($CDCl_3$) δ 14.2, 16.3, 65, 81.6, 99.8, 153.8; GC-MS (CI with NH_3), m/z (relative intensity) 252/254/256/258 ($MNH4^+$, 100/94.7/30.5/3.1), 220 (1.9), 218 (2.4). Anal. Calcd for $C_6H_9Cl_3O_3$: C, 30.60; H, 3.85; Cl 45.16. Found: C, 30.43; H, 3.81; Cl, 45.10.

1-Phenyl-4,4-dichloro-1,3-butadiene (10a): ^1H NMR ($CDCl_3$) δ 6.8 (3 H, m), 7.6 (5 H, m); GC-MS, m/z (relative intensity) 198/200/202 (M^+, 35.2/20.5/2.9), 165 (4.4), 164 (5.8), 163 (17.6), 162 (10.2), 129 (10.2), 128 (100), 127 (85.2), 126 (13.2), 115 (2.9).

1-Phenyl-1,1-dichlorohexane (4b): ^1H NMR ($CDCl_3$) δ 0.85 (3 H, m), 1.3 (4 H, m), 1.6 (2 H, m), 2.83 (2 H, t, J = 7.5 Hz), 7.45 (3 H, m), 7.8 (2 H, m). Anal. Calcd for $C_{12}H_{16}Cl_2$: C, 62.35; H, 6.98; Cl, 30.67. Found: C, 62.53; H, 7.03; Cl, 30.55.

Methyl 3-phenyl-3,3-dichloropropanoate (5b): IR ($CDCl_3$) 2960, 1750, 1600, 1445, 1435, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (3 H, s), 3.63 (2 H, s), 7.3 (3 H, m), 7.7 (2 H, m); HRMS 232.0065, calcd for $C_{10}H_{10}Cl_2O_2$ 232.0058.

Methyl 2-Methyl-3,3-dichloro-3-phenylpropanoate (6b). Compound **6b** was found not stable as pure sample and was analyzed in presence of **9b**: ^1H NMR ($CDCl_3$) δ 1.34 (3 H, d, J = 7 Hz), 3.4 (3 H, s), 3.45 (1 H, q, J = 7 Hz), 7.25 (3 H, m), 7.4 (2 H, m); GC-MS (CI with NH_3), m/z (relative intensity) 264/266/268 (MNH_4^+, 32.7/21.5/3.6), 232 (3.7), 230 (16), 228 (16.6), 213 (14.6), 211 (41.5), 192 (100). Treatment of **6b** (120 mg) with 1 N alcoholic NaOH gave **9b** (95 mg).

Methyl 2-methyl-3-chlorocinnamate (9b): GC analysis, two isomers in 3/1 ratio; stereochemistry not determined; IR (neat) 1750, 1600, 1490, 1460, 1450, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (3 H, s), 3.5 (3 H, s), 7.33 (5 H, s); GC-MS (CI with NH_3), m/z (relative intensity) 228/230 (MNH_4^+, 100/34.7), 211/213 (MH^+, 61.9/19.9), 175 (13), 115 (13); HRMS 210.0435, calcd for $C_{11}H_{11}ClO_2$ 210.0444.

1-Chloro-1-phenyl-1-hexene (11b): ^1H NMR ($CDCl_3$) δ 0.85 (3 H, m), 1.35 (4 H, m), 2.31 (2 H, m), 6.1 (1 H, t, J = 8 Hz), 7.3 (3 H, m), 7.5 (2 H, m). Anal. Calcd for $C_{12}H_{15}Cl$: C, 74.02; H, 7.76; Cl, 18.20. Found: C, 74.09; H, 7.75; Cl, 18.10.

Ethyl 1-methyl-2,2-dichloropropyl carbonate (7d): ^1H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz), 1.46 (3 H, d, J = 6.7 Hz), 2.05 (3 H, s), 4.18 (2 H, q, J = 7 Hz), 5.04 (1 H, q, J = 6.7 Hz); GC-MS (CI with NH_3), m/z (relative intensity) 232/234/236 (MNH_4^+, 100/66.6/10.3). Anal. Calcd for $C_7H_{12}Cl_2O_3$: C, 39.09; H, 5.62; Cl, 32.97. Found: C, 39.22; H, 5.60; Cl, 33.09.

3-Phenyl-2,2-dichloro-1,1,1-trifluoropropane (1e): ^1H NMR ($CDCl_3$) δ 3.53 (2 H, s), 7.37 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 45.2, 114.9, 128.2, 128.4, 128.7, 131.1, 131.3. Anal. Calcd for $C_9H_7Cl_2F_3$: C, 44.47; H, 2.90; Cl, 29.17. Found: C, 44.46; H, 2.89; Cl, 29.20.

Acknowledgment. We thank the Société Nationale des Poudres et Explosifs and the CNRS for financial support.

Registry No. **1a**, 3883-13-4; **1b**, 53617-93-9; **1c**, 4412-39-9; **1e**, 115395-69-2; **1f**, 1552-80-3; **2f**, 55039-88-8; **3a**, 115560-82-2; **4b**, 115560-84-4; **5a**, 20618-02-4; **5b**, 30693-80-2; **6a**, 115560-83-3; **6b**, 115560-86-6; **7a**, 115395-70-5; **7d**, 115395-68-1; **8a**, 2257-46-7; **8b**, 87541-87-5; **9a**, 86164-40-1; **9b**, 115560-87-7; **10a**, 56772-77-1; **11b**, 115560-85-5; **12b**, 1460-06-6; **13**, 115560-88-8; THF, 109-99-9; TMU, 632-22-4; Mg, 7439-95-4; Al, 7429-90-5; Zn, 7440-66-6; NBu_4BF_4, 429-42-5; NBu_4I, 311-28-4; $ZnBr_2$, 7699-45-8; $PhCH_2Br$, 100-39-0; $PhCH{=}CHCH_2Br$, 4392-24-9; $BrCH_2CO_2Me$, 96-32-2; $CH_3CHBrCO_2Me$, 5445-17-0; $CH_3CHClOCO_2Et$, 50893-36-2; $PhCCl_3$, 98-07-7; CCl_3CO_2Me, 598-99-2; CH_3CCl_3, 71-55-6; CF_3CCl_3, 354-58-5; $HCCl_3$, 67-66-3; $CH_3(CH_2)_3CH_2Br$, 110-53-2; $BrCH(CH_3)CO_2Me$, 5445-17-0; $CH_2{=}CHCH_2Br$, 106-95-6; $ClCH(CH_3)OCO_2Et$, 50893-36-2; $PhCH_2Cl$, 100-44-7; $PhCH_2CH_2Ph$, 103-29-7.

