A New Stereoselective Synthesis of (−)-Isoavenaciolide and (−)-Avenaciolide

Carmen M. Rodríguez, Tomás Martín, and Victor S. Martín*

Instituto Universitario de Bio-Orgánica "Antonio González", Universidad de La Laguna Carretera de La Esperanza, 2, 38206 La Laguna, Tenerife, Spain

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The synthesis of isoavenaciolide and avenaciolide in their natural enantiomeric forms are described. In both syntheses, α-(phenylthio)-β-[(methoxycarbonyl)methyl]-γ-lactones obtained by the base-induced cyclization of enantiomerically enriched γ-[(phenylthio)acyl] α,β-unsaturated esters were used as starting materials. In the isoavenaciolide synthesis the key step is the stereoselective hydroxylation of the enolate generated in the (methoxycarbonyl)methyl chain that permits the bis-lactonization by a double transesterification. The configuration in the quaternary center vicinal to the carbonyl group in the ring was critical in order to obtain successfully the α-methylene lactone. In avenaciolide, the stereoselective synthesis of the bis-lactone unit was performed taking advantage of the presence of the phenyl sulfide group which by previous activation was used as leaving group to obtain the fused ring by an intramolecular substitution utilizing the carboxylate of the β-substituent as nucleophile. In this case, the α-methylene lactone was obtained by previously reported methodology.

Introduction

Avenaciolide (**1**)[1] and isoavenaciolide (**2**)[2] are naturally occurring secondary metabolites isolated from cultures of *Aspergillus* and *Penicillium* species. The bis-lactonic structure exhibited by these compounds as well as the potent biological activity manifested by avenaciolide[1a] have attracted a great deal of attention, and numerous syntheses of such compounds have been reported.[3]

A particularly interesting approach for us to the synthesis of these compounds is the one reported by Burke et al.[3] in which both compounds are obtained in a stereodivergent manner using the common intermediate **3** mainly by use of a series of lactone rearrangements. Considering our recently reported methodology to the synthesis of highly substituted γ-butyro lactones in their enantiomeric forms,[4] we decided to explore the synthesis of both avenaciolide and isoavenaciolide following the synthetic design outlined in Scheme 1 through the synthon **6** potentially available from **4**.[4b]

As depicted in the retrosynthesis in Scheme 1, a key step is the stereoselective hydroxylation of **4**. Gratifyingly, the enolate of the highly substituted γ-butyrolactone **4** was stereoselectively hydroxylated with MoOPH[5] to the α-hydroxy ester **6** in 85% yield as the only stereoisomer detected by NMR. The great stereoselectivity observed in this reaction is attributed to the more stable conformation adopted by the enolate **5**[4b] in which the hydrogen of the sp^2 carbon is oriented inside the ring of the γ-lactone forcing the reactions with electrophiles to occur using the *re* face since the *si* face is sterically

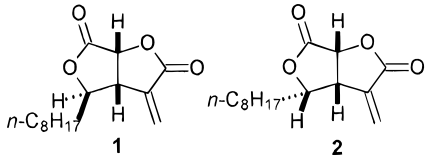
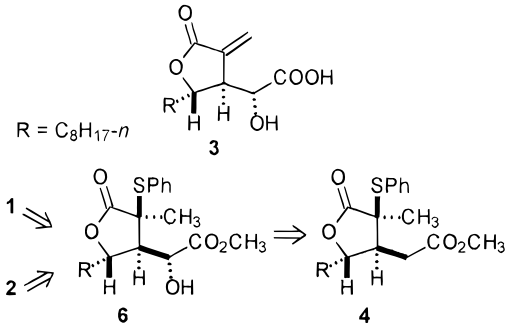


Figure 1.

Scheme 1



hindered by the substituents of the carbon vicinal to the carbonyl lactone (Scheme 2). The treatment of **6** with catalytic CSA in refluxing toluene for 72 h yielded **7** in 83% yield and a remaining amount of the starting material (≈12%). The stereochemistry of the stereocenters in **7** was clearly determined by NOE studies. Thus, the irradiation of the proton located at C3a showed NOE enhancements in the C6a and C4 protons. The *cis*-relative positions of the protons located at C3a and C6a were also deduced from the NOE between the protons of such carbons when the proton at C6a was irradiated. In order to obtain the desired α-methylene lactone **2**, the sulfide **7** was oxidized almost quantitatively to the sulfoxide **8** which decomposed to a mixture of uncharacterized compounds upon heating. This result was accounted by us as the effect of the preferential elimination of the proton situated in the bridge carbon which is situated *syn* relative to the sulfoxide group.[6]

With this consideration in mind, we expected that the elimination step would be controlled by changing the

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(3) (a) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *Tetrahedron Lett.* **1986**, *27*, 3345. (b) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *J. Org. Chem.* **1992**, *57*, 2228, and references cited therein.

(4) (a) Rodríguez, C. M.; Martín, V. S. *Tetrahedron Lett.* **1991**, *32*, 2165. (b) Rodríguez, C. M.; Martín, T.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **1994**, *59*, 4461.

