Chemistry of Aryloxazolines. Applications to the Synthesis of Lignan Lactone Derivatives

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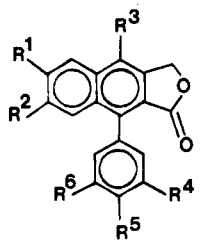
The syntheses of several lignan lactone derivatives using aryloxazolines as the pivotal intermediates have been investigated. Metalations on napthyloxazolines followed by electrophilic addition gave one of the appropriate substituents, whereas methoxy displacement with organometallics introduced the remaining substituents. Metalations on naphthalene systems were shown to be precarious and poorly related to metalation in the benzene series.

The versatility of aryl oxazoline as a means in introducing various substituents into the aromatic nucleus has been amply demonstrated in recent years.[2] Thus, aryl carboxylic acids **1** (Chart I) are transformed into their oxazolines **2**, which serves both as a protecting group and an activating group, and metalated to furnish the *o*-lithio intermediate. Treatment with a wide variety of electrophiles provides the ortho-substituted oxazolines **3** which lead to the elaborated benzoic acids **4** after hydrolytic removal of the oxazoline. Similarly, *o*-methoxy benzoic acid **5**, after conversion to the oxazoline **6**, react readily with nucleophiles, displacing the methoxyl group leading to the ortho-substituted oxazolines **7**. Hydrolysis of the latter furnishes the ortho-substituted benzoic acids **8**. In this fashion, aromatic nuclei can be elaborated via their oxazoline derivatives to a wide variety of compounds in either an electrophilic or nucleophilic process, free of any regioisomers. Although a number of aromatic substituents have served as activating groups toward ortho metalation, in particular *N,N*-diethylbenzamide,[3] these do not function as an activating group toward nucleophilic displacement.

We describe in this report the use of the oxazoline moiety as a unique functional protecting group in allowing synthetic approaches to aromatic lignan lactones. Lignan lactones occur widely in nature and have also been synthetically reached by several laboratories.[4] We have chosen as targets systems related to taiwanin C (**9**), jus-



9, R^1, R^2 = OCH_2O, R^4,R^5 = OCH_2O, R^3, R^6 = H

10, R^1, R^2 = OCH_2O, R^4,R^5 = OCH_2O, R^6 = H, R^3 = OCH_3

11, R^1,R^2,R^6 = H, R^4,R^5 = OCH_2O, R^3 = OCH_3

12, R^1,R^2,R^3,R^6 = H, R^4, R^5 = OCH_3

ticidin F (**10**), justicidin A/F (**11**), and chinensin (**12**) to demonstrate both the electrophilic and nucleophilic substitutions possible with aryl oxazolines. Specific natural products were not prepared due to undue difficulties in reaching various alkoxy-substituted naphthalenes. The key steps in the preparation of these lignan-type lactones can be seen in Scheme I. The retrosynthetic approach to **9**–**12** requires the acquisition of the four intermediates A–D, shown without the appropriate ring substituents. The synthetic route would begin with an *o*-methoxynaphthoic acid, A, which would be transformed into the oxazoline B. The latter now possesses the requisite substituent to introduce an aryl Grignard, via methoxide displacement to produce C. Metalation of C would serve to introduce the hydroxylmethyl group (D) which would furnish the lactones **9**–**12** on acidic hydrolysis. This scheme illustrates nucleophilic introduction of a substituent (B to C) and electrophilic introduction of another substituent (C to D), both ortho to the oxazoline.

In order to establish the feasibility of the nucleophilic addition to B and electrophilic addition to C, we performed model studies. A number of Grignard and organolithium reagents were added to B and resulted in smooth displacement of the methoxy group. Details will be given for this process elsewhere.[5] The electrophilic addition to lithioaryloxazolines containing an ortho phenyl substituent was examined. The presence of the ortho phenyl group was of concern since metalation may be hindered due to the inability of the oxazoline to assume coplanarity during the metalation step. A model system, **13**, was therefore examined. Metalation with *n*-butyllithium followed by dimethylformamide gave the air-sensitive aldehyde **14a** in quantitative yields which was immediately reduced to the

(1) Abstracted from the Ph.D. Thesis of W.B.A., Colorado State University, 1981.

(2) Early studies in the synthetic versatility of oxazolines have been reviewed: Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. Reports since the appearance of this review are as follows. Orthometalation–alkylation: (a) Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4465; (b) Meyers, A. I.; Gabel, R. A. *Heterocycles* **1978**, *11*, 133; (c) Meyers, A. I.; Gabel, R. A. *Tetrahedron Lett.* **1978**, 227; (d) Meyers, A. I.; Avila, W. B. *Ibid.* **1980**, 3335; (e) Meyers, A. I.; Campbell, A. L. *Ibid.* **1979**, 4155, 4159; (f) Houbian, J. A.; Miles, J. A.; Paton, J. A. *Org. Prep. Proc. Int.* **1979**, *11*, 27; (g) Newman, M. S.; Kumar, S. *J. Org. Chem.* **1978**, *43*, 370; Newman, M. S.; Kannan, R. *Ibid.* **1979**, *44*, 3388; (i) Newman, M. S.; Kanna, J. M.; Kanakerajan, K.; Kumar, S. *Ibid.* **1978**, *43*, 2553; (j) Harris, T. D.; Neuschwender, B.; Boekelheide, V. *Ibid.* **1978**, *43*, 727; (k) Ellefson, C. R. *Ibid.* **1979**, *44*, 1533; (l) Ziegler, F. E.; Chliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Shinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790; (m) Djuric, S.; Sarkar, T.; Magnus, P. *Ibid.* **1980**, *102*, 6886; (n) Hauck, A. E.; Giam, C. S. *J. Chem. Soc. Perkin Trans. 1* **1980**, 2070; (o) Reinecke, M. G.; Chen, L. J.; Almquist, A. *J. Chem. Soc., Chem. Commun.* **1980**, 585. Nucleophilic substitution: (p) Meyers, A. I.; Gabel, R. A.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372; (q) Meyers, A. I.; Gabel, R. A. *Ibid.* **1977**, *42*, 2653; (r) Meyers, A. I.; Williams, B. E. *Tetrahedron Lett.* **1978**, 223; (s) Meyers, A. I.; Gabel, R. A.; Reuman, M. *J. Org. Chem.* **1981**, *46*, 783; (t) Tanaka, H.; Itoh, Y.; Ikushima, H.; Okamoto, M.; Kawai, Y.; Imanaka, H. *Tetrahedron Lett.* **1980**, 4359.

