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# Highly Stereoselective Epoxidation of α-Methyl-γ-hydroxy-α,β-unsaturated Esters: Rationalization and Synthetic Applications

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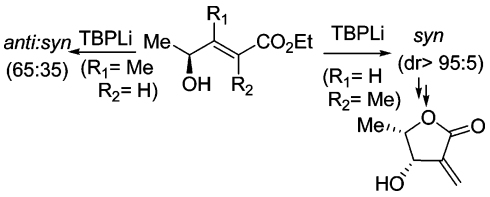
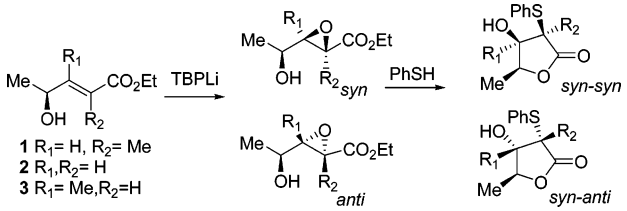



The diastereoselectivity of the nucleophilic epoxidation of γ-hydroxy-α,β-unsaturated esters having a methyl substituent at the α- or β-position was investigated. Epoxidation of the α-methyl-substituted enoate was highly stereoselective, giving rise to the *syn* isomer. This finding was used to perform an enantioselective synthesis of a natural product having a β-hydroxy-α-methylene-γ-butyrolactone motif. The nucleophilic epoxidation of enoates was found to be irreversible. Models to explain the observed stereoselectivities are proposed.

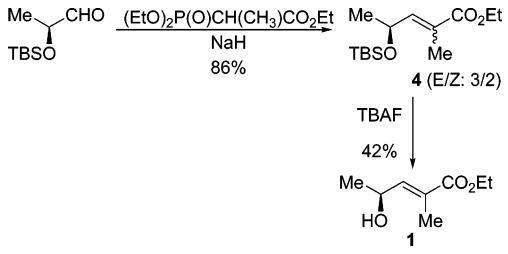
Stereoselective synthesis of α,β-epoxyesters is of considerable synthetic interest because a number of compounds can be obtained by the opening of the oxirane ring.[1] A convenient method for the preparation of α,β-epoxyesters is via nucleophilic epoxidation of γ-chiral α,β-unsaturated esters.[2] We previously reported the stereoselectivity of the epoxidation of nonsubstituted γ-hydroxy-α,β-unsaturated esters,[2] and we now report that the stereoselectivity depends highly on the substitution of the double bond and that high *syn* stereoselectivity (dr >19:1) is observed for the α-methyl-substituted enoates. This finding has synthetic applications and provided for the synthesis of a β-hydroxy-α-methylene-γ-butyrolactone that is a natural product.

Furthermore, it was determined that the nucleophilic epoxidation of enoates is an irreversible process. The enolization of a β-peroxyester afforded the corresponding α,β-epoxyester but not enoate or hydroperoxide. Our previous reports describing the epoxidation of non-ene-branched enoates were unable to propose kinetic models to explain the observed selectivities because it was unknown whether the reaction was kinetically or thermodynamically controlled. However, in the present study the observed stereoselectivities can be rationalized through models combining chelation and allylic strain.

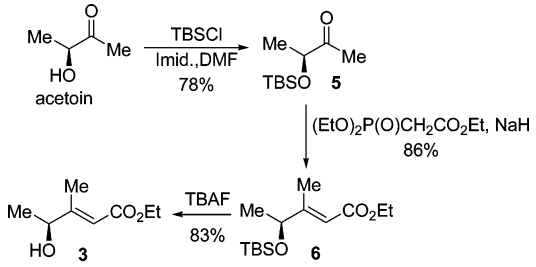
**SCHEME 1. General Scheme of Reactions**




**SCHEME 2. Preparation of Substrate 1**




**SCHEME 3. Preparation of Substrate 3**




The epoxidation reactions of the α-methyl- and β-methyl-substituted unsaturated esters **1** and **3**, respectively, were assayed, and the resulting stereoselectivities were compared with that of the nonsubstituted ester **2**. The stereochemistries of the α,β-epoxyesters were assigned by their derivatization into α-sulfphenyl-γ-butyrolactones using thiophenol (Scheme 1).

