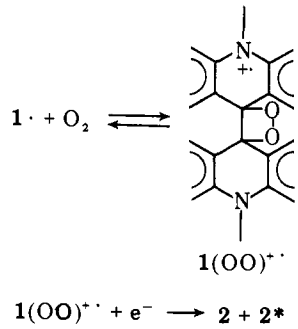
Scheme IV



predict (1) a rate of disappearance of **1** which would possess a first-order dependence upon $[HO^-]$ at lower pHs and a dependence upon $[HO^-]^2$ at higher pHs; (2) identical rates for CL (k_b) and non-CL (k_{obsd}) reactions since the concentrations of CL pathway intermediates would be controlled by the concentrations of **1**, **1**(OH), and **1**$(OH)_2$; (3) both the CL reaction and buildup of radicals would be biphasic; (4) constant Φ_{CL} with increasing pH since both CL and non-CL paths involve one or two hydroxide additions; (5) a first-order increase in Φ_{CL} with increasing [**1**] since two molecules of **1** or its derivatives such as **1**(OH), **1**$(OH)_2$, **3**, or **4** are required in the comproportionation reactions (eq 10, 14–17); (6) radicals would be formed, some, such as **1**· and **1**(OH)· which have been previously detected and identified.[3a]

Legg and Hercules[5] have shown that the reaction of superoxide (O_2^-·) with **1** results in CL. A similar conclusion was reached by Fridovich[12] since CL had been observed upon the addition of **1** to a xanthine–xanthine oxidase system, which is known to produce O_2^-. We have found that addition of superoxide dismutase to a solution of **1** in aerobic 0.1 M carbonate (pH 10.7) decreased the amount of light produced (Table VII), but on the other hand so did the addition of bovine serum albumin. Superoxide could arise on reaction of molecular oxygen with the various radical species formed in the present system. Direct participation of O_2^-· in the CL reaction of this study could arise from the reactions

$$\mathbf{1}\cdot + O_2 \rightleftarrows \mathbf{1} + O_2^-\cdot \quad (18)$$

$$\mathbf{1}\cdot + O_2^-\cdot \rightarrow \mathbf{1}(OO) \rightarrow \mathbf{2} + \mathbf{2}^* \quad (19)$$

Addition of potassium superoxide to solutions of **1** at various pHs did not increase either maximum light intensity or quantum yield (Table VIII). A mechanism consistent with the kinetic and quantum yield data, which does not invoke O_2^-·, is presented in Scheme IV.

Acknowledgment. This work was supported by grants from the National Science Foundation and the National Institutes of Health.

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Total Synthesis of (±)-Pederamide

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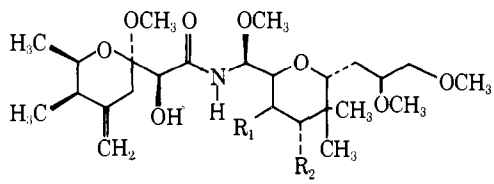
Abstract: The synthesis of (±)-pederamide (**2**), a key intermediate in the projected total synthesis of pederin (**1a**), a vesicant component of the hemolymph of the staphylinid beetle *Paederus fuscipes*, is described. The preparation of **2** is accomplished in 16 steps, starting from *trans*-2-butene epoxide.

Pederin, **1a**, a vesicant component in the hemolymph of many species of staphylinid beetle (genus *Paederus*), is a powerful inhibitor of protein synthesis in eucaryotic cells.[2]



1a, R_1 = H; R_2 = OH
b, R_1 = OH; R_2 = H

Although the marked vesicatory effect of these beetles on man and animals was described as early as 1912,[3] it was not until 1949 that the principle responsible for this action was isolated by A. Ueta.[4] Pavan and Bo, in an independent study, obtained the active component contained in the hemolymph of *Paederus fuscipes* in crystalline form, and named it "pederin".[5]

Pederin was initially formulated as **1b**, based primarily on degradative studies.[6] Detailed NMR spectral analysis,[7] however, suggested that the structure was better represented as **1a**; this was confirmed by two independent X-ray crystallographic studies, carried out on the corresponding bis(*p*-bromobenzoate) of pederin. This work also established the absolute configuration of **1a**.[8]

Investigations of the acid-catalyzed hydrolysis of pederin have yielded, as the major products, pederamide (**2**), pederenal (**3**), and meropederin acetal (**4**), depending on the choice of

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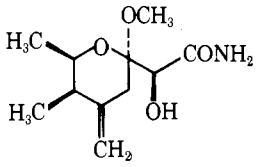

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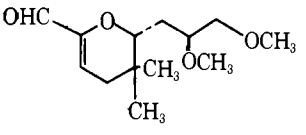

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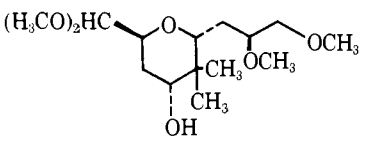
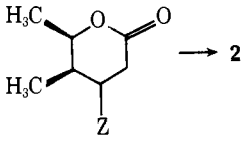


4

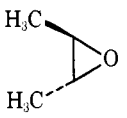
reaction conditions.[9,10] We decided to attempt a convergent synthesis of pederin involving construction of the amide and aldehyde (or acetal) portions of the molecule, followed by a coupling of the two components to generate the centrally located *O*-methylcarbinolamide functionality. This paper reports the synthesis of (±)-pederamide (**2**), a key intermediate in our projected synthesis of **1a**.[11]

Strategy directed toward the synthesis of **2** may be divided into several parts: construction of a unit bearing two cis, vicinal methyl groups, introduction of an exocyclic methylene group, and introduction of the geminal methoxy and hydroxyacetamido substituents. We thought that, if a suitably substituted δ-valerolactone were prepared, methods could be developed both for introduction of the exocyclic methylene and for replacement of the lactonic carbonyl group with the appropriate substituents (eq 1).



(1)

Opening of the epoxide ring of *trans*-2-butene epoxide (**5**)[12] with the ethylenediamine complex of lithium acetylide in dimethyl sulfoxide provides, in 77% yield, a product (**6**) with the



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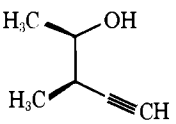
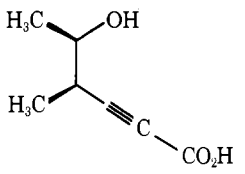


6

desired erythro relationship unambiguously established. Acetylenic alcohol **6** was further elaborated according to the general method of Haynes and Jones,[13] allowing construction of α,β-unsaturated lactone **7** (eq 2) in the following manner.



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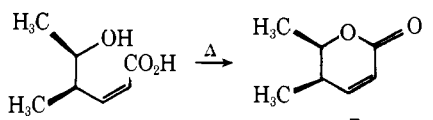


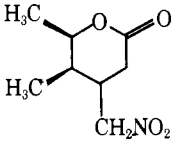
(2)

7

The bis-anion of **6** was generated in THF by addition of 2 equiv of *n*-butyllithium at −40 °C. Carboxylation of the acetylenic anion with gaseous carbon dioxide, followed by treatment with aqueous acid, gave acetylenic acid **8** in 56% yield.

Hydrogenation of **8** over 5% palladium on barium sulfate, poisoned with quinoline, gave the desired cis olefin.[14-16] Distillation of the crude olefinic acid at reduced pressure resulted in lactonization, giving **7** in 82% yield.