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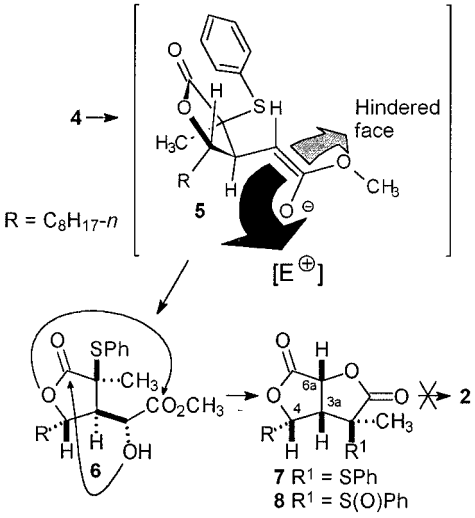
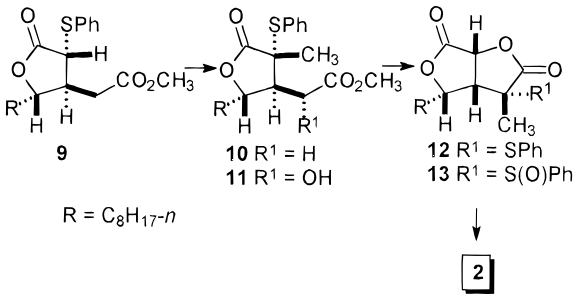
Scheme 2



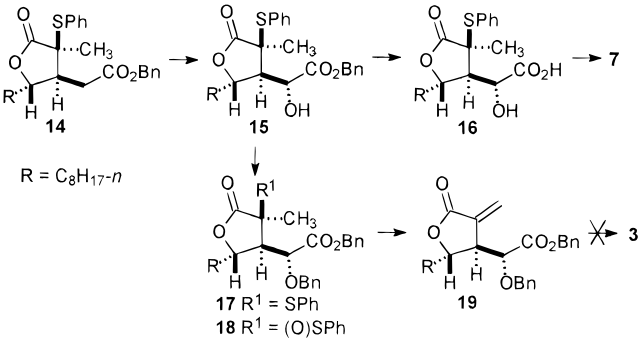
Scheme 3



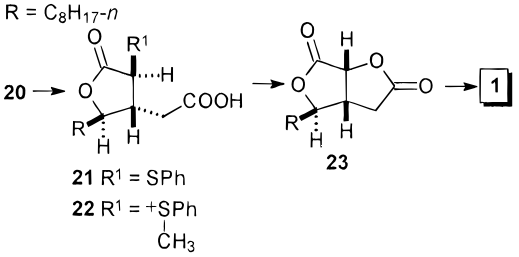
stereochemistry at the carbon in which the phenyl sulfide group is located. Thus, we decided to recommence the synthetic sequence using the diastereoisomer of **4** in such an epimeric center. The alkylation of the readily available butyrolactone **9**[4b] under newly developed conditions,[7] using $LiN(TMS)_2$ as base and with addition of MeI at −90 °C, furnished the diastereoisomeric γ-lactone **10** as the only detectable stereoisomer by NMR analysis. As expected, the hydroxylation of **10** proceeded following the same stereochemical course relative to the vicinal stereocenter, regardless of the stereochemistry in the quaternary carbon adjacent to the carbonyl butyrolactone, cleanly affording **11**, which when heated with a catalytic amount of CSA in toluene for 72 h yielded the bis-lactone **12** in 76% isolated yield and unreacted **11** (≈15%). The oxidation of **12** with MCPBA cleanly yielded the sulfoxide **13** in 96% yield, that when heated in refluxing toluene afforded isoavenaciolide (**2**) in 85% yield, mp 126−127 °C, $[\alpha]^{25}_D$ −154 (*c* 1.1, EtOH) [lit.[3] mp 128−129 °C, $[\alpha]^{25}_D$ −155.83 (*c* 0.5, EtOH)].

We decided to explore the synthesis of avenaciolide (**1**) by a similar sequence to that used for the synthesis of **2**, essentially performing the bis-lactonization over the free α-hydroxy acid instead of the methyl ester since, in such cases, the stereochemical course of the bis-annelation[3] would be an inversion of configuration in the carbon where the oxygen of the γ-lactone is located. In order to obtain the free acid under very mild conditions, we decided to prepare the benzyl ester **15** using the same general sequence outlined in Scheme 4. The cleavage of

Scheme 4



Scheme 5



the benzyl ester using $FeCl_3$[8] cleanly yielded the free α-hydroxy acid **16** in an almost quantitative manner. Unfortunately, when **16** was submitted to refluxing toluene in the presence of catalytic CSA, **7** was again obtained by the double transesterification sequence. The failure to produce the desired inversion in the oxygenated secondary carbon in the lactone ring was attributed to the presence of a quaternary center vicinal to the carbonyl γ-lactone. Thus, we decided to try to prepare directly the known α-methylene lactone **3**. Consequently, we protected the hydroxy group in **15** as benzyl ether, and the sulfide **17** was oxidized under standard conditions using a 1 equiv amount of MCPBA, obtaining the sulfoxide **18** which when heated yielded the α-methylene lactone **19** in 75% yield. Disappointingly, all attempts to obtain the free α-hydroxy acid **3** proved unsuccessful.