(3) For recent reviews on metalated benzamides and related systems, see: Snieckus, V. *Heterocycles* **1980**, *14*, 1649. Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. Gschwend, H. W.; Rodriquez, H. R. *Org. React.* **1979**, *26*, 1.

(4) Plauman, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 354. de Silva, S. O.; St. Dennis, D.; Rodrigo, R. *Ibid.* **1980**, 995 and earlier references cited.

(5) Meyers, A. I.; Lutomski, K., research in progress.

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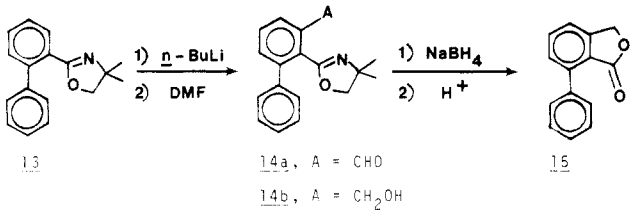
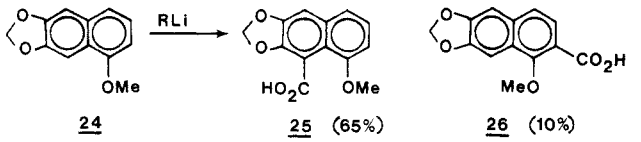


benzyl alcohol **14b** (97.5%). Acidic hydrolysis gave the lactone **15** in 96.4% yield, attesting to the feasibility of regioselective metalation of over encumbered aryloxazolines such as **13**.

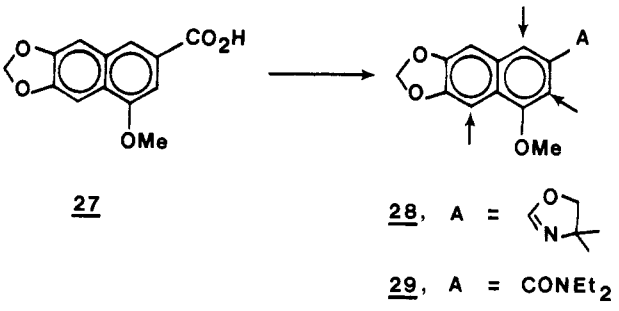
With the model experiments successfully completed, the total synthesis of a chinensin analogue **12** was accomplished as shown in Scheme II. Metalation[6] of 1-methoxynaphthalene followed by addition of carbon dioxide gave the naphthoic acid **16** (94%) which was transformed, by using 2-amino-2-methylpropanol and thionyl chloride, into the oxazoline **17** in 74% yield. Addition of 4-lithioveratrole, from 4-bromoveratrole, gave smooth arylation of **18** in 90% yield. The final substituent was introduced by treating **18** with *sec*-butyllithium–TMEDA in THF at −78 °C. In contrast to the model system **13**, *n*-butyllithium–THF gave only 26% lithiation. A systematic study led to the use of the *sec*-butyllithium–TMEDA metalation system. Hydrolysis of **19** with aqueous acid gave the chinensin derivative **12** in 94% yield.

Synthesis of the justicidin A/F system **11** began with 1,4-dimethoxynaphthalene (Scheme III). Metalation with *n*-butyllithium in cyclohexane[6] followed by addition of carbon dioxide gave the dimethoxynaphthoic acid **20** (92%) which was transformed into the oxazoline **21** (79%) as before. Nucleophilic methoxide displacement in **21** was performed by using either the lithio or Grignard derivative of 4-bromo-1,2-(methylenedioxy)benzene and afforded the arylated product **22** in 77–79% yield. Metalation to introduce the hydroxymethyl substituent once again was contrary to the results previously acquired in the model study on **13**. The presence of the *m*-methoxy substituent in **22** although advantageous for ring metalation also introduces additional steric factors to hinder the ortho-metalation–alkylation. Thus, *n*-butyllithium in THF at −78 °C metalates **22** in ~90% yield, as determined by addition of methyl iodide, to give **23**. However, DMF proved to be too bulky to enter that position. Utilization of paraformaldehyde gave the intermediate hydroxymethyl derivative which was hydrolyzed directly to the desired lactone **11** in 46.3% yield.

The synthesis of taiwan C (**9**) and justicidin F (**10**), natural lignans containing the methylenedioxy substituents on the naphthalene ring (R^1, R^2 = CH_2OCH_2) added complications not anticipated in our model studies due to the lability of the methylenedioxy group to strong bases (e.g., *n*-BuLi).[7] Furthermore, the regioselective metalation of **24**[8] under a variety of conditions gave primarily **25** and



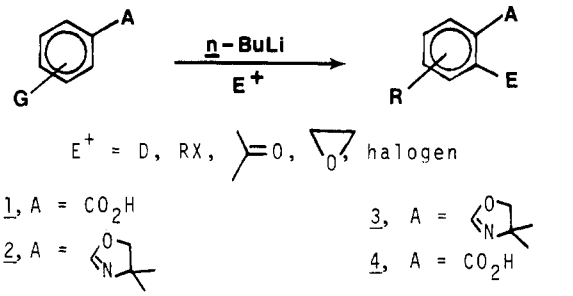
only a few percent of the desired acid **26**. Thus, metalations in the naphthalene series continued to exhibit behavior hardly comparable to that of the benzene series. Further attempts to introduce the requisite functionality for taiwanin C focused on the naphthoic acid **27**[8] which



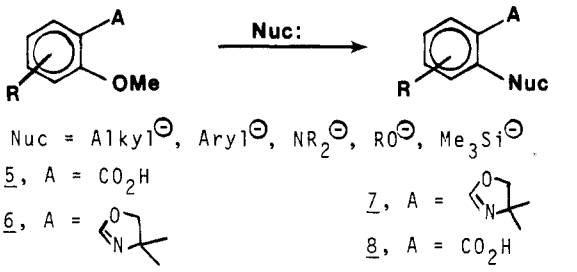
was converted into the oxazoline **28** and the *N,N*-diethyl amide **29**. Repeated metalations under various conditions failed to provide an appropriate substituent between the methoxyl and the oxazoline or the amide function. Mixtures were obtained (indicated by arrows) for both **28** and **29**. Snieckus[3] has already commented on the regiometalation of *N,N*-diethyl amides as being limited in the naphthalene series. The approach finally taken to overcome these difficulties was based on the work of Hauser,[9]