Consideration of the reactivity of an α,β-unsaturated lactone led to the conclusion that a functional group amenable to further conversion to the required exocyclic methylene group might be introduced by a Michael addition reaction. Pursuing this idea, the anion of nitromethane, generated with Triton-B, was found to add smoothly to lactone **7** at room temperature, giving nitrolactone **9** in 88% yield. It is interesting to note that



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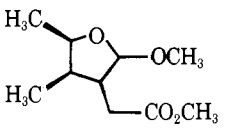
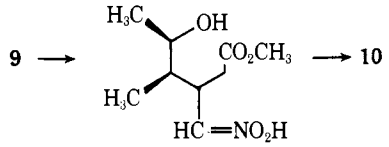


10

the ^{1}H NMR spectrum and chromatographic evidence indicate that only one isomer of **9** is formed under these reaction conditions. While this detail is not significant for the ultimate stereochemistry of pederamide, it does make analysis of the isomeric mixtures produced in later reactions much easier.

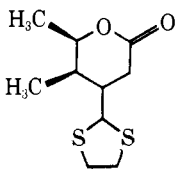
We hoped to convert the nitromethylene group of **9** to an aldehyde or acetal function using the Nef reaction[17,18] as modified by Jacobson.[19] Toward this end, **9** was converted into its *aci*-nitro anion by dissolving it in 0.5 N sodium methoxide at room temperature. The solution of nitronate salt was quickly added to cold (−35 °C) methanolic sulfuric acid. The product isolated proved not to be the desired dimethyl acetal, but was the rearranged ketal **10** (98% yield). This product apparently arises from initial methanolysis of the lactone with sodium methoxide to give a nitronate hydroxy ester (eq 3), the intra-



(3)

molecular hydroxyl group of which then participates in the Nef process in place of 1 mol of methanol. Acetal **10** is formed as a mixture of two epimers.

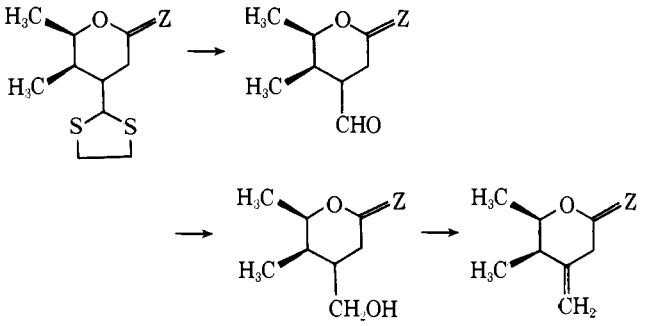
The rearranged acetal, **10**, proved to be a useful intermediate, since it was possible to regenerate the six-membered ring from it. Thus, using the reaction conditions suggested by Seebach and Corey[20] for the conversion of acetals to thioacetals, we found that compound **11** could be generated from **10**



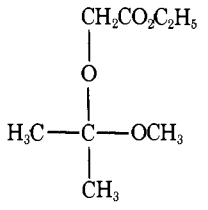
11a, oily isomer
b, crystalline isomer

in good yield. Acetal **10** was dissolved in chloroform and the solution was cooled to −35 °C. Hydrogen chloride gas was bubbled into the solution for 0.5 h and then an equivalent of ethanedithiol was added; the mixture was warmed to room temperature and allowed to stand for 10 h. This procedure resulted in isolation of **11a** in 96% yield. Allowing **10** to stand in chloroform–hydrogen chloride solution for 10 h before adding ethanedithiol resulted in isolation of **11b**, a crystalline isomer of the dithiolane lactone, in 85% yield. Whereas the solid isomer is readily purified by recrystallization, it was inconvenient to use in later experiments due to its tendency to crystallize from moderately concentrated tetrahydrofuran (THF) solutions. Therefore, the oily isomer was used for continuation of the synthetic sequence.

Dithiolane lactone **11** seemed to be an ideal substrate for our elaboration of the pederamide side chain. It possesses the necessary vicinal *cis*-dimethyl substituents, and the dithiolane ring provides a masked exocyclic methylene group which may be converted into the desired double bond at an appropriate time, for example, as suggested by the sequence of transformations outlined below:



When dithiolane lactone **11a** was treated with the lithium enolate of **12** in THF at −75 °C, adduct **13** was isolated in 84% yield. The alcohol protecting group was removed in essentially quantitative yield by treatment with hydrochloric acid in THF, giving hemiketal alcohol **14** as a mixture of epimers.



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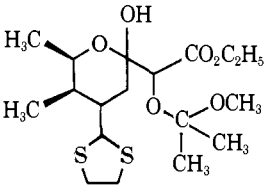

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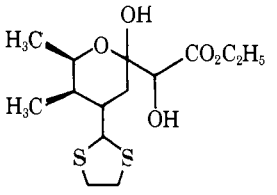

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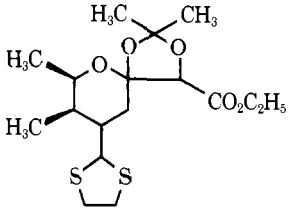
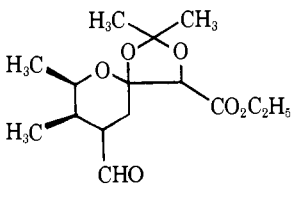


15

Preliminary experiments had indicated that the hemiketal functionality was quite labile under reaction conditions to be used later in the synthetic sequence. It was deemed necessary, therefore, to protect this sensitive group at as early a stage as possible. We decided to take advantage of the fact that our condensation products were α-hydroxyhemiketals, possessing the reactivity of 1,2-diols. Consequently hemiketal alcohol **14** was converted to acetonide **15** as a mixture of epimers with acetone and phosphorus pentoxide in 81% yield.

The dithiolane ring of **15** was cleaved by using the oxidative hydrolysis conditions of Seebach.[21,22] Compound **15** was dissolved in 4:1 acetonitrile-water. To this solution were added 1.5 equiv of red mercuric oxide and 2 equiv of mercuric chloride. This suspension was heated at 62 °C for 8 h. The red color of the mercuric oxide was gradually discharged; when the suspension became tan-colored, the reaction was complete. After the workup, a 92% yield of aldehyde **16** was obtained.



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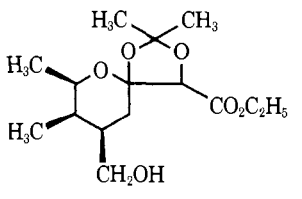
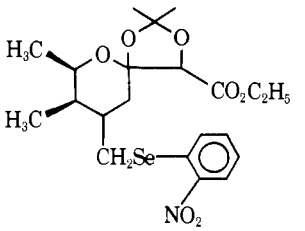


17

This aldehyde was immediately reduced with sodium borohydride in ethanol at 0 °C to give alcohol **17** in quantitative yield.

