Synthesis of Ethisolide, Isoavenaciolide, and Avenaciolide

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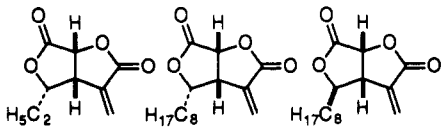
Syntheses of the trio of related mold metabolites ethisolide (1), isoavenaciolide (2), and avenaciolide (3) in racemic and optically active forms are described. Glycolate Claisen rearrangements governed by chelation control of enolate geometry and diastereofacial bias in the [3,3] shifts establish the functional and stereochemical details in butyrolactone precursors (**15b**, **22**, and **19**) of the natural products. Lactone rearrangements via complementary bis(transesterification) (**22** → **23**) and carboxylate displacement/lactonization (**26** → **27** → **3**) reactions provided the diastereomeric isoavenaciolide and avenaciolide structures. Differential reactivities among potential transacylation substrates **15a**, **15b**, **21**, **22**, **24**, and **26** are attributed to steric interactions or strain in bridged bicyclic intermediates **32**, **34**, and **36**.

Ethisolide (**1**),[1] isoavenaciolide (**2**),[1] and avenaciolide (**3**)[2] constitute a trio of secondary metabolites isolated from fermentation broths of *Aspergillus* and *Penicillium* species. Of these, avenaciolide exhibits the most diverse and potent biological activity, including inhibition of fungal spore germination,[2a] antibacterial action,[2a] and inhibition of glutamate transport in rat liver mitochondria.[3] Although not structurally complex by current standards, the densely functionalized frameworks of these bislactones have attracted numerous synthetic efforts that are notable in their strategic diversity. In the 15 published syntheses of avenaciolide,[2e-s] at least nine distinct approaches are discernable. Specifically, these works have employed Fittig condensation,[2e] carbohydrate modification,[2f-h] nucleophilic addition to butenolides,[2i-l] furan [4 + 2] cycloaddition,[2m,n] furan–aldehyde [2 + 2] cycloaddition,[2o] glycolate Claisen rearrangement,[2p,q] epoxy alcohol rearrangement,[2r] radical cyclization,[2h] and the carbonyl ene reaction.[2s]



1 ethisolide **2** isoavenaciolide **3** avenaciolide

The generalized structure **4** (Scheme I) possesses the C(4) stereochemistry present in ethisolide and isoavenaciolide.[4] Embedded therein is a γ,δ-unsaturated carbonyl structural unit, suggesting a Claisen rearrangement approach.[5] Antithetic manipulation via the indicated rotations in the bis(hydroxy ester) **5** leads to the substituted α-methylene lactone **6**, expected to arise from substrate **7** via a glycolate Claisen rearrangement.[5c-g] The rearrangement topology was expected to favor conformation **9b** over **9a**, involving the less encumbered face of the butenolide. In concert with the precedented control of enolate geometry by chelation,[5c-f] the relative stereochemistry at the C(4), C(3a), and C(6a) centers in **10** would thus be established. The sequential bis(transacylation) indicated for the lactone and ester moieties would convert **10** into ethisolide (**4**, $R_1 = C_2H_5$) or isoavenaciolide (**4**, $R_1 = C_8H_{17}$). Direct access to the relative stereochemistry present in avenaciolide (**3**) would require rearrangement via conformer **9a**, which was not expected. An inversion at C(4) in **10** (or its equivalent) would therefore be required for avenaciolide. Implementation of this plan for the total synthesis of the three title compounds in racemic and natural forms is described here in full detail.[6] Striking differences in reactivity among several related structures are described and rationalized.

As depicted in the retrosynthesis in Scheme I, the Claisen rearrangement substrate **7** was expected to arise from the generalized β-hydroxy-α-methylene lactone **8**. The specific lactones **11a,b** (Scheme II) were prepared by the method of Seebach.[7] Addition of the dianion of methyl 3-nitropropionate to racemic α-[(*tert*-butyldi-

* To whom correspondence should be addressed at the University of Wisconsin.

(1) Isolation and structure of ethisolide and isoavenaciolide: (a) Aldridge, D. C.; Turner, W. B. *J. Chem. Soc. C* **1971**, 2431. Syntheses of isoavenaciolide: (b) Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1977**, 2865; *J. Org. Chem.* **1985**, *50*, 4781. (c) Damon, R. E.; Schlessinger, R. H. *Ibid.* **1975**, 4551. (d) Yamada, K.; Kato, M.; Iyoda, M.; Hirata, Y. *J. Chem. Soc., Chem. Commun.* **1973**, 499. (e) Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchihashi, G.-i. *Tetrahedron Lett.* **1986**, *27*, 6237. (f) McDonald, C. E.; Dugger, R. W. *Ibid.* **1988**, *29*, 2413.

(2) Isolation and structure of avenaciolide: (a) Brookes, D.; Tidd, B. K.; Turner, W. B. *J. Chem. Soc.* **1963**, 5385. (b) Ellis, J. J.; Stodola, F. H.; Vesonder, R. F.; Glass, C. A. *Nature (London)* **1964**, *203*, 1382. (c) Brookes, D.; Sternhell, S.; Tidd, B. K.; Turner, W. B. *Aust. J. Chem.* **1965**, *18*, 373. (d) Hughes, D. L. *Acta Crystallogr.* **1978**, *B34*, 3674. Syntheses of avenaciolide: (e) Parker, W. L.; Johnson, F. *J. Org. Chem.* **1973**, *38*, 2489; *J. Am. Chem. Soc.* **1969**, *91*, 7208. (f) Anderson, R. C.; Fraser-Reid, B. *Ibid.* **1975**, *97*, 3870; *J. Org. Chem.* **1985**, *50*, 4781. (g) Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1975**, 3657. (h) Sharma, G. V. M.; Vepachedu, S. R. *Tetrahedron Lett.* **1990**, *31*, 4931. (i) Herrmann, J. L.; Berger, M. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1544; **1973**, *95*, 7923. (j) Kido, F.; Tooyama, Y.; Noda, Y.; Yoshikoshi, A. *Chem. Lett.* **1983**, 881. (k) Takei, H.; Fukuda, Y.; Taguchi, T.; Kawara, T.; Mizutani, H.; Mukuta, T. *Chem. Lett.* **1980**, 1311. (l) Sakai, T.; Horikawa, H.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 2039. (m) Murai, A.; Takahashi, K.; Taketsuru, H.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1981**, 221. (n) Kotsuki, H.; Ohnishi, H.; Akitomo, Y.; Ochi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3881. (o) Schreiber, S. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1984**, *106*, 7200. (p) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *Tetrahedron Lett.* **1986**, *27*, 3345. (q) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1985**, *50*, 1128. (r) Reference 1e. (s) Mikami, K.; Shimizu, M.; Nakai, T. *J. Org. Chem.* **1991**, *56*, 2952.

(3) (a) Meyer, J.; Vignais, P. M. *Biochim. Biophys. Acta* **1973**, *325*, 375. (b) McGivan, J. D.; Chappell, J. B. *Biochim. J.* **1970**, *116*, 37P.

(4) The atom numbering in structure **4** is employed throughout the schemes and does not correspond to systematic nomenclature for all intermediates.

(5) For a recent review of the aliphatic Claisen rearrangement, see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. For a detailed description of the Ireland–Claisen rearrangement, see: (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. For enolate Claisen rearrangements of glycolate esters, see: (c) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (d) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Ibid.* **1982**, *47*, 3941. (e) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. (f) Kallmerten, J.; Gould, T. J. *Ibid.* **1983**, *24*, 5177. For an example giving the nonchelated enolate geometry, see: (g) Barrish, J. C.; Lee, H. L.; Baggiolini, E. G. Uskokovic, M. R. *J. Org. Chem.* **1987**, *52*, 1372.

(6) Communications from our laboratory describing syntheses of racemic ethisolide, isoavenaciolide, and avenaciolide have appeared. See ref 2p and Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445.

(7) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705.