Compound **1** was prepared from *O*-protected (*S*)-lactaldehyde by a Horner−Emmons reaction using triethyl 2-phosphonopropionate, which furnished **4** as a 3:2 mixture of *E*/*Z* isomers. Upon desylilation of **4** and chromatographic separation, (*E*)-α-methyl-γ-hydroxy-α,β-unsaturated ester **1** was obtained (Scheme 2).

Compound **2** was obtained readily by treatment of ethyl (*E*)-4-oxo-2-butenoate[2a] with methylmagnesium bromide. Compound **3** was prepared from acetoin by protection, Horner−Emmons reaction, and deprotection (Scheme 3). Enoates **2** and **3** were obtained as racemates and used as such in the epoxidation reactions.

Enoates were epoxidized using lithium *tert*-butylperoxide in THF as the oxidizing reagent. For compound **3**, the reaction needed to take place at room temperature to proceed to completion. The stereoselectivity of epoxidation of these compounds was highly dependent on the substitution of the

(1) (a) Chong, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1985**, *26*, 4683−4686. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4435−4436. (c) Saito, S.; Takahashi, N.; Ishikawa, T.; Moriwake, T. *Tetrahedron Lett.* **1991**, *32*, 667−670. (d) Lanier, M.; Pastor, R. *Tetrahedron Lett.* **1995**, *36*, 2491−2492. (e) Righi, G.; Rumboldt, G.; Bonini, C. *J. Org. Chem.* **1996**, *61*, 3557−3560. (f) Concellón, J. M.; Bardales, E. *Org. Lett.* **2002**, *4*, 189−191. (g) Concellón, J. M.; Bardales, E.; Llavona, R. *J. Org. Chem.* **2003**, *68*, 1585−1588 and refs cited therein.

(2) (a) Rodríguez, S.; Vidal, A.; Monroig, J. J.; González, F. V. *Tetrahedron Lett.* **2004**, *45*, 5359−5361. (b) Rodríguez, S.; Izquierdo, F.; López, I.; González, F. V. *Tetrahedron* **2006**, *62*, 11112−11123.

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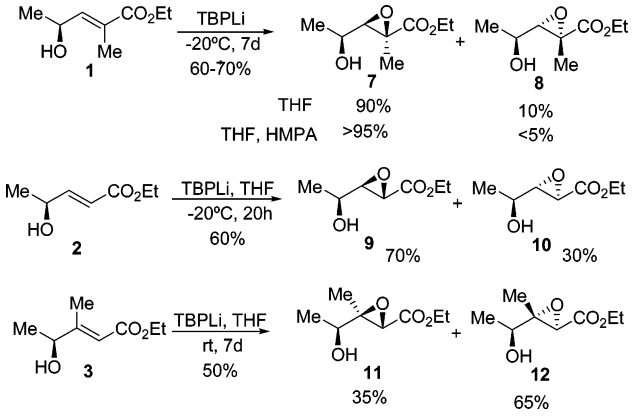
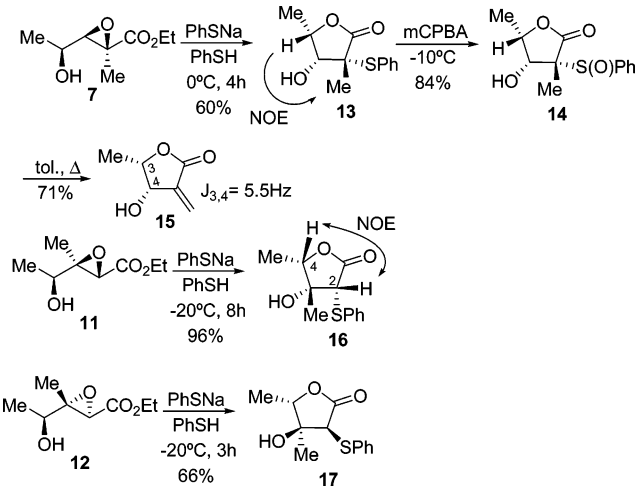
**SCHEME 4. Epoxidation of α,β-Unsaturated Esters**