Total Synthesis of (±)-Wikstromol

John L. Belletire* and Douglas F. Fry

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221-0172

Received February 24, 1988

The antineoplastic prototype lignan natural product wikstromol was synthesized in racemic form by a straightforward sequence involving, as its key transformations, oxidative coupling of a carboxylic acid dianion, generation and stereoselective oxidation of a potassium enolate, and a deprotection step. The overall yield for nine steps is 29%. Depending on the choice of oxidants for the enolate, considerable modification in the ratio of stereoisomeric products is possible.

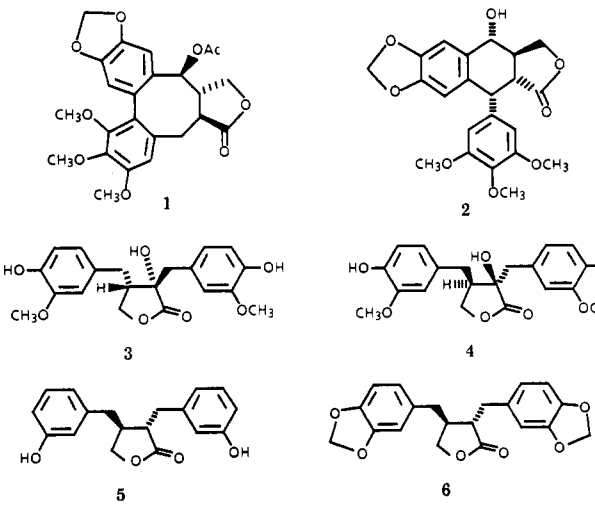
The lignans,[1] an important class of natural products derived formally from the dimerization of substituted 3-phenylpropane precursors,[2] exhibit many useful biological activities.[3] Medicinal chemists have been especially intrigued by those lignans that display cytotoxicity since such compounds may serve as valuable leads in the search for novel antitumor agents.[4] Complex lignan prototypes such as steganacin (**1**),[5] and podophyllotoxin (**2**),[6] as well as simpler lignans, have attracted considerable synthetic attention.[7]

In Chinese medical folklore "Nan-Ling-Jao-Hua" or "Po-Lun", *Wikstroemia indica* C. A. Mey (Thymelaeaceae), has been recommended as a herbal remedy for a number of maladies including cancer.[8] Recent work by Lee[9] has demonstrated that methanolic extracts of the stems of this plant have inhibitory activity in vivo against Ehrlich ascites carcinoma and P-388 lymphocytic leukemia. Several antitumor constituents were isolated as pure substances by a combination of solvent extraction followed by chromatography. Wikstromol ((+)-nortrachelogenin), a lignan of unusual structure, is a particularly interesting constituent. Additional studies by Lee confirmed the significant antineoplastic activity of wikstromol. Other

(1) Rao, C. B. S. *Chemistry of Lignans*; Andhra University Press: Andhra Pradesh, 1978.
(2) Geissman, T. A.; Crout, D. H. *Organic Chemistry of Secondary Plant Metabolism*; Freeman, Cooper, & Co.: San Francisco, 1969; pp 398-399.
(3) (a) Pratt, W. B.; Ruddon, R. W. *The Anticancer Drugs*; Oxford University Press: New York, 1979; pp 221-235. (b) MacRae, W. D.; Towers, G. H. N. *Phytochemistry* **1984**, *23*, 1207.
(4) For example: Glinski, M. B.; Freed, J. C.; Durst, T. *J. Org. Chem.* **1987**, *52*, 2749.
(5) Becker, D.; Hughes, L. R.; Raphel, R. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1674 and references cited within.
(6) Van der Eycken, J.; DeClercq, P.; Vandewalle, M. *Tetrahedron Lett.* **1985**, *26*, 3871 and references cited within.
(7) Ward, R. S. *Chem. Soc. Rev.* **1982**, 75.
(8) Sugi, M.; Nagashio, Y. In *Cancer Therapy in Modern China*; Kondo, K., Ed.; Shizen Sha: Japan, 1977; p 256.
(9) Lee, K.-H.; Tagahara, K.; Suzuki, H.; Wu, R.-Y.; Haruna, M.; Hall, I. H.; Huang, H.-C.; Ito, K.; Iida, T.; Lai, J.-S. *J. Nat. Prod.* **1981**, *44*, 530.

0022-3263/88/1953-4724$01.50/0 © 1988 American Chemical Society

Chart I



1 2 3 4 5 6

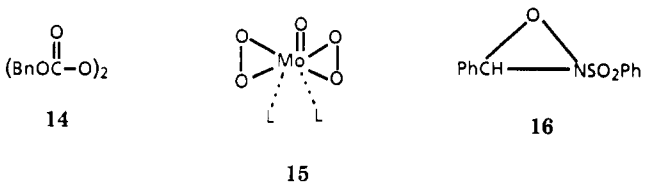
workers have also shown that wikstromol is an active constituent of *Wikstroemia foetida* var. *oahuensis* and *Wikstroemia uva-ursi*.[10]

Considerable effort has been devoted to the structure elucidation of wikstromol. Nishibe's group conducted pioneering studies[11] to elucidate the overall structure of nortrachelogenin. Later work by Kato[12] established that (−)-nortrachelogenin is the enantiomer of wikstromol. The configurations of the two chiral centers in (−)-nortrachelogenin are based upon a circular dichroism study performed by Nishibe that indicated that this substance could be correlated with the known configuration of dimethylmatairesinol.[13] Apparently, no single-crystal X-ray crystallographic investigation has yet been performed on either wikstromol or (−)-nortrachelogenin. The presently accepted structures for (−)-nortrachelogenin and for (+)-nortrachelogenin/wikstromol are **3** and **4**, respectively.[14]

An efficient synthetic approach to racemic wikstromol required the solution of three significant problems. First, a protection/deprotection sequence was required to avoid side reactions of the phenolic hydroxyl groups during assembly of the molecular framework. Second, some procedure had to be chosen that would afford the overall butyrolactone-containing lignan skeleton. Third, a convenient method for the introduction of tertiary hydroxyl functionality α to the lactone carbonyl group was needed.

