Asymmetric Functionalization of Chromium Carbene-Derived Optically Active 4,4-Disubstituted Butenolides

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Optically active 4,4-disubstituted butenolides were readily prepared by photolysis of chromium alkoxycarbene complexes with optically active ene carbamates, followed by Baeyer–Villiger oxidation/oxazolidinone elimination. These butenolides underwent clean 1,3-dipolar cycloaddition reactions with cyclic nitrones exclusively from the more hindered face of the butenolide. Azomethine ylides were considerably less stereoselective. Conjugate addition reactions also occurred from the more hindered face, while *cis* hydroxylation occurred from the opposite face.

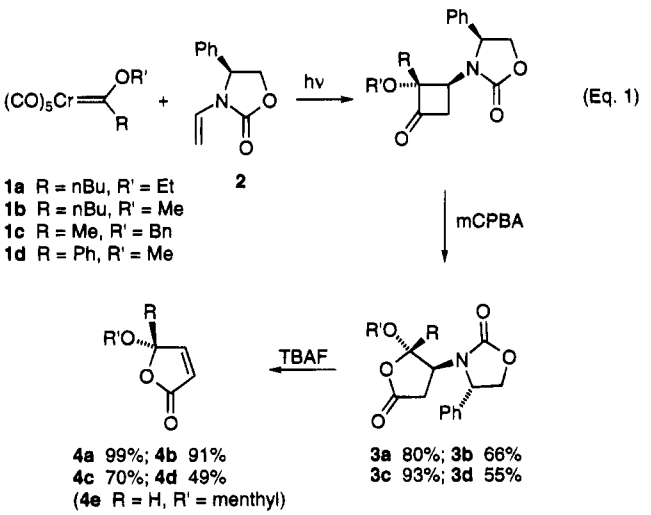
Introduction

Because of their high intrinsic chemical reactivity, optically active butenolides (γ-substituted-2(5*H*)-furanones) have been extensively developed as chiral templates for the synthesis of a wide range of biologically active compounds. Two general classes of these compounds have been studied. Hanessian[1] synthesized (*S*)-5-(hydroxymethyl)furan-2(5*H*)-one from (*S*)-glutamic acid in five steps and an overall 42% yield[2] and used this as a template for asymmetric conjugate additions, α-enolate chemistry, and cycloadditions and in the synthesis of polypropionates, 1,3-polyols, and other biologically active compounds.[2] Feringa[3] developed the chemistry of γ-alkoxy-2(5*H*)-furanones, synthesized in good yield and excellent optical purity[4] by singlet oxygen oxidation of furfural followed by diastereoselective acetalization of the resulting 5-hydroxy-2(5*H*)-furanone with menthol. In this way, either enantiomer was available enantiomerically pure, after recrystallization, by acetalizing with either *d*- or *l*-menthol. Again, conjugate addition[5] and cycloaddition reactions[6] of these substrates were extensively studied. Other approaches to this general class of compounds are also known[7] but are less broadly studied.

Butenolides that contain both a 4-alkoxy and a 4-alkyl substituent are less common but do occur in nature,[8] often from marine algae[9] or sponges.[10] Racemic syntheses include singlet oxygen oxidation of substituted furans[11] and intramolecular acetalizations,[12] while syntheses of optically active materials have been achieved by resolution[13] or by oxidation of carbohydrate-derived furan derivatives.[14] Recently, an efficient synthesis of optically active 5-alkoxy-5-alkyl-2(5*H*)-furanones has been reported from these laboratories,[15] and the procedure was used to synthesize (+)-tetrahydrocerulenin and two butenolides from the marine sponge *Plakortis lita*.[16] Herein we report asymmetric 1,3-dipolar cycloaddition reactions, conjugate addition reactions, and oxidations of this class of compounds.