**SCHEME 5. Derivatization of Epoxyesters**



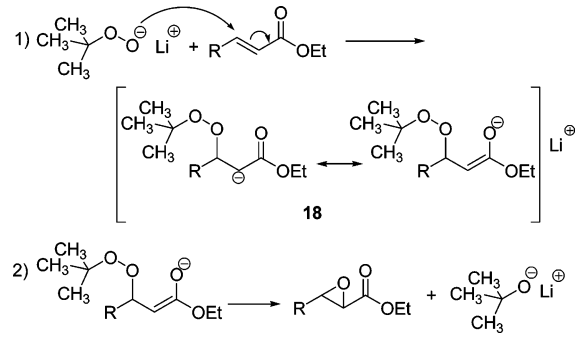

double bond: compound **1** afforded higher stereoselection than **2**, with the *syn* isomer predominating in both cases[3] (Scheme 4). If the reaction was carried out using lithium *tert*-butylperoxide in the presence of HMPA, then a better selectivity was observed.[2b] On the other hand, compound **3** provided poor stereoselectivity, with the *anti* isomer predominating.

The stereochemistries of epoxides were assigned by treatment with sodium thiophenolate to afford the corresponding diastereomeric γ-butyrolactones. Stereochemical assignment was performed by NOE experiments (Scheme 5).

The *syn* epoxyester **7** was transformed into the lactone **13**, which exhibited an NOE effect between H-4 and the methyl group in the 2-position. Compound **13** was then treated with *m*-chloroperbenzoic acid, curiously furnishing sulfoxide **14** as a single stereoisomer.[4] Heating of the sulfoxide provided **15**, a natural product isolated from plants of the Lauraceae[5] family.

The spectroscopic data for **15** were identical to those described previously, showing a coupling constant $J_{3,4}$ of 5.5 Hz that denoted relative *syn* stereochemistry. β-Hydroxy-α-alkylidene-γ-butyrolactone motifs such as **15** are present in many natural products with interesting biological properties.[5,6]

**SCHEME 6. Mechanism of Nucleophilic Epoxidation of Enoates**



Epoxides **11** and **12** were separated by column chromatography and derivatized into lactones **16** and **17**, respectively. Lactone **16** exhibited an NOE effect between H-2 and H-4, whereas **17** did not (Scheme 5).

A nucleophilic epoxidation reaction is thought to proceed by the addition of a *tert*-butylperoxy anion to the activated double bond, giving rise to enolate **18** (Scheme 6). Upon elimination of *tert*-butoxide from **18**, the epoxide is furnished.[7]

To conduct a meaningful analysis of transition states, it was necessary to determine whether the initial Michael addition of the peroxy anion to the enoate is kinetic (irreversible) or reversible. If the enolate intermediate is prepared by an alternate route and enoate and/or *tert*-butylperoxy anion is detected, this result would prove reversibility of the reaction.

*tert*-Butylperoxyether **19** was prepared from ethyl 3-hydroxybutanoate by a two-step sequence.[8] Then, **19** was treated with LDA or LHMDS to generate the desired enolate **18**. Careful analysis of the $^1$H NMR spectrum of the crude reaction mixture showed (*E*)-ethyl 2-butenoate oxide **20** and (*E*)-*tert*-butyl-2-butenoate oxide in a 3:1 ratio as the sole product of the reaction.[9] The same result was obtained when ethyl *trans*-crotonate was epoxidized by using lithium *tert*-butylperoxide (Scheme 7).

A competition experiment was performed to examine the reversibility of the epoxidation reaction. The peroxide intermediate and a second, different enone/enoate acceptor were mixed to determine whether the epoxide of the second unsaturated acceptor is formed, which would definitively prove reversibility of the reaction.