Several effective strategies for generation of the substituted γ-butyrolactone systems commonly found in lignans are available.[15] Exploitation of the Stobbe condensation as pioneered by Haworth[16] and the butenolide-based

Chart II



14 15 16

routes as employed by Schlessinger[17] and by Asano[18] provide sequences of reasonable synthetic success. More recently, an alternative methodology developed by our group,[19] oxidative coupling of a suitable carboxylic acid dianion followed by straightforward desymmetrization/lactonization chemistry, has proven suitable for the preparation of several lignan prototypes. Using this approach, the cytotoxic lignan enterolactone (**5**)[20] and the widespread phytolignan hinokinin (**6**)[21] were prepared in overall yields of 51% and 60%, respectively, via oxidative coupling of suitable precursors. For lignan natural products possessing identically substituted benzyl side chains at C-2 and C-3 about the butyrolactone backbone, this type of coupling provides an especially straightforward preparative technique.

After hydrogenation of commercially available cinnamic acid **7**, the resulting hydrocinnamic acid was combined with excess benzyl chloride in a refluxing slurry of granular potassium carbonate/potassium iodide in acetone to provide the desired ether ester **8**. Saponification of the benzyl ester functionality leads to the protected benzyl ether acid **9** in an overall yield (two steps) of 87% (Scheme I).

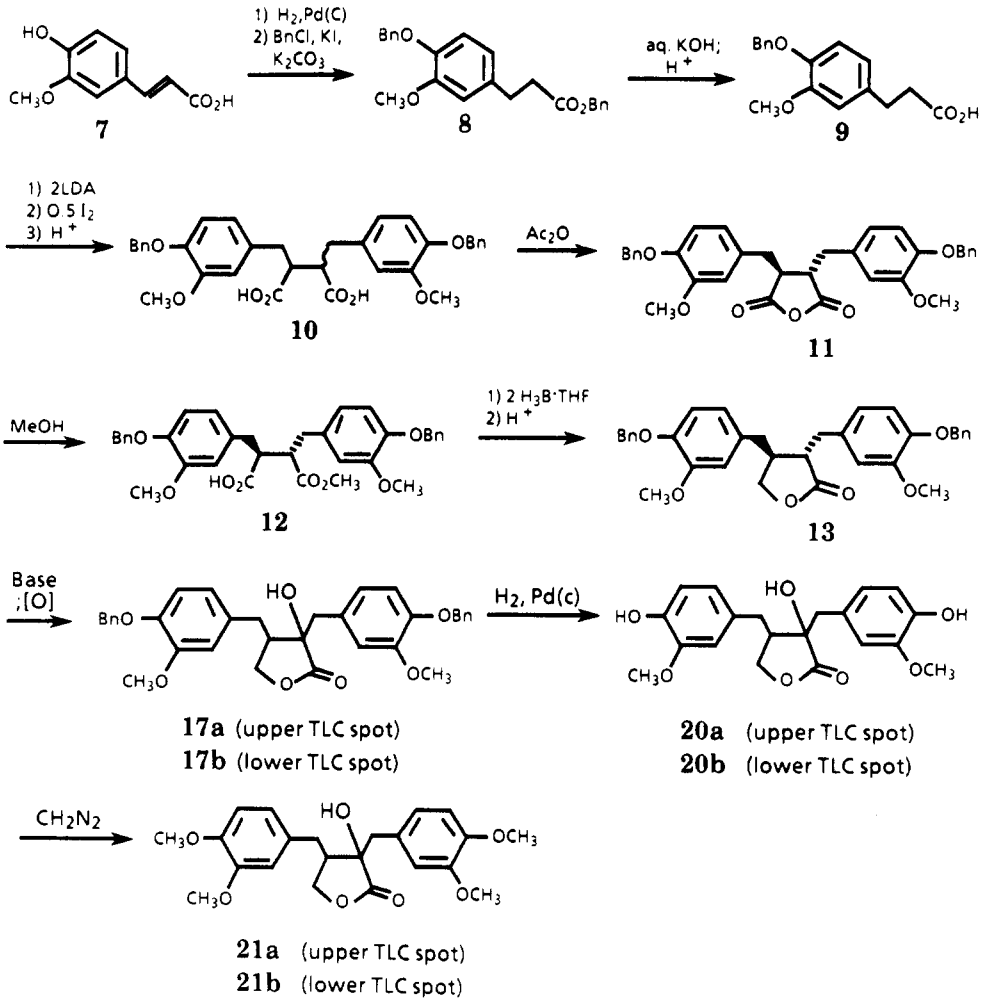
When applied to the dianion derived from protected acid **9**, iodine-mediated coupling occurs smoothly. Treatment of the crude diacid **10** with acetic anhydride at reflux affords the cyclic anhydride **11** in high yield. By NMR spectroscopy, anhydride **11** is a *single* diastereoisomer. Methanolysis of the cyclic anhydride to give ester acid **12** followed by selective reduction with borane and careful exposure to concentrated HCl gives the desired, highly crystalline lactone **13** in 60% overall yield, in what is essentially a one-pot procedure from the crude diacid.

The third major challenge presented in devising a practical synthesis of wikstromol was to effect smooth generation of the tertiary alcohol. α hydroxylation of a carbonyl species generally involves oxidation of an electron-rich intermediate such as an enol ether or an enolate.[22] Conditions for optimal transformation of **13** into the corresponding butyrolactone enolate were explored via simple quenching with iodomethane. Complete, if somewhat slow, conversion to the sterically hindered lithium salt occurs upon mixing **13** with LDA. Alternatively, potassium hexamethyldisilazide (prepared from potassium hydride and hexamethyldisilazane) is a convenient source of the highly reactive potassium enolate.[23]

A variety of oxidants have been developed for hydroxylation α to carbonyl functionality. Although a systematic investigation of all these reagents was not per-