Alcohol **17** was converted to aryl selenide **18** by treatment with *o*-nitrophenylselenocyanate and tri-*n*-butylphosphine in THF in 94% yield, after purification by silica gel column chromatography.[23] Selenide **18** was then transformed to the



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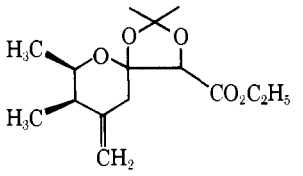

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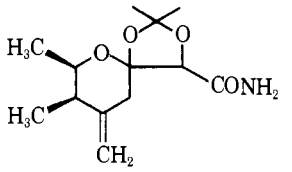

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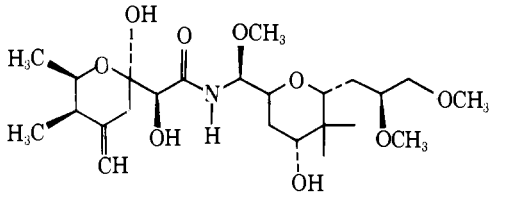
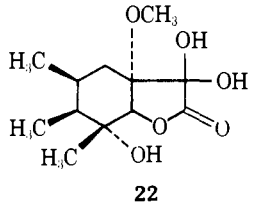


21

exocyclic olefin, **19**, by oxidation with hydrogen peroxide. By stirring with concentrated ammonium hydroxide in methanol, **19** was converted to the corresponding amide, **20**. This amide was treated with anhydrous hydrochloric acid in methanol in an attempt to remove the acetonide protecting group and generate pederamide, **2**. Under these conditions, it was expected that the hemiketal would be converted stereospecifically into the α-methoxy-containing ketal. This expectation was based on an observation by Cardani[10] that pseudopederin, **21**, captures methanol stereospecifically from its α face to generate pederin. However, instead of the desired ketal, a rearranged product was isolated; this product was identified as pederinolactone, **22**, a known degradation product of pederin.[10,24]

It is believed that a key step in the formation of pederinolactone from pederin is an allylic oxidation, presumably due to traces of atmospheric oxygen.[10] To test the applicability of this observation to our case, the methanolysis of **20** was conducted in a system from which oxygen was rigorously excluded. While pederinolactone formation was undetected, only decomposition products were isolated.



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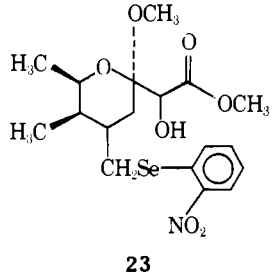


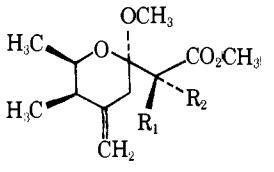
23

For successful removal of the acetonide, it was necessary to return to an intermediate in which the exocyclic double bond had not yet been introduced. Aryl selenide **18** was therefore subjected to treatment with acidic methanol. The acetonide

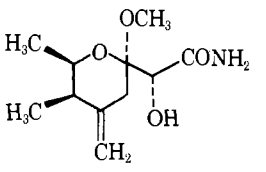
was smoothly removed, giving ketal alcohol **23** in excellent yield. The ethyl ester group had transesterified under the reaction conditions, giving the methyl ester.

Oxidation of the selenium atom of **23** with hydrogen peroxide, followed by thermal elimination of the aryl selenyl residue at room temperature, generated the exocyclic olefin in 52% overall yield.[25] The product was a mixture of methyl pederate (**24**) and methyl *epi*-pederate (**25**); the isomers were formed in about equal amounts. The epimeric mixture was separated by column chromatography by using deactivated silica gel. Stereochemical assignments were made based on the published proton NMR spectra.[11b]

Methyl pederate (**24**) was dissolved in anhydrous methanol and placed in a pressure reaction tube. After bubbling ammonia through the solution for 20 min, the tube was sealed. Heating at 100 °C for 48 h converted **20** to racemic pederamide (**2**) in quantitative yield. Under identical reaction conditions, methyl *epi*-pederate (**25**) was converted to *epi*-pederamide (**26**) in 81% yield.



24, R_1 = OH; R_2 = H
25, R_1 = H; R_2 = OH



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Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise noted, all reactions were conducted in an atmosphere of argon. Solvent mixtures are described as ratios by volume, and removal of solvents was performed at reduced pressure by using a rotary evaporator.

Tetrahydrofuran (THF) and *p*-dioxane were freshly distilled from sodium benzophenone ketyl; benzene and dimethyl sulfoxide were distilled from calcium hydride. Pentane was filtered through silica gel and distilled.

Microanalyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark, or Galbraith Laboratories, Knoxville, Tenn.

Infrared (IR) spectra were obtained on a Perkin-Elmer Model 257 spectrometer. Proton nuclear magnetic resonance (NMR) spectra were determined in deuteriochloroform containing 5% tetramethylsilane as an internal standard. The NMR spectra were obtained either on a Varian EM-390, Varian A-60A, Bruker HX-90, or Bruker HX-270 spectrometer. NMR data are expressed in parts per million (ppm) downfield from Me_4Si (δ = 0).

Mass spectra were recorded by using either an AEI-MS-902 mass spectrometer or a Finnigan Model 3300 gas chromatograph–mass spectrometer. Unless otherwise noted, electron impact mass spectra (EIMS) were obtained at 70 eV and chemical ionization mass spectra (CIMS) were determined by using methane as the ionizing gas.

(2*R,3*R**)-2,3-Dimethylethylene Oxide (5).** This compound was prepared as described in the literature.[13]

(3*R,4*R**)-3,4-Dimethyl-1-butyn-4-ol (6).** In a flask equipped with a dry ice condenser were placed lithium acetylide (commercially available from Alfa Inorganics, Inc., as the ethylenediamine complex, 375 g, 1.25 mol) and 800 mL of dimethyl sulfoxide. The solution was cooled to 0 °C and *trans*-2-butene epoxide, **5** (90 g, 1.25 mol), was added dropwise over a 1-h period. The reaction mixture was held at 0 °C for 24 h and then allowed to warm to room temperature. After 1 week, the reaction mixture was quenched with water and diluted with pentane. The aqueous layer was saturated with ammonium chloride. Continuous extraction with pentane for 3 days gave crude product which distilled at 55–57 °C (25 Torr) to give 67 g (55%) of a colorless liquid: IR ($CHCl_3$) 3560, 3450, 3300, 2950 cm^{-1}; NMR ($CDCl_3$) 1.15 (d, 3 H, J = 5 Hz), 1.25 (d, 3 H, J = 4 Hz), 2.15 (s, 1 H), 2.45 (m, 1 H), 3.45 (s, 1 H), 3.60 (m, 1 H) ppm; CIMS, *m/e* (rel intensity) 99 (5, $M^+ + 1$), 81 (100), 67 (10).

(4*R, 5*R**)-4,5-Dimethyl-5-hydroxypent-2-ynoic Acid (8).** In a flask equipped with a mechanical stirrer were placed 1 L of THF and acetylenic alcohol **6** (37.9 g, 0.387 mol). The solution was cooled to −40 °C. *n*-Butyllithium (360 mL of a 2.4 M solution in hexane, 2.3 equiv) was added dropwise, with stirring. The reaction temperature was maintained at −40 °C for 1 h after completion of the *n*-butyllithium addition. Carbon dioxide gas was then bubbled through the solution via a gas dispersion tube for 0.5 h. The reaction mixture was poured onto crushed dry ice and acidified with 6 N hydrochloric acid. The aqueous layer was extracted three times with diethyl ether and the combined ether solution was dried over magnesium sulfate. Filtration followed by concentration at reduced pressure gave an oil that crystallized upon standing. The crystals were washed with hexane to give 30.7 g (56%) of acetylenic acid **8.** Recrystallization of a small sample from 1:1 chloroform–hexane gave white crystals: mp 91–93 °C; IR ($CHCl_3$) 3500, 2980, 2600, 2210, 1770 cm^{-1}; NMR ($CDCl_3$) 1.2 (d, 3 H, J = 4 Hz), 1.3 (d, 3 H, J = 3 Hz), 2.65 (m, 1 H), 3.75 (m, 1 H), 7.35 (bs, 1 H) ppm; CIMS, *m/e* (rel intensity) 143 (2, $M^+ + 1$), 125 (100).