At this point of the synthesis, we decided to reconsider our strategy and focused our attention on the enantiomer of the sulfide **9** (**20**),[4b] in which we pondered the possibility of performing the synthesis of the desired bis-lactone skeleton taking advantage of the presence of a sulfide group as a potential leaving group.[9] Thus, **20** was submitted to basic hydrolysis yielding the free carboxylic acid **21** in 92% yield. With this compound in our hands we performed the synthesis of the bis-lactone **23**, that was neatly accomplished by a one-pot procedure with treatment of **21** with Me_3O^+ BF_4^- to generate the sulfonium salt **22** and further basic treatment with KOBu-*t*, in 86% overall yield. Finally, the methylenation of **23** with Stiles's reagent[10] yielded natural avenaciolide (**1**) in 68% yield, mp 49−50 °C, $[\alpha]^{25}_D$ −41.1 (*c* 1.1, EtOH) [lit.[3] mp 51−52 °C, $[\alpha]^{25}_D$ −39.7 (*c* 1.28, EtOH)].

In conclusion, we have described efficient routes to the natural enantiomers of avenaciolide (**1**) and isoavenaciolide (**2**), using as starting materials α-(phenylthio)-β-[(methoxycarbonyl)methyl]-γ-lactones easily obtained with absolute stereochemical control by the base-induced

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(7) Rodríguez, C. M.; Martín, T.; Ramírez, M. A.; Martín V. S. *J. Org. Chem.* **1994**, *59*, 8081.
(8) Padrón, J. I.; Vázquez, J. T. *Tetrahedron: Asymmetry* **1995**, *6*, 857.
(9) Bravo, P.; Resnati, G.; Viani, F. *Tetrahedron Lett.* **1985**, *26*, 2913.
(10) Parker, W. L.; Johnson, F. *J. Org. Chem.* **1973**, *38*, 2489.

cyclization of enantiomerically enriched γ-[(phenylthio)-acyl] α,β-unsaturated esters. The methodology could be easily extended to other related natural products such as ethisolide[2] simply by the proper choice of the length of the alkyl group of the precursor **9** (R = C_2H_5-*n*).

Experimental Section

Materials and Methods. Essentially similar to those used in ref 4b.

Preparation of Methyl (2*S*,3*S*,4*S*)-[4-Methyl-2-octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetate (4). The γ-butyrolactone was obtained for the general procedure used in ref 4b using the nonyl aldehyde as the starting material. (See supporting information).

General Procedure for the Hydroxylation of β-[(Alkoxycarbonyl)methyl]-γ-lactones. Preparation of Methyl 2-[(2*R*)-Hydroxy]-2-[(2*S*,3*S*,4*S*)-4-methyl-2-octyl-5-oxo-4-(phenylthio)-tetrahydrofuran-3-yl]acetate (**6**). To a solution of hexamethyldisilazane (0.3 mL, 1.4 mmol) in THF (1.6 mL) was added *n*-butyllithium (0.8 mL, 1.6 M in *n*-hexane, 1.3 mmol) at 0 °C with stirring. After the mixture was stirred for 15 min, the solution was then cooled to −78 °C, and the γ-butyrolactone **4** (250 mg, 0.6 mmol) was added in THF (1.6 mL) over a period of 5 min. The mixture was additionally stirred at this temperature for 30 min and then treated with solid oxodiperoxomolybdenum−pyridine−HMPA complex (MoOPH) (554 mg, 1.3 mmol) in a single portion. The temperature was allowed to warm to −50 °C and stirred for 2 h. The resulting blue-green solution was poured into ether (10 mL) and freshly prepared saturated $NaHSO_3$ solution (10 mL). The organic layer was washed with H_2O (2 × 8 mL), dried over $MgSO_4$, and concentrated to provide a crude mixture. Purification by silica gel column chromatography afforded the α-hydroxy lactone **6** (222 mg, 85% yield) as an oil: $[\alpha]^{25}_D$ −54.1 (*c* 1.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, *J* = 6.8 Hz, 3 H), 1.30 (m, 12 H), 1.42 (s, 3 H), 1.54 (m, 2 H), 2.61 (dd, *J* = 10.1, 2.8 Hz, 1 H), 3.05 (d, *J* = 4.2 Hz, 1 H), 3.88 (s, 3 H), 4.65 (dd, *J* = 4.2, 2.8 Hz, 1 H), 4.80 (m, 1 H), 7.40 (m, 3 H), 7.55 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ: 14.1 (q), 22.2 (q), 22.6 (t), 25.5 (t), 29.1 (t), 29.2 (t), 29.3 (t), 31.8 (t), 33.9 (t), 53.3 (q), 54.0 (s), 55.7 (d), 67.0 (d), 76.7 (d), 128.4 (s), 128.8 (d), 130.0 (d), 137.7 (d), 174.1 (s), 174.4 (s); IR ($CHCl_3$) (cm^{-1}): 3525, 3025, 2956, 1763; MS *m*/*z* (relative intensity): 408 $(M)^+$ (2), 251 (78), 182 (22), 109 (93); HRMS calcd for $C_{22}H_{32}O_5S$ $(M)^+$: 408.1971, found 408.1981.