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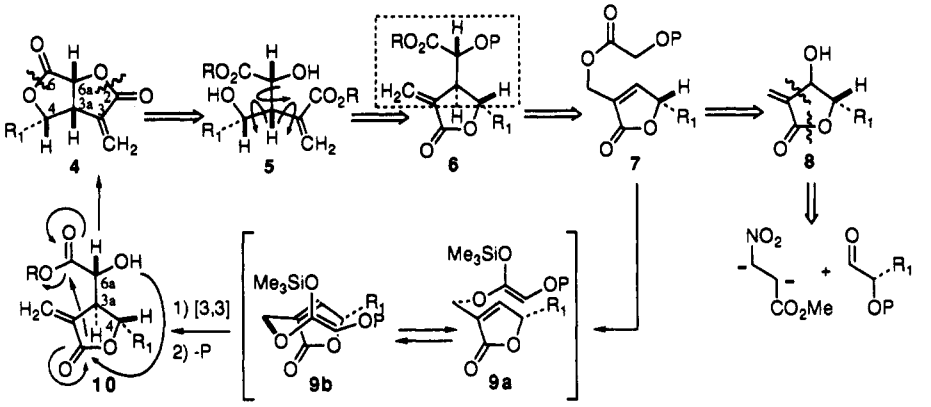
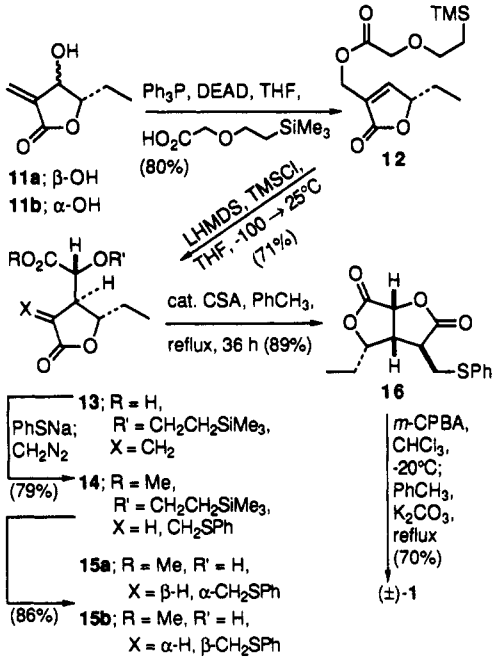
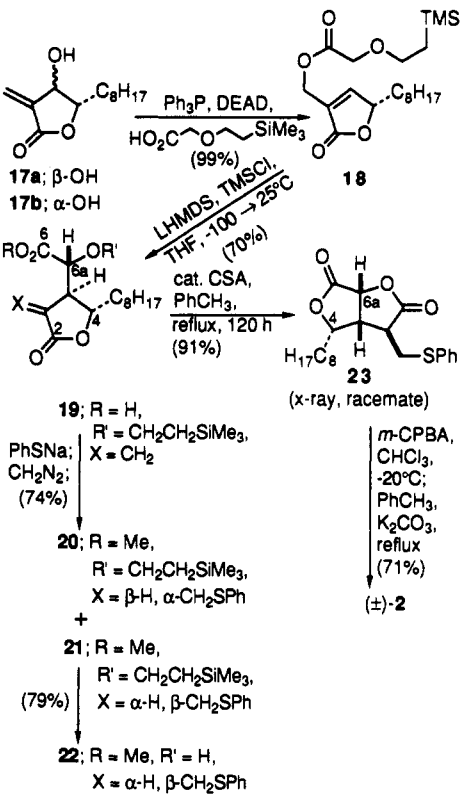
Scheme I



Scheme II



Scheme III



methylsilyl)oxy]propionaldehyde and elimination of the elements of nitrous acid with DBU gave a 4:1 mixture of diastereomeric β-hydroxy-α-methylene esters,[8] which were converted to **11a,b** (Scheme II) by desilylation with aqueous HF in acetonitrile,[9b] then acid-catalyzed lactonization. This mixture of allylic alcohols converged to the single butenolide **12** upon Mitsunobu coupling[10] with *O*-2-[(trimethylsilyl)ethyl]glycolic acid.[11] Clean S_N2' displacement was observed, facilitated by the unhindered nature of the olefin terminus and the Michael acceptor properties of the α-methylene lactone. Deprotonation of the α-alkoxy ester at −100 °C with lithium hexamethyldisilazide (LiHMDS) in the presence of Me_3SiCl[12] and warming to room temperature afforded only diastereomer **13**,[13] arising via a reactive conformer generalized as **9b**. The glycolate Claisen rearrangement thus served to establish the relative stereochemistry at the three asymmetric centers; use of scalemic[14] **11a,b** provided access to the optically active series (vide infra).

As depicted in the generalized transformation **10** → **4**, two sequential transacylations involving the C(6a) and C(4) hydroxyls were expected to give the ethisolide bislactone. Curiously, the α-methylene unit present in transacylation substrates **10** for the ethisolide and isoavenaciolide series prevented this skeletal reorganization (vide infra). Rehybridization at the C(3) center was accomplished by thiophenoxide addition[15] to **13**, giving Michael addition products **14** after diazomethane esterification. Cleavage of the β-(trimethylsilyl)ether[16] with $BF_3{\cdot}Et_2O$ afforded the

(8) Although this mixture converges in a subsequent transformation, the stereoisomers were readily distinguished by the method of Banfi: Banfi, L.; Potenza, D.; Ricca, G. S. *Org. Magn. Reson.* **1984**, *22*, 224.

(9) (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. For hydrolysis of TBS ethers using aqueous HF in acetonitrile, see: (b) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(10) Mitsunobu, O. *Synthesis* **1981**, 1.

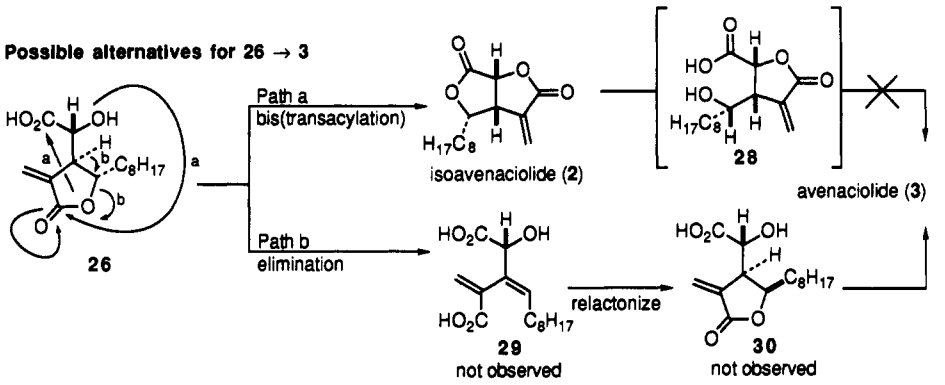
(11) None of the β-acyloxy-α-methylene lactones that would arise via direct S_N2 displacement were detected. Such products, prepared independently via carbodiimide coupling, did not undergo allylic rearrangement at room temperature.

(12) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(13) No diastereomeric product could be detected by ^1H NMR at 400 MHz. Selectivity is ≥20:1 by this criterion.

(14) For the definition and first use of this term, see ref 8 in: Heathcock, C. H.; Finkelstein, B. L.; Jarvi, E. T.; Radel, P. A.; Hadley, C. R. *J. Org. Chem.* **1988**, *53*, 1922.

(15) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1975**, *40*, 1181.

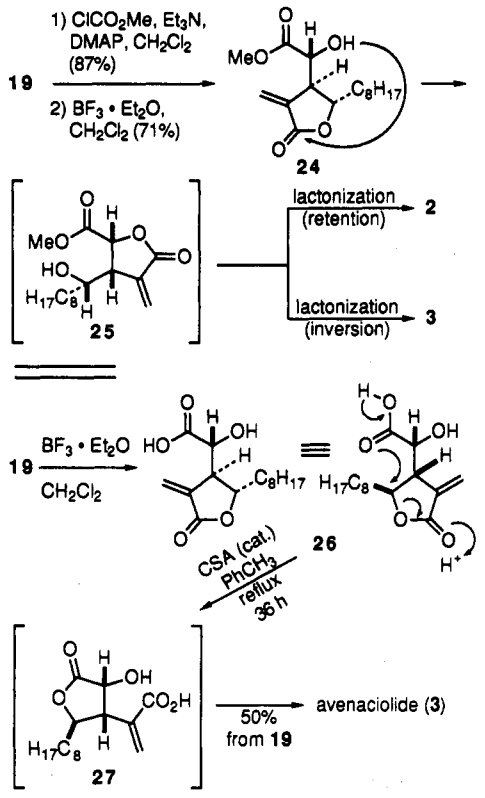


alcohols **15a,b** (1:1), which were separated. These C(3) epimers showed a striking reactivity difference. Isomer **15a** failed to undergo intramolecular transacylation upon heating with camphorsulfonic acid (CSA) in toluene at reflux (vide infra). However, diastereomer **15b** gave the crystalline bislactone **16** in 89% yield after heating for 36 h with CSA in toluene. Completion of the first recorded synthesis of (±)-ethisolide (**1**) required only oxidation of **16** to the sulfoxide and thermolysis.[15] The crystalline material (mp 108–110 °C) so produced in 70% overall yield exhibited spectroscopic data fully in accord with those published for the natural product.[1a]

The diastereofacial preference[17] exhibited in the conversion of the butenolide glycolate **12** to the α-methylene lactone **13** was also exploited in a route to isoavenaciolide (**2**). Mitsunobu S_N2' coupling of the β-hydroxy-α-methylene lactones **17a,b**[18] with the protected glycolic acid used previously gave in nearly quantitative yield the Claisen rearrangement substrate **18** (Scheme III). Again, chelation-controlled enolate formation, in situ trapping[12] as the silyl ketene acetal, and selective involvement of the less encumbered face of the butenolide provided rearrangement product **19** as the only discernable stereoisomer.[13] Sequential treatment of this α-methylene lactonic acid with sodium phenylthiolate[15] and diazomethane gave the separable epimeric esters **20** and **21** (1:1), which were individually treated with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 to unmask the C(6a) hydroxyl functionality. As in the ethisolide sequence, only stereoisomer **22** underwent the bis(transesterification), yielding the bislactonic sulfide **23**, for which X-ray crystallographic data confirmed the structure.[19] The alcohol derived from isomer **20** was unreactive under these conditions (vide infra). Oxidation of sulfide **23** and elimination under standard conditions gave racemic isoavenaciolide, mp 101–102 °C (lit. mp 99–99.5 °C,[1c] 99–101 °C[1d]) in 71% yield. ^1H NMR, IR, and mass spectrometric criteria agreed with published data.[1]