Anal. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.04. Found: C, 58.98; H, 7.02.

(5*R,6*R**)-5,6-Dimethyl-5,6-dihydro-2*H*-pyran-2-one (7).** Acid **8** (11 g, 0.078 mol) was dissolved in 300 mL of methanol. Palladium (5%) on barium sulfate (1.5 g) and quinoline (0.75 g) were added to the solution. The acetylenic acid was semihydrogenated at 1 atmosphere hydrogen pressure until 95% of the theoretical amount of hydrogen was taken up. The solution was filtered through Celite and the methanol was removed by evaporation at reduced pressure. The resulting oil was heated to 95 °C at a pressure of 2 Torr. Material boiling between 75 and 100 °C was collected. This material was redistilled and the fraction boiling at 52–53 °C (0.2 Torr) was collected. This fraction afforded 8.06 g (82%) of lactone **7:** IR ($CHCl_3$) 2990, 1715, 1695, 1375, 1365, 1245, 1085, 985, 820 cm^{-1}; NMR ($CDCl_3$) 1.01 (d, 3 H, J = 8 Hz), 1.33 (d, 3 H, J = 7 Hz), 2.4 (m, 1 H), 4.6 (m, 1 H), 5.88 (d, 1 H, J = 10 Hz), 6.98 (d of d, 1 H, J = 10 Hz, 6 Hz) ppm; EIMS, *m/e* (rel intensity) 126 (1, M^+), 82 (100), 54 (29), 53 (22). CIMS, *m/e* (rel intensity) 127 (100, $M^+ + 1$), 110 (7), 109 (85), 82 (14); CIMS (He charge exchange), *m/e* (rel intensity) 82 (100), 81 (22).

(5*R,6*R**)-Tetrahydro-4-nitromethyl-5,6-dimethyl-2*H*-pyran-2-one (9).** Lactone **7** (4.0 g, 0.032 mol) was dissolved in 100 mL of reagent grade nitromethane and Triton-B (benzyltrimethylammonium hydroxide, as a 40% solution in methanol, 0.5 mL) was added to the solution. The reaction mixture was stirred at room temperature for 10 h and then diluted with 250 mL of diethyl ether. The organic phase was washed once each with 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate solution, water, and saturated aqueous sodium chloride solution. The organic material was dried over magnesium sulfate, filtered, and concentrated at reduced pressure. Traces of nitromethane were removed by evaporation at high vacuum (0.01 Torr) for several hours. The resulting oil was essentially pure nitrolactone (5.2 g, 88%). A small sample was purified by Kugelrohr distillation (bp 150–160 °C at 0.2 Torr): IR ($CHCl_3$) 3040, 3000, 2945, 1730, 1550, 1425, 1260, 1090, 1000, 965 cm^{-1}; NMR ($CDCl_3$) 1.03 (d, 3 H, J = 7 Hz), 1.3 (d, 3 H, J = 6 Hz), 1.9 (m, 2 H), 2.55 (m, 2 H), 4.6 (m, 3 H) ppm. CIMS, *m/e* (rel intensity) 188 (62, $M^+ + 1$), 170 (21), 158 (25), 157 (12), 155 (5), 142 (11), 141 (100), 140 (18), 128 (51), 127 (17), 123 (31), 99 (9), 95 (12).

Anal. Calcd for $C_8H_{13}O_4N$: C, 51.33; H, 6.95; N, 7.48. Found: C, 51.56; H, 7.10; N, 7.34.

Methyl (4*R,5*R**)-Tetrahydro-2-methoxy-4,5-dimethyl-3-furan Acetate (10).** The nitronate salt of nitrolactone **9** was generated by dissolving nitrolactone **9** (9.5 g, 0.051 mol) in 120 mL of a 0.5 N solution of sodium methoxide in methanol. Concentrated sulfuric acid (120 mL) was dissolved in 450 mL of methanol and the solution was cooled to −35 °C. The nitronate salt solution was added dropwise to the cold, acidic methanol over a 10-min period. After addition was complete, the reaction mixture was warmed to room temperature, poured into 600 mL of methylene chloride and washed twice with 300 mL portions of water, three times with 150 mL portions of 10% aqueous sodium hydroxide solution, and once with 100 mL of saturated aqueous sodium chloride solution. The organic material was dried over potassium carbonate, filtered, and concentrated at reduced pressure to give 10.1 g (98%) of acetal ester **10** as an epimeric mixture. This product was shown to be pure by GLC analysis (3% OV-1 on Gaschrom-Q). A small sample was Kugelrohr distilled: bp 105–110 °C at 0.8 Torr; IR ($CHCl_3$) 2990, 1730, 1430, 1380, 1270, 1170, 1080,

990 cm^{-1}; NMR ($CDCl_3$) (major isomer) 0.75 (d, 3 H, J = 7 Hz), 1.13 (d, 3 H, J = 6 Hz), 2.47 (m, 4 H), 3.30 (s, 3 H), 3.68 (s, 3 H), 4.23 (m, 1 H), 4.6 (d, 1 H, J = 5 Hz); (minor isomer) 0.86 (d, 3 H, J = 6 Hz), 1.15 (d, 3 H, J = 6 Hz), 2.47 (m, 4 H), 3.25 (s, 3 H), 3.68 (s, 3 H), 4.23 (m, 1 H), 4.78 (d, 1 H, J = 5 Hz) ppm; EIMS, *m/e* (rel intensity) 201 (2.4, $M^+ - 1$), 171 (100, $M^+ - OCH_3$), 158 (68), 142 (61), 139 (56).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.41; H, 8.91. Found: C, 59.31; H, 8.96.

(5*R,6*R**)-Tetrahydro-4-(1,3-dithiolan-2-yl)-5,6-dimethyl-2*H*-pyran-2-one, Oily Isomer (11a).** Acetal ester **10** (4.2 g, 0.021 mol) was dissolved in 100 mL of chloroform and placed in a flask equipped with a low-temperature thermometer and a calcium sulfate drying tube. The solution was cooled to −35 °C and hydrogen chloride gas (dried by passing through concentrated sulfuric acid) was added to the solution through a tube opening below the surface of the liquid. After 20 min, hydrogen chloride addition was stopped and ethanedithiol (2 g, 0.021 mol) was added in one portion. The reaction mixture was stirred an additional 30 min at −35 °C and was then warmed to room temperature. The flask was tightly stoppered and allowed to stand for 10 h. The reaction mixture was washed once with water, once with 10% aqueous potassium hydroxide solution, twice with water, and once with saturated aqueous sodium chloride solution. All organic material was dried over magnesium sulfate, filtered, and concentrated at reduced pressure to give 5.2 g of crude dithiolane lactone **11a** as an oil. Column chromatography (silica gel, 30% ether in pentane) gave 4.68 g (96%) of pure dithiolane lactone **11a.** A small sample was purified by Kugelrohr distillation (bp 130–140 °C at 0.05 Torr): IR ($CHCl_3$) 2940, 1730, 1500, 1380, 1260, 1110, 1000 cm^{-1}; NMR ($CDCl_3$) 1.0 (d, 3 H, J = 7 Hz), 1.31 (d, 3 H, J = 6 Hz), 2.0 (m, 2 H), 2.65 (d of d, 2 H, J = 8 Hz), 3.25 (s, 4 H), 4.54 (m, 1 H), 4.76 (d, 1 H, J = 5 Hz) ppm; EIMS, *m/e* (rel intensity) 127 (12, M^+ − dithiolane), 105 (100, dithiolane$^+$), 82 (13).