General Procedure for the Thermal Bis-Cyclization of β-[Hydroxy(alkoxycarbonyl)methyl]-γ-lactones. Preparation of (3*S*,3a*R*,4*S*,6a*R*)-3-Methyl-4-octyl-3-(phenylthio)dihydrofuro[3,4-*b*]furan-2,6-dione (**7**). To a solution of **6** (160 mg, 0.4 mmol) in dry toluene (3.9 mL, 0.1 M) was added a catalytic amount of camphorsulfonic acid. The reaction mixture was submitted to reflux for 72 h. Then, the solvent was evaporated, and the obtained residue was purified by silica gel column chromatography yielding the bis-lactone **7** (123 mg, 83% yield) as an oil and remaining starting material **6** (19 mg, 12%). Compound **7**: $[\alpha]^{25}_D$ −27.3 (*c* 1.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, *J* = 6.8 Hz, 3 H), 1.29 (m, 12 H), 1.55 (m, 1 H), 1.65 (s, 3 H), 1.92 (m, 1 H), 3.31 (dd, *J* = 8.0, 5.9 Hz, 1 H), 4.61 (m, 1 H), 4.88 (d, *J* = 8.0 Hz, 1 H), 7.44 (m, 3 H), 7.55 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ: 14.1 (q), 20.9 (q), 22.6 (t), 26.8 (t), 29.1 (t), 29.2 (t), 29.3 (t), 30.3 (t), 31.8 (t), 47.6 (d), 52.6 (s), 73.9 (d), 80.3 (d), 129.0 (s), 129.5 (d), 130.5 (d), 136.9 (d), 170.2 (s), 175.4 (s); IR ($CHCl_3$) (cm^{-1}): 2928, 2856, 1792, 1281; MS *m*/*z* (relative intensity): 376 $(M)^+$ (3), 109 (82), 55 (100); HRMS calcd for $C_{21}H_{28}O_4S$ $(M)^+$: 376.1708, found 376.1700.

General Procedure for the Thermal Elimination of the Phenylthio Group. Oxidation and Pyrolysis of 7. To a stirred solution of **7** (100 mg, 0.27 mmol) in dry CH_2Cl_2 (2.7 mL) was added MCPBA (66 mg, 0.27 mmol) at −20 °C. The reaction was stirred for 1 h at this temperature and then quenched with potassium fluoride (62 mg, 1.06 mmol) and vigorously stirred for 0.5 h. The mixture was filtered through a pad of Celite and washed with ether (3 × 10 mL). The resulting solution was concentrated, and the crude isomeric mixture of sulfoxides **8** (100 mg) was used without purification.

A solution of the mixture of sulfoxides **8** (100 mg, 0.25 mmol) in dry toluene (2.5 mL, 0.1 M) was submitted to reflux for 1 h. After this period, TLC showed the end of the reaction showing the formation of an irresolvable mixture of compounds.

Preparation of Methyl (2*S*,3*S*,4*R*)-[2-octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetate (9). **9** was obtained by the general procedure used in ref 4b using the nonyl aldehyde as the starting material (see supporting information).

Preparation of Methyl (2*S*,3*S*,4*R*)-[4-Methyl-2-octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetate (10). To a solution of hexamethyldisilazane (0.3 mL, 1.45 mmol) in THF:HMPA (4:1, 2.6 mL:0.7 mL) was added *n*-butyllithium (0.8 mL, 1.6 M in *n*-hexane, 1.32 mmol) at 0 °C and the mixture stirred for 15 min. The solution was then cooled to −90 °C and **9** (250 mg, 0.66 mmol) added in THF:HMPA (4:1, 2.6 mL: 0.7 mL) over a period of 5 min. The mixture was additionally stirred for 15 min and iodomethane (82 μL, 1.32 mmol) added dropwise. After the addition, the reaction was maintained with stirring for 4 h at this temperature. Then, the reaction mixture was poured into HCl aqueous solution (15% w/v, 25 mL), ice, and ether (25 mL) and vigorously stirred. After 5 min, the mixture was extracted with ether (2 × 15 mL), and the combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL) and brine (15 mL), dried, and concentrated. Purification by column chromatography gave the α-methyl-γ-butyrolactone **10** (238 mg, 92% yield) as an oil: $[\alpha]^{25}_D$ −26.3 (*c* 3.61, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.86 (t, *J* = 7.0 Hz, 3 H), 1.23 (m, 12 H), 1.37 (s, 3 H), 1.53 (m, 2 H), 2.29 (m, 1 H), 2.60 (m, 2 H), 3.72 (s, 3 H), 4.02 (m, 1 H), 7.36 (m, 3 H), 7.58 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ: 14.1 (q), 18.2 (q), 22.6 (t), 24.6 (t), 29.1 (t), 29.2 (t), 29.3 (t), 31.8 (t), 32.1 (t), 33.1 (t), 43.8 (d), 52.0 (q), 55.7 (s), 81.4 (d), 129.0 (d), 129.5 (s), 129.9 (d), 137.1 (d), 171.6 (s), 176.5 (s); IR ($CHCl_3$) (cm^{-1}): 2955, 2857, 1767, 1737, 1439; MS *m*/*z* (relative intensity): 392 $(M)^+$ (48), 283 (100), 251 (78); HRMS calcd for $C_{22}H_{32}O_4S$ $(M)^+$: 392.2021, found 392.2027.