(10) Torrance, S. J.; Hoffmann, J. J.; Cole, J. R. *J. Pharm. Sci.* **1979**, *68*, 664.
(11) (a) Nishibe, S.; Hisada, S.; Inagaki, I. *Phytochemistry* **1971**, *10*, 2231; (b) *Chem. Pharm. Bull. (Tokyo)* **1973**, *21*, 1108.
(12) Kato, A.; Hashimoto, Y.; Kidokoro, M. *J. Nat. Prod.* **1979**, *42*, 159.
(13) (a) Inagaki, I.; Hisada, S.; Nishibe, S. *Chem. Pharm. Bull. (Tokyo)* **1972**, *20*, 2710. (b) Haworth, R. D.; Woodcock, D. *J. Chem. Soc.* **1939**, *154*; (c) *J. Chem. Soc.* **1939**, 1054. (d) But note: Capon, R. J.; MacLeod, J. K. *J. Org. Chem.* **1987**, *52*, 5059.
(14) There is considerable confusion in the literature as to the correct depiction of (−)-nortrachelogenin (**3**) and (+)-nortrachelogenin/wikstromol (**4**). We are following the convention of Lee (ref 9 of this paper). In our synthesis, we have produced only the racemic product. Wikstromol is one of those relatively rare natural products in which the two enantiomers have different names. Since the term "wikstromol" is more familiar to medicinal chemists, we have used this name for the racemic material. It could just as easily have been called racemic "nortrachelogenin".
(15) Haynes, L. J. *Q. Rev. Chem. Soc.* **1948**, *2*, 46.
(16) Haworth, R. D.; Woodcock, D. *J. Chem. Soc* **1938**, 1985.
(17) Damon, R. E.; Schlessinger, R. H.; Blount, J. F. *J. Org. Chem.* **1976**, *41*, 3772.
(18) Asano, Y.; Kamikawa, T.; Tokoroyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3232.
(19) (a) Belletire, J. L.; Spletzer, E. G.; Pinhas, A. R. *Tetrahedron Lett.* **1984**, *25*, 5969. (b) Belletire, J. L.; Spletzer, E. G. *Ibid.* **1986**, *27*, 131.
(20) Belletire, J. L.; Fremont, S. L. *Tetrahedron Lett.* **1986**, *27*, 127.
(21) Belletire, J. L.; Fry, D. F. *J. Org. Chem.* **1987**, *52*, 2549.
(22) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (b) Rubottom, G. M.; Gruber, J. M.; Marrero, R.; Juve, H. D., Jr..; Kim, C. W. *J. Org. Chem.* **1983**, *48*, 4940. (c) Adam, W.; Fierro, J. D. *Ibid.* **1978**, *43*, 1159.
(23) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

Scheme I



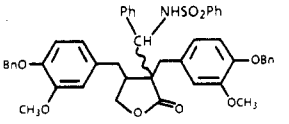
formed, successful oxidation of the enolate derived from **13** takes place with several oxidants *albeit* with significant variation in both overall yield and in product outcome.

The least promising results were found with the diacyl peroxide **14**.[24] Use of this reagent results in a complex product mixture. Therefore, this approach was not pursued further.

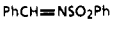
Much more successful were enolate oxidations with molecular oxygen/triethyl phosphite,[25] with MoOPH **15**,[26] and with oxaziridine **16**.[27]

Reaction of the potassium enolate with molecular oxygen in a THF solution containing 1 equiv of triethyl phosphite produces the diastereoisomeric alcohols **17a** (the upper (i.e. nonpolar) TLC spot) and **17b** (the lower (i.e. polar) TLC spot). From examination of the analytical TLC results as well as integration of proton NMR spectra of the crude reaction mixtures and as confirmed by chromatographic isolation of the isomeric products, these two tertiary alcohols are formed in high yield as essentially a 1:1 mixture with no starting material remaining.

Chart III



18



19

Addition of MoOPH to the lithium enolate failed to afford detectable conversion to **17a** and/or **17b**. However, a preliminary experiment involving the reaction between potassium enolate and MoOPH successfully leads to formation of **17a** and **17b** as a 2:1 mixture in 43% yield (if recovered starting material is taken into account, the overall yield is 87%).

Treatment of the lithium enolate with oxaziridine **16** leads to a similar mixture of **17a** and **17b** (but in the ratio of 6:1, respectively) along with formation, in significant (ca. 15%) yield, of a byproduct (**18**) that was tentatively assigned (by analogy to the reported observations of Davis[27] and of Evans[28]) as an adduct[29] between the enolate derived from **13** and sulfonimine **19** (itself the result of oxygen transfer from the oxaziridine **16**). The yield of the tertiary alcohol mixture is ca. 40%. In contrast, when oxaziridine

(24) Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700.
(25) (a) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352. (b) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *Ibid.* **1968**, *33*, 3294.
(26) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(27) (a) Davis, F. A.; Mancinelli, P. A.; Balasubramanian, K.; Nadir, U. K. *J. Am. Chem. Soc.* **1979**, *101*, 1044. (b) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774. (c) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *Ibid.* **1984**, *49*, 3241. (d) Davis, F. A.; Lamendale, J., Jr.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000.
(28) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.
(29) A separate experiment involving direct reaction of the enolate derived from **13** and authentic **19** leads to the same complex mixture of diastereoisomers. The ^{1}H NMR spectrum of this mixture is virtually identical with the proton spectrum of the byproduct **18** isolated by chromatography from the oxidation attempts.

16 is added to the potassium enolate, a rapid and remarkably clean oxidation of the enolate occurs to form a 6:1 mixture of **17a** and **17b** in better than 75% yield. Of particular interest, use of the potassium enolate produces no more than a trace of byproduct **18**.

While the mixture of **17a** and **17b**, with effort, could be separated chromatographically, hydrogenolysis of the mixture of diastereoisomers (using standard conditions: 10% Pd(C)/EtOAc/H_2 at 1 atm) leads to the more easily separable diastereoisomeric trihydroxy derivatives **20a** (the upper TLC spot) and **20b** (the lower TLC spot).

Careful examination of the spectral data for all synthetic intermediates, especially **20a** and **20b**, was instructive. Besides IR, mass spectral, and proton NMR patterns all of which are consistent with the two desired racemic products—wikstromol and epiwikstromol—the major isomer **20a** resulting from both MoOPH and oxaziridine oxidation exhibits a ^{13}C NMR spectrum that is very close to that of dimethylwikstromol as published by Kato.[12] As confirmation of the successful synthesis of wikstromol, we converted **20a** to the same ether (**21a**) by prolonged exposure to ethereal diazomethane. The ^{13}C NMR spectrum of the resulting product is *identical* with Kato's.[12] The minor isomer, **20b**, as well as its diazomethane-derived derivative (**21b**), gives ^{13}C NMR patterns whose chemical shift values were in considerable variance with those of authentic wikstromol. By TLC, diastereoisomer **21a** is less polar than diastereoisomer **21b**.

With a 29% overall yield for nine steps and with easily separable mixtures of products, our route to racemic wikstromol is quite convenient. By appropriate choice of reagents, wikstromol can be secured as a highly favored reaction product. Alternatively, the previously unknown epiwikstromol (whose biological activity is obviously of considerable interest) may readily be obtained from the molecular oxygenation procedure. Thus, we have demonstrated practical syntheses for both of these targets.