Our original intention had been to employ a common intermediate for the production of both isoavenaciolide and avenaciolide, which differ only in their C(4) stereochemistry. To that end (Scheme IV), the Ireland–Claisen rearrangement product **19** was esterified by the procedure of Kim[20] and then treated with $BF_3{\cdot}Et_2O$ to cleave the β-(trimethylsilyl)ethyl ether. Interconversion of α-methylene lactones **24** and **25** by the indicated transacylation was expected to lead to isoavenaciolide (**2**) by lactonization with retention at C(4) and to avenaciolide (**3**) by lactonization with inversion at that center. Although various conditions to effect conversion of **24** to **25** failed (vide infra), an alternative mode of reactivity did provide stereodivergent syntheses of isoavenaciolide *and* avenaciolide from common intermediate **19**.

Scheme IV



Deprotection of the C(6a) hydroxyl with $BF_3{\cdot}OEt_2$ gave the hydroxy acid **26** (Scheme IV), also shown in a conformation more suggestive of its observed reactivity. Upon treatment of **26** with catalytic CSA in refluxing toluene for 36 h, (±)-avenaciolide (**3**) resulted, presumably via **27**. The C(4) stereochemistry in **26** had thus been inverted, and the mechanism we favor is that indicated.

Alternative mechanistic pathways for the conversion of **26** to **3** were considered. For example, bis(transacylation)

(16) For similar uses of the β-(trimethylsilyl)ethyl ether protecting group, see: (a) Jansson, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1986**, *27*, 753. (b) Hoffmann, R. W.; Kemper, B.; Metternich, R.; Lehmeier, T. *Liebigs Ann. Chem.* **1985**, 2246. (c) Trost, B. M.; Quayle, P. *J. Am. Chem. Soc.* **1984**, *106*, 2469. (d) Pyne, S. G.; Spellmeyer, D. C.; Chen, S.; Fuchs, P. L. *Ibid.* **1982**, *104*, 5728. (e) Lipshutz, B.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603.

(17) For selected cases of diastereofacial selectivity in Claisen rearrangements, see: (a) Takahashi, S.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 515. (b) Ireland, R. E.; Marshall, J. A.; Church, R. F. *J. Org. Chem.* **1962**, *27*, 1118. (c) Kurth, M. J.; Yu, C.-M. *Ibid.* **1985**, *50*, 1840.

(18) Prepared by the method described earlier for **11a,b**.

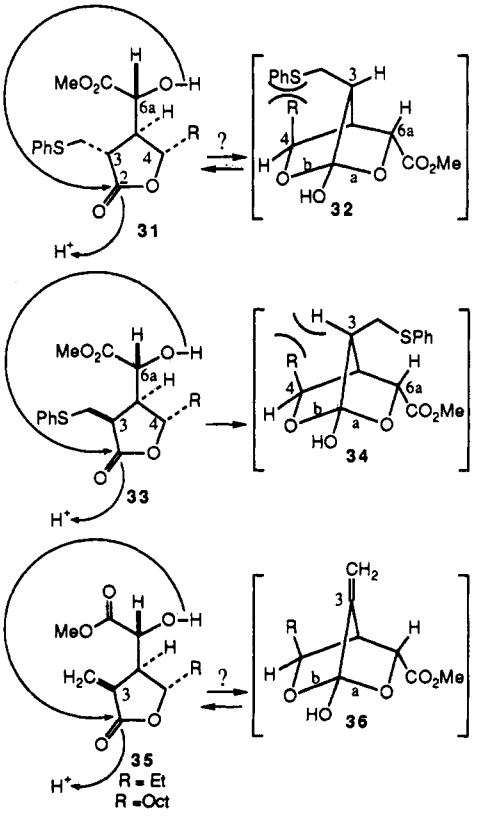
(19) We are grateful to Dr. Lukasz Lebioda (University of South Carolina) for this crystallographic structure confirmation.

(20) Kim, S.; Kim, Y. C.; Lee, J. I. *Tetrahedron Lett.* **1983**, *24*, 3365.

of **26** to give isoavenaciolide (**2**) and then the bracketed intermediate **28** (path a) could lead to avenaciolide (**3**). This was discounted by treating synthetic isoavenaciolide with CSA in refluxing toluene for 72 h, at which time it was recovered unchanged. Elimination via path b, stereoselective relactonization, and transacylation/lactonization (**26** → **29** → **30** → **3**) is considered unlikely, in that **29** and/or **30** were never detected, and analogous rearrangements (e.g., **26** → **2**) never occurred.

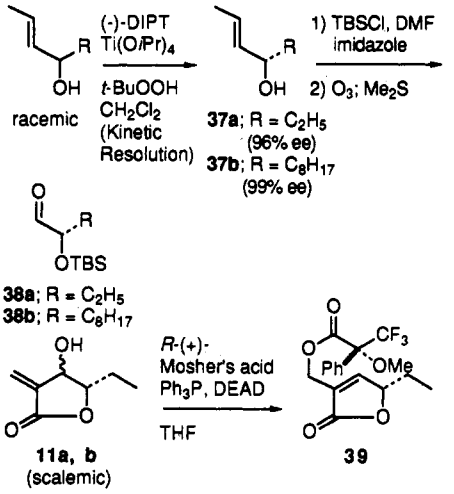
Although surprising at first encounter, the reactivity differences observed for transacylation substrates generalized as **31**, **33**, and **35** can be understood by evaluating transient structures **32**, **34**, and **36**. In each case, the tetrahedral intermediate in the first transacylation is a dioxabicyclo[2.2.1]heptane structure. Unreactive C(3) epimer **31** would achieve structure **32** by formation of bond "a". However, a serious steric conflict between the C(4) and C(3) substituents would result. The analogous tetrahedral intermediate **34**, resulting from **33** by bond a formation, suffers no similar interaction between the C(3) substituent and either of those at C(4) or C(6a). Epimer **33** was thus reactive in both the ethisolide and isoavenaciolide series, with bond b cleavage completing the first transacylation in each. Epimer **31** was not reactive in either series.

The curious involvement of the α-methylene unit in **35** as a "protecting group" for the lactone carbonyl against the intramolecular attack shown is similarly explained by considering the tetrahedral intermediate **36**. The added strain resulting from a trigonal (vis à vis sp^3) carbon in analogous bridged bicyclic structures (e.g., 7-methylenenorbornane, 7-norbornanone) is large (22 kcal/mol, MM2, for the latter).[21] We therefore believe that bracketed intermediate **36**, like **32**, is kinetically inaccessible.



(21) (a) Schneider, H.-J.; Schmidt, G.; Thomas, F. *J. Am. Chem. Soc.* **1983**, *105*, 3556. In 7-norbornanone, the C–CO–C angle has been calculated to be 86°: (b) Durand, R.; Geneste, P.; Lamaty, G.; Roque, J. P. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 131.

Production of ethisolide, isoavenaciolide, and avenaciolide in their natural, levorotatory forms was accomplished by synthetic sequences analogous to those employed for the racemates. The C(4) stereocenter in **8** (R_1 = Et or *n*-Oct) was set by employing a scalemic[14] α-siloxy aldehyde as the electrophilic partner in the Seebach β-nitropropionate dianion addition.[7] Kinetic resolution of (*E*)-(±)-hex-2-en-4-ol[22] by the Sharpless asymmetric epoxidation[23] with (−)-diisopropyl tartrate afforded the (*S*)-allylic alcohol **37a** in 96% enantiomeric excess (ee).[24]



Similarly, (*E*)-(±)-dodec-2-en-4-ol[25] gave the 4*S* isomer **37b** in 99% ee[24] after kinetic resolution via the Sharpless method. Alcohol protection as the *tert*-butyldimethylsilyl (TBS) ethers[9] and ozonolysis gave aldehydes **38a** and **38b**,[26] substrates for the synthesis of β-hydroxy-α-methylene lactones **11a,b** and **17a,b**, respectively, in scalemic form.

The (−)-ethisolide (mp 121–122 °C (lit.[1a] mp 122–123 °C)) resulting from executing the route shown in Scheme II with scalemic **11a,b** had physical data closely corresponding to that reported by Turner,[1a] except for optical rotation in ethanol. We found that the α-methylene lactone unit in ethisolide reacts slowly with ethanol to give the hydroxy ester, thus invalidating rotational data in this solvent and precluding any meaningful comparison with Turner's value.[27] Returning to a point in the synthetic sequence after which C(4) epimerization was unlikely, we subjected racemic and scalemic allylic alcohols **11a,b** to the Mitsunobu S_N2' reaction using (*R*)-(+)-Mosher's acid.[28] Comparison of the ^1H NMR spectrum (400 MHz) for the product **39** from scalemic **11a,b** with that from the race-

(22) Prepared in 65% yield from ethylmagnesium bromide and crotonaldehyde. See: *Organic Syntheses*; Wiley, New York 1955; Collect. Vol. III, p 696.