Results and Discussion

The requisite optically active butenolides **4a–d** were synthesized in the usual manner[16] in fair yield and with high diastereoselectivity (eq 1). Their reactivity toward 1,3-dipolar cycloaddition was first addressed. Nitrones and azomethine ylides were chosen as 1,3-dipolar species to allow direct comparisons with the corresponding



monosubstituted 4-(menthyloxy)butenolides (e.g., **4e**, R = H, R[1] = menthyl) of Feringa.[6a] Cyclic nitrones **5**, **6** (eq 2), and **9** (eq 3) added cleanly, giving high yields of a

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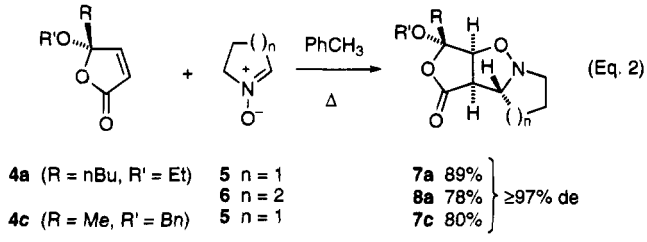
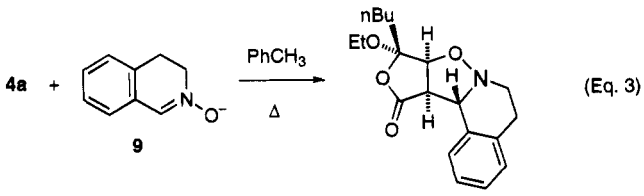
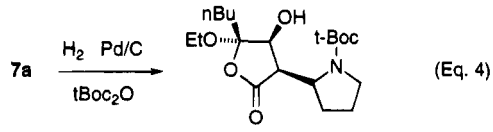
single diastereoisomer of the cycloaddition product. The regioselectivity was as expected,[6a] with the nitrone oxygen adding to the β-carbon of the butenolide. Clean *exo* addition was evidenced by the lack of coupling ($J_{trans} \approx 0$) between the methine proton adjacent to the carbonyl group and that adjacent to nitrogen. The addition of the nitrone occurred from the face *opposite* the alkoxy group, and this was confirmed by determining the X-ray crystal structure of compound **7a**. This corresponds to attack from the sterically *more* hindered face (R > OR^1) of the butenolide and may reflect an electronic rather than a steric bias in these systems (see below). Nitrones derived from proline, diethylamine, and homopiperidine failed to undergo this cycloaddition reaction. The nitrone decomposed and the butenolide was recovered unchanged. Hydrogenolysis of **7a** produced β-hydroxy lactone **11** in excellent yield (eq 4).







In contrast, the monosubstituted butenolide **4e** was reported[6a] to undergo 1,3-dipolar cycloaddition to a range of both cyclic and acyclic nitrones. Attack always occurred from the *less* sterically hindered face which, however, corresponds to the face *opposite* the alkoxy group, as observed above. With nitrone **5**, an 89:11 mixture of exo/endo was observed in the monosubstituted system.

Azomethine ylides underwent cycloaddition with **4a** with considerably lower diastereoselectivity (eq 5), and the use of an optically active azomethine ylide had little