(5*R,6*R**)-Tetrahydro-4-(1,3-dithiolan-2-yl)-5,6-dimethyl-2*H*-pyran-2-one, Crystalline Isomer (11b).** Allowing acetal ester **10** to stand in chloroform–hydrogen chloride solution for 10 h before proceeding with dithioacetalization, as described in the previous experiment, results in isolation of a crystalline isomer of dithiolane lactone, mp 108–109 °C (recrystallized from 1:1 methylene chloride–heptane), in 85% yield; IR ($CHCl_3$) 2990, 2910, 1715, 1385, 1335, 1205, 1105, 1000, 970 cm^{-1}; NMR ($CDCl_3$) 0.88 (d, 3 H, J = 7 Hz), 1.33 (d, 3 H, J = 6 Hz), 2.2 (m, 3 H), 2.8 (m, 1 H), 3.25 (s, 3 H), 4.44 (m, 2 H) ppm; EIMS, *m/e* (rel intensity): 232 (3, M^+), 142 (15), 127 (30), 107 (22), 106 (12), 105 (100); CIMS, *m/e* (rel intensity) 233 (25, $M^+ + 1$), 107 (38), 106 (21), 105 (100), 89 (12).

Anal. Calcd for $C_{10}H_{16}O_2S_2$: C, 51.72; H, 6.89; S, 27.58. Found: C, 51.80; H, 6.97; S, 27.47.

Ethyl *O*-(2-Methoxy-2-propyl)glycolate (12). Freshly distilled ethyl glycolate (116 g, 1.12 mol) was mixed with 2-methoxypropene (93.6 g, 1.3 mol). The solution was cooled to 0 °C and concentrated hydrochloric acid (0.2 mL) was added. The reaction mixture was warmed to room temperature and allowed to stand for 7 h. The solution was then poured into 300 mL of hexane and washed once with saturated aqueous sodium bicarbonate solution. The organic material was dried with potassium carbonate, filtered, and concentrated at reduced pressure. Distillation gave 170.7 g (87%) of ester **12:** bp 58–60 °C at 2.5 Torr; IR ($CHCl_3$) 2990, 1745, 1455, 1370, 1300, 1190, 1140, 1100, 1055, 835, 815 cm^{-1}; NMR ($CDCl_3$) 1.3 (t, 3 H, J = 7 Hz), 1.4 (s, 6 H), 3.25 (s, 3 H), 4.08 (s, 2 H), 4.23 (q, 2 H, J = 7 Hz) ppm; CIMS, *m/e* (rel intensity) 145 (100, $M^+ - OCH_3$).

Ethyl (5*R,6*R**)-Tetrahydro-2-hydroxy-4-(1,3-dithiolan-2-yl)-5,6-dimethyl-2*H*-pyran-2-[α-(2-methoxyprop-2-yl)oxy]acetate (13).** In a flame-dried flask were placed 5 mL of THF and diisopropylamine (0.74 g, 0.009 mol), and the solution was cooled to 0 °C. *n*-Butyllithium (3.6 mL of a 2.2 M solution in hexane, 0.008 mol) was added dropwise over a 5-min period. The reaction mixture was stirred for 0.5 h and then cooled to −75 °C. Ester **12** (1.62 g, 0.009 mol) was dissolved in 3 mL of THF and added dropwise to the cold lithium diisopropylamide solution. One hour after ester addition, dithiolane lactone **11a** (1.43 g, 0.006 mol), dissolved in 4 mL of THF, was added in 1-mL portions to the ester enolate solution. The reaction mixture was maintained at −75 °C for an additional 2 h, then slowly warmed to −20 °C and quenched by addition of 2 mL of ethanol. The quenched reaction mixture was diluted with diethyl ether and poured into water. The aqueous layer was extracted twice with diethyl ether and the combined ether solution was washed once with water and dried over potassium carbonate. Filtration followed by concentration at reduced pressure gave 2.4 g (84%) of hemiketal **13** which was essentially pure by TLC: IR ($CHCl_3$) 3850, 3000, 1730, 1380, 1370, 1090, 820 cm^{-1}; NMR ($CDCl_3$) 1.08 (m, 6 H), 1.35 (m, 9 H), 1.9 (m, 4 H), 3.21 (m, 7 H), 4.2 (m, 4 H), 5.25 (d, 1 H, J = 10 Hz) ppm.

Ethyl (5*R,6*R**)-Tetrahydro-2-hydroxy-4-(1,3-dithiolan-2-yl)-5,6-dimethyl-2*H*-pyran-2-glycolate (14).** Hemiketal **13** (0.11 g, 0.03 mmol) was dissolved in 10 mL of THF. One drop of concentrated hydrochloric acid was added and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution was added. The combined aqueous material was extracted twice with diethyl ether and the organic extract was dried over magnesium sulfate. Filtration followed by concentration at reduced pressure gave 0.09 g (99%) of hemiketal alcohol **14:** IR ($CHCl_3$) 3580, 3000, 2960, 1735, 1100 cm^{-1}; NMR ($CDCl_3$) epimeric mixture, 0.9 (m, 6 H), 1.28 (t, 3 H, J = 9 Hz), 1.95 (m, 3 H), 2.65 (m, 1 H), 3.24 (s, 3 H), 4.3 (m, 4 H), 4.75 (d, 1 H, J = 6 Hz, epimer A), 5.05 (d, 1 H, J = 6 Hz, epimer B) ppm; EIMS, *m/e* (rel intensity) 336 (5, M^+), 335 (12), 334 (41), 316 (10), 226 (20), 214 (12), 213 (100), 208 (41), 195 (28), 155 (11), 153 (35), 127 (13), 125 (16), 111 (23), 109 (18), 105 (70), 97 (12), 95 (14), 81 (17), 79 (11), 77 (26). EIMS exact mass determination calcd for $C_{14}H_{23}O_5S_2^+$ ($M^+ - 1$): 335.0987. Found: 335.0956.

Ethyl (7*R,8*R**)-9-(1,3-Dithiolan-2-yl)-2,2,7,8-tetramethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxylate (15).** Hemiketal alcohol **14** (1.67 g, 0.005 mol) was dissolved in 100 mL of acetone (previously dried over potassium carbonate and distilled) and a small amount of phosphorus pentoxide was added. The reaction mixture was stirred at room temperature for 10 h. A second portion of phosphorus pentoxide was added and stirring was continued for an additional 5 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution was added. The aqueous material was extracted three times with diethyl ether and the combined extract was dried over potassium carbonate. The solution was filtered and concentrated at reduced pressure to remove ether and acetone. The residue was diluted with chloroform and filtered through Florisil to give 1.5 g (81%) of acetonide ester **15.** A small sample was further purified by TLC (silica gel, 1:1 pentane–diethyl ether): IR ($CHCl_3$) 2950, 2920, 1755, 1380, 1370, 1110, 995 cm^{-1}; NMR ($CDCl_3$), epimeric mixture 0.95 (d, 3 H, J = 7 Hz), 1.03 (d, 3 H, J = 6 Hz), 1.4 (m, 3 H), 1.43 (s, 3 H), 1.58 (s, 3 H), 2.1 (bm, 4 H), 3.2 (s, 4 H), 4.2 (bm, 1 H), 4.23 (q, 2 H, J = 7 Hz), 4.27 (s, 1 H), 5.02 (bs, 1 H, epimer A), 5.2 (bs, 1 H, epimer B) ppm. A small sample was purified by Kugelrohr distillation (bp 100–110 °C, 0.2 Torr).