Chart I

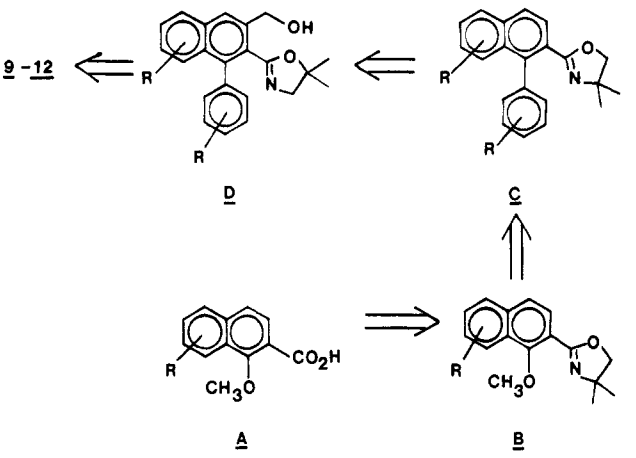
electrophilic substitution



nucleophilic substitution

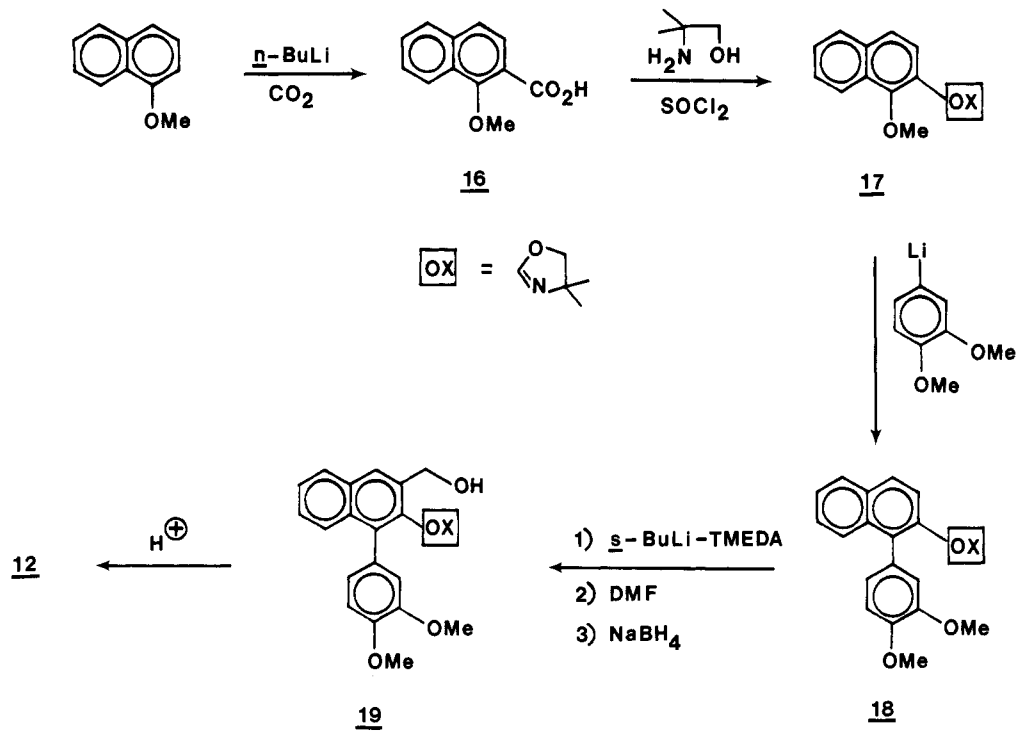


Scheme I

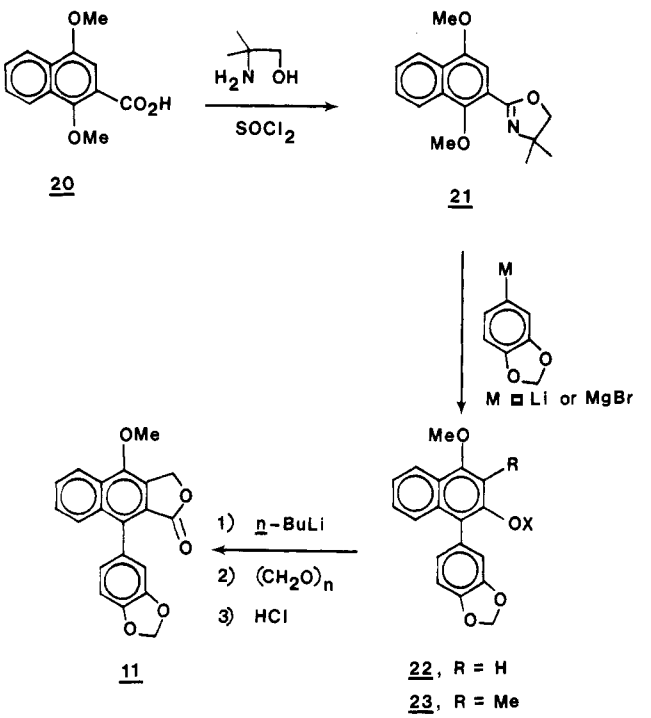


(6) Shirley, D. A.; Cheng, C. F. *J. Organomet. Chem.* **1969**, *20*, 251.
(7) Nalliah, B.; Amed, Q. A.; Manske, R. F. H. *Can. J. Chem.* **1972**, *50*, 1819.
(8) El-Assal, L. S.; El-Wahhan, S. A. *J. Chem. Soc.* **1960**, 849.