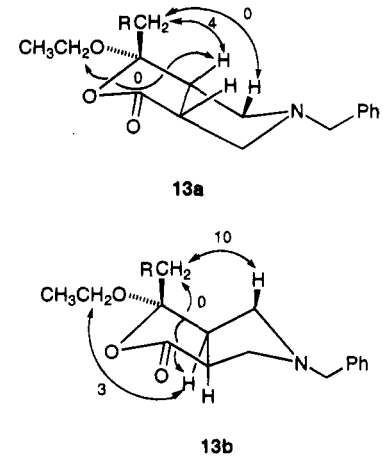
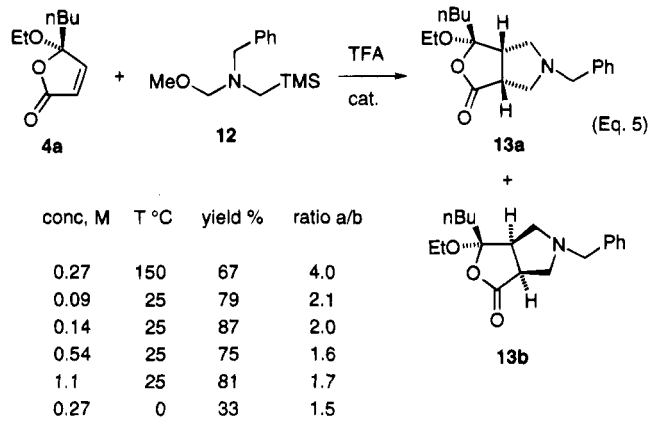
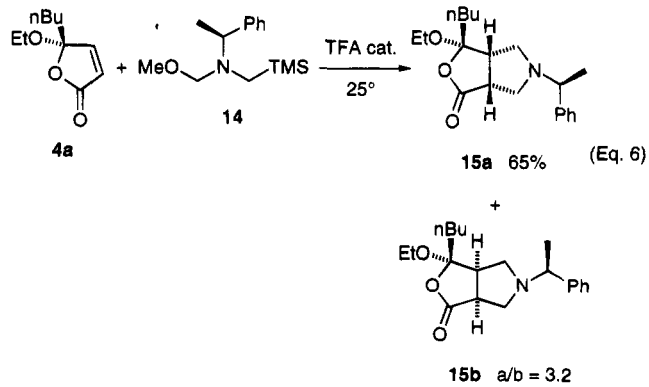


Figure 1. NOE effects in compounds **13a** and **13b**.

effect on stereoselectivity (eq 6). The best results were obtained at high temperature. The diastereoisomers were easily separated, and the stereochemistry was assigned on the basis of NOE measurements (Figure 1). In contrast to the nitrone cycloadditions, the major diastereoisomer resulted from attack of the face opposite the butyl group and from the same side as the alkoxy group. For comparison, monosubstituted butenolide **4e**





has been reported[6a] to undergo cycloaddition to the same azomethine ylide exclusively from the face opposite the alkoxy group to give a single diastereoisomer of the adduct. (This also corresponds to the sterically less hindered face for this system.)

To determine if the dependence of product ratio on temperature for the reaction in eq 5 was due to reversibility of the reaction, resulting in thermodynamic vs kinetic control, the minor diastereoisomer **13b** was subjected to the reaction conditions for 15 h and recovered

(11) For example: (a) Yamamoto, M.; Munakata, H.; Kishikawa, K.; Kokmoto, S.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2366. (b) Gollnik, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057. (c) Feringa, B. L.; Butselaar, R. J. *Tetrahedron Lett.* **1983**, *24*, 1193 and references therein.

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(16) Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779.

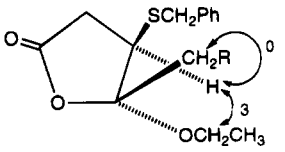
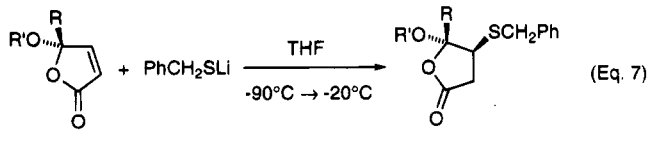


Figure 2. NOE measurements for compound **16a**.

unchanged, indicating that the minor product could not convert to the major after formation. To check for reversibility, the minor diastereoisomer was heated at reflux in toluene in the presence of *N*-phenylmaleimide and a catalytic amount of trifluoroacetic acid, in an attempt to trap any azomethine ylide resulting from retrocycloaddition. Only unchanged starting materials were recovered, indicating irreversibility.

Nucleophilic Michael addition to 4-monosubstituted butenolides has been extensively studied with a very wide range of nucleophiles. In *all* cases, the nucleophile attacked from the face *opposite* the substituent in the 4-position, whether it was an alkyl group[12] or an alkoxy group.[3-5] This selectivity was attributed to steric hindrance of one face of the butenolide π system by the 4-substituent, directing the nucleophile to the other face. Remarkably, although 4-alkylbutenolides were generally reactive toward organocuprates,[12] the 4-alkoxy systems failed to react with either cuprates or zincates,[3b] implying some electronic impediment to cuprate additions in these systems.