(23) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(24) Enantiomeric excesses were determined by coupling the racemic and scalemic alcohols with (+)-Mosher's acid using dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP): (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. Separation of the diastereomeric esters was accomplished in each case by glass capillary GC, using a 25-m column coated with SUPEROX-4 (Alltech Associates, Inc., Deerfield, IL).

(25) Prepared in 97% yield from octylmagnesium bromide and crotonaldehyde. See ref 22.

(26) For the preparation of α-alkoxy aldehydes in this way, see: Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846.

(27) In contrast, neither isoavenaciolide nor avenaciolide react with ethanol at room temperature at an appreciable rate. Their literature rotations in this solvent are valid.

(28) ^1H NMR spectra at 400 MHz are sufficient to differentiate and quantitate the diastereomers. See: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

mate showed **39** to be ≥90% optically pure. Synthetic (−)-ethisolide obtained here, $[\alpha]_D^{21.5}$ −188.13° (*c* 0.21, $CHCl_3$), should be of similarly high ee.

Enantioselective synthesis of (−)-isoavenaciolide (**2**) proceeded from scalemic **17a,b** as described for the racemic series (Scheme III). Notably, the structure for scalemic **21** was secured by X-ray diffraction.[19] In combination with the crystallographic proof of structure for racemic **23**, this formed the basis for the preceding discussion of the reactivity differential in diastereomeric pairs **20/21** and **15a/15b**. The (−)-isoavenaciolide produced by this sequence, mp 128–129 °C, $[\alpha]_D^{22}$ −155.8° (*c* 0.5, EtOH) [lit. mp 129–130 °C,[1a] 127–128 °C;[1b] $[\alpha]_D^{27}$ −154° (*c* 1.1, EtOH),[1a] $[\alpha]_D^{20}$ −167.2° (*c* 1.2, EtOH)[1b]] was structurally identical to the natural substance by IR, 400-MHz ^1H NMR, MS, and combustion analysis.

(−)-Avenaciolide (**3**) was also produced by the route shown (Scheme IV) for the racemate, involving scalemic **19** as an intermediate in common with the isoavenaciolide synthesis. Synthetic (−)-avenaciolide from the sequence **19** → **26** → **3**, mp 51–52 °C, $[\alpha]_D^{24}$ −39.77° (*c* 1.28, EtOH) [lit. mp 49–50, 54–56;[2a] 50–51;[1b,2f] 54–56 °C,[2g] $[\alpha]_D^{26.5}$ −41.6° (*c* 1.2, EtOH),[2d] $[\alpha]_D^{29.5}$ −41.8° (*c* 0.274, EtOH),[1b,2f] $[\alpha]_D^{25}$ −41.6° (*c* 1.0, EtOH)[2g]] had spectroscopic and analytical data consistent with those published.[2]

In summary, a general route to the three bislactone mold metabolites ethisolide (**1**), isoavenaciolide (**2**), and avenaciolide (**3**) has been developed, yielding the title compounds in racemic and natural, optically active forms. The glycolate Claisen rearrangement[5c-g] served to establish the relative stereochemical details. Complementary butyrolactone rearrangements were devised to give the diastereomeric isoavenaciolide and avenaciolide structures from a common intermediate.

Experimental Section

General. Infrared (IR) absorption maxima are reported in wavenumbers (cm^{-1}) and are standardized to the 1601 cm^{-1} reference peak of polystyrene. Chemical shifts for proton and carbon NMR resonances are reported in parts per million (δ) relative to Me_4Si (δ 0.0). Analytical glass capillary GC analyses were done using a 25-m capillary column coated with SUPEROX-4 (Alltech Associates, Inc., Deerfield, IL). Melting points were recorded in open-ended capillaries and, along with boiling points, are uncorrected.

Moisture-sensitive reactions were carried out in flame-dried glassware under a positive pressure (balloon) of argon. Analytical TLC was done on Analtech plates precoated with silica gel GHLF (250-mm-layer thickness). Gravity column chromatography was done on E. Merck silica gel 60 (70–230 mesh) ASTM. Flash chromatography was performed as described by Still.[29]

THF was distilled from potassium benzophenone ketyl immediately before use. CH_2Cl_2 was passed through a column of alumina (activity grade I) and stored over 4-Å molecular sieves. Chlorotrimethylsilane, DBU, and DMPU were distilled from CaH_2 and stored over 4-Å molecular sieves. Triethylamine, diisopropylamine, and hexamethyldisilazane were distilled from CaH_2 and stored over KOH pellets. Boron trifluoride etherate was distilled and stored under Ar at −20 °C. Hexanes were purified by distillation. All other reagents were used as received.

***trans*- and *cis*-5-Ethyldihydro-4-hydroxy-3-methylene-2(3*H*)-furanone (11a, 11b).** To a solution of 612 mg (2.13 mmol) of a mixture of (*R**,*S**)- and (*S**,*S**)-3-hydroxy-4[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenehexanoic acid methyl esters[8,31] in 20 mL of CH_3CN at 25 °C was added 10 drops of 48% aqueous HF.[9b] The reaction mixture was stirred at 25 °C for 1 h, quenched with ca. 5 mL of saturated aqueous $NaHCO_3$, and stirred for 10 min. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude diols obtained were dissolved in 30 mL of PhH and, after the addition of a catalytic amount of camphorsulfonic acid, were heated at reflux under a Dean-Stark condenser for 1 h. Concentration under reduced pressure followed by chromatography on 35 g of silica gel (elution with 2:1 CH_2Cl_2–ether) gave 183 mg (61%) of lactones **11a** (major) and **11b** (minor) in a 4:1 ratio, as determined by integration of distinctive resonances in the 400-MHz ^1H NMR spectrum.

Data for **11a**: R_f 0.66 (1:1 CH_2Cl_2–ether); IR (neat film) 3430, 2988, 1755, 1671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (d, 1 H, *J* = 2.3 Hz), 5.97 (d, 1 H, *J* = 2.0 Hz), 4.52 (ddd, 1 H, *J* = 4.3, 2.2, 2.2 Hz), 4.21 (ddd, 1 H, *J* = 7.4, 5.6, 4.4 Hz), 2.75 (br s, 1 H), 1.72 (m, 2 H), 1.04 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 169.49, 138.85, 126.05, 86.85, 72.12, 26.43, 9.02; MS (15 eV) parent peak +1 143, base peak 84. Anal. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.09. Found: C, 58.99; H, 7.24.

Data for **11b**: R_f 0.66 (1:1 CH_2Cl_2–ether); ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, 1 H, *J* = 1.8 Hz), 5.97 (d, 1 H, *J* = 1.7 Hz), 4.84 (ddd, 1 H, *J* = 5.6, 1.6, 1.6 Hz), 4.37 (dt, 1 H, *J* = 8.2, 5.7 Hz), 2.75 (br s, 1 H), 1.79 (m, 2 H), 1.06 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 169.49, 138.85, 126.14, 84.12, 68.82, 21.79, 9.61.

***O*-[2-(Trimethylsilyl)ethyl]glycolic Acid.** To a slurry of 2.90 g (95.4 mmol) of NaH (80% dispersion in oil) in 10 mL of THF at 0 °C was added a solution of 3.75 g (31.8 mmol) of 2-(trimethylsilyl)ethanol[30] in 15 mL of THF. The mixture was stirred at 0 °C for 15 min then a solution of 4.42 g (31.8 mmol) of bromoacetic acid in 20 mL of THF was added. The mixture was stirred at 0 °C for 15 min then heated at reflux for 18 h. The reaction mixture was cooled to 0 °C, quenched with ca. 10 mL of H_2O, and then added to 20 mL of H_2O and extracted once with ether. The aqueous layer was acidified with concentrated HCl then extracted three times with ether. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography on 150 g of silica gel (elution with 3:1 hexanes–ether, 1% HOAc) gave 3.00 g (54%) of the product acid as an oil, homogeneous by TLC and spectroscopic criteria: R_f 0.77 (1:1 ether–hexanes, 1% HOAc); IR (neat film) 3500, 3150, 2960, 1740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 9.40 (br s, 1 H), 4.10 (s, 2 H), 3.65 (t, 2 H, *J* = 8.4 Hz), 1.00 (t, 2 H, *J* = 8.4 Hz), 0.05 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 175.43, 69.27, 67.05, 3.26, −1.54; MS (15 eV) parent peak +1 177, base peak 105.