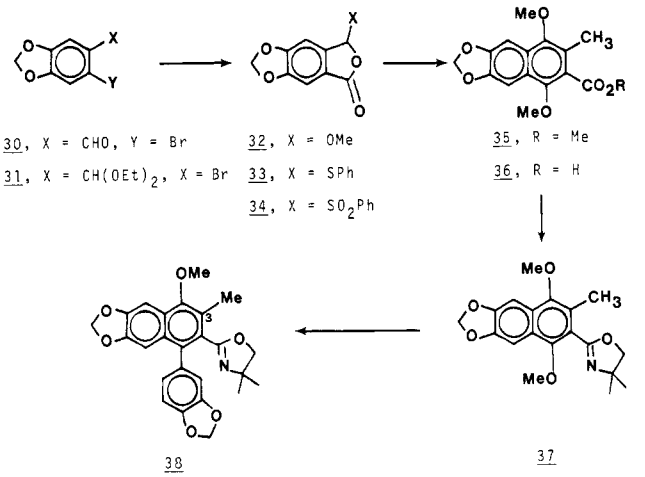
Scheme II



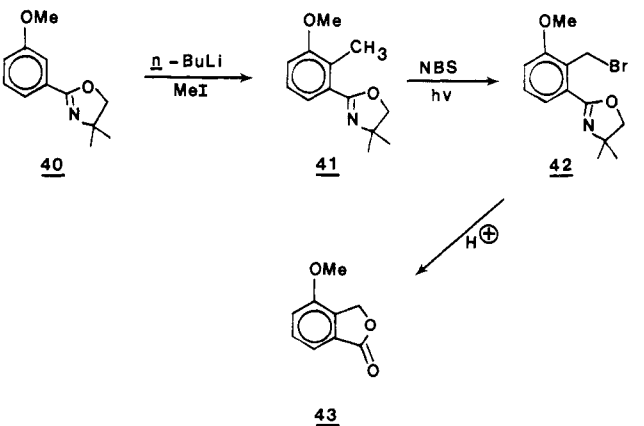
Scheme III



Scheme IV



Scheme V



who described a versatile method to reach polysubstituted naphthalenes. In this fashion, with some modifications, the hexasubstituted naphthalene **35** was obtained (see Scheme IV). Hydrolysis to the acid **36** was followed by oxazoline formation to **37** which was now equipped for introduction of the aryl substituent and also contained the methyl group for further elaboration. Treatment of **37** with the Grignard reagent from 4-bromo-1,2-(methylenedioxy)benzene gave **38** in 85% yield. This sequence therefore circumvents the lack of regioselective metalation encountered in the naphthalenes **24**, **28**, and **29**. The presence of the methyl group at C-3 in **38** should now allow elaborations to the hydroxymethyl substituent which would lead ultimately to the lignan lactones **9** and **10**.

(9) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061 and earlier references cited.

Toward this end, another model study was undertaken to assess the feasibility of transforming the C-3 methyl into a group suitable for lactone formation. The oxazoline **40** was treated with *n*-butyllithium at −45 °C followed by addition of methyl iodide to give the methyl derivative **41** in 90% yield (Scheme V). Bromination using *N*-bromosuccinimide and peroxide,[10] gave the (bromomethyl)oxazoline **42** in high yield, as an unstable oil, which was hydrolyzed in aqueous acid to the lactone **43** in 94% yield. The successful implementation of **40** to **43** now encourages further work to transform the justacidin F precursor **38** into the natural material, **10**.

Experimental Section

2-[2-Phenyl-6-(hydroxymethyl)phenyl]-4,4-dimethyl-2-oxazoline (14b). 2-(2-Phenylphenyl)-4,4-dimethyl-2-oxazoline[11] (**13**; 0.319 g, 1.27 mmol) and 20 mL of anhydrous THF were placed in a 100-mL three-necked flask with a magnetic stir bar. The system was flushed with nitrogen and cooled to −50 to −45 °C by using an acetone/dry ice bath. *n*-Butyllithium (0.55 mL, 2.62 M solution in hexane) was added via syringe, and the reaction mixture turned a reddish color. The mixture was stirred at −50 to −45 °C for 1.75 h then cooled to −78 °C. Dimethylformamide (0.20 mL, distilled from calcium oxide) was added via a syringe and the mixture stirred at −78 °C for 1.25 h. The reaction mixture was warmed to −50 °C and stirred for 1.25 h at which time the reddish color disappeared. The reaction mixture (−50 °C) was quenched with 5 mL of methanol and stirred for 10 min, and 0.0881 g of sodium borohydride in 5 mL of 100% ethanol was added. Stirring was continued for 15 min, and then the mixture was warmed to room temperature and stirred for 18 h. Water was added, and the mixture was then extracted with ether. This organic phase was washed once with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 0.349 g (97.5%) of **14b** as a solid which was purified by silica gel PLC (ether/hexane, 50/50): 0.212 g (59.2%); mp 107–110 °C; ^{1}H NMR ($CDCl_3$) δ 7.26 (s, 9), 5.28 (br s, 1), 4.47 (s, 2), 3.63 (s, 2), 1.32 (s, 6); IR (film) 1664 cm^{-1}.

6-Phenyl-2-(hydroxymethyl)benzoic Acid Lactone (15). Oxazoline **14b** (0.0980 g, 0.348 mmol) and 5 mL of 6 N HCl were stirred at room temperature for 5 h and then heated at reflux for 18 h. The reaction mixture was cooled to room temperature, and the white solid was removed by filtration and dried to give 0.0193 g (96.4%) of the lactone **15**: mp 159–161 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (m, 8), 5.36 (s, 2); IR (film) 1770 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 79.78; H, 4.77.

2-(1-Methoxy-2-naphthyl)-4,4-dimethyl-2-oxazoline (17). 1-Methoxy-2-naphthoic acid (**16**;[6] 9.94 g, 49.2 mmol) and 11 mL of thionyl chloride were heated at reflux for 50 min. The mixture was cooled to room temperature, and the excess thionyl chloride was removed on the rotary evaporator to give a dark brown oil which was distilled (8 torr, 210 °C pot temperature) to give 4.22 g of the acid chloride as a yellow liquid which solidified on standing. The crude acid chloride (4.22 g, 19.1 mmol) was treated with 2-amino-2-methyl-1-propanol (3.49 g, 39.2 mmol) in CH_2Cl_2 at 0–25 °C to give 5.17 g (99.1%) of the amide as a dark yellow oil: ^{1}H NMR ($CDCl_3$) δ 8.82–7.30 (m, 6), 3.92 (s, 3), 3.67 (br s, 2), 1.40 (s, 6). The amide (5.15 g, 18.9 mmol) was cyclized[11] by using 6.0 mL of thionyl chloride (25 °C) to give 3.75 g (77.9%) of the oxazoline **17** as a yellow liquid after neutralization at 0 °C with 20% NaOH. Purification by Kugelrohr distillation [120–126 °C (0.1–0.8 torr)] gave 3.59 g (74.7%, 73.7% based on the acid chloride) of **17** as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 8.42–8.10 (m, 1), 8.00–7.32 (m, 5), 4.15 (s, 2), 4.00 (s, 3), 1.42 (s, 6); IR (film) 1650 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}O_2N$: C, 75.31; H, 6.48; N, 5.49. Found: C, 75.27; H, 6.71; N, 5.49.