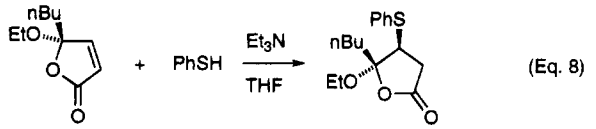
In light of this, it was not surprising that cuprates failed to add to 4,4-disubstituted butenolide **4a**, since both faces are shielded by a substituent and one of them is an alkoxy group. Addition of trimethylsilyl iodide failed to promote efficient addition, in contrast to acyclic γ-alkoxy-α,β-unsaturated esters.[17] In contrast to cuprates, thiolate anions added cleanly and in high yield, giving a single diastereoisomer, corresponding to additions anti to the smaller alkoxy group and syn to the larger alkyl group (eqs 7 and 8). This unexpected stereoselectivity was confirmed by NOE measurements (Figure 2) and parallels that previously observed[16] in the



(Eq. 7)

4a
4b

16a R = nBu, R' = OEt 75%
16b R = nBu, R' = OMe 79%

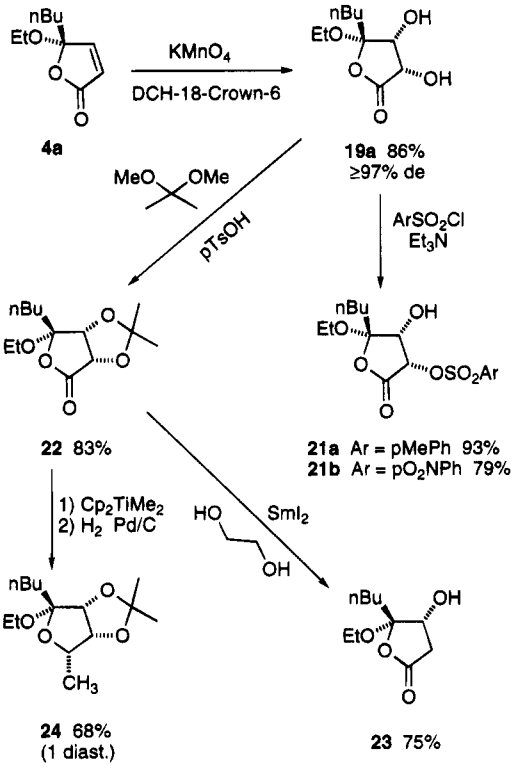


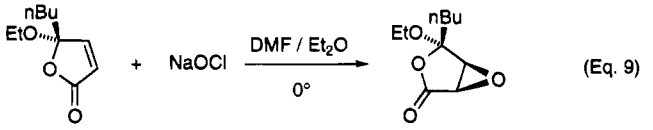
(Eq. 8)

4a **17** 95%

nucleophilic (NaOCl) epoxidation of similar butenolides. Butenolide **4a** also underwent nucleophilic epoxidation from the more hindered face (eq 9), suggesting that an alkoxy group in the 4-position exerted electronic control over Michael addition reactions.[18] (The low yields of epoxidation of these butenolides observed here and previously[16] reflect poor conversion (≈50% recovery of starting butenolide) and the instability of these compounds to both the basic conditions required for nucleophilic epoxidation and chromatographic purification.) Finally, piperidine underwent clean conjugate addition to **4a**.[19] However all attempts to purify this adduct resulted in retro conjugate addition followed by attack of the amine at the carbonyl group to give ring-opened material.