Consideration of the expected steric course of enolate oxidation indicates that virtually no preference should be seen with the smallest oxidant (molecular oxygen). This is just what was observed. In contrast, both MoOPH and the oxaziridine reagent afford considerable selectivity (2:1 and 6:1 diastereoisomer ratios, respectively). If the assumption is made that the structure of wikstromol is as generally accepted, then one must postulate that for these two reagents the enolate reacts in such a way that at least one of the benzyl side chains remains *cis* to the incoming oxidant. Logically, one would expect that the two benzyl chains would tend to be as far away from the oxidant as possible, and, therefore, the prediction would be for favored formation of the *unnatural* (i.e. epiwikstromol) diastereoisomer, just the opposite of what occurs. Literature precedent (e.g., in work reported by Grieco[30] and by Davis[27c]) strongly suggests that MoOPH and the oxaziridine give the product derived from attack from the least hindered face of the enolate. Formation of the apparently *anomalous* stereoisomer in our experiments implies one of two possibilities. Either some subtle electronic interaction (possibly caused by the electron-rich aromatic ring) leads to delivery of the bulky electrophile from the "wrong" side *or* the accepted structure of wikstromol is in need of revision. Thus, the simplest (but not necessarily correct) explanation for the unexpected results seen with both MoOPH and oxaziridine assumes that sterically governed addition is occurring and that wikstromol actually has the two benzyl side chains cis to one another. Obviously, the next stage in this research is an independent structure determination of our two reaction products **20a** (wikstromol) and **20b** (epiwikstromol) via a definitive technique. To this end we are engaged in a follow-up investigation involving attempts to grow appropriate crystals for a single-crystal X-ray study. While we have obtained several crystalline derivatives from racemic wikstromol and racemic epiwikstromol, as yet we do not have suitable crystals in hand.

(30) (a) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. (b) Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Jaw, J. Y.; Tu, S. *J. Org. Chem.* **1987**, *52*, 3346.

Experimental Section

Materials and General Procedures. Melting points are uncorrected. The multiplicity of ^{13}C NMR spectra was determined by off-resonance proton decoupling. All reactions were run under dry N_2 unless otherwise specified. Glassware for the dianion reactions was assembled hot from a 115 °C oven, purged with N_2, and then flame-dried under vacuum. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use. Diisopropylamine was distilled from barium oxide immediately prior to use. Ligroin, chloroform, and ethyl acetate were distilled before use.

3-Methoxy-4-(phenylmethoxy)benzenepropanoic Acid (9). Routine atmospheric hydrogenation of commercially available (Aldrich) 4-hydroxy-3-methoxycinnamic acid using 10% Pd(C) as catalyst (approximately 5% by weight) in ethyl acetate was followed by filtration through Celite, evaporation, and Kugelrohr distillation (bp ca. 110 °C (1.3×10^3 Pa)) to afford the hydrocinnamic acid as a crystalline product, which was used without further purification (yield ca. 100%).

A mixture of the hydrocinnamic acid (4.00 g, 20.4 mmol), benzyl chloride (9.4 mL, 82 mmol), KI (13.5 g, 81.6 mmol), K_2CO_3 (11.3 g, 81.6 mmol), and acetone (45 mL) was refluxed for 2 days and then cooled, 20% NaOH (50 mL) was added, and the mixture was refluxed for an additional 2 days. The solution was poured into a separatory funnel containing 150 mL of H_2O and 25 mL of Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (25 mL). The aqueous layer was cooled in ice and acidified with concentrated HCl to a pH of 1. The acidic aqueous layer was extracted with $CHCl_3$ (2×75 mL), the $CHCl_3$ layer was washed with saturated brine (25 mL), dried over $MgSO_4$, and filtered, and the volatiles were removed by rotary evaporation to leave a powdery white solid (6.36 g), which was recrystallized from EtOAc (in 2 crops) to yield 5.08 g (87%) of the benzyl ether acid **9** as colorless plates (mp 98–99 °C): IR ($CHCl_3$) 3000 (br s), 1710 (s), 1590 (s), 1510 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.25 (m, 5 H), 6.85–6.65 (m, 3 H), 5.10 (s, 2 H), 3.85 (s, 3 H), 2.87 (t, 2 H, J = 7.7 Hz), 2.63 (t, 2 H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.23 (s), 149.51 (s), 146.63 (s), 137.19 (s), 133.32 (s), 128.41 (d), 127.69 (d), 127.20 (d), 120.02 (d), 114.17 (d), 112.15 (d), 71.04 (t), 55.86 (q), 35.76 (t), 30.13 (t); MS (EI), m/z (relative intensity) 286 (100), 195, 149, 91; exact mass (M^+) calcd 286.1205, found 286.1230. Anal. Calcd for $C_{17}H_{14}O_4$: C, 71.31; H, 6.34. Found: C, 70.93; H, 6.21.

2,3-Bis[[3-methoxy-4-(phenylmethoxy)phenyl]methyl]-butanedioic Acid (10). A 100-mL Schlenk tube (flame-dried under vacuum and refilled with N_2) equipped with a stirring bar was charged with THF (25 mL). The THF was cooled to 0 °C with stirring and diisopropylamine (1.12 mL, 8.0 mmol) was added followed by *n*-BuLi (5.33 mL, 1.5 M, 8.0 mmol). After being stirred at 0 °C for 15 min, the LDA solution was cooled to −78° C and acid **9** (1.14 g, 4 mmol) in THF (5 mL) was added over 1.5 min. The resulting waxy-white mixture was stirred at −78 °C for 0.5 h, at 0 °C for 3 h, and at room temperature for 1.5 h. The dianion solution at this time was clear and dark pink. After the dianion solution was cooled to −78 °C, I_2 (0.508 g, 2.0 mmol) in THF (5 mL) was added over 1.5 min, resulting in a clear deep yellow solution, which was allowed to warm to room temperature over 18 h. The volatiles were removed in vacuo and to the residue were added 1 N HCl (20 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer reextracted with EtOAc (20 mL). The EtOAc layers were combined, washed with $NaHSO_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and reduced by rotary evaporation to leave a yellow paste. Removal of the last traces of solvent in vacuo afforded 1.157 g of an

amorphous yellow solid. For wikstromol the diacid was used as is. An analytical sample (mp 171–172 °C) was prepared by recrystallization from methanol: IR (Nujol mull) 1700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, DMSO-d_6) δ 7.53–7.25 (m, 10 H), 6.85–6.65 (m, 6 H), 5.11 (s, 4 H), 3.85 (s, 6 H), 3.05–2.80 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, DMSO-d_6) δ 175.5 (s), 149.3 (s), 146.6 (s), 137.4 (s), 132.2 (s), 128.5 (d), 127.7 (d), 127.3 (d), 121.0 (d), 113.9 (d), 112.9 (d), 71.0 (t), 55.9 (q), 49.9 (d), 36.1 (t); MS (EI), m/z (relative intensity) 552, 461, 416, 268, 227, 181, 137, 91 (100); exact mass ($M^+ - H_2O$) calcd 552.2149, found 552.2127. Anal. Calcd for $C_{34}H_{34}O_8$: C, 71.56; H, 6.01. Found: C, 71.43; H, 5.98.