When peroxide **19** was subjected to basic treatment in the presence of methyl acrylate or chalcone, (*E*)-2-butenoate oxides were obtained, and methyl acrylate or chalcone was recovered.[10]

(3) Similar selectivities have been reported in the conjugate addition of amides to nonsubstituted and α-methyl-substituted γ-methoxyenoates: (a) Yamamoto, Y.; Chounan, Y.; Nishii, S.; Ibuka, T.; Kitahara, H. *J. Am. Chem. Soc.* **1992**, *114*, 7652−7660. (b) Asao, N.; Shimada, T.; Sudo, T.; Tsukada, N.; Yazawa, K.; Gyoung, Y. S.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 6274−6282.

(4) This reaction had been previously conducted by C. Benezra et al. (see ref 5e) reporting a mixture of sulfoxides; however, we observed only one sulfoxide although, if the reaction is conducted with an excess of oxidant, then a mixture of sulfoxide and sulfone is obtained.

(5) (a) Martínez, J. C. V.; Yoshida, M.; Gottlieb, O. R. *Phytochemistry* **1981**, *20*, 459−464. (b) Martínez, J. C. V.; Yoshida, M.; Gottlieb, O. R. *Tetrahedron Lett.* **1979**, *20*, 1021−1024. (c) Niwa, M.; Iguchi, M.; Yamamura, S. *Chem. Lett.* **1977**, 581−582. (d) Takeda, K.; Sakurawi, K.; Ishi, H. *Tetrahedron* **1972**, *28*, 3757−3766. For other syntheses of **15** see: (e) Barbier, P.; Benezra, C. *J. Org. Chem.* **1983**, *48*, 2705−2709. (f) Adam, W.; Klug, P. *Synthesis* **1994**, 567−572.

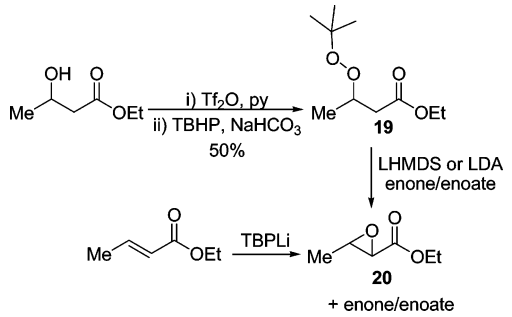
(6) Hanson, R. L.; Lardy, H. A.; Kupchan, S. M. *Science* **1970**, *168*, 376−380.

(7) (a) Meth-Cohn, O.; Moore, C.; Taljaard, H. C. *J. Chem. Soc., Perkin Trans. I* **1988**, 2663−2674. (b) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, 5845−5848.

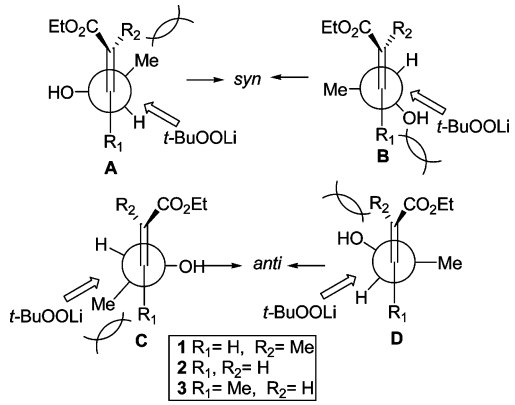
(8) Salomon, M. F.; Salomon, R. G.; Gleim, R. D. *J. Org. Chem.* **1976**, *41*, 3983−3987.

(9) Only *trans*-epoxyesters were observed.

**SCHEME 7. Reversibility Experiment**




**SCHEME 8. Kinetic Models to Explain Stereoselectivity**




The epoxidation of the acrylate or the chalcone was never observed, demonstrating the irreversibility of the reaction.

The synthesis of the peroxide and its transformation into an epoxide represents a new approach to synthesizing α,β-epoxyesters from β-hydroxyesters.

The stereoselectivity in epoxidation of compounds **1**, **2**, and **3** can be accounted for by a modified Felkin−Anh model[3] (Scheme 8). We previously reported that *O*-protected γ-hydroxy-α,β-unsaturated esters are less reactive and less selective than unprotected esters.[2b] Thus, a free hydroxyl would chelate lithium, thereby directing the attack of the nucleophile.