Scheme 1





(Eq. 9)

4a **18** 23%
(48% vs. recovered **3a**)

Butenolide **4a** underwent clean *cis*-hydroxylation with potassium permanganate from the *same* face as the alkoxy group (Scheme 1) to give good yields of a single diastereoisomer of the desired diol **19a**. With 4-alkylbutenolides, *cis*-hydroxylation under these conditions occurred predominantly but not exclusively from the less hindered face, opposite the alkyl group.[20] When sodium periodate and a catalytic amount of ruthenium chloride were used for the *cis*-hydroxylation[21] of butenolide **4a**, a 93:7 mixture of **19a** and its other *cis* diastereoisomer **19b** was formed in 75% yield. The major diastereomer was still **19a**.

(17) Hannessian, S.; Sumi, K. *Synthesis* **1991**, 1083 and references therein.

(18) Wipf and Kim recently provided experimental evidence for electrostatic control of nucleophilic additions to 4,4-disubstituted dienones. In all cases, attack *anti* to the oxygen substituents at C-4, regardless of the steric factors, was observed; Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678.

(19) Feringa has reported direct β-amination of 5-alkoxy-2(5*H*)-furanones followed by lactone cleavage to give a variety of useful compounds: de Lange, B.; van Bolhius, F.; Feringa, B. L. *Tetrahedron* **1989**, *45*, 6799.

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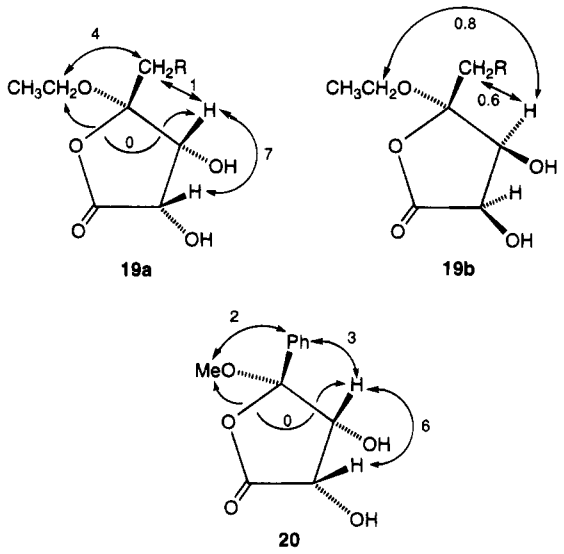

Figure 3. NOE measurements for diol lactones.

To aid in the assignment of the stereochemistry of the *cis*-hydroxylation products **19**, the phenyl analog **20** was prepared using the $KMnO_4$ procedure. These diol lactones were subjected to NOE studies, and the results are summarized in Figure 3. Although all NOE effects in these compounds were weak, they were consistently observed. The most important interactions in the diols resulting from oxidation from the same face as the alkoxy group, **19a** and **20**, are those between the *syn*-C-3 methine and the C-4 alkyl or aryl group. This, coupled with the *lack* of interaction of this same methine with the *anti*-C-4 alkoxy group, argues for the stereochemistry shown. In contrast, in the minor diastereoisomer **19b**, the C-3 methine interacted with the C-4 alkoxy group but also with the C-4 alkyl group. Taken together, these data argue for the stereochemistry assigned. Crystals suitable for X-ray studies could not be obtained.

Diol **17a** was selectively sulfonated, and its acetonide was cleanly deoxygenated α to the carbonyl group by samarium(II) iodide[22] and was methylenated/reduced to form compound **24**[23] (Scheme 1), both of importance for planned applications in nucleoside analog syntheses.

In summary, 4,4-disubstituted butenolides undergo a variety of reactions with high but unpredictable stereoselectivity. The use of these functionalized lactones in the synthesis of nucleoside analogs is under current study.