2-[1-(3,4-Dimethoxyphenyl)-2-naphthyl]-4,4-dimethyl-2-oxazoline (18). 4-Bromoveratrole (Aldrich, 97%; 0.205 g, 0.942 mmol) and 5 mL of anhydrous THF were placed in a 50-mL three-necked flask with a magnetic stir bar. The system was purged with nitrogen and then cooled to −78 °C with dry ice/acetone bath. *n*-Butyllithium (0.41 mL, 2.25 M in hexane) was added via syringe, and the mixture was stirred for 30 min during which time a white precipitate of the lithio compound formed. A solution of 2-(1-methoxy-2-naphthyl)-4,4-dimethyl-2-oxazoline (**17**; 0.228 g, 0.0894 mmol) in 4 mL of anhydrous THF was added dropwise, and the mixture was stirred for an additional 30 min. The reaction mixture was warmed to −15 to −10 °C, stirred for 45 min, warmed to room temperature, and stirred for 4 h. The reaction mixture was quenched with water and extracted with ether. Drying over anhydrous magnesium sulfate and removal of solvent gave 0.359 g of **18** as a yellow liquid. Purification by silica gel PLC (50/50, hexane/ether) gave the following: 0.292 g (90.4%); ^{1}H NMR ($CDCl_3$) δ 7.99–7.20 (m, 6), 6.92 (br s, 3), 3.95 (s, 3), 3.81 (s, 3), 3.74 (s, 2), 1.22 (s, 6); IR (film) 1665 cm^{-1}.

Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.44; H, 6.41. Found: C, 76.22; H, 6.38.

2-[1-(3,4-Dimethoxyphenyl)-3-(hydroxymethyl)-2-naphthyl]-4,4-dimethyl-2-oxazoline (19). Oxazoline **18** (0.112 g, 0.309 mmol; nitrogen atmosphere) was dissolved in 5.0 mL of anhydrous THF. The reaction mixture was cooled to −78 °C, and then TMEDA (0.05 mL) and *sec*-butyllithium (0.15 mL, 2.25 M in hexane) were added via syringe. The reaction mixture was stirred at −78 °C for 30 min, 1.2 equiv of DMF was added, and the mixture was stirred for 30 min. The reaction was quenched with 1 mL of methanol and stirred an additional 5 min. Solid sodium borohydride (0.073 g) was added, and the mixture was stirred for 5 min, at which time the cold bath was removed and the mixture was stirred at room temperature for 18 h. Water was added to the reaction mixture, and it was extracted with ether. A standard workup gave 0.127 g of a yellow liquid. Purification by silica gel PLC (100% ether) gave 0.715 g (53%) of **19** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 8.06–7.32 (m, 5), 5.52–5.02 (br, 1), 4.75 (br s, 2), 3.99 (s, 3), 3.87 (s, 3), 3.71 (s, 2), 1.29 (s, 6); IR (film) 3260 (br), 1670 cm^{-1}.

1-(3,4-Dimethoxyphenyl)-3-(hydroxymethyl)-2-naphthoic Acid Lactone (12). A solution of **19** (0.155 g, 0.397 mmol) and 10 mL of 6 N HCl was stirred at room temperature for 18 h and heated at reflux for 4.5 h. The reaction mixture was then cooled to room temperature and stirred for an additional 6 h. The mixture was extracted with methylene chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 0.119 g (93%) of **12** as a pale yellow solid: mp 208.0–208.5 °C (hexane/$CHCl_3$) (lit.[12] mp 208.5–209.5 °C); ^{1}H NMR ($CDCl_3$) δ 8.10–7.32 (m, 5), 7.11–6.79 (m, 3), 5.43 (br s, 2), 3.98 (s, 3), 3.85 (s, 3); IR (KBr) 1760 cm^{-1}.

2-(1,4-Dimethoxy-2-naphthyl)-4,4-dimethyl-2-oxazoline (21). 1,4-Dimethoxy-2-naphthoic acid (**20**;[6] 0.556 g, 2.39 mmol) was converted to the acid chloride with thionyl chloride (2 mL) at room temperature (21 h) to give 0.602 g (quantitative) of the acid chloride as a brown solid. The acid chloride was converted to the amide (0.718 g, 98.5%) in the standard manner: ^{1}H NMR ($CDCl_3$) δ 8.56–7.93 (m, 2), 7.73–7.44 (m, 2), 7.38 (s, 1), 3.99 (s, 3), 3.90 (s, 3), 3.71 (s, 2), 1.45 (s, 6). The above amide (0.718 g, 2.36 mmol) was cyclized with thionyl chloride to give 0.655 g (97.3%) of the oxazoline **21** as a brown oil. The oxazoline was purified by using silica gel PLC (ether/hexane, 50/50; three elutions) to give 0.533 g (79.1%) of **21** as an orange-brown oil: ^{1}H NMR ($CDCl_3$) δ 8.51–8.05 (m, 2), 7.83–7.50 (m, 2), 7.22 (s, 1), 4.21 (s, 2), 4.05 (s, 3), 3.92 (s, 3), 1.45 (s, 6); IR (film) 1649 cm^{-1}.

An alternate purification method involves bulb-to-bulb distillation [85–93 °C (0.002 torr)] or silica gel PLC (30/70, ethyl acetate/hexane) which gives **21** as a pale yellow liquid. Anal. Calcd for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71. Found: C, 71.27; H, 6.74.

2-[1-[3,4-(Methylenedioxy)phenyl]-4-methoxy-2-naphthyl]-4,4-dimethyl-2-oxazoline (22). The Grignard reagent prepared from 0.977 g (4.86 mmol) of 4-bromo-1,2-(methylenedioxy)benzene (Aldrich) and 0.173 g (7.09 mmol) of magnesium in 3.5 mL of THF (I_2 initiator) was transferred via cannula into a solution of 1.14 g (3.99 mmol) of oxazoline **21** in 10 mL of THF. The reaction mixture was stirred at room temperature for 21.5 h. Addition of saturated aqueous ammonium chloride, followed by ether extraction and a standard workup gave 1.65 g of **22** as a yellow oil. Purification by silica gel column chromatography

(10) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1977**, *42*, 4155.
(11) Meyers, A. I.; Gabel, R. A.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.

(30/70, ethyl acetate/hexane) gave 1.15 g (76.8%) of **22** as a cream-colored solid: mp 152.8–153.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.47–8.20 (m, 1), 7.87–7.32 (m, 3), 7.12 (s, 1), 6.98–6.78 (m, 3), 5.98 (s, 2), 4.05 (s, 3), 3.78 (s, 2), 1.26 (s, 6); IR (film) 1661 cm^{-1}.

Anal. Calcd for $C_{23}H_{21}O_4N$: C, 73.59; H, 5.63. Found: C, 73.75; H, 5.56.