(±)-5-Ethyl-3-[[2-[2-(trimethylsilyl)ethoxy]acetoxy]methyl]-2(5*H*)-furanone (12). To a solution of 511 mg (1.95 mmol) of triphenylphosphine, 213 mg (1.50 mmol) of a mixture of alcohols **11a** and **11b**, and 343 mg (1.95 mmol) of *O*-[(2-trimethylsilyl)ethyl]glycolic acid in 7.5 mL of THF at 0 °C was added 0.31 mL (1.95 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred at 0 °C for 5 min then warmed to 25 °C and stirred 45 min. Concentration under reduced pressure followed immediately by flash chromatography (elution with 1:1 ether–hexanes) afforded 359 mg (80%) of butenolide **12** as an oil, homogeneous by TLC and spectroscopic criteria: R_f 0.38 (1:1 ether–hexanes); IR (neat film) 2958, 1765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 1 H, *J* = 1.0 Hz), 4.93 (brm, 1 H), 4.91 (t, 2 H, *J* = 1.3 Hz), 4.10 (s, 2 H), 3.60 (t, 2 H, *J* = 8.4 Hz), 1.76 (m, 2 H), 0.99 (t, 3 H, *J* = 7.4 Hz), 0.98 (t, 2 H, *J* = 8.4 Hz), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.19, 169.86, 151.63, 129.12, 82.55, 68.99, 67.27, 57.36, 26.06, 17.86, 8.79, 1.67; MS (15 eV) base peak 73. Anal. Calcd for $C_{14}H_{24}O_5Si$: C, 55.97; H, 8.05. Found: C, 55.67; H, 8.11.

(2α,3β(*R))-(±)-2-Ethyltetrahydro-4-methylene-α-[2-(trimethylsilyl)ethoxy]-5-oxo-3-furanacetic Acid (13).** To a solution of 0.77 mmol of lithium hexamethyldisilazide in 2 mL of THF at −100 °C was added 1.5 mL of the supernatant from the centrifugation of a 1:1 mixture of Me_3SiCl and Et_3N. After stirring at −100 °C for 5 min, a solution of 154 mg (0.51 mmol) of ester **12** in 1.5 mL of THF was introduced. The reaction mixture was stirred at −100 °C for 1.5 h then allowed to warm to 25 °C over 12 h. The reaction mixture was acidified with 5% aqueous HCl then the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (elution with 5:1 hexanes–acetone, 1% HOAc) afforded 110 mg (71%) of acid **13** as an oil, homogeneous by TLC and spectroscopic criteria: R_f 0.53 (3:1 hexanes–acetone, HOAc); IR (neat film) 3200, 2955, 1760,

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(30) Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039.
(31) Prepared by the method described by Seebach in ref 7.

1665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (br s, 1 H), 6.38 (d, 1 H, J = 2.3 Hz), 5.76 (d, 1 H, J = 2.0 Hz), 4.57 (m, 1 H), 3.96 (d, 1 H, J = 4.7 Hz), 3.75 (ddd, 1 H, J = 8.3, 8.3, 8.3 Hz), 3.47 (ddd, 1 H, J = 8.5, 8.4, 8.4 Hz), 3.13 (br m, 1 H), 1.64 (m, 2 H), 0.96 (t, 3 H, J = 7.3 Hz), 0.92 (dd, 2 H, J = 8.1, 8.1 Hz), -0.01 (s, 9 H); ^{13}C NMR ($CDCl_3$) 174.59, 169.72, 135.55, 124.18, 79.89, 79.80, 69.76, 53.39, 46.47, 29.01, 18.11, 8.88, -1.47; MS (15 eV) base peak 73.

(2α,3β(*R),4α)- and (2α,3β(*R**),4β)-(±)-2-Ethyltetrahydro-α-[2-(trimethylsilyl)ethoxy]-5-oxo-4-[(phenylthio)methyl]-3-furanacetic Acid Methyl Ester (14).** To a solution of NaOEt (6.90 mmol) in 3 mL of absolute EtOH at 25 °C was added 1.10 mL (10.4 mmol) of thiophenol. After being stirred at 25 °C for 10 min, the mixture was cooled to 0 °C and a solution of 520 mg (1.73 mmol) of acid **13** in 6 mL of absolute EtOH was added. The reaction mixture was stirred at 0 °C for 10 min then warmed to 25 °C and stirred 1 h. After quenching with ca. 1.5 mL of HOAc and ca. 1 mL of H_2O, the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude mixture of acids was dissolved in 50 mL of ether and esterified with an ethereal solution of diazomethane. Chromatography on 50 g of silica gel (elution with 4:1 hexanes–ether) gave 581 mg (79%) of an inseparable mixture of esters **14**: R_f 0.48 (3:1 hexanes–ether); IR (neat film) 2960, 1780, 1755 cm^{-1}; MS (70 eV) parent peak 424, base peak 73. Anal. Calcd for $C_{21}H_{35}O_5SSi$: C, 59.40; H, 7.60. Found: C, 59.28; H, 7.45.

(2α,3β(*R),4β)- and (2α,3β(*R**),4α)-(±)-2-Ethyltetrahydro-α-hydroxy-5-oxo-4-[(phenylthio)methyl]-3-furanacetic Acid Methyl Ester (15b, 15a).** To a solution of 46 mg (0.11 mmol) of the mixture of protected alcohols **14** in 0.5 mL of CH_2Cl_2 at 0 °C was added 40 μL (0.33 mmol) of BF_3 etherate. The reaction mixture was stirred at 0 °C for 5 min, warmed to 25 °C, and stirred 1 h, and then quenched with ca. 0.5 mL of H_2O. The layers were separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (elution with 1:1 ether–hexanes) gave 15.5 mg (44%) of alcohol **15b** and 14.5 mg (41%) of alcohol **15a** as oils, homogeneous by TLC and spectroscopic criteria.

Data for **15b**: R_f 0.20 (1:1 ether–hexanes); IR (neat film) 3490, 2970, 1775, 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 4.65 (br s, 1 H), 4.11 (dt, 1 H, J = 7.1, 1.0 Hz), 3.85 (s, 3 H), 3.65 (dd, 1 H, J = 13.6, 3.6 Hz), 3.17 (dd, 1 H, J = 13.7, 11.8 Hz), 2.98 (m, 2 H), 2.80 (dt, 1 H, J = 8.9, 1.6 Hz), 1.65 (m, 1 H), 1.49 (m, 1 H), 0.90 (t, 3 H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 175.93, 173.60, 134.34, 129.82, 129.15, 126.82, 80.26, 68.89, 52.94, 42.99, 39.11, 29.60, 27.41, 9.23; MS (70 eV) parent peak 324, base peak 123. Anal. Calcd for $C_{16}H_{20}O_5S$: C, 59.24; H, 6.22. Found: C, 59.11; H, 6.29.

Data for **15a**: R_f 0.17 (1:1 ether–hexanes); IR (neat film) 3485, 2975, 1770, 1748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 4.44 (t, 1 H, J = 3.6 Hz), 4.32 (ddd, 1 H, J = 7.7, 7.7, 4.0 Hz), 3.77 (s, 3 H), 3.57 (m, 1 H), 3.12 (m, 3 H), 2.65 (ddd, 1 H, J = 8.1, 8.1, 3.0 Hz), 1.50 (m, 2 H), 0.97 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 175.78, 173.56, 134.81, 130.03, 129.19, 126.88, 78.82, 68.88, 52.77, 47.99, 42.23, 34.71, 27.98, 9.38; MS (70 eV) parent peak 324, base peak 110.

(3α,3aα,4β,6aα)-(±)-4-Ethyldihydro-3-[(phenylthio)methyl]furo[3,4-*b*]furan-2,6(3*H*,4*H*)-dione (16). A solution of 15.5 mg (0.048 mmol) of hydroxy ester **15b** and a catalytic amount of camphorsulfonic acid in 4 mL of $PhCH_3$ was heated at reflux for 36 h. Concentration under reduced pressure followed by flash chromatography (elution with 1:1 ether–hexanes) gave 12.5 mg (89%) of bislactone **16** as a solid, mp 125.0–126.0 °C, homogeneous by TLC and spectroscopic criteria: R_f 0.48 (3:1 ether–hexanes); IR ($CHCl_3$) 3030, 2965, 2930, 1795, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 5.12 (d, 1 H, J = 8.6 Hz), 4.52 (dt, 1 H, J = 8.6, 5.5 Hz), 3.54 (ddd, 1 H, J = 8.6, 8.6, 5.8 Hz), 3.35 (d, AB_q, 2 H, $\Delta\nu_{AB}$ = 28 Hz, J_{AB} = 14.0 Hz, J_{AX} = 47 Hz, J_{BX} = 5.8 Hz), 3.00 (ddd, 1 H, J = 8.5, 5.2, 5.2 Hz), 1.62 (m, 2 H), 1.05 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 174.53, 170.32, 134.25, 130.46, 129.36, 127.40, 80.63, 75.42, 43.36, 39.02, 34.60, 24.80, 10.53; MS (70 eV) parent peak 292, base peak 123.