Experimental Section

General Procedures. Melting points are uncorrected. The NMR spectra (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) are recorded in $CDCl_3$, and chemical shifts are given in δ relative to $CDCl_3$ (δ 7.24 for ^1H and δ 77.0 for ^{13}C) unless otherwise indicated. Other general procedures are the same as those in previous literature.[16] Trimethyloxonium tetrafluoroborate, chromium hexacarbonyl, TBAF, and samarium(II) iodide were used as received. Organolithium reagents were titrated according to the procedure described by Watson and Eastham.[24]

The following materials were prepared according to literature methods: [(methoxy)(butyl)carbene]pentacarbonylchromium(0) **(1b)**,[25] [(benzyloxy)(methyl)carbene]pentacarbonylchromium(0) **(1c)**,[26] [(methoxy)(phenyl)carbene]pentacarbonylchromium(0) **(1d)**,[27] (benzyloxy)(methyl)cyclobutanone,[27] (methoxy)(phenyl)cyclobutanone,[27] (benzyloxy)(methyl) lactone **3c**,[27] *N*-benzyl-*N*-(methoxymethyl)-*N*-(trimethylsilyl)methylamine **(12)**,[28] 3-vinyl-(*S*)-4-phenyl-2-oxazolidinone **(2)**,[16] (*S*)-methyl-*N*-benzyl*N*-(methoxymethyl)-*N*-(trimethylsilyl)methylamine **(14)**,[29] and dimethyltitanocene.[30]

[(Ethoxy)(butyl)carbene]pentacarbonylchromium-(0) (1a). A 1.3 M solution of *n*-butyllithium in hexanes (11.5 mL, 15.0 mmol) was slowly added to a solution of chromium hexacarbonyl (3.00 g, 13.6 mmol) in 30 mL of ether. The reaction was stirred at rt for 18 h. Methanol was slowly added to protonate any unreacted *n*-butyllithium. The solvents were removed, and water was added to the remaining dark residue. Triethyloxonium tetrafluoroborate was added until the pH was 3. The water layer was extracted several times with hexanes until no orange color was seen in the organic layer. The organic layers were combined and dried over $MgSO_4$. The solvent was removed, and the crude carbene complex was purified by flash column chromatography using hexanes as the eluent to give 3.56 g of an orange oil (85%): ^1H NMR δ 0.88 (m, 3H), 1.24–1.52 (m, 4H), 1.60–1.65 (t, 3H, J = 7.1 Hz), 3.25 (m, 2H), 5.04 (q, 2H, J = 7.1 Hz); ^{13}C NMR δ 360.4, 223.3, 216.5, 77.2, 62.8, 28.3, 22.3, 14.8, 13.7; IR (thin film) ν 2051, 1935 cm^{-1}.

Cycloaddition Reactions. The carbene complex and the (*S*)-ene carbamate **2** in CH_2Cl_2 (degassed) in a Fisher Porter pressure tube were flushed with CO gas, and 90 psi of CO was left in the tube. The reaction was irradiated for 18 h. The CO pressure was slowly released, and the solvent was removed. The residue was placed in a sublimation apparatus and heated to 50 °C under reduced pressure (ca. 1 mmHg) to remove all chromium hexacarbonyl. The remaining material was purified by flash chromatography using the appropriate eluent. When the carbene complex **1d** was used, glass beads were placed in the pressure tube and the irradiation time was doubled.

(Ethoxy)(butyl)cyclobutanone. The carbene complex **1a** (1.09 g, 3.57 mmol) and the (*S*)-ene carbamate **2** (450 mg, 2.37 mmol) were subjected to the reaction conditions above. Flash chromatography (1:5 ethyl acetate:hexanes) gave the (*R*,*S*,*S*) diastereomer as a white solid (625 mg, 83%): mp 78–81 °C; ^1H NMR δ 0.88 (t, 3H, J = 6.8 Hz), 1.02 (t, 3H, J = 6.9 Hz), 1.21–1.32 (m, 3H), 1.43–1.49 (m, 1H), 1.83 (m, 2H), 2.51 (dd, 1H, J = 10.1, 18.0 Hz), 3.24–3.31 (m, 3H), 4.19 (dd, 1H, J = 5.2, 8.7 Hz), 4.31 (t, 1H, J = 9.8 Hz), 4.66 (t, 1H, J = 8.6 Hz), 4.87 (dd, 1H, J = 5.2, 8.5 Hz), 7.24–7.41 (m, 5H); ^{13}C NMR δ 206.3, 157.8, 138.7, 129.4, 129.3, 126.5, 98.5, 70.0, 61.8, 60.2, 48.0, 42.2, 29.9, 25.3, 22.9, 15.2, 13.9; IR (thin film) ν 1790, 1741 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.03; H, 7.73; N, 4.20. $[\alpha]^{25}_D$ = +67.1° (c = 0.785 in ether).