Anal. Calcd for $C_{17}H_{28}O_5S_2$: C, 54.26; H, 7.45; S, 17.02. Found: C, 54.36; H, 7.58; S, 16.95.

Ethyl (7*R,8*R**)-9-Formyl-2,2,7,8-tetramethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxylate (16).** Acetonide ester **15** (1.03 g, 0.0027 mol) was dissolved in 12.5 mL of 4:1 acetonitrile–water. To this solution were added mercuric oxide (red, 0.89 g, 0.0041 mol) and mercuric chloride (1.46 g, 0.0054 mol). The suspension was heated to 62 °C and stirred for 8 h. At the end of this time, the red color of the mercuric oxide had been discharged and a TLC analysis showed that the starting material had been consumed. The reaction mixture was filtered through Celite and the filter cake was washed with diethyl ether. The ether solution was washed four times with 5 M aqueous ammonium acetate solution, and once each with water, saturated aqueous sodium bicarbonate solution, again with water and finally with saturated aqueous sodium chloride solution. The ether solution was dried over magnesium sulfate, filtered, and concentrated at reduced pressure to give 0.75 g (92%) of aldehyde **16:** IR ($CHCl_3$) 2965, 2720, 1760, 1730, 1460, 1445, 1385, 1370, 1200, 1120, 1065, 995, 890 cm^{-1}; NMR ($CDCl_3$) 1.1 (m, 6 H), 1.3 (m, 3 H), 1.5 (m, 6 H), 2.2 (m, 4 H), 4.2 (m, 1 H), 4.3 (q, 2 H, J = 7 Hz), 4.35 (s, 1 H), 9.7 (d, 1 H, J = 6 Hz) ppm.

Ethyl (7*R,8*R**)-9-Hydroxymethyl-2,2,7,8-tetramethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxylate (17).** Aldehyde **16** (0.613 g, 0.002 mol) was dissolved in 10 mL of ethyl alcohol and the solution was cooled to 0 °C. Sodium borohydride (0.076 g, 0.002 mol, 4 equiv) was added to the cold solution in one portion. After 15 min, TLC analysis indicated that all of the aldehyde had been consumed. The reaction mixture was quenched by addition of dilute, aqueous ammonium chloride solution. Ethyl alcohol was removed by evaporation at reduced pressure and the aqueous residue was extracted with diethyl

ether. The ether solution was washed once with water and once with saturated, aqueous sodium chloride solution. The organic material was dried over magnesium sulfate, filtered and concentrated at reduced pressure to give 0.62 g (100%) of alcohol **17:** IR ($CHCl_3$) 3600, 3500, 2965, 2920, 2880, 1775, 1455, 1385, 1375, 1200, 1115, 1000, 885 cm^{-1}; NMR ($CDCl_3$) 0.74 (d, 3 H, J = 7 Hz), 1.02 (d, 3 H, J = 7 Hz), 1.29 (t, 3 H, J = 8 Hz), 1.41 (s, 3 H), 1.58 (s, 3 H), 2.1 (bm, 4 H), 2.85 (s, 1 H), 3.55 (m, 2 H), 4.25 (q, 2 H, J = 8 Hz), 4.29 (s, 1 H), 4.3 (m, 1 H) ppm; EIMS, *m/e* (rel intensity) 287 (38, $M^+ - CH_3$), 241 (19), 227 (21, $M^+ - O{-}C(CH_3){=}CH_2 - H_2O$), 226 (11), 223 (20), 200 (48), 197 (18), 189 (13), 187 (10), 186 (73), 171 (37), 155 (26), 144 (30), 114 (10), 113 (100), 97 (37), 95 (11), 87 (29), 59 (67), 57 (11), 56 (12), 55 (42); CIMS, *m/e* (rel intensity) 285 (25, $(M^+ + 1) - H_2O$), 246 (14), 245 (100, $M^+ - O{-}C(CH_3){=}CH_2$), 227 (36).

Ethyl (7*R,8*R**)-9-[(2-Nitrophenylselenyl)methyl]-2,2,7,8-tetramethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxylate (18).** Alcohol **17** (1.0 g, 0.0033 mol) was dissolved in 20 mL of THF containing *o*-nitrophenylselenocyanate (0.9 g, 0.004 mol) and the solution was cooled to 0 °C. Tri-*n*-butylphosphine (0.81 g, 0.004 mol) was added dropwise. During the addition, the reaction mixture turned deep red; the color gradually changed to yellow as the reaction proceeded. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 12 h. The solvent was removed by evaporation at reduced pressure and the residue was purified by column chromatography (grade III silica gel, 3:1 hexane–diethyl ether) to give 1.5 g (94%) of aryl selenide **18** as a mixture of epimers: IR ($CHCl_3$) 3020, 2980, 1760, 1595, 1570, 1515, 1455, 1395, 1385, 1335, 1305, 1110, 905 cm^{-1}; NMR ($CDCl_3$) 0.9 (d, 3 H, J = 6 Hz), 1.05 (d, 3 H, J = 7 Hz), 1.28 (t, 3 H, J = 7 Hz), 1.45 (s, 3 H), 1.56 (s, 3 H), 1.9 (bm, 4 H), 3.26 (m, 2 H), 4.25 (q, 2 H, J = 7 Hz), 4.25 (m, 1 H), 4.29 (s, 1 H), 7.85 (bm, 4 H) ppm; CIMS, *m/e* (rel intensity) 487 (2, $M^+ + 1$), 432 (21), 431 (21), 430 (100, $(M^+ + 1) - O{-}C(CH_3){=}CH_2$), 429 (10), 428 (53), 427 (19), 426 (20), 412 (27), 410 (13), 243 (13), 227 (77), 210 (11), 209 (59), 202 (18), 191 (12), 173 (28), 59 (59).