To explain the *syn* selectivity observed for **1** and **2**, transition-state geometry **A** (Scheme 8) would be electronically favored because the hydroxyl group is *anti*. However, there is 1,3-allylic strain between the inside methyl group and an olefinic hydrogen (in **2**) or a methyl group (in **1**). The transition-state geometry **B** might be the most favorable due both to the chelation factor and minimal allylic strain. In the case of transition-state geometry **C**, there is steric repulsion between the incoming reagent and the methyl group. Transition-state geometry **D** would be the most unfavorable due to 1,3-allylic strain between the hydroxyl group and vinylic hydrogen group (in **2**) or a methyl group (in **1**) and to the presence of the methyl group at the *anti* position.

The *syn* selectivity observed for compounds **1** and **2** would be then explained by transition state **B**, and the higher *syn* selectivity in **1** compared to **2** would be due to the different size of $R_2$ group (methyl in **1** and hydrogen in **2**) making less favored transition state **D** in **1** compared to that in **2**.

For compound **3**, the 1,2-allylic strain between the methyl group in the β-position and the hydroxyl group would make geometry **B** less favorable than **D**, resulting in a slight preference for the *anti* isomer.

In summary, the nucleophilic epoxidation of α-methyl-substituted γ-hydroxy-α,β-unsaturated esters is a diastereoselective reaction that favors the *syn* isomer. In contrast, the reaction of β-methyl-substituted γ-hydroxy-α,β-unsaturated esters is less stereoselective, and the *anti* isomer predominates. The nucleophilic epoxidation of enoates is an irreversible process because the enolization of a β-peroxyester gives only the α,β-epoxyester. The observed *syn* selectivity for epoxides **1** and **2** can be explained by a Felkin−Anh model assisted by chelation with the nucleophile. The enantioselective synthesis of a natural product having a β-hydroxy-α-methylene-γ-butyrolactone motif was accomplished.

## Experimental Section

**General Experimental Procedure for the Epoxidation.** To a −78 °C cold THF (3.5 mL) was added TBHP (3.3 M in toluene)[12] (2.2 mmol) and then ethyllithium (0.5 M in benzene/cyclohexane (9/1)) (1.61 mmol). The resulting mixture was stirred at −78 °C for 15 min, and then a solution of the unsaturated ester (1.46 mmol) in THF (2 mL) was added dropwise; the mixture was than stirred at the required temperature and time (see Scheme 4). Solid $Na_2SO_3$ (120 mg) was then added in one portion with stirring for 15 min, followed by dilution with saturated aqueous $NH_4Cl$ solution and extraction with $Et_2O$ (3 × 30 mL). The organic layers were washed (brine), dried ($Na_2SO_4$), and concentrated. The crude oil was purified through chromatography (silica gel, hexanes/EtOAc (7:3), (6:4), (1:1), (1:2) and EtOAc).

Spectroscopy data for **7** and **8**: $^1$H NMR (500 MHz, $CDCl_3$) δ 4.20 (2H, m, **7** and **8**), 3.69 (1H, dq, $J$ = 8.5, 6.5 Hz, **7** and **8**), 3.16 (1H, d, $J$ = 8.0 Hz, **7**), 3.15 (1H, d, $J$ = 8.0 Hz, **8**), 1.54 (1H, s, **8**), 1.53 (1H, s, **7**), 1.28 (3H, t, $J$ = 7.5 Hz, **7** and **8**), 1.27 (1H, d, $J$ = 6.5 Hz, **7** and **8**). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.5 (**7** and **8**), 69.4 (**7**), 66.4 (**8**), 65.7 (**8**), 61.9 (**8**), 61.0 (**7**), 19.6 (**7**), 19.2 (**8**), 14.1 (**8**), 13.8 (**8**), 12.8 (**7**). IR (NaCl) ν 3449, 2981, 2928, 1734, 1446, 1371, 1294, 1181, 1089, 1058, 1021, 930, 878, 760 cm$^{-1}$. HRMS *m*/*z* calcd for $C_8H_{14}O_4Na$ [M + $Na^+$]: 197.0790, found: 197.0790. For **7**: $[\alpha]^{25}_D$ = −8.82 ($c$ = 5.4, $CHCl_3$).