(Methoxy)(butyl)cyclobutanone. The carbene complex **1b** (700 mg, 2.4 mmol) and the (*S*)-ene carbamate **2** (349 mg, 1.8 mmol) were subjected to the reaction conditions above. Flash chromatography (4:1 hexanes:ethyl acetate) gave the (*R*,*S*,*S*) diastereomer in 67% yield (403 mg): mp 112–114 °C; ^1H NMR δ 0.89 (t, 3H, J = 8.0 Hz), 1.24–1.49 (m, 4H), 1.83 (m, 2H), 2.52 (dd, 1H, J = 10.1, 18.0 Hz), 3.15 (s, 3H), 3.23 (dd, 1H, J = 9.2, 17.9 Hz), 4.20 (dd, 1H, J = 5.0, 8.7 Hz), 4.34 (t, 1H, J = 9.5 Hz), 4.67 (t, 1H, J = 8.6 Hz), 4.88 (dd, 1H, J = 4.8, 9.0 Hz), 7.24–7.28 (m, 2H), 7.37–7.41 (m, 3H); ^{13}C NMR δ 205.7, 157.8, 138.7, 129.5, 129.4, 126.4, 98.7, 70.1, 61.6, 52.4, 47.3, 42.6, 29.5, 25.2, 23.0, 13.9. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.27; H, 7.37; N, 4.27. $[\alpha]^{25}_D$ = +63.2° (c = 0.212 in CH_2Cl_2).

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Lactones. *m*-CPBA was added in small portions to a CH_2Cl_2 solution containing the cyclobutanone and Na_2HPO_4. The mixture was stirred at rt for 18 h. A saturated aqueous solution of $Na_2S_2O_3$ was added, and the biphasic mixture was stirred vigorously for 1 h. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were washed with aqueous saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was removed, and the lactone was purified by flash column chromatography using the appropriate eluent.

Ethoxy Butyl Lactone 3a. The ethoxybutylcyclobutanone (815 mg, 2.46 mmol), Na_2HPO_4 (873 mg, 6.15 mmol), and *m*-CPBA (972 mg, 4.43 mmol, 80% mixture) were combined as described above. Purification of the lactone by flash chromatography (1:2 ethyl acetate:hexanes) gave a white solid (824 mg, 96%): mp 131–133 °C; ^{1}H NMR δ 0.91 (m, 3H), 1.11 (t, 3H, J = 7.0 Hz), 1.31–1.41 (m, 4H), 1.59–1.64 (m, 1H), 1.86 (d, 1H, J = 18.3 Hz), 2.15 (m, 1H), 2.78 (dd, 1H, J = 8.2, 18.1 Hz), 3.70 (m, 2H), 4.19 (dd, 1H, J = 2.3, 8.7 Hz), 4.57–4.72 (m, 3H), 7.22–7.25 (m, 2H), 7.35–7.40 (m, 3H); ^{13}C NMR δ 174.2, 157.8, 139.9, 129.6, 126.3, 112.3, 71.0, 58.3, 58.1, 56.7, 32.4, 29.7, 24.3, 22.8, 15.2, 13.7. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.48; H, 7.21; N, 3.92. $[\alpha]^{25}_D$ = +41.1° (c = 0.095 in CH_2Cl_2).