Preparation of Methyl 2-[(2*R*)-Hydroxy]-[(2*S*,3*S*,4*R*)-4-methyl-2-octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetate (11). The general hydroxylation procedure (used above to obtain **6**) was applied to **10** on a 200 mg (0.51 mmol) scale to −50 °C for 2 h, affording **11** (162 mg, 78% yield) as an oil: $[\alpha]^{25}_D$ −29.4 (*c* 1.97, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, *J* = 6.9 Hz, 3 H), 1.22 (m, 12 H), 1.39 (m, 2 H), 1.55 (s, 3 H), 2.59 (d, *J* = 10.1 Hz, 1 H), 2.99 (br s, 1 H), 3.83 (s, 3 H), 4.4 (m, 1 H), 4.48 (bs, 1 H), 7.39 (m, 3 H), 7.55 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ: 14.1 (q), 19.4 (q), 22.6 (t), 24.6 (t), 29.1 (t), 29.2 (t), 29.3 (t), 31.8 (t), 34.1 (t), 50.1 (d), 53.1 (q), 54.5 (s), 67.6 (d), 76.7 (d), 128.9 (d), 130.0 (d), 136.9 (s), 137.1 (d), 174.4 (s), 176.1 (s); IR ($CHCl_3$) (cm^{-1}): 3525, 3025, 2956, 1763; MS *m*/*z* (relative intensity): 408 $(M)^+$ (2), 251 (78), 109 (93); HRMS calcd for $C_{22}H_{32}O_5S$ $(M)^+$: 408.1971, found 408.1981.

Preparation of (3*R*,3a*R*,4*S*,6a*R*)-3-Methyl-4-octyl-3-(phenylthio)dihydrofuro[3,4-*b*]furan-2,6-dione (12). The general thermal bis-cyclization procedure (used above to obtain **7**) was applied to **11** on a 150 mg (0.37 mmol) scale for 72 h, yielding **12** (105 mg, 76% yield) as an oil and remaining starting material **11** (30 mg, 15%). Compound **12**: $[\alpha]^{25}_D$ +21.1 (*c* 1.75, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, *J* = 7.2 Hz, 3 H), 1.30 (m, 12 H), 1.60 (s, 3 H), 2.06 (m, 1 H), 2.55 (m, 1 H), 3.33 (dd, *J* = 8.0, 4.9 Hz, 1 H), 4.69 (ddd, *J* = 8.0, 8.0, 4.9 Hz, 1 H), 5.04 (d, *J* = 8.0 Hz, 1 H), 7.36 (m, 3 H), 7.47 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ: 14.0 (q), 22.6 (t), 23.5 (q), 26.6 (t), 29.1 (t), 29.3 (t), 29.6 (t), 29.8 (t), 31.8 (t), 51.8 (s), 53.1 (d), 73.6 (d), 78.9 (d), 127.6 (s), 129.0 (d), 130.7 (d), 137.9 (d), 170.5 (s), 172.4 (s); IR ($CHCl_3$) (cm^{-1}): 2928, 2856, 1792, 1281; MS *m*/*z* (relative intensity): 376 $(M)^+$ (3), 182 (3), 55 (100); HRMS calcd for $C_{21}H_{28}O_4S$ $(M)^+$: 376.1708, found 376.1700.

Preparation of (−)-Isoavenaciolide (2). The general thermal elimination used above for **7** was applied to **12** on a 100 mg (0.27 mmol) scale, yielding isoavenaciolide (**2**) (59 mg, 82% yield), as a solid: mp 126−127 °C, $[\alpha]^{25}_D$ −154° (*c* 1.1, EtOH) [lit.[3b] mp 128−129 °C, $[\alpha]^{25}_D$ −155.8° (*c* 0.5, EtOH)]; ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, *J* = 6.6 Hz, 3 H), 1.27 (m, 12 H), 1.61 (m, 2 H), 3.98 (m, 1 H), 4.75 (m, 1 H), 5.10 (d, *J* = 8.8 Hz, 1 H), 5.87 (d, *J* = 2.1 Hz, 1 H), 6.61 (d, *J* = 2.4 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ: 14.0 (q), 22.6 (t), 26.0 (t), 29.1 (t), 29.2 (t),

29.3 (t), 31.7 (t), 32.4 (t), 41.7 (d), 74.6 (d), 80.3 (d), 128.8 (t), 130.8 (s), 167.7 (s), 169.8 (s); IR ($CHCl_3$) (cm^{-1}): 2956, 2929, 2857, 1788; MS *m/z* (relative intensity): 267 $(M + 1)^+$ (5), 124 (21), 96 (100).