Ethyl (7*R,8*R**)-9-Methylene-2,2,7,8-tetramethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxylate (19).** Alcohol **17** (0.62 g, 0.002 mol) and *o*-nitrophenylselenocyanate (0.55 g, 0.0024 mol) were dissolved in 15 mL of THF. The solution was cooled to 0 °C and tri-*n*-butylphosphine (0.49 g, 0.0024 mol, distilled) was added dropwise. During the addition, the reaction mixture turned deep red; the color gradually changed to yellow as the reaction proceeded. After the addition was completed, the reaction mixture was warmed to room temperature. After 6 h, TLC analysis indicated that the alcohol had been consumed. Solvent was removed by evaporation at reduced pressure and the residue was chromatographed (silica gel, 3:1 hexane–diethyl ether) to give 1.2 g of a yellow oil. This oil was dissolved in 15 mL of THF and cooled to 0 °C. Hydrogen peroxide (30% aqueous solution, 2.3 mL, 0.02 mol) was added dropwise over a 10-min period. The reaction mixture was then warmed to room temperature. After 10 h, water was added and the reaction mixture was extracted three times with benzene. The benzene extract was washed three times with saturated aqueous sodium bicarbonate solution, once with water and once with saturated aqueous sodium chloride solution. The organic material was dried over magnesium sulfate, filtered, and concentrated at reduced pressure. The residue was diluted with methylene chloride and chromatographed (alumina, activity grade I, methylene chloride) and 0.047 g (83%) of exocyclic olefin **19** was obtained as a mixture of isomers: IR ($CHCl_3$) 2965, 2930, 1755, 1650, 1455, 1380, 1370, 1200, 1105, 1010, 895 cm^{-1}; TLC (silica gel, 1:1 pentane–diethyl ether) was used to separate the major and minor (16:1) isomers for NMR spectra (R_f: major isomer, 0.47; minor isomer, 0.53); NMR ($CDCl_3$, $CHCl_3$ reference) (major isomer) 0.99 (d, 3 H, J = 7 Hz), 1.05 (d, 3 H, J = 7 Hz), 1.3 (t, 3 H, J = 7 Hz), 1.4 (s, 3 H), 1.6 (s, 3 H), 2.15 (m, 1 H), 2.22 (d, 1 H, J = 14 Hz), 3.0 (d of t, 1 H, J = 14, 2 Hz), 4.1 (m, 1 H), 4.28 (q, 2 H, J = 7 Hz), 4.34 (s, 1 H), 4.82 (d of t, 2 H, J = 10, 2 Hz) ppm; (minor isomer) 1.05 (d, 3 H, J = 7 Hz), 1.13 (d, 3 H, J = 7 Hz), 1.33 (t, 3 H, J = 7 Hz), 1.33 (t, 3 H, J = 7 Hz), 1.52 (s, 3 H), 1.6 (s, 3 H), 1.98 (d, 1 H, J = 13 Hz), 2.26 (m, 1 H), 2.64 (d of t, 1 H, J = 14, 2 Hz), 4.12 (m, 1 H), 4.25 (m, 2 H), 4.63 (s, 1 H), 4.8 (d of t, 2 H, J = 11, 2 Hz) ppm; EIMS, *m/e* (rel intensity) 284 (0.5, M^+), 269 (12), 241 (12), 240 (75), 210 (13), 209 (100), 189 (10), 185 (24), 167 (13), 161 (11), 153 (42), 144 (19), 137 (48), 136 (31), 125 (10), 109 (47), 108 (31), 104 (15), 96 (42), 95 (22), 87 (38), 81 (63), 79 (14), 68 (24), 67 (23), 59 (81), 55 (34), 53 (20).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 63.38; H, 8.45. Found: C, 63.31; H, 8.54.

(7*R,8*R**)-9-Methylene-2,2,7,8-tetramethyl-1,3,6-trioxaspiro[4.5]decane-4-carboxamide (20).** Acetonide ester **19** (0.02 g, 0.07 mmol) was dissolved in 4 mL of ethanol and 5 mL of concentrated ammonium hydroxide solution was added. The reaction mixture was stirred at room temperature for 6 days. Solvent was removed by evaporation at reduced pressure to give 0.019 g of crude product. TLC purification (silica gel, 1:1 pentane–diethyl ether) gave 0.014 g (78%) of pure acetonide amide **20:** IR ($CHCl_3$) 3500, 3385, 2965, 1695, 1570, 1380, 1370, 1170, 1090, 1080, 1010, 950, 895 cm^{-1}; NMR ($CDCl_3$) 0.98 (d, 3 H, J = 6 Hz), 1.05 (d, 3 H, J = 4.5 Hz), 1.41 (s, 3 H), 1.55 (s, 3 H), 2.2 (m, 3 H), 2.2 (d, 1 H, J = 15 Hz), 3.08 (d of t, 1 H, J = 14, 3 Hz), 4.13 (s, 1 H), 4.4 (m, 1 H), 4.79 (d of t, 2 H, J = 8, 3 Hz), 5.73 (bs, 1 H), 6.46 (bs, 1 H) ppm; EIMS, *m/e* (rel intensity) 255 (1.4, M^+), 212 (14), 211 (100, $M^+ - CONH_2$), 198 (15), 180 (19), 167 (15), 153 (29), 137 (10), 136 (33), 115 (43), 109 (31), 108 (17), 86 (17), 81 (21), 75 (13), 67 (14), 59 (23), 58 (13), 55 (14), 53 (12). EIMS exact mass determination, calcd for $C_{13}H_{21}O_4N^+$: 255.1470. Found: 255.1469.

Methyl (αR*,2R*,5R*,6R*)-Tetrahydro-2-methoxy-5,6-dimethyl-4-methylene-2*H*-pyran-2-glycolate (Methyl *epi*-Pederate) (21) and Methyl (αR*,2S*,5S*,6S*)-Tetrahydro-2-methoxy-5,6-dimethyl-4-methylene-2*H*-pyran-2-glycolate (Methyl Pederate) (20). Aryl selenide **18** (1.5 g, 0.0031 mol) was dissolved in 40 mL of anhydrous methanol (dried over magnesium ethoxide and distilled) and 2 mL of acetyl chloride was added (to make a 3% solution of anhydrous hydrochloric acid in methanol). The solution was stirred at room temperature for 10 h and then quenched by addition of 6 mL of triethylamine, with cooling. The methanol and excess triethylamine were removed by evaporation at reduced pressure, giving a gummy solid. The solid was triturated five times with diethyl ether. The ether solution was dried over magnesium sulfate, filtered, and concentrated at reduced pressure to give 1.37 g (99% recovery) of ketal selenide **23.** Selenide **23** was redissolved in 50 mL of THF and cooled to 0 °C. Hydrogen peroxide (5 mL, 0.03 mol, 30% aqueous solution) was added to the cold THF solution. After the addition was complete, the reaction mixture was warmed to room temperature and allowed to stand for 15.5 h. The solution was then diluted with water and extracted three times with diethyl ether. The ether solution was washed three times with 10% aqueous sodium carbonate solution, once with water and once with saturated aqueous sodium chloride solution. The extract was dried over magnesium sulfate, filtered, and concentrated at reduced pressure to give 0.65 g of crude, epimeric methyl pederates (89% recovery). This mixture was separated into its two main constituents by silica gel column chromatography (grade III, 10% diethyl ether–hexane, gradually increased to 20% diethyl ether in hexane). The stereochemistry of these components was assigned on the basis of a comparison of their NMR spectra with published data.[11b] Epimer "A" (high R_f compound, 0.144 g) was shown to be methyl *epi*-pederate **25.** Epimer "B" (low R_f compound, 0.13 g) was identified as methyl pederate **24.** The yield of the mixture of esters was 46%: IR ($CHCl_3$) (methyl *epi*-pederate) 3540, 2970, 1740, 1650, 1445, 1395, 1285, 1080, 1040, 1035, 900 cm^{-1}; (methyl pederate) 3530, 2970, 1730, 1650, 1445, 1100, 905 cm^{-1}; NMR ($CDCl_3$) (methyl *epi*-pederate) 1.05 (d, 3 H, J = 7 Hz), 1.18 (d, 3 H, J = 7 Hz), 1.85 (d, 1 H, J = 14 Hz), 2.23 (m, 1 H), 2.81 (m, 2 H), 3.32 (s, 3 H), 3.82 (s, 3 H), 3.95 (m, 1 H), 4.45 (d, 1 H, J = 4 Hz), 4.8 (d of t, 2 H, J = 14, 2 Hz) ppm; (methyl pederate) 0.98 (d, 3 H, J = 7 Hz), 1.29 (d, 3 H, J = 7 Hz), 2.2 (m, 1 H), 2.37 (bs, 2 H), 3.14 (d, 1 H, J = 6 Hz), 3.31 (s, 3 H), 3.82 (s, 3 H), 3.9 (m, 1 H), 4.49 (d, 1 H, J = 6 Hz), 4.81 (d of t, 2 H, J = 10, 1 Hz) ppm; EIMS, *m/e* (rel intensity) (methyl *epi*-pederate) 212 (47, $M^+ - CH_3OH$), 200 (33), 195 (27, $M^+ - CH_3OH - OH$), 184 (14), 155 (87, $M^+ - HC(OH)C(=O)OCH_3$), 153 (92, $M^+ - CO_2CH_3 - CH_3OH$), 149 (13), 140 (19), 125 (24), 124 (10), 123 (69), 113 (13), 111 (23), 109 (29), 107 (24), 97 (24), 96 (33), 95 (100), 91 (17), 89 (14), 87 (21), 81 (89), 79 (30), 77 (15), 68 (20), 67 (41), 59 (20), 56 (14), 55 (53), 54 (14), 53 (28); (methyl pederate) 212 (55, $M^+ - CH_3OH$), 197 (14), 183 (10), 155 (14, $M^+ - HC(OH)C(=O)OCH_3$), 154 (11), 153 (100, $M^+ - CO_2CH_3 - CH_3OH$), 152 (14), 125 (19), 123 (35), 109 (43), 107 (20), 96 (18), 95 (42), 91 (15), 90 (11), 81 (32), 79 (22), 77 (12), 67 (25), 59 (11), 55 (29), 53 (21); CIMS, *m/e* (rel intensity) (methyl *epi*-pederate) 243 (1, $M^+ - 1$), 213 (53), 212 (10), 201 (14), 196 (21), 195 (100), 155 (10); (methyl pederate) 243 (1, $M^+ - 1$), 213 (45), 196 (13), 195 (100).