1-[3,4-(Methylenedioxy)phenyl]-4-methoxy-3-(hydroxymethyl)-2-naphthoic Acid Lactone (11). 2-[1-[3,4-(Methylenedioxy)phenyl]-4-methoxy-2-naphthyl]-4,4-dimethyl-2-oxazoline (**22**; 0.110 g, 0.294 mmol) was placed in a 25-mL flask with a magnetic stir bar. The system was purged with argon. Tetrahydrofuran (5.0 mL) was added, and the reaction mixture was cooled to −78 °C with an acetone/dry ice bath. *n*-Butyllithium (0.12 mL, 2.69 M in hexane) was added, and the mixture was stirred at −78 °C for 1 h. Paraformaldehyde (dried over P_2O_5, 0.13 g) was added, and the bath was allowed to gradually warm to room temperature (total stirring time was 21.6 h). Water, ether, and saturated ammonium chloride were added, and the reaction mixture was extracted with ether. A standard workup gave 0.136 g of the hydroxymethyl compound as an orange-brown oil. To this were added 1.5 mL of THF and 15 mL of 6 N hydrochloric acid. This mixture was stirred at room temperature for 4 h and then extracted with ether, and the organic phase was washed once with 5% sodium bicarbonate. A standard workup gave 0.119 g of a brown oil. Trituration with ether gave 0.0455 g (46.3%) of the lactone **11** as an off-white solid. Purification by silica gel PLC (ethyl acetate/hexane, 30/70) gave 0.0387 g of **11** as a white solid: mp 198–200 °C (ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$) δ 8.45–8.19 (m, 1), 7.99–7.41 (m, 3), 7.09–6.65 (m, 3), 6.02 (s, 2), 5.55 (s, 2), 4.05 (s, 3); IR (KBr) 1760 cm^{-1}.

Anal. Calcd for $C_{20}H_{14}O_5$: C, 71.81; H, 4.22. Found: C, 71.74; H, 4.41.

Metalation of 2-[1-[3,4-(Methylenedioxy)phenyl]-4-methoxy-2-naphthyl]-4,4-dimethyl-2-oxazoline To Give 23. The title oxazoline, **22** (0.0702 g, 0.187 mmol), was dissolved in 5.0 mL of THF (argon atmosphere). The mixture was cooled to −78 °C with an acetone/dry ice bath. *n*-Butyllithium (0.075 mL, 2.69 M in hexane) was added, and the reaction mixture was stirred at −78 °C for 1 h. Methyl iodide (0.20 mL) was added, the bath was removed, and the reaction mixture was stirred at room temperature for 1 h. Water was added and the mixture extracted with ether. A standard workup gave 0.0880 g of **23** as yellow oil which was purified by silica gel PLC (ethyl acetate/hexane 30/70) to give 0.0616 g (84.6%) of **23** as a clear oil which solidified to a yellow solid: mp 95.5–99 °C; ^{1}H NMR ($CDCl_3$) δ 8.31–8.06 (m, 1), 7.78–7.21 (m, 3), 6.89 (s, 3), 6.00 (s, 2), 3.95 (s, 3), 3.84 (s, 2), 2.52 (s, 3), 1.19 (s, 6); ir (KBr) 1678 cm^{-1}.

Anal. Calcd for $C_{24}H_{23}O_4N$: C, 74.02; H, 5.95. Found: C, 74.16; H, 6.16.

2-[1-Methoxy-6,7-(methylenedioxy)-3-naphthyl]-4,4-dimethyl-2-oxazoline (28). 1-Methoxy-6,7-(methylenedioxy)-3-naphthoic acid (**27**;[8] 0.724 g, 2.94 mmol) and 5 mL of thionyl chloride were heated at reflux for 1 h. Workup gave the acid chloride as a brown solid. The crude acid chloride in 40 mL of THF and 5 mL of methylene chloride was added dropwise to a stirred solution of 2-amino-2-methyl-1-propanol (0.566 g, 6.35 mmol) in 30 mL of methylene chloride at 0 °C. The reaction mixture was then stirred at room temperature for 16.8 h. The solvent was removed on the rotary evaporator, methylene chloride was added, and the solution was extracted with water. A standard workup gave 0.910 g (96.8%) of the amide as a tan solid: ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 2), 7.15 (s, 1), 7.11 (s, 1), 6.09 (s, 2), 6.32 (br s, 1), 4.01 (s, 2), 3.82 (br s, 1), 1.45 (s, 6); IR (film) 1645 cm^{-1}. The above crude amide (0.824 g, 2.59 mmol) was cyclized with 3 mL of thionyl chloride at room temperature (22 min). The excess thionyl chloride was removed on the rotary evaporator. The reaction mixture was cooled to 0 °C, water was added, and the mixture was made basic with 20% sodium hydroxide. The aqueous mixture was extracted with methylene chloride, and the organic phase was dried over anhyrous magnesium sulfate, filtered, and concentrated to give 0.747 g (96.2%) of the oxazoline **28** as a white solid: mp 189–190 °C (PLC, 90/10 CH_2Cl_2/Et_2O); ^{1}H NMR ($CDCL_3$) δ 7.88 (br m, 1), 7.75 (s, 1), 7.27 (s, 1), 7.11 (s, 1), 6.03 (s, 2), 4.12 (s, 2), 4.01 (s, 3), 1.41 (s, 6); IR (film) 1655 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72. Found: C, 68.09; H, 5.70.

6-Bromo-3,4-(methylenedioxy)benzaldehyde Dimethyl Acetal (31). 6-Bromo-3,4-(methylenedioxy)benzaldehyde[12] (1.47 g, 6.42 mmol), 15 mL of trimethyl orthoformate (Aldrich, 98%), and a small amount of *p*-toluenesulfonic acid were heated at reflux for 21 h. The mixture was cooled to room temperature, ether was added, and the mixture was washed several times with water and then once with 1 M aqueous sodium hydroxide. A standard workup of the organic phase, followed by bulb-to-bulb distillation [91–99 °C (0.1–0.06 torr)] gave 1.78 g of **31** as a clear liquid: ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 1), 7.02 (s, 1), 6.00 (s, 2), 5.49 (s, 1), 3.41 (s, 6).

Preparation of Methoxyphthalide 32. Acetal **31** (2.05 g, 7.48 mmol) was dissolved in 35 mL of ether (argon atmosphere) and then cooled to −78 °C (acetone/dry ice). *n*-Butyllithium (2.9 mL, 2.69 M in hexane) was added, and the mixture was stirred for 30 min. Ether (10 mL) was added to the resulting opague solution, and then dry carbon dioxide gas (dried over P_2O_5) was bubbled into the solution. The bath was removed, and the mixture was allowed to warm to room temperature. The mixture was extracted with water, and the aqueous phase was cooled to 0 °C and acidified with saturated aqueous oxalic acid. Extraction with methylene chloride followed by the standard workup gave 1.58 g (95.6%) of **32** as a white solid: mp 113–114 °C; ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 1), 6.91 (s, 1), 6.18 (s, 1), 6.14 (s, 2), 360 (s, 3); IR (film) 1765 cm^{-1}. This compound was used without further purification.