(*R*,R)-(±)-2,3-Bis[[3-methoxy-4-(phenylmethoxy)-phenyl]methyl]butanedioic acid, Monomethyl Ester (12).** Crude diacid (2.0 mmol) was refluxed for 24 h as a dilute solution in acetic anhydride (20 mL). Removal of the Ac_2O at reduced pressure gives the cyclic anhydride **11**, which was used without further purification: IR ($CHCl_3$) 2940 (w), 1825 (m), 1785 (s), 1515 (m) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.5–7.2 (m, 10 H), 6.9–6.3 (m, 6 H), 5.2 (s, 4 H), 3.8 (s, 6 H), 3.2–2.6 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 150.1, 147.6, 137.0, 128.8, 128.6, 127.9, 127.3, 121.4, 114.4, 112.8, 71.1, 56.0, 46.0, 34.7; MS (EI), m/z (relative intensity) 552, 286, 227, 181, 137, 91 (100); exact mass MS (M^+) calcd 552.2149, found 552.2147.

The crude anhydride (ca. 2.0 mmol) was dissolved in MeOH (20 mL), heated at 80 °C for 24 h, cooled to room temperature, and concentrated by rotary evaporation to a brown syrup, which was put in vacuo overnight. For wikstromol: the acid ester was used as is in the next step. An analytical sample can be prepared by crystallization from EtOAc to give the acid ester as a white powder (mp 135–136 °C): IR ($CHCl_3$) 3600–2300 (br m), 1730 (s), 1710 (s), 1600 (s), 1515 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (m, 10 H), 6.80–6.50 (m, 6 H), 5.12 (s, 4 H), 3.80 (s, 6 H), 3.63 (s, 3 H), 3.10–2.85 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.884 (s), 173.918 (s), 149.483 (s), 146.827 (s), 146.764 (s), 137.219 (s), 131.418 (s), 131.233 (s), 128.515 (d), 127.803 (d), 127.221 (d), 120.977 (d), 113.902 (d), 112.582 (d), 70.983 (t), 55.836 (q), 51.871 (q), 47.251 (d), 47.093 (d), 35.265 (t), 34.975 (t); MS (EI), m/z (relative intensity) 552, 461, 268, 227, 181, 137, 91 (100); exact mass ($M^+ - CH_3OH$) calcd 552.2149, found 552.2117. Anal. Calcd for $C_{35}H_{36}O_8$: C, 71.90; H, 6.21. Found: C, 72.00; H, 6.34.

***trans*-(±)-Dihydro-3,4-bis[[3-methoxy-4-(phenylmethoxy)phenyl]methyl]-2(3*H*)-furanone (13).** A clear, brown solution of the crude acid ester (1.17 g, ca. 2 mmol) in THF (20 mL) was cooled to −17 °C with stirring, and BH_3·THF (1.0 M in THF; 4.0 mL, 4.0 mmol) was added dropwise over 1 min. The resulting solution was stirred at −17 °C for 5 min, at 0 °C for 2.5 h, and at room temperature for 0.5 h. After the solution had been cooled back down to 0 °C, concentrated HCl (1 mL) in THF (10 mL) was added *slowly*, and the resulting mixture was stirred at 0 °C for 1 h. The volatiles were removed by rotary evaporation, and MeOH was added and removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 and filtered through SiO_2 (5 g), reduced in vacuo, and then purified by flash chromatography (50 g of SiO_2, 2% Et_2O/CH_2Cl_2) to afford the lactone as an oil (0.657 g; 61.0%), which could be crystallized from EtOAc/pentane as a light yellow powder (mp 126–127 °C): IR ($CHCl_3$) 3010 (m), 2960 (m), 1775 (s), 1600 (s), 1520 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.27 (m, 10 H), 6.85–6.43 (m, 6 H), 5.11 (s, 4 H), 4.10 (dd, 1 H, $J \sim 13$, 12 Hz), 3.88 (dd, 1 H, partially obscured by OMe singlets), 3.82 (s, 3 H), 3.81 (s, 3 H), 3.02–2.82 (m, 2 H), 2.38–2.70 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.65 (s), 149.79 (s), 149.73 (s), 147.08 (s), 146.99 (s), 137.11 (s), 131.09 (s), 130.88 (s), 128.52 (d), 127.82 (d), 127.25 (d), 121.33 (d), 120.56 (d), 114.30 (d), 114.12 (d), 112.94 (d), 112.46 (d), 71.20 (t), 71.11 (t), 55.97 (q), 46.49 (d), 41.05 (d), 38.16 (t), 34.52 (t); MS (EI), m/z (relative intensity) 538, 447, 233, 181, 137, 91 (100); exact mass (M^+) calcd 538.2356, found 538.2374. Anal. Calcd for $C_{34}H_{34}O_6$: C, 75.82; H, 6.36. Found: C, 75.99; H, 6.50.

Dihydro-3-hydroxy-3,4-bis[[3-methoxy-4-(phenylmethoxy)phenyl]methyl]-2(3*H*)-furanone (17a and 17b). Oxaziridine Approach. To a 25-mL Schlenk tube (flame-dried under vacuum and refilled with N_2) were added THF (3 mL) and KHMDS in THF (1.5 mL of a 0.5 M solution, prepared from KH and hexamethyldisilazane (HMDS)). The basic solution was cooled to −78 °C and the lactone **13** (0.269 g, 0.5 mmol) in THF (5 mL) was added over 1.5 min. The resulting clear deep yellow solution was stirred at −78 °C for 1 h, at 0 °C for 1.5 h, and then cooled back down to −78 °C. Oxaziridine **16** (0.131 g, 0.5 mmol) in THF (2 mL) was added over 1 min, the solution was stirred at −78 °C for 15 min, and saturated NH_4Cl solution (3 mL) was added. The solution was allowed to warm to room temperature, the volatiles were removed, and the residue was extracted with Et_2O (2 × 10 mL). The Et_2O was washed with brine (3 mL), dried over $MgSO_4$, and filtered, and the volatiles were removed by rotary evaporation to leave a pale yellow paste. Purification by radial chromatography (2-mm plate, 10% Et_2O/CH_2Cl_2) provided the hydroxy lactone (0.210 g, 75.7%) as a white foam. Analysis of the ^1H NMR spectrum of the lactonic fraction revealed this material to consist of a mixture of the two diastereoisomers (5.8:1). These isomers could be separated by a second chromatography.