**4-Hydroxy-3,5-dimethyl-3-phenylsulfanyl-dihydro-furan-2-one, 13.** An ice-bath cold suspension of sodium hydride (60% in mineral oil) (60 mg, 1.50 mmol) in THF (12 mL) was treated with thiophenol (308 μL, 3.0 mmol). The mixture was stirred at this temperature for 15 min and then was cooled to −10 °C; a solution of **7** (174 mg, 1.00 mmol) in THF (15 mL) was added dropwise, and the mixture was stirred at −10 °C for 80 min. Then brine was added and extracted with $Et_2O$ (3 × 20 mL), and the organic layers were washed (brine), dried ($Na_2SO_4$), and concentrated. The crude oil was purified through chromatography (silica gel, hexanes/EtOAc (7:3), and ethyl acetate) to afford 175 mg (60%) of a white solid (mp 102−104 °C); $[\alpha]^{25}_D$ = −54.66 ($c$ = 1.1, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) δ 7.63−7.64 (m, 2H), 7.40−7.46 (m, 3H), 4.70 (1H, dq, $J$ = 7.0, 4.0 Hz), 3.93 (1H, t, $J$ = 3.5 Hz), 3.40 (1H, d, $J$ = 3.0 Hz), 1.56 (3H, d, $J$ = 6.5 Hz), 1.5 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.4, 136.5, 129.9, 129.4, 127.8, 77.9, 74.9, 61.4, 21.1, 14.5. IR (NaCl) δ 3459, 2931, 1766, 1440, 1096, 945, 753, 692 cm$^{-1}$. HRMS *m*/*z* calcd for $C_{12}H_{14}O_3SNa$ [M + $Na^+$]: 261.0561, found: 261.0540.

**(3*R*,4*R*,5*S*)-Dihydro-4-hydroxy-3,5-dimethyl-3-(phenylsulfinyl)-furan-2(3H)-one, 14.** To a −10 °C cold solution of compound **13** (100 mg, 0.34 mmol) in $CH_2Cl_2$ (3 mL) was added a solution of

(10) In the presence of chalcone, a by-product (a mixture of isomers) resulting from the conjugate addition of enolate to chalcone was also formed.

(11) The preparation of *O*-*tert*-butyldimethylsilyl lactaldehyde was performed according to: Marshall, J. A.; Shiping, X. *J. Org. Chem.* **1995**, *60*, 7230−7237.

(12) Preparation of *tert*-butylhydroperoxide solution: Hill, J. G.; Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3607−3608.

*m*-CPBA (77% pure) (76 mg, 0.34 mmol) in $CH_2Cl_2$ (2 mL). The resulting mixture was stirred at −10 °C for 30 min, then was quenched with a saturated aqueous solution of sodium bicarbonate, and extracted with $CH_2Cl_2$ (3 × 15 mL); the organic layers were subsequently washed with brine and a saturated aqueous solution of sodium bicarbonate and water and were dried ($Na_2SO_4$) and concentrated. The crude was directly purified through recrystallization from $CH_2Cl_2$/hexane to give colorless needles (73 mg, 84%) (mp 171−173 °C); $[\alpha]^{20}_D = -234.88$ ($c = 1.3$, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.90−7.91 (m, 2H), 7.58−7.60 (m, 3H), 5.30 (br s, 1H), 4.66 (1H, dq, $J = 6.0$, 3.5 Hz), 4.34 (1H, d, $J = 3.5$ Hz), 1.54 (3H, d, $J = 6.5$ Hz), 1.18 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.0, 137.4, 132.3, 129.0, 127.3, 78.9, 78.0, 67.9, 14.2, 13.8. IR (NaCl) $\delta$ 3406, 2976, 1759, 1639, 1442, 1389, 1337, 1303, 1264, 1194, 1156, 1080, 1050, 1031, 1006, 949, 878, 755, 741, 688 cm$^{-1}$. HRMS *m*/*z* calcd for $C_{12}H_{14}O_4SNa$ [M + $Na^+$]: 277.0510, found: 277.0544.