(3aα,4β,6aα)-(±)-4-Ethyldihydro-3-methylenefuro[3,4-*b*]-furan-2,6(3*H*,4*H*)-dione ((±)-1) [(±)-Ethisolide]. To a solution of 21 mg (0.072 mmol) of bislactonic sulfide **16** in 1 mL of $CHCl_3$ at -20 °C was added a solution of 16 mg (0.076 mmol) of *m*-CPBA in 0.8 mL of $CHCl_3$. The reaction mixture was stirred at -20 °C for 30 min and then quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was washed once with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude sulfoxide obtained was dissolved in 6 mL of $PhCH_3$ then, after the addition of 40 mg (0.29 mmol) of solid K_2CO_3, the mixture was heated at reflux for 6 h. Concentration under reduced pressure followed by flash chromatography (elution with 3:1 hexanes–acetone) gave 9.2 mg (70%) of (±)-ethisolide ((±)-1) as a solid. Recrystallization from hexanes–acetone afforded white elongated plates, mp 108.0–110.0 °C, homogeneous by TLC and spectroscopic criteria: R_f 0.20 (3:1 hexanes–acetone), IR ($CHCl_3$) 3035, 2982, 2946, 1788, 1663 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, 1 H, J = 2.7 Hz), 5.89 (d, 1 H, J = 2.3 Hz), 5.13 (d, 1 H, J = 8.8 Hz), 4.70 (ddd, 1 H, J = 10.1, 7.9, 3.8 Hz), 4.02 (m, 1 H), 1.76 (m, 1 H), 1.60 (m, 1 H), 1.12 (t, 3 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 170.11, 167.83, 130.87, 128.78, 81.91, 74.88, 41.62, 25.58, 10.52; MS (70 eV) parent peak +1 183, base peak 96. Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.11, H, 5.40.

(3a*R*-(3aα,4β,6aα))-4-Ethyldihydro-3-methylenefuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((-)-1) [(-)-Ethisolide]. The procedure for the conversion of **16** to (±)-**3** was followed. Flash chromatography (elution with 3:1 hexanes–acetone) gave 6.6 mg (35%) of (-)-ethisolide ((-)-1) as a solid. Recrystallization from hexanes–acetone afforded white needles, mp 121.0–122.0 °C (lit.[1a] mp 122–123 °C), homogeneous by TLC and spectroscopic criteria: R_f 0.22 (3:1 hexanes–acetone); $[\alpha]_D^{21.5}$ -188.13° (*c* 0.21, $CHCl_3$) [lit.[1a,32] $[\alpha]_D^{27}$ -214° (*c* 1.2, EtOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.60 (d, 1 H, J = 2.6 Hz), 5.89 (d, 1 H, J = 2.2 Hz), 5.13 (d, 1 H, J = 8.8 Hz), 4.70 (ddd, 1 H, J = 10.0, 8.0, 3.8 Hz), 4.02 (m, 1 H), 1.76 (m, 1 H), 1.60 (m, 1 H), 1.12 (t, 3 H, J = 7.3 Hz).

***trans*- and *cis*-Dihydro-4-hydroxy-3-methylene-5-octyl-2(3*H*)-furanone (17a, 17b).** To a solution of 942 mg (2.53 mmol) of a mixture of (*R**,*S**)- and (*S**,*S**)-3-hydroxy-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-methylenedodecanoic acid methyl esters[31,8] in 20 mL of CH_3CN at 25 °C was added 10 drops of 40% aqueous HF.[9b] The reaction mixture was stirred at 25 °C for 1 h, quenched with ca. 10 mL of saturated aqueous $NaHCO_3$, and stirred 10 min. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude diols were dissolved in 60 mL of PhH and, after the addition of a catalytic amount of camphorsulfonic acid, were heated at reflux under a Dean-Stark condenser for 1 h. Concentration under reduced pressure followed by chromatography on 25 g of silica gel (elution with 2:1 CH_2Cl_2–ether) gave 506 mg (88%) of lactones **17a** (major) and **17b** (minor) in an 8:1 ratio, as determined by integration of distinctive resonances in the 400-MHz ^{1}H NMR spectrum.

Data for **17a**: R_f 0.74 (1:1 CH_2Cl_2–ether); IR (neat film) 3440, 2925, 2860, 1704, 1674 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, 1 H, J = 2.3 Hz), 5.96 (d, 1 H, J = 2.0 Hz), 4.51 (ddd, 1 H, J = 8.8, 4.4, 2.2 Hz), 4.25 (ddd, 1 H, J = 7.8, 5.5, 4.4 Hz), 2.50 (br s, 1 H), 1.68 (m, 2 H), 1.46 (m, 2 H), 1.26 (br s, 10 H), 0.87 (t, 3 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 169.59, 138.96, 126.04, 82.69, 69.20, 31.76, 29.37, 29.13, 28.56, 25.31, 22.57, 14.01; MS (70 eV) parent peak + 1 227, base peak 56. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.60; H, 9.88.

Data for **17b**: R_f 0.74 (1:1 CH_2Cl_2–ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, 1 H, J = 2.2 Hz), 5.95 (d, 1 H, J = 2.0 Hz), 4.80 (br s, 1 H), 4.41 (dt, 1 H, J = 8.2, 5.5 Hz), 3.15 (br s, 1 H), 1.66 (m, 2 H), 1.45 (m, 2 H), 1.26 (br s, 10 H), 0.86 (t, 3 H, J = 6.7 Hz).

(±)-3-[[2-[2-(Trimethylsilyl)ethoxy]acetoxy]methyl]-5-octyl-2(5*H*)-furanone (18). To a solution of 1.68 g (6.40 mmol) of triphenylphosphine, 1.12 g (4.96 mmol) of a mixture of alcohols **17a** and **17b**, and 1.13 g (6.40 mmol) of *O*-[(2-trimethylsilyl)-ethyl]glycolic acid in 50 mL of THF at 0 °C was added 1.08 mL (6.40 mmol) of diethyl azodicarboxylate. The reaction mixture was stirred at 0 °C for 15 min and then warmed to 25 °C and stirred 1 h. Concentration under reduced pressure followed im-

(32) See text for discussion of unsuitability of EtOH for this measurement.

mediately by flash chromatography (elution with 4:1 hexanes–ethyl acetate) afforded 1.40 g (99%) of ester **18** as an oil, homogeneous by TLC and spectroscopic criteria: R_f 0.39 (4:1 hexanes–ethyl acetate); IR (neat film) 2955, 2928, 2858, 1762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, 1 H, J = 1.4 Hz), 4.97 (m, 1 H), 4.90 (d, 2 H, J = 1.3 Hz), 4.11 (s, 2 H), 3.62 (t, 2 H, J = 8 Hz), 1.68 (br m, 2 H), 1.42 (br m, 2 H), 1.26 (br s, 10 H), 0.99 (t, 2 H, J = 8 Hz), 0.87 (br t, 3 H, J = 7 Hz), 0.02 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.21, 169.90, 151.98, 128.94, 81.69, 69.06, 67.34, 57.42, 33.01, 31.60, 29.11, 28.93, 24.81, 22.41, 17.93, 13.86, -1.56, -1.63; MS (15 eV) parent peak 384, base peak 123. Anal. Calcd for $C_{20}H_{36}O_5Si$: C, 62.46; H, 9.44. Found: C, 62.23; H, 9.62.

(2α,3β(R*))-(±)-Tetrahydro-4-methylene-α-[2-(trimethylsilyl)ethoxy]-2-octyl-5-oxo-3-furanacetic Acid (19). To a solution of 0.86 mmol of lithium hexamethyldisilazide in 4 mL of THF at -100 °C was added 1.0 mL of the supernatant from the centrifugation of a 1:1 mixture of Me_3SiCl and Et_3N. After the solution was stirred at -100 °C for 5 min, a solution of 237 mg (0.62 mmol) of ester **18** in 3 mL of THF was introduced. The reaction mixture was stirred at -100 °C for 1 h then allowed to warm to 25 °C over 14 h. The reaction mixture was acidified with 5% aqueous HCl, stirred 15 min, then the aqueous phase was extracted several times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (elution with 4:1 hexanes–ethyl acetate, 1% HOAc) afforded 166 mg (70%) of acid **19** as an oil, homogeneous by TLC and spectroscopic criteria: R_f 0.40 (3:1 hexanes–ethyl acetate, 1% HOAc); IR (neat film) 3450, 2960, 2928, 2860, 1768, 1662, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, 1 H, J = 2.3 Hz), 5.74 (d, 1 H, J = 1.9 Hz), 4.64 (m, 1 H), 3.97 (d, 1 H, J = 4.6 Hz), 3.74 (ddd, 1 H, J = 8.4, 8.3, 8.3 Hz), 3.44 (ddd, 1 H, J = 8.0, 8.0, 8.0 Hz), 3.11 (br m, 1 H), 1.59 (br m, 2 H), 1.38 (br m, 2 H), 1.25 (br s, 10 H), 0.93 (dd, 2 H, J = 8.1, 8.1 Hz), 0.87 (t, 3 H, J = 6.7 Hz), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 174.74, 169.86, 135.40, 124.29, 79.74, 78.97, 69.54, 46.90, 36.11, 31.74, 29.29, 29.11, 24.59, 22.55, 18.04, 13.99, -1.50; MS (15 eV) base peak 73.