Preparation of Benzyl (2*S*,3*S*,4*S*)-[4-Methyl-2-octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetate (14). The γ-butyrolactone **14** was obtained for the general procedure used in ref 4b using the nonyl aldehyde as the starting material. (See supporting information).

Preparation of Benzyl 2-[(2*R*)-Hydroxy]-2-[(2*S*,3*S*,4*S*)-4-methyl-2-octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetate (15). The general hydroxylation procedure (used above to obtain **6**) was applied to **14** on a 825 mg (1.76 mmol) scale to −50 °C for 2 h, affording the α-hydroxy lactone **15** (648 mg, 76% yield) as an oil: $[\alpha]^{25}_D$ −42.1 (*c* 1.9, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, *J* = 6.9 Hz, 3 H), 1.32 (m, 12 H), 1.41 (s, 3 H), 1.48 (m, 2 H), 2.57 (dd, *J* = 10.04, 2.8 Hz, 1 H), 3.19 (d, *J* = 4.3 Hz, 1 H), 4.66 (dd, *J* = 4.3, 2.8 Hz, 1 H), 4.77 (m, 1 H), 5.19 (d, *J* = 11.9 Hz, 1 H), 5.34 (d, *J* = 11.9 Hz, 1 H), 7.32 (m, 3 H), 7.40 (m, 5 H), 7.52 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ: 14.1 (q), 22.2 (q), 22.7 (t), 25.6 (t), 29.1 (t), 29.2 (t), 29.4 (t), 31.8 (t), 33.9 (t), 53.9 (s), 55.8 (d), 67.1 (d), 68.3 (t), 76.7 (d), 127.5 (s), 128.5 (d), 128.7 (d), 128.8 (d), 129.0 (d), 130.0 (d), 134.4 (s), 137.7 (d), 173.6 (s), 174.3 (s); IR ($CHCl_3$) (cm^{-1}): 3524, 3018, 2927, 1762; MS *m/z* (relative intensity): 485 $(M + 1)^+$ (2), 393 (2), 91 (100); HRMS calcd for $C_{28}H_{37}O_5S$ $(M + 1)^+$: 485.2362, found 485.2367.

Alternative Preparation of 7. To a stirred solution of **15** (300 mg, 0.62 mmol) in dry CH_2Cl_2 (12.4 mL) under argon was added anhydrous $FeCl_3$ (200 mg, 1.24 mmol) at 0 °C. The reaction was stirred for 1 h, until starting material was not detected by TLC. Then, the reaction was quenched by addition of water (15 mL) and diluted with CH_2Cl_2 (10 mL). The mixture was stirred for 10 min and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to provide the α-hydroxy acid lactone **16**, which was used without purification.

To a solution of crude **16** in dry toluene (6.2 mL) was added a catalytic amount of CSA. The reaction mixture was submitted to reflux for 72 h. Then, the solvent was evaporated and the obtained residue was purified by silica gel column chromatography yielding **7** (140 mg, 60% yield) and remaining starting material **15** (105 mg, 35%).

Preparation of Benzyl 2-[(2*R*)-Benzyloxy]-2-[(2*S*,3*S*,4*S*)-4-methyl-2-octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetate (17). To a suspension of NaH (22 mg, 0.74 mmol, 80% in mineral oil) in dry DMF (3.1 mL) under argon was added dropwise **15** (300 mg, 0.62 mmol) in dry DMF (3.1 mL) at 0 °C. The reaction mixture was stirred for 15 min, after which time was added benzyl bromide (110 μL, 0.93 mmol). The reaction was allowed to warm to rt and stirred for 1 h. After this period, TLC showed complete conversion. Then, to the reaction mixture were added AcOH (200 μL) and H_2O (10 mL), and it was extracted with ether (3 × 10 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography, yielding **17** (327 mg, 92% yield) as an oil: $[\alpha]^{25}_D$ −11.1 (*c* 3.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, *J* = 7.0 Hz, 3 H), 1.23 (m, 12 H), 1.34 (s, 3 H), 1.42 (m, 2 H), 2.61 (dd, *J* = 9.8, 4.4 Hz, 1 H), 4.44 (d, *J* = 4.4 Hz, 1 H), 4.62 (d, *J* = 10.5 Hz, 1 H), 4.65 (m, 1 H), 4.71 (d, *J* = 10.5 Hz, 1 H), 5.21 (d, *J* = 12.0 Hz, 1 H), 5.32 (d, *J* = 12.0 Hz, 1 H), 7.39 (m, 15 H); ^{13}C-NMR ($CDCl_3$) δ: 14.1 (q), 22.3 (q), 22.7 (t), 25.6 (t), 29.1 (t), 29.2 (t), 29.3 (t), 31.8 (t), 34.3 (t), 53.7 (s), 55.0 (d), 67.3 (t), 72.7 (t), 75.2 (d), 78.5 (d), 128.1 (d), 128.2 (d), 128.3 (d), 128.5 (d), 128.6 (d), 128.7 (d), 128.8 (d), 130.1 (d), 135.0 (s), 136.8 (s), 137.2 (s), 137.6 (d), 171.1 (s), 174.5 (s); IR ($CHCl_3$) (cm^{-1}): 3015, 2975, 1750, 1457; MS *m/z* (relative intensity): 483 $(M - 91)^+$ (1), 135 (12), 91 (100); HRMS calcd for $C_{28}H_{35}O_5S$ $(M - 91)^+$: 483.2205, found 483.2223.