**(4*S*,5*S*)-Dihydro-4-hydroxy-5-methyl-3-methylenefuran-2(3H)-one, 15.** A solution of sulfoxide **14** (62 mg, 0.24 mmol) in toluene (4 mL) was refluxed for 30 min, and then the solvent was removed under vacuum,The resulting crude oil was purified through chromatography (silica gel, hexanes/EtOAc (1:1), (1:2)) to afford 22 mg of a colorless oil (71%). $[\alpha]^{20}_D = -97.26$ ($c = 1.3$, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.41 (1H, d, $J = 2.1$ Hz), 5.97 (1H, d, $J = 1.5$ Hz), 4.83 (1H, d, $J = 5.7$ Hz), 4.65 (1H, dq, $J = 6.0$, 6.6 Hz), 1.34 (3H, d, $J = 6.6$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.9, 138.8, 126.3, 78.4, 69.7, 14.3. IR (NaCl) $\delta$ 3439, 3015, 2930, 1756, 1672, 1387, 1263, 1186, 1103, 1045, 958, 910, 861, 821, 784 cm$^{-1}$. HRMS *m*/*z* calcd for $C_6H_8O_3Na$ [M + $Na^+$]: 151.0371, found: 151.0354.

Spectroscopy data for **11**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.26 (2H, m), 3.66 (1H, q, $J = 6.6$ Hz), 3.61 (1H, s), 2.60 (1H, s), 1.36 (3H, s), 1.31 (3H, t, $J = 7.0$ Hz), 1.29 (1H, d, $J = 6.6$ Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.4, 68.0.2, 65.3, 61.5, 54.5, 18.4, 14.3, 13.6. IR (NaCl) $\nu$ 3422, 2925, 1753, 1446, 1371, 1294, 1181, 1089, 1058, 1021, 930, 878, 760 cm$^{-1}$. HRMS *m*/*z* calcd for $C_8H_{14}O_4Na$ [M + $Na^+$]: 197.0790, found: 197.0787.

Spectroscopy data for **12**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.26 (2H, m), 3.86 (1H, q, $J = 6.5$ Hz), 3.64 (3H, s), 2.05 (1H, s), 1.36 (3H, s), 1.33 (3H, t, $J = 7.0$ Hz), 1.27 (1H, d, $J = 6.5$ Hz). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.4, 68.0.2, 65.3, 61.5, 54.5, 18.4, 14.3, 13.6. IR (NaCl) $\nu$ 3490, 2982, 1751, 1384, 1298, 1199, 1033, 923, 873, 736 cm$^{-1}$. HRMS *m*/*z* calcd for $C_8H_{14}O_4Na$ [M + $Na^+$]: 197.0790, found: 197.0752.

**(3*R*,4*R*,5*S*)-Dihydro-4-hydroxy-4,5-dimethyl-3-(phenylthio)-furan-2(3H)-one, 16.** An ice-bath cold suspension of sodium hydride (60% in mineral oil) (44 mg, 1.10 mmol) in THF (7 mL) was treated with thiophenol (225 $\mu$L, 2.19 mmol). The mixture was stirred at this temperature for 30 min and then was cooled to −20 °C; then a solution of **11** (127 mg, 0.73 mmol) in THF (3 mL) was added dropwise, and the mixture was stirred at −20 °C for 8 h. Then brine was added and extracted with $Et_2O$ (3 × 15 mL), and the organic layers were washed (brine), dried ($Na_2SO_4$), and concentrated. The crude oil was purified through chromatography (silica gel, hexanes/EtOAc (6:4), (1:1) and ethyl acetate) to afford 166 mg (96%) of a white solid. Recrystallization from hexanes/EtOAc gave a white solid (mp 104−106 °C). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.60−7.61 (m, 2H), 7.30−7.38 (m, 3H), 4.33 (1H, q, $J = 6.0$ Hz), 3.91 (1H, s), 2.45 (1H, br s), 1.43 (3H, d, $J = 6.5$ Hz), 1.27 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.4, 68.0.2, 65.3, 61.5, 54.5, 18.4, 14.3, 13.6. IR (NaCl) $\delta$ 3484, 3063, 2981, 2937, 1762, 1584, 1481, 1441, 1385, 1324, 1256, 1172, 1090, 1064, 1016, 958, 914, 865, 795, 743, 692, 649 cm$^{-1}$. HRMS *m*/*z* calcd for $C_{12}H_{14}O_3SNa$ [M + $Na^+$]: 261.0561, found: 261.0554.