(2α,3β(R*))-(±)-Tetrahydro-α-hydroxy-4-methylene-2-octyl-5-oxo-3-furanacetic Acid Methyl Ester (24). To a solution of 55.5 mg (0.14 mmol) of acid **19** in 0.5 mL of CH_2Cl_2 at 0 °C was added 60 μL (0.44 mmol) of triethylamine, then 32 μL (0.39 mmol) of methyl chloroformate, and finally 2 mg (0.014 mmol) of 4-(dimethylamino)pyridine (DMAP).[20] The reaction mixture was stirred at 0 °C for 1.5 h, warmed to 25 °C and stirred 3 h, and then quenched with ca. 1 mL of saturated aqueous NH_4Cl. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography on 30 g of silica gel (elution with 3:1 hexanes–ether) gave 50 mg (87%) of the methyl ester as an oil, homogeneous by TLC and spectroscopic criteria: R_f 0.71 (1:1 ether–hexanes); IR (neat film) 2960, 2930, 2860, 1770, 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (d, 1 H, J = 2.4 Hz), 5.63 (d, 1 H, J = 2.0 Hz), 4.59 (m, 1 H), 3.88 (d, 1 H, J = 5.8 Hz), 3.76 (s, 3 H), 3.68 (ddd, 1 H, J = 8.8, 8.8, 7.8 Hz), 3.41 (ddd, 1 H, J = 9.0, 8.3, 7.7 Hz), 3.06 (dddd, 1 H, J = 5.7, 3.3, 2.3, 2.3 Hz), 1.56 (m, 2 H), 1.25 (br s, 12 H), 0.90 (dd, 2 H, J = 8.3, 7.9 Hz), 0.87 (t, 3 H, J = 6.8 Hz), 0.00 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 171.05, 169.51, 135.51, 123.79, 80.14, 78.92, 69.07, 51.91, 47.15, 36.16, 31.80, 29.35, 29.19, 29.15, 24.66, 22.60, 18.04, 14.03, -1.45; MS (15 eV) base peak 73. Anal. Calcd for $C_{21}H_{38}O_5Si$: C, 63.28; H, 9.61. Found; C, 63.09; H, 9.48.

To a solution of 53 mg (0.13 mmol) of the methyl ester derived from **19** in 0.7 mL of CH_2Cl_2 at 0 °C was added 66 μL (0.53 mmol) of boron trifluoride etherate. The reaction mixture was stirred at 0 °C for 10 min, warmed to 25 °C and stirred 1.5 h, and then quenched with ca. 0.5 mL of H_2O. The layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (elution with 3:2 ether–hexanes) gave 28 mg (71%) of alcohol **24** as an oil, homogeneous by TLC and spectroscopic criteria: R_f 0.22 (1:1 ether–hexanes); IR (neat film) 3470, 2955, 2927, 2860, 1750, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.37 (d, 1 H, J = 2.5 Hz), 5.76 (d, 1 H, J = 2.2 Hz), 4.49 (ddd, 1 H, J = 7.7, 5.1, 4.0 Hz), 4.38 (t, 1 H, J = 3.9 Hz), 3.81 (s, 3 H), 3.10 (m, 2 H), 1.60 (m, 1 H), 1.53 (m, 1 H), 1.26 (br s, 12 H), 0.87 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.83, 169.41, 135.27, 124.06, 78.19, 72.12, 52.87, 47.71, 36.12, 31.77, 29.34, 29.22, 29.12, 24.65, 22.58, 14.02; MS (15 eV) parent peak 298, base peak 209. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.22; H, 9.04.

(2α,3β(R*),4β)- and (2α,3β(R*),4α)-(±)-Tetrahydro-α-[2-(trimethylsilyl)ethoxy]-2-octyl-5-oxo-4-[(phenylthio)methyl]-3-furanacetic Acid Methyl Ester (21, 20). To a solution of NaOEt (0.52 mmol) in 0.5 mL of absolute EtOH at 0 °C was added 80 μL (0.78 mmol) of thiophenol. After the solution was stirred at 0 °C for 10 min, a solution of 100 mg (0.26 mmol) of acid **19** in 1 mL of absolute EtOH was added. The reaction mixture was stirred at 0 °C for 10 min and then warmed to 25 °C and stirred 1 h. After quenching with ca. 0.5 mL of HOAc and ca. 0.5 mL of H_2O, the aqueous layer was extracted several times with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude mixture of acids was dissolved in 20 mL of ether and esterified with an ethereal solution of diazomethane. Flash chromatography (elution with 5:1 hexanes–ether) afforded 44 mg (33%) of sulfide **21** and 35 mg (27%) of sulfide **20**, homogeneous by TLC and spectroscopic criteria.

Data for **21**: R_f 0.33 (5:1 hexanes–ether); IR (neat film) 3062, 2958, 2930, 2860, 1777, 1755, 1582 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 4.49 (t, 1 H, J = 7.0 Hz), 4.20 (d, 1 H, J = 2.1 Hz), 3.77 (s, 3 H), 3.76 (m, 1 H), 3.61 (dd, 1 H, J = 13.3, 3.4 Hz), 3.29 (ddd, 1 H, J = 11.0, 8.9, 4.9 Hz), 2.92 (m, 1 H), 2.80 (dd, 1 H, J = 13.1, 11.8 Hz), 2.69 (br d, 1 H, J = 8.7 Hz), 1.57 (br m, 2 H), 1.38 (br m, 2 H), 1.24 (br s, 10 H), 0.98 (m, 1 H), 0.87 (t, 3 H, J = 6.8 Hz), 0.85 (m, 1 H), -0.01 (s, 9 H); MS (15 eV) parent peak 508, base peak 227. Anal. Calcd for $C_{27}H_{44}O_5SSi$: C, 63.74; H, 8.72. Found: C, 63.78; H, 8.94.

Data for **20**: R_f 0.24 hexanes–ether); hexane–ether); IR (neat film) 3062, 2958, 2930, 2860, 1775, 1755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5 H), 4.47 (m, 1 H), 4.07 (d, 1 H, J = 3.3 Hz), 3.73 (s, 3 H), 3.64 (m, 2 H), 3.15 (ddd, 1 H, J = 10.5, 8.9, 5.5 Hz), 3.03 (m, 2 H), 2.57 (ddd, 1 H, J = 8.4, 7.6, 3.3 Hz), 1.45 (br m, 2 H), 1.25 (br s, 12 H), 0.87 (t, 3 H, J = 6.9 Hz), 0.80 (ddd, 1 H, J = 13.8, 10.6, 6.5 Hz), 0.72 (ddd, 1 H, J = 13.8, 10.6, 5.5 Hz), -0.04 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 176.02, 171.50, 134.81, 129.17, 126.55, 76.89, 68.73, 51.80, 48.57, 41.71, 35.57, 34.44, 31.77, 29.28, 29.12, 25.21, 22.55, 18.00, 13.98, -1.46; MS (15 eV) parent peak 508, base peak 299. Anal. Calcd for $C_{27}H_{44}O_5SSi$: C, 63.74; H, 8.72. Found: C, 64.03; H, 9.02.

(2α,3β(R*),4β)-(±)-Tetrahydro-α-hydroxy-2-octyl-5-oxo-4-[(phenylthio)methyl]-3-furanacetic Acid Methyl Ester (22). To a solution of 78 mg (0.15 mmol) of protected alcohol **21** in 0.8 mL of CH_2Cl_2 at 0 °C was added 95 μL (0.77 mmol) of $BF_3{\cdot}Et_2O$. The reaction mixture was stirred at 0 °C for 5 min, warmed to 25 °C, and stirred 2.5 h, and then quenched with ca. 0.5 mL H_2O. The layers were separated, and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated. Chromatography on 20 g of silica gel (elution with 2:1 ether–hexanes) gave 49.5 mg (79%) of alcohol **22** as an oil, homogeneous by TLC and spectroscopic criteria: R_f 0.51 (2:1 ether–hexanes); IR (neat film) 3510, 3060, 2930, 2858, 1775, 1740, 1585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 4.64 (dd, 1 H, J = 3.8, 2.1 Hz), 4.18 (t, 1 H, J = 7.0 Hz), 3.85 (s, 3 H), 3.65 (dd, 1 H, J = 13.6, 3.6 Hz), 3.17 (dd, 1 H, J = 13.6, 11.8 Hz), 2.97 (m, 2 H), 2.78 (d, 1 H, J = 8.8 Hz), 1.60 (m, 2 H), 1.43 (br m, 2 H), 1.25 (br s, 10 H), 0.88 (t, 3 H, J = 6.9 Hz); MS (70 eV) parent peak 408, base peak 110.