(αR*,2S*,5S*,6S*)-Tetrahydro-2-methoxy-5,6-dimethyl-4-methylene-2H-pyran-2-glycolamide (Pederamide) 2. Methyl pederate **20** (0.056 g, 0.00023 mol) was dissolved in 5 mL of anhydrous methanol (dried over magnesium ethoxide and distilled), placed in a pressure reaction tube (Fischer-Porter Co.), and cooled to 0 °C. Anhydrous ammonia was bubbled into the solution for 20 min and the tube was then sealed. The reaction mixture was heated at 100 °C for 48 h. After recooling to 0 °C, the tube was cautiously opened and warmed to room temperature. Methanol was removed by evaporation at reduced pressure. Pederamide (0.053 g, single TLC spot) was obtained in quantitative yield. The solid was recrystallized twice from diethyl ether to give a sample showing mp 129–129.5 °C (lit.[11b] mp 128.5–129.5 °C): IR ($CHCl_3$) 3490, 3440, 3370, 2970, 1690, 1655, 1580, 1140, 1105, 1040, 1010, 900 cm^{-1}; NMR ($CDCl_3$) 0.97 (d, 3 H, J = 6 Hz), 1.14 (d, 3 H, J = 6 Hz), 2.24 (m, 4 H), 3.29 (s, 3 H), 4.0 (m, 1 H), 4.24 (s, 1 H), 4.78 (d of t, 2 H, J = 10, 2 Hz), 5.9 (bs, 1 H), 6.75 (bs, 1 H) ppm; EIMS, *m/e* (rel intensity) 198 (40), 139 (11), 134 (45), 125 (21), 124 (12), 123 (49), 121 (10), 113 (13), 109 (36), 107 (24), 97 (12), 96 (14), 95 (87), 93 (15), 91 (20), 81 (56), 79 (29), 77 (15), 75 (13), 74 (12), 67 (36), 56 (11), 55 (46), 54 (11), 53 (29), 45 (11), 44 (27), 43 (41), 41 (60); CIMS, *m/e* (rel intensity) 226 (13), 199 (11), 198 (100), 181 (12), 180 (89).

Anal. Calcd for $C_{11}H_{19}O_4N$: C, 57.64; H, 8.30; N, 6.11. Found: C, 57.49; H, 8.36; N, 6.05.

(αR*,2R*,5R*,6R*)-Tetrahydro-2-methoxy-5,6-dimethyl-4-methylene-2H-pyran-2-glycolamide (*epi*-Pederamide) 26. Methyl *epi*-pederate **25** (0.067 g, 0.00028 mol) was dissolved in 5 mL of anhydrous methanol (dried over magnesium ethoxide and distilled) and was treated with ammonia as described for the synthesis of pederamide **2.** Crude *epi*-pederamide (0.051 g, 81% yield, one TLC spot) was obtained. This solid was recrystallized twice from diethyl ether to give a sample of **26,** mp 131–132 °C: IR ($CHCl_3$) 3510, 3480, 3395, 2970, 1690, 1655, 1580, 1120, 900 cm^{-1}; NMR ($CDCl_3$) 1.03 (d, 3 H, J = 6 Hz), 1.18 (d, 3 H, J = 6 Hz), 2.24 (m, 2 H), 2.28 (d, 1 H, J = 12 Hz), 2.55 (bs, 1 H), 3.35 (s, 3 H), 3.99 (m, 1 H), 4.15 (s, 1 H), 4.8 (d of t, 2 H, J = 12, 2 Hz), 6.12 (bs, 1 H), 6.79 (bs, 1 H) ppm; EIMS, *m/e* (rel intensity) 198 (11), 197 (51), 180 (10), 155 (74), 153 (100), 152 (10), 139 (10), 134 (90), 125 (22), 123 (49), 121 (12), 109 (34), 107 (27), 97 (12), 96 (26), 95 (94), 93 (11), 91 (20), 85 (20), 83 (37), 81 (83), 79 (36), 77 (17), 75 (15), 74 (22), 68 (17), 67 (40), 65 (10), 56 (18), 55 (48), 54 (17), 53 (37), 44 (32), 43 (61), 41 (72); CIMS, *m/e* (rel intensity) 226 (14), 199 (11), 198 (100), 181 (10), 180 (74).

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Total Synthesis of the Yohimbines

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Abstract: A recently introduced scheme of indole alkaloid synthesis has been utilized for the six-step construction of pseudoyohimbine from methyl β-(β-pyridyl)acrylate. Thus the interaction of the *N*-tryptophyl salt of the latter with dimethyl sodiomalonate, followed by acid-catalyzed ring closure, affords an indoloquinolizidine, whose monodecarbomethoxylation and hydrogenation produce a diester, which on base-induced cyclization and hydrogenation leads to the pentacyclic alkaloid. The interconversion of the intermediate tri- and diesters results in formal total syntheses of also the alkaloids yohimbine, β-yohimbine, alloyohimbine, and α-yohimbine. A ^{13}C NMR analysis of all indoloquinolizidines permits their ready conformational analysis.

The yohimbines comprise a group of natural, pentacyclic indole alkaloids containing five chiral centers illustrated by general formula **1,** various stereoisomers of which have been synthesized in the last two decades.[2] In view of the recent introduction of a new method of construction of the indoloquinolizidine unit, a structure moiety common to the yohimbines, and its successful exploitation in the total synthesis of the natural ajmalicinoid bases (**4**)[3,4] the yohimbines appeared to

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