Preparation of Sulfide Lactone 33. The methoxyphthalide **32** (1.54 g, 7.40 mmol), 120 mL of toluene, 1.0 mL (9.71 mmol) of thiophenol (Eastman), and a trace of *p*-toluenesulfonic acid were heated at reflux for 11 h with azeotropic removal of methanol. The reaction mixture was cooled to room temperature, and the solvent was removed on a rotary evaporator to give a yellow oil which was then dissolved in ethyl acetate. The mixture was washed successively with water, saturated aqueous sodium bicarbonate, and brine. A standard workup of the organic phase gave 2.13 g of a pale yellow solid which was purified by silica gel column chromatography (methylene chloride) to give 1.72 g (81.2%) of **33** as a white solid: mp 139.5–141 °C; ^{1}H NMR (acetone-d_6) δ 7.78–6.98 (m, 5), 7.12 (s, 1), 7.02 (s, 1), 6.85 (s, 1), 6.22 (s, 2); ^{1}H NMR ($CDCl_3$) δ 7.78–7.18 (m, 5), 7.09 (s, 1), 7.00 (s, 1), 6.56 (s, 1), 6.12 (s, 2); IR (film) 1785 cm^{-1}.

Preparation of Sulfone Lactone 34. The sulfide lactone **33** (0.729 g, 2.55 mmol) and 7.6 mL of glacial acetic acid were heated until the lactone had dissolved. The mixture was cooled to room temperature, and 0.96 mL of 30% hydrogen peroxide was added. The reaction mixture was heated to 100–105 °C for 1 h, cooled to room temperature, quenched with 32 mL of water, and then cooled in the refrigerator for 2.75 h. The resulting white solid was filtered from the mixture and dried overnight in vacuo (P_2O_5) to yield 0.725 g (89.5%) of **34**: mp 218–222 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 8.12–7.52 (m, 5), 7.37 (s, 1), 7.32 (s, 1), 7.05 (s, 1), 6.35 (s, 2); IR (KBr) 1765 cm^{-1}; mass spectrum (CH_4/CI), *m/e* 319 (M + 1).

Methyl 1,4-Dimethoxy-6,7-(methylenedioxy)-3-methylnaphthoate (35). Lithium diisopropylamide was prepared from diisopropylamine (0.20 mL) and 0.56 mL of *n*-butyllithium (2.55 M in hexane) in 2.6 mL of THF at 0 °C (0.5 h, argon atmosphere). The mixture was cooled to −78 °C (dry ice/acetone), and a slurry of the sulfone lactone **34** in 3.2 mL of THF was added, followed by an additional 4.5 mL of THF. The reaction mixture was stirred at −78 °C for 0.5 h, methyl crotonate (0.175 mL) was added, and the mixture was stirred for 3 min. The bath was removed, and the reaction mixture was stirred at room temperature for 1 h and then heated at reflux for 2 h. The reaction mixture was cooled to room temperature and made acidic by addition of glacial acetic acid (13.5 mL). The solvent was removed on a rotary evaporator, and the residue was dissolved in 50 mL of ethyl acetate. The mixture was washed with water, aqueous sodium dithionite (50 mL/2 g of mixture), and brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give a dark residue which was dissolved in 17 mL of acetone. Potassium carbonate (0.56 g) and 0.40 mL of dimethyl sulfate were added to the acetone solution, and the mixture was heated at reflux for 21 h. The reaction mixture was cooled to room temperature, filtered, and

(12) Klemm, L. H.; Gopinath, K. W.; Lee, D. N.; Kelley, F. W.; Trodd, E.; McGuire, T. M. *Tetrahedron* **1966**, *22*, 1797.

concentrated to give a yellow oil which was dissolved in 20 mL of ether. Triethylamine (0.60 mL) was added to the ether solution, and the mixture was allowed to stand at room temperature for 30 min. The ether solution was washed with water, 10% hydrochloric acid, and brine, dried ($MgSO_4$), filtered, and concentrated to give 0.329 g of an orange-brown oil. Purification by silica gel PLC (25/75 ethyl acetate/hexane) gave 0.181 g (88.5%) of **35** as a pale yellow solid: mp 83–86 °C; ^1H NMR ($CDCl_3$) δ 7.37 (s, 2), 6.08 (s, 2), 4.01 (s, 3), 3.93 (s, 3), 3.83 (s, 3), 2.38 (s, 3); IR (KBr) 1730 cm^{-1}.

1,4-Dimethoxy-3-methyl-6,7-(methylenedioxy)-2-naphthoic Acid (36). Compound **35** (0.159 g, 0.523 mmol) and 3.0 mL of 16% aqueous potassium hydroxide were heated (methanol added to give a homogeneous solution) at reflux for 3.0 h. The mixture was cooled to room temperature and the methanol removed in vacuo. The resulting aqueous solution was cooled to 0 °C and acidified with concentrated hydrochloric acid. The cold solution was filtered to remove the acid which was then dried in vacuo (P_2O_5) to give 0.135 g of **36** as a white solid: total yield of **36** (based on recovered **35**) 0.111 g (85.8%); IR (KBr) 1695 cm^{-1}.

2-[1,4-Dimethoxy-3-methyl-6,7-(methylenedioxy)-2-naphthyl]-4,4-dimethyl-2-oxazoline (37). Acid **36** (0.133 g, 0.457 mmol) and 1.5 mL of thionyl chloride were heated at reflux for 30 min. Removal of the excess thionyl chloride gave the acid chloride which was reacted with 2-amino-2-methyl-1-propanol (0.151 g, 1.69 mmol) to give the amide as a yellow solid (0.162 g). The amide was cyclized (0 °C, 1.25 h) by using 0.10 mL of thionyl chloride to give 0.143 g of a yellow oil. Separation by silica gel PLC (30/70 ethyl acetate/hexane, twice) gave 0.024 g of ester **35** and 0.114 g (88.7% from the acid based on recovered **35**) of **37** as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.48 (s, 2), 6.11 (s, 2), 4.22 (s, 2), 4.00 (s, 3), 3.88 (s, 3), 2.40 (s, 3), 1.52 (s, 6); IR (film) 1670 cm^{-1}.