Major isomer **17a**: oil; IR ($CHCl_3$) 3620–3160 (m br), 3020 (m), 2940 (m), 1770 (s), 1590 (s), 1500 (s), 1450 (s), 1420 (s), 1375 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.5–7.2 (m, 10 H), 6.9–6.5 (m, 6 H), 5.114 (s, 2 H), 5.105 (s, 2 H), 3.991 (m, 2 H), 3.822 (s, 6 H), 3.14–3.02 (m, 1 H), 2.98–2.80 (m, 3 H), 2.62–2.40 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.44 (s), 149.73 (s), 149.60 (s), 147.49 (s), 146.86 (s), 137.10 (s), 136.98 (s), 131.61 (s), 128.46 (d), 127.76 (d), 127.34 (s), 127.18 (d), 122.39 (d), 120.75 (d), 114.38 (d), 113.96 (d), 113.92 (d), 112.79 (d), 76.32 (s), 71.10 (t), 71.00 (t), 70.14 (t), 55.96 (q), 43.64 (d), 41.89 (t), 31.47 (t); MS (EI), m/z (relative intensity) 554, 317, 227, 137, 91 (100); exact mass (M^+) calcd 554.2305, found 554.2318. Anal. Calcd for $C_{34}H_{34}O_7$: C, 73.63; H, 6.18. Found: C, 73.27; H, 6.21.

Minor isomer **17b**: crystalline (mp 127–128 °C (EtOAc/ligroin)); IR ($CHCl_3$) 3540 (m), 3020 (m), 2950 (m), 1780 (s), 1600 (s), 1510 (s), 1460 (s), 1430 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55–7.25 (m, 10 H), 6.9–6.55 (m, 6 H), 5.134 (s, 4 H), 4.162 (m, 2 H), 3.873 (s, 6 H), 3.18–3.06 (m, 1 H), 3.00–2.84 (m, 3 H), 2.76–2.58 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.72 (s), 149.98 (s), 149.60 (s), 147.86 (s), 147.14 (s), 130.90 (s), 128.54 (d), 127.83 (d), 127.26 (d), 126.01 (s), 122.61 (s), 120.38 (d), 114.43 (d), 114.14 (d), 113.95 (d), 112.15 (d), 75.73 (d), 71.17 (t), 71.05 (t), 69.33 (t), 56.07 (q), 47.96 (d), 38.23 (t), 32.02 (t); MS (EI), m/z (relative intensity) 554, 317, 227, 137, 91 (100); exact mass (M^+) calcd 554.2305, found 554.2309. Anal. Calcd for $C_{34}H_{34}O_7$: C, 73.63; H, 6.18. Found: C, 73.24; H, 6.05.

MoOPH Approach. To a 25-mL Schlenk tube (flame-dried under vacuum and refilled with N_2) was added THF (3 mL) followed by a KHMDS solution (1.50 mL of a 0.5 M solution of KHMDS in THF). The base mixture was cooled to −78 °C. Lactone **13** (0.269 g, 0.5 mmol) in THF (5 mL) was added over 2.5 min to give a dark yellow clear solution, which was stirred at −78 °C for 1 h and then at 0 °C for 1 h. The enolate solution was cooled back down to −78 °C. MoOPH (bright yellow crystalline commercial (Aldrich) powder which smelled of pyridine (0.326 g, 0.75 mmol)) was added through the top of the Schlenk tube under purge of N_2. Over a few minutes the solution became a deep green color, but remained heterogeneous with crystals of MoOPH still visible suspended in the solution. After the heterogeneous mixture had been stirred at −78 °C for 2 h, 5 mL of a saturated Na_2SO_3 solution was added. The mixture (blue with a white precipitate) was stirred at room temperature for 0.5 h, then 5 mL H_2O was added, and the solution was stirred for an additional 15 min. The solution was poured into a separatory funnel, 10 mL of H_2O and 20 mL of Et_2O were added, and the layers were separated. The aqueous layer (pH ~8) was reextracted with Et_2O (20 mL). The Et_2O layers were combined and washed with 1 N HCl (10 mL), dried over $MgSO_4$, and filtered, the solvent was evaporated, and the residue was placed in vacuo overnight.

The crude hydroxy lactone was purified by radial chromatography (1 mm plate, 10% Et_2O/CH_2Cl_2). Two fractions were obtained in a total weight of 0.119 g (42.9%) which, by ^1H NMR analysis, were ca. 2:1 **17a**:**17b**. Also recovered was 0.136 g of starting material (50.6%).

Molecular Oxygen/Triethyl Phosphite Approach. To a 25-mL Schlenk tube (flame-dried under vacuum and refilled with N_2) was added THF (3 mL) and a KHMDS solution (1.5 mL of a 0.5 M solution in THF). The solution was cooled to −78 °C and the lactone **13** (0.269 g, 0.5 mmol) in 5 mL of THF was added dropwise over 2.5 min. The resulting clear, deep yellow solution was stirred at −78 °C for 1 h and at 0 °C for 1.5 h and then cooled

back to −78 °C. Triethyl phosphite (0.086 mL, 0.5 mmol) was added, the N_2 was shut off, and oxygen was bubbled through the enolate solution with stirring for 1 h. At this time the reaction was quenched with 3.5 mL of saturated NH_4Cl solution. The mixture was stirred at room temperature until all solids had dissolved, the volatiles were removed in vacuo, and the residue was extracted with Et_2O (2 × 10 mL). The Et_2O layer was washed with 3 mL of brine, dried over $MgSO_4$, and filtered, and the solvent was evaporated and exposed to high vacuum to leave a yellow syrup.

The crude product was dissolved in $CHCl_3$ and filtered through 5 g of SiO_2. The filtrated was reduced in vacuo to a cloudy yellow oil.