(3α,3aα,4β,6aα)-(±)-Dihydro-4-octyl-3-[(phenylthio)methyl]furo[3,4-*b*]furan-2,6(3*H*,4*H*)-dione (23). A solution of 174 mg (0.43 mmol) of hydroxy ester **22**, and a catalytic amount of camphorsulfonic acid in 35 mL of $PhCH_3$ was heated at reflux for 120 h. Concentration under reduced pressure followed by flash chromatography (elution with 1:1 ether–hexanes) afforded 146 mg (91%) of bislactone **23** as a solid. Recrystallization from 3:1 hexanes–ethyl acetate gave colorless plates, mp 120.5–121.5 °C, homogeneous by TLC and spectroscopic criteria: R_f 0.28 (1:1 ether–hexanes); IR ($CHCl_3$) 3020, 2930, 2860, 1795 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 5.11 (d, 1 H, J = 8.6 Hz), 4.56 (m, 1 H), 3.52 (ddd, 1 H, J = 8.6, 8.6, 5.8 Hz), 3.35 (ABX, 2 H, $\Delta\nu_{AB}$ = 51 Hz, J_{AB} = 14.1 Hz, J_{AX} = 4.6 Hz, J_{BX} = 6.1 Hz), 3.00 (ddd, 1 H, J = 6.0, 6.0, 4.6 Hz), 1.55 (br m, 2 H), 1.25 (br s, 12 H), 0.89 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) 174.57, 170.35, 134.23, 130.28, 129.39, 127.34, 79.23, 75.40, 43.57, 38.91, 34.56, 31.73, 31.50, 29.20, 29.09, 25.99, 22.57, 14.01; MS (70 eV) parent peak

376, base peak 110. Anal. Calcd for $C_{21}H_{28}O_4S$: C, 66.99; H, 7.50. Found: C, 66.77; H, 7.59.

(3aα,4β,6aα)-(±)-Dihydro-3-methylene-4-octylfuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((±)-2) [(±)-Isoavenaciolide]. To a solution of 15 mg (0.04 mmol) of bislactonic sulfide **23** in 0.5 mL of $CHCl_3$ at −20 °C was added a solution of 8.6 mg (0.04 mmol) of *m*-CPBA in 0.5 mL of $CHCl_3$. The reaction mixture was stirred at −20 °C for 40 min and then quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was washed once with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude sulfoxide was dissolved in 5 mL of $PhCH_3$. After the addition of 6.9 mg (0.05 mol) of solid K_2CO_3, the mixture was heated at reflux for 5 h. Concentration under reduced pressure followed by flash chromatography (elution with 3:1 hexanes–acetone) afforded 7.5 mg (71%) of (±)-isoavenaciolide ((±)-**2**) as a solid. Recrystallization from hexanes–ethyl acetate gave white needles, mp 101.0–102.0 °C (lit. mp 99–101,[1d] 99–99.5 °C[1c]), homogeneous by TLC and spectroscopic criteria: R_f 0.21 (4:1 ether–hexanes); IR ($CHCl_3$) 3022, 2960, 2932, 2860, 1785, 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (d, 1 H, J = 2.6 Hz), 5.88 (d, 1 H, J = 2.3 Hz), 5.12 (d, 1 H, J = 8.8 Hz), 4.76 (m, 1 H), 4.00 (m, 1 H), 1.60 (br m, 2 H), 1.25 (br s, 12 H)) 0.88 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 170.25, 167.92, 130.78, 128.93, 80.52, 74.87, 41.64, 32.25, 31.71, 29.28, 29.08, 26.01, 22.55, 14.00; MS (70 eV) parent peak +1 267, base peak 96. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.42; H, 8.50.

(3a*R*-(3aα,4β,6aα))-Dihydro-3-methylene-4-octylfuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((−)-2) [(−)-Isoavenaciolide]. The procedure for the conversion of **23** to (±)-**2** was followed. Concentration under reduced pressure followed by flash chromatography (elution with 3:1 hexanes–acetone) gave 13 mg (61%) of (−)-isoavenaciolide ((−)-**2**) as a solid. Recrystallization from hexanes–ethyl acetate afforded white needles, mp 128.0–129.0 °C (lit. mp 127.0–128.0,[1b] 129.0–130.0 °C[1a]), homogeneous by TLC and spectroscopic criteria: R_f 0.21 (3:1 hexanes–acetone); $[\alpha]_D^{22}$ −155.83° (*c* 0.50, EtOH) [lit. $[\alpha]_D^{20}$ −167.2° (*c* 1.2, EtOH),[1b] $[\alpha]_D^{27}$ −154° (*c* 1.1, EtOH)[1a]]; ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (d, 1 H, J = 2.6 Hz), 5.88 (d, 1 H, J = 2.3 Hz), 5.12 (d, 1 H, J = 8.8 Hz), 4.76 (m, 1 H), 4.00 (m, 1 H), 1.61 (m, 2 H), 1.26 (br s, 12 H), 0.88 (t, 3 H, J = 6.6 Hz).

(3aα,4α,6aα)-(±)-Dihydro-3-methylene-4-octylfuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((±)-3) [(±)-Avenaciolide]. To a solution of 295 mg (0.77 mmol) of acid **19** in 4 mL of CH_2Cl_2 at 0 °C was added 0.47 mL (3.84 mmol) of $BF_3{\cdot}Et_2O$. The reaction mixture was stirred at 0 °C for 15 min and then warmed to 25 °C and stirred for 1.5 h. After concentration under reduced pressure, crude hydroxy acid **26** was dissolved in 35 mL of $PhCH_3$. A catalytic amount of camphorsulfonic acid was added, and the mixture was heated at reflux for 36 h. Concentration under reduced pressure followed by flash chromatography (elution with 4:1 hexanes–ethyl acetate) gave 102 mg (50%) of (±)-avenaciolide ((±)-**3**) as a solid. Recrystallization from pentane–ether afforded white needles, mp 56.0–57.0 °C (lit.[2e,i] mp 55–56 °C), homogeneous by TLC and spectroscopic criteria: R_f 0.33 (4:1 hexanes–ethyl acetate); IR ($CHCl_3$) 3025, 2960, 2933, 2862, 1790, 1665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, 1 H, J = 2.5 Hz), 5.88 (d, 1 H, J = 2.3 Hz), 5.06 (d, 1 H, J = 8.5 Hz), 4.42 (ddd, 1 H, J = 7.2, 6.0, 3.9 Hz), 3.56 (m, 1 H), 1.80 (m, 2 H), 1.45 (br m, 2 H), 1.28 (br s, 10 H), 0.88 (t, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 169.77, 167.47, 134.64, 126.11, 85.19, 74.30, 44.11, 35.95, 31.69, 29.24, 29.04, 24.76, 22.52, 13.97; MS (15 eV) parent peak + 1 267, base peak 96. Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.53; H, 8.55.

(3a*R*-(3aα,4α,6aα))-Dihydro-3-methylene-4-octylfuro[3,4-*b*]furan-2,6(3*H*,4*H*)-dione ((−)-3) [(−)-Avenaciolide]. The procedure for the conversion of **19** to (±)-**3** was followed. Concentration under reduced pressure followed by flash chromatography (elution with 4:1 hexanes–ethyl acetate) gave 123 mg (59%) of (−)-avenaciolide ((−)-**3**) as a solid. Recrystallization from pentane–ether gave white needles, mp 51.0–52.0 °C (lit. mp 49–50, 54–56;[2a] 50–51;[1b,2f] 54–56 °C[2g]), homogeneous by TLC and spectroscopic criteria: R_f 0.40 (4:1 Et_2O–hexanes); $[\alpha]_D^{24}$ −39.77° (*c* 1.28, EtOH) [lit. $[\alpha]_D^{26.5}$ −41.6° (*c* 1.2, EtOH),[2d] $[\alpha]_D^{29.5}$ −41.08° (*c* 0.274, EtOH),[1b,2f] $[\alpha]_D^{25}$ −41.6° (*c* 1.0, EtOH)[2g]]; ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (d, 1 H, J = 2.5 Hz), 5.88 (d, 1 H, J = 2.2 Hz), 5.05 (d, 1 H, J = 8.5 Hz), 4.42 (ddd, 1 H, J = 6.6, 6.5, 3.9 Hz), 3.56 (m, 1 H), 1.80 (m, 2 H), 1.27 (br s, 12 H), 0.88 (t, 3 H, J = 6.7 Hz).

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Synthesis of the Lower Subunit of Rhizoxin

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Full details of a study leading to a synthesis of the optically active C13–C26 lower subunit of rhizoxin including the side-chain chromophore characteristic of the full class of antimitotic agents are described. A key element of the synthesis is the stereoselective introduction of the C18–C19 trisubstituted olefin through use of a Wadsworth–Horner–Emmons condensation of **3** with β-keto phosphonate **38** bearing resident functionality suitable for the diastereoselective introduction of C15–C17 employing a hydroxyl-directed reduction of the resultant β-hydroxy ketone.

Rhizoxin **1** (NSC-332598), a 16-membered macrolide isolated from *Rhizopus chinensis*, constitutes the most extensively examined member of a new class of agents that has been shown to possess antimicrobial activity, antifungal activity, potent in vitro cytotoxic activity, and confirmed in vivo antitumor activity including a pronounced efficacy against vincristine and adriamycin resistant tumor cell lines. The cytotoxic and antitumor activity of rhizoxin and its homologues[2] is believed to be

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