2-[1-[3,4-(Methylenedioxy)phenyl]-4-methoxy-3-methyl-6,7-(methylenedioxy)naphthyl]-4,4-dimethyl-2-oxazoline (38). Oxazoline **37** (0.109 g, 0.319 mmol) was dissolved in 5.0 mL of THF (argon atmosphere). To this solution was added the Grignard prepared from 4-bromo-1,2-(methylenedioxy)benzene (Aldrich; 0.103 g, 0.511 mmol, distilled prior to use) and 0.0305 g of magnesium in 5.0 mL of THF. The reaction mixture was stirred at room temperature for 24.5 h. Water was added to the mixture, and it was extracted with ether. A standard workup, followed by silica gel PLC (30/70 ethyl acetate/hexane), gave 0.115 g of a yellow oil which was a mixture of **37** and **38** (by ^1H NMR). The above procedure was repeated on this mixture except that it was stirred at room temperature for 19 h and then heated at reflux for 24 h. Workup and silica gel PLC as above gave 0.118 g (85.3%) of **38** as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.49 (s, 1), 6.97 (s, 1), 6.94 (s, 3), 6.08 (s, 4), 3.92 (s, 3), 3.87 (s, 2), 2.44 (s, 3), 1.19 (s, 6); IR (film) 1670 cm^{-1}; mass spectrum, m/e 433 (M^+).

2-(3-Methoxyphenyl)-4,4-dimethyl-2-oxazoline (40). 3-Methoxybenzoic acid (6.16 g, 40.5 mmol) and 8.8 mL of thionyl chloride were reacted as above to give 6.77 g (98.1%) of the acid chloride as a yellow liquid. The acid chloride (6.77 g, 39.7 mmol) and 7.18 g (80.5 mmol) of 2-amino-2-methyl-1-propranol were reacted as above to give the amide (9.47 g, quantitative) as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.48–6.88 (m, 4), 6.61–6.35 (br s, 1), 5.05 (s, 1), 3.81 (s, 3), 3.63 (s, 2), 1.41 (s, 6); IR (film) 1650 cm^{-1}. The amide (8.96 g, 40.1 mmol) was cyclized as previously described to give 7.72 g (92.9% from the acid) of **40** as a yellow liquid. Kugelrohr distillation [70–73 °C (0.05 torr)] gave **40** as a yellow liquid: ^1H NMR ($CDCl_3$) δ 7.71–6.88 (m, 4), 4.09 (s, 2), 3.82 (s, 3), 1.39 (s, 6); IR (film) 1653 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}O_2N$: C, 70.23; H, 7.36. Found: C, 69.91; H, 7.33.

2-(2-Methyl-3-methoxyphenyl)-4,4-dimethyl-2-oxazoline (41). A solution of **40** (0.305 g, 1.48 mmol) in 5 mL of THF was metalated at −45 °C for 1.5 h with *n*-butyllithium (0.70 mL, 2.24 M) in hexane. Addition of 0.5 mL of methyl iodide was followed by removal of the cooling bath, and the reaction was allowed to reach room temperature. The reaction mixture was quenched in 20 mL of water, and the mixture was then extracted with ether, dried ($MgSO_4$), and concentrated to give 0.337 g of a yellow oil: ^1H NMR ($CDCl_3$) δ 7.49–6.80 (m, 4), 4.08 (s, 2), 3.82 (s, 3), 2.40 (s, 3), 1.38 (s, 3). GC analysis gave 97% **41**, 0.5% **40**, and 2.5% unidentified material. A portion of crude **41** was hydrolyzed (6 N HCl, reflux, 6 h) to give 2-methyl-3-methoxybenzoic acid, mp 141–143 °C (lit.[13] mp 145–146 °C).

Bromination of 41 and Preparation of Lactone 43. A solution of **41** (52.4 mg) in 5 mL of carbon tetrachloride was treated with 47.4 mg of *N*-bromosuccinimide and 1 mg of benzoyl peroxide and then heated to reflux. A 200-W light bulb was placed outside the flask and irradiation continued throughout the reflux period (1 h). Solid succinimide appeared in the solution and after cooling was removed by filtration. The solution was concentrated, leaving 83.7 g of a yellow oil which solidified. This material, assumed (by ^1H NMR) to be **42**, was immediately dissolved in 10 mL of 6 N hydrochloric acid and heated to reflux overnight. After the mixture was cooled and extracted with methylene chloride and the extract dried ($MgSO_4$) and concentrated, there was obtained 37.8 mg (96.4%) of a pale yellow solid: IR (KBr) 1780 cm^{-1}; mass spectrum, m/e 164 (M^+).

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Registry No. **11**, 78265-07-3; **12**, 6258-44-2; **13**, 57598-40-0; **14a**, 78265-08-4; **14b**, 78265-09-5; **15**, 57677-70-0; **16**, 883-21-6; **16** acid chloride, 51439-63-5; **17**, 78265-10-8; **18**, 78265-11-9; **19**, 78265-12-0; **20**, 78265-13-1; **20** acid chloride, 78265-14-2; **21**, 78265-15-3; **22** (R = H), 78265-16-4; **22** (R = CH_2OH), 78265-17-5; **23**, 78265-18-6; **24**, 78265-19-7; **25**, 78265-20-0; **26**, 78265-21-1; **27**, 78265-22-2; **27** acid chloride, 78265-23-3; **28**, 78265-24-4; **30**, 15930-53-7; **31**, 78265-25-5; **32**, 78265-26-6; **33**, 78265-27-7; **34**, 78265-28-8; **35**, 78265-29-9; **36**, 78265-30-2; **36** acid chloride, 78265-31-3; **37**, 78265-32-4; **38**, 78265-33-5; **40**, 73453-77-7; **41**, 72623-17-7; **42**, 78265-34-6; **43**, 4792-33-0; 2-amino-2-methyl-1-propanol, 124-68-5; *N*-(2-methyl-2-propan-1-ol)-1-methoxy-2-naphthalenecarboxamide, 78265-35-7; 4-bromoveratrol, 2859-78-1; 4-lithioveratrole, 14005-70-0; *N*-(2-methyl-2-propan-1-ol)-1,4-dimethoxy-2-naphthalenecarboxamide, 78265-36-8; 4-bromo-1,2-(methylenedioxy)benzene, 2635-13-4; *N*-(2-methyl-2-propan-1-ol)-6,7-(methylenedioxy)-2-naphthalenecarboxamide, 78265-37-9; methyl crotonate, 18707-60-3; *N*-(2-methyl-2-propan-1-ol)-1,4-dimethoxy-3-methyl-6,7-(methylenedioxy)-2-naphthalenecarboxamide, 78265-38-0; 3-methoxybenzoic acid, 586-38-9; 3-methoxybenzoyl chloride, 1711-05-3; *N*-(2-methyl-2-propan-1-ol)-3-methoxybenzamide, 78265-39-1; 2-methyl-3-methoxybenzoic acid, 55289-06-0.

(13) Weissbach, O. "Beilsten Guide"; Springer-Verlag: West Berlin, 1976; Vol. 10, p 494.