Preparation of Benzyl 2-[(2*R*)-Benzyloxy]-2-[(2*S*,3*S*)-4-methylene-2-octyl-5-oxotetrahydrofuran-3-yl]acetate (19). The general thermal elimination used above for **7** was applied to **17** on a 300 mg (0.52 mmol) scale, yielding the methylene lactone **19** (181 mg, 75% yield) as an oil: $[\alpha]^{25}_D$ +58.6 (*c* 0.7, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, *J* = 6.9 Hz, 3 H), 1.29 (m, 12 H), 1.42 (m, 2 H), 3.05 (d, *J* = 1.9 Hz, 1 H), 4.0 (d, *J* = 5.1 Hz, 1 H), 4.38 (d, *J* = 11.8 Hz, 1 H), 4.57 (m, 1 H), 4.71 (d, *J* = 11.8 Hz, 1 H), 5.17 (d, *J* = 12.0 Hz, 1 H), 5.21 (d, *J* = 12.0 Hz, 1 H), 5.41 (d, *J* = 1.9 Hz, 1 H), 6.22 (d, *J* = 2.2 Hz, 1 H), 7.23 (m, 3 H), 7.32 (m, 2 H), 7.38 (m, 5 H); ^{13}C-NMR ($CDCl_3$) δ: 14.1 (q), 22.6 (t), 24.7 (t), 29.1 (t), 29.2 (t), 29.3 (t), 31.8 (t), 36.1 (t), 47.0 (d), 67.2 (t), 72.8 (t), 78.7 (d), 78.8 (d), 124.1 (t), 128.2 (d), 128.3 (d), 128.4 (d), 128.7 (d), 128.8 (d), 128.9 (d), 134.9 (s), 135.1 (s), 136.3 (s), 169.5 (s), 170.1 (s); IR ($CHCl_3$) (cm^{-1}): 3031, 2929, 2857, 1756; MS *m/z* (relative intensity): 300 $(M - 164)^+$ (2), 107 (3), 91 (100); HRMS calcd for $C_{20}H_{28}O_2$ $(M - 164)^+$: 300.2089, found 300.2080.

Preparation of Methyl (2*R*,3*R*,4*S*)-[2-Octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetate (20). The γ-butyrolactone **20** was obtained for the general procedure used in ref 4b using the nonyl aldehyde as the starting material. (See supporting information).

Preparation of (2*R*,3*R*,4*S*)-2-[2-Octyl-5-oxo-4-(phenylthio)tetrahydrofuran-3-yl]acetic Acid (21). To a stirred solution of **20** (200 mg, 0.53 mmol) in THF:H_2O (4:1, 4.2 mL:1.1 mL) was added NaOH (85 mg, 2.12 mmol) at 0 °C. The reaction was stirred for 1 h, until starting material was not detected by TLC. Then concentrated HCl was added at 0 °C until pH ≈ 1 was reached and the reaction mixture extracted with AcOEt (2 × 20 mL). The combined organic phases were washed with 50 mL of a saturated solution of brine, dried over $MgSO_4$, evaporated in vacuo, and purified by column chromatography to give the acid **21** (177 mg, 92% yield) as an oil: $[\alpha]^{25}_D$ +3.3 (*c* 3.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.87 (t, *J* = 6.9 Hz, 3 H), 1.22 (m, 12 H), 1.59 (m, 2 H), 2.38 (ddd, *J* = 10.2, 7.0, 3.5 Hz, 1 H), 2.65 (d, *J* = 7.0 Hz, 2 H), 3.76 (d, *J* = 10.2 Hz, 1 H), 4.18 (ddd, *J* = 8.1, 8.1, 3.5 Hz, 1 H), 7.32 (m, 3 H), 7.55 (m, 2 H); ^{13}C-NMR ($CDCl_3$) δ: 14.0 (q), 22.6 (t), 25.0 (t), 29.1 (t), 29.2 (t), 29.3 (t), 31.8 (t), 33.9 (t), 42.5 (d), 51.2 (d), 82.5 (d), 129.2 (d), 131.0 (s), 133.2 (d), 134.4 (d), 173.9 (s), 176.5 (s); IR ($CHCl_3$) (cm^{-1}): 3027, 2857, 1768, 1715; MS *m/z* (relative intensity): 364 $(M)^+$ (52), 238 (7), 109 (99). Anal. Calcd for $C_{20}H_{28}O_4S$: C, 65.90; H, 7.75; S, 8.78. Found: C, 65.58; H, 8.00; S, 8.43.