Further purification was accomplished by radial chromatography (1-mm plate, 70% Et_2O/ligroin). The sample was introduced in CH_2Cl_2 (~3 mL). The plate was then dried by N_2 flow (1500 mL/min) for 20 min. The ether/ligroin solvent mixture was then used to elute the plate. The less polar fraction (**17a**) came off in a broad band, but the more polar fraction (**17b**) crystallized on the plate and would not move. After all the less polar fraction was off the plate, the polar material was eluted with EtOAc. The respective fractions were concentrated in vacuo to leave pale yellow oils, which were put in vacuo overnight. Weights of recovered fractions: **17a** = 0.129 g; **17b** = 0.114 g.

Dihydro-3-hydroxy-3,4-bis[(4-hydroxy-3-methoxyphenyl)methyl]-2(3*H*)-furanone (20a and 20b). A suspension of Pd(C) (25 mg) in a solution of hydroxy lactone **17** (0.210 g, 0.38 mmol (mixture of diastereoisomers)) in EtOAc (5 mL) was stirred under an H_2 atmosphere (1 atm) for 20 h, then the Pd(C) was removed by filtration through Celite. The filtrate was reduced in vacuo, and the residue was purified by radial chromatography (1-mm plate, 60% EtOAc/ligroin) to give wikstromol (0.121 g, 85%) and epiwikstromol (0.021 g, 15%) as glasses.

Wikstromol (20a): IR ($CHCl_3$) 3550 (s br), 3010 (m), 2950 (m), 1770 (s), 1610 (s), 1520 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90–6.55 (m, 6 H), 5.75 (s, 1 H), 5.70 (s, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 4.05 (m, 2 H), 3.25 (s, 1 H), 3.05–2.90 (m, 3 H), 2.55 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.72 (s), 146.55 (s), 144.86 (s), 144.19 (s), 130.28 (s), 126.14 (s), 123.07 (d), 121.36 (d), 114.49 (d), 114.27 (d), 112.70 (d), 111.45 (d), 76.44 (s), 70.27 (t), 55.89 (q), 55.83 (q), 43.66 (d), 41.82 (t), 31.47 (t); MS (EI), m/z (relative intensity) 374, 332, 313, 286, 207, 137 (100); exact mass (M^+) calcd 374.1366, found 374.1370.

Epiwikstromol (20b): IR ($CHCl_3$) 3550 (s), 3015 (m), 2950 (m), 1780 (s), 1610 (s), 1515 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95–6.60 (m, 6 H), 5.65 (s, 1 H), 5.55 (s, 1 H), 4.20 (dd, 1 H, J ~ 13, 13 Hz), 3.91 (s, 3 H), 3.90 (s, 3 H), 3.89 (dd, 1 H, obscured by OMe singlets), 3.15 (dd, 1 H, J ~ 13, 7 Hz), 2.95 (m, 3 H), 3.85 (s, 1 H), 2.65 (dd, 1 H, J ~ 14, 13 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.89 (s), 146.83 (s), 146.54 (s), 145.27 (s), 144.53 (s), 129.61 (s), 124.70 (s), 123.37 (d), 121.11 (d), 114.60 (d), 114.42 (d), 112.88 (d), 110.76 (d), 75.78 (s), 69.40 (t), 55.99 (q), 48.12 (d), 38.28 (t), 32.09 (t); MS (EI); m/z (relative intensity) 374, 164, 137 (100), 122, 94; exact mass (M^+) calcd 374.1366; found 374.1362.

3,4-Bis[(3,4-dimethoxyphenyl)methyl]dihydro-3-hydroxy-2(3*H*)-furanone (21a and 21b). Wikstromol (**20a**) (0.068 g, 0.18 mmol) was dissolved in Et_2O and transferred to a flask containing freshly distilled diazomethane in Et_2O. The flask was capped, covered with aluminum foil, and allowed to stand at room temperature. The progress of the reaction was checked periodically by TLC. After 3 weeks the volatiles were evaporated, the residue was dissolved in EtOAc and filtered through Celite, and the filtrate was evaporated. Radial chromatography (1-mm plate, 15% Et_2O/CH_2Cl_2) provides the dimethyl ether **21a** as a glass (18 mg, 25%): IR ($CHCl_3$) 3560 (m), 3020 (m), 2950 (m), 1780 (s), 1600 (s), 1515 (s), 1465 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.85–6.60 (m, 6 H), 4.03 (m, 2 H), 3.856 (s), 3.845 (s) (12 H total), 3.20–2.88 (m, 3 H), 2.67 (s, 1 H), 2.60–2.44 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.38, 149.04, 148.91, 148.38, 147.76, 130.94, 126.63, 122.43, 120.80, 113.31, 112.16, 111.36, 111.09, 76.38, 70.05, 55.89, 55.84, 43.83, 42.06, 31.54 (^{13}C NMR superimposable on Kato's published[12] spectrum); MS (EI), m/z (relative intensity) 402, 177, 151 (100), 107; exact mass (M^+) calcd 402.1679, found 402.1680.

Similar treatment of epiwikstromol (**20b**) also gives the dimethyl ether **21b** as a glass (ca. 25% yield after radial chromatography): IR ($CHCl_3$) 3550 (m), 3010 (m), 2950 (m), 1785 (s), 1600 (s), 1515 (s), 1460 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86–6.69 (m, 6 H), 4.19 (1 H, dd, J = 8.8, 8.1 Hz), 3.88 (s, 12 H), 3.15 (dd, 1 H, J = 13.5, 3.9 Hz), 3.01–2.88 (m, 2 H), 2.74–2.62 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.71, 149.34, 148.97, 148.68, 148.05, 130.29, 125.44, 122.67, 120.41, 113.65, 111.63, 111.26, 75.76, 69.36, 55.97, 55.90, 48.03, 38.22, 32.03; MS (EI), m/z (relative intensity) 402, 151 (100), 107; exact mass (M^+) calcd 402.1679, found 402.1656.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health and the donors of Petroleum Research Fund, administered by the American Chemical Society. This investigation was supported by PHS Grant 1 RO1 CA40105-02 awarded by the National Cancer Institute, DHHS. D.F.F. thanks the University Research Council of the University of Cincinnati for a summer fellowship. Preliminary research on this project was funded by grants from the Lalor Foundation, The American Cancer Society, and the Research Corporation. The 300-MHz NMR spectrometer used in this study was purchased with the aid of an NSF instrumentation grant (CHE-8102974). The Kratos mass spectrometer used in this study was purchased with the aid of an NSF instrumentation grant (PCM-8219912). We thank K.-H. Lee, S. Nishibe, and A. Kato for providing spectra and comparison samples. Technical assistance of D. Dunco is acknowledged.

Supplementary Material Available: ^{13}C NMR spectra of **21a** and **21b** (2 pages). Ordering information is given on any current masthead page.