**(3S,4*S*,5*S*)-Dihydro-4-hydroxy-4,5-dimethyl-3-(phenylthio)furan-2(3H)-one, 17.** An ice-bath cold suspension of sodium hydride (60% in mineral oil) (95 mg, 2.38 mmol) in THF (16 mL) was treated with thiophenol (489 $\mu$L, 4.76 mmol). The mixture was stirred at this temperature for 30 min and was cooled to −20 °C. Then a solution of **12** (276 mg, 1.59 mmol) in THF (6 mL) was added dropwise, and the mixture was stirred at −20 °C for 3 h. Then brine was added and extracted with $Et_2O$ (3 × 10 mL); the organic layers were washed (brine), dried ($Na_2SO_4$), and concentrated. The crude oil was purified through chromatography (silica gel, hexanes/EtOAc (7:3), (6:4) and EtOAc) to afford 250 mg (66%) of an oil. Recrystallization from $CH_2Cl_2$/hexane gave a white solid (mp 90−93 °C). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.58−7.62 (m, 2H), 7.25−7.35 (3H, m), 4.47 (1H, q, $J = 7.0$ Hz), 3.78 (1H, s), 1.56 (3H, d, $J = 6.5$ Hz), 1.50 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.7, 132.8, 132.7, 129.5, 128.6, 83.5, 77.0, 58.9, 21.6, 15.8. IR (NaCl) $\delta$ 3468, 3059, 2927, 2855, 1769, 1580, 1478, 1440, 1383, 1345, 1323, 1158, 1091, 1049, 1024, 953, 924, 869, 808, 741, 690 cm$^{-1}$. HRMS *m*/*z* calcd for $C_{12}H_{14}O_3SNa$ [M + $Na^+$]: 261.0561, found: 261.0569.

**Ethyl 3-(*tert*-Butylperoxy)butanoate, 19.** A −20 °C cold solution of ethyl 3-hydroxybutanoate (165 mg, 1.24 mmol) in dichloromethane (2 mL) was treated with pyridine (121 $\mu$L, 1.50 mmol) and then with trifluoromethansulfonic anhydride (230 $\mu$L, 1.36 mmol). The resulting mixture was stirred at this temperature for 35 min and then was quenched with water; the organic layer was separated, dried ($MgSO_4$), and concentrated. Then the crude oil was solved in dichloromethane (2 mL), and the resulting mixture was treated with sodium hydrogencarbonate (310 mg, 3.70 mmol) and *tert*-butylhydroperoxide (5 M in decanes) (310 $\mu$L, 1.60 mmol) and stirred at room temperature for 3.5 h and then was quenched with water and extracted with dichloromethane (3 × 10 mL), dried ($Na_2SO_4$), and concentrated. The crude oil was purified through chromatography (silica gel, hexanes/EtOAc (8:2)) to afford 126 mg (50%) of an oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.35 (1H, dq, $J = 6.3$ Hz), 4.02 (2H, q, $J = 7.2$ Hz), 2.63 (1H, dd, $J = 6.3$, 15.0 Hz), 2.22 (1H, dd, $J = 6.3$, 15.0 Hz), 1.17 (3H, t, $J = 7.2$ Hz), 1.14 (3H, d, $J = 6.3$ Hz), 1.11 (9H, s). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.1, 79.8, 76.0, 60.1, 40.1, 26.1, 18.1, 14.0. HRMS *m*/*z* calcd for $C_{10}H_{20}O_4Na$ [M + $Na^+$]: 227.1259, found: 227.1246.

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**Supporting Information Available:** Description of the general experimental procedures and graphical NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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