Preparation of (3a*S*,4*R*,6a*R*)-4-Octyldihydrofuro[3,4-*b*]furan-2,6-dione (23). To a stirred solution of lactone **21** (150 mg, 0.41 mmol) in a mixture of CH_2Cl_2:CH_3NO_2 (1:1, 2.1 mL:2.1 mL) was added trimethyloxonium tetrafluoroborate (61 mg, 0.41 mmol) at −5 °C. The temperature was allowed to warm to rt and stirred for 1 h. Then the solvent was removed in vacuum at 0 °C, and the crude sulfonium salt **22** was dissolved in dimethylformamide (8.2 mL, 0.05 M). The solution was then cooled to −45 °C, and solid potassium *tert*-butoxide (50 mg, 0.41 mmol) was added. The temperature was allowed to warm to 0 °C and stirred for 1 h. The resulting solution was poured into ether (20 mL) and washed with saturated solution of NH_4Cl (25 mL), dried over $MgSO_4$, concentrated, and purified by column chromatography to give **23** (90 mg, 86% yield), as an oil: $[\alpha]^{25}_D$ −2.45 (*c* 1.96, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, *J* = 6.7 Hz, 3 H), 1.27 (m, 12 H), 1.69 (m, 2 H), 2.54 (dd, *J* = 18.1, 3.8 Hz, 1 H), 2.93 (dd, *J* = 18.1, 9.4 Hz, 1 H), 3.05 (m, 1 H), 4.34 (m, 1 H), 5.0 (d, *J* = 7.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 13.9 (q), 22.5 (t), 24.8 (t), 29.0 (t), 29.1 (t), 29.2 (t), 31.6 (t), 32.6 (t), 35.1 (t), 39.9 (d), 77.2 (d), 85.1 (d), 170.4 (s), 174.2 (s); IR ($CHCl_3$) (cm^{-1}): 2956, 2929, 1795, 1782; MS *m/z* (relative intensity): 355 $(M + 1)^+$ (18), 212 (3), 55 (100).

Preparation of (−)-Avenaciolide (1). **23** (75 mg, 0.3 mmol) in dry DMF (1.5 mL) was added to a 2 M solution of methyl methoxymagnesium carbonate (0.8 mL, 1.53 mmol) in DMF and the mixture heated under a slow stream of dry argon at 120 °C for 5 h, until TLC showed the end of the reaction. The resulting solution was poured into a mixture of ice cold 6 N HCl (10 mL) and ether (10 mL) and shaken until all of the precipitated solid had dissolved. The ether phase was washed with water (10 mL) and brine (10 mL) and then dried over magnesium sulfate. Removal of the ether under reduced pressure afforded the bis-lactonic acid, which was used without purification.

The crude diacid was treated with 5 mL/mmol of compound of a stock solution (prepared from 4 mL of acetic acid, 2.9 mL of 37% formaldehyde in water, 1 mL of diethylamine, and 105 mg of NaOAc) and stirred vigorously under argon at rt for 2 h, until evolution of carbon dioxide ceased. The resulting solution was poured into water (10 mL) and ether (10 mL). The ether phase was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried, and concentrated. Purification by column chromatography gave (−)-avenaciolide (**1**) (53 mg, 68% yield), as a solid: mp 49−50 °C, $[\alpha]^{25}_D$ −41.1° (*c* 1.1, EtOH) [lit.[3b] mp 51−52 °C, $[\alpha]^{25}_D$ −39.7° (*c* 1.28, EtOH)]; ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, J = 6.7 Hz, 3 H), 1.28 (m, 12 H), 1.80 (m, 2 H), 3.55 (m, 1 H), 4.43 (ddd, J = 6.5, 6.5, 4.0 Hz, 1 H), 5.04 (d, J = 8.5 Hz, 1 H), 5.87 (d, J = 2.1 Hz, 1 H), 6.48 (d, J = 2.4 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ: 14.0 (q), 22.6 (t), 24.8 (t), 29.1 (t), 29.3 (t), 29.6 (t), 31.8 (t), 36.0 (t), 44.2 (d), 74.2 (d), 85.1 (d), 126.2 (t), 134.6 (s), 167.4 (s), 169.6 (s); IR ($CHCl_3$) (cm^{-1}): 2956, 2929, 2857, 1788; MS *m*/*z* (relative intensity): 267 $(M + 1)^+$(3), 191 (6), 124 (23), 96 (100).

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Supporting Information Available: Copies of ^{13}C-NMR spectra for the new and final compounds, and experimental details for the synthesis of **4**, **9**, **14**, and **20** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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