Methoxy Butyl Lactone 3b. The methoxybutylcyclobutanone (700 mg, 2.21 mmol), Na_2HPO_4 (784 mg, 5.53 mmol), and *m*-CPBA (871 mg, 3.97 mmol, 80% mixture) were added together as described above. Purification of the lactone by flash chromatography (1:3 ethyl acetate:hexanes) gave a white foam (728 mg, 99%): mp 121–122 °C; ^{1}H NMR δ 0.92 (m, 3H), 1.28–1.49 (m, 4H), 1.57–1.68 (m, 1H), 1.87 (d, 1H, J = 18.2 Hz), 2.11–2.22 (m, 1H), 2.77 (dd, 1H, J = 8.1, 18.3 Hz), 3.26 (s, 3H), 4.21 (dd, 1H, J = 2.3, 8.1 Hz), 4.58–4.71 (m, 3H), 7.21–7.25 (m, 2H), 7.35–7.38 (m, 3H); ^{13}C NMR δ 174.0, 157.8, 139.8, 129.6, 126.3, 112.3, 71.0, 58.3, 56.5, 49.9, 32.4, 29.0, 24.1, 22.7, 13.6. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 65.09; H, 7.04; N, 4.15. $[\alpha]^{25}_D$ = +50.0° (c = 0.240 in CH_2Cl_2).

Methoxy Phenyl Lactone 3d. The methoxyphenylcyclobutanone (455 mg, 1.35 mmol), Na_2HPO_4 (1.34 g, 9.45 mmol), and *m*-CPBA (711 mg, 2.43 mmol, 60% mixture) were added together as described above. Purification of the lactone by flash chromatography (1:3 ethyl acetate:hexanes) gave a white solid (367 mg, 77%): mp 167–168 °C; ^{1}H NMR δ 1.98 (d, 1H, J = 18.2 Hz), 2.92 (dd, 1H, J = 8.6, 18.4 Hz), 3.07 (s, 3H), 3.38–3.50 (m, 1H), 3.74 (dd, 1H, J = 3.2, 8.5 Hz), 4.14 (dd, 1H, J = 3.0, 8.6 Hz), 5.06 (broad s, 1H), 7.12–7.15 (m, 2H), 7.31–7.36 (m, 3H), 7.45-7.52 (m, 3H), 7.58–7.65 (m, 2H); ^{13}C NMR δ 173.7, 157.8, 133.1, 130.0, 129.5, 129.4, 128.8, 126.6, 126.3, 112.2, 70.6, 58.9, 57.0, 51.4, 32.3; MS (FAB) 354 (M + 1), 277 (100); HRMS calcd 354.1341, found 354.1349; $[\alpha]^{25}_D$ = +9.2° (c = 0.274 in CH_2Cl_2).

Butenolides. A 1.0 M solution of TBAF in THF was slowly added to a solution of the lactone in THF. The solution turned a bright yellow color. The reaction was stirred for 1 h at rt. Water and ether were added, and the water layer was extracted with ether. The organics layers were combined and dried over $MgSO_4$. The solvent was removed, and purification was accomplished by flash chromatography in the appropriate eluent.

Ethoxy Butyl Butenolide 3a. The lactone **3a** (750 mg, 2.16 mmol) and the TBAF solution (3.78 mmol) were allowed to react together as described above. Flash column chromatography (1:5 ethyl acetate:hexanes) gave a clear oil (395 mg, 99%): ^{1}H NMR δ 0.87 (t, 3H, J = 6.9 Hz), 1.16 (t, 3H, J = 7.0 Hz), 1.28–1.35 (m, 4H), 1.86–1.91 (m, 2H), 3.28–3.38 (m, 1H), 3.42–3.52 (m, 1H), 6.16 (d, 1H, J = 5.7 Hz), 7.12 (d, 1H, J = 5.7 Hz); ^{13}C NMR δ 169.9, 153.9, 124.2, 111.0, 59.2, 36.8, 25.2, 22.4, 15.0, 13.6; IR (thin film) ν 1770 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.30; H, 8.63. $[\alpha]^{25}_D$ = +35.7° (c = 0.185 in ether).

Methoxy Butyl Butenolide 3b. The lactone **3b** (351 mg, 1.05 mmol) and the TBAF solution (1.84 mmol) were allowed to react together in the method described above. Flash column chromatography (1:2 ethyl acetate:hexanes) gave a clear oil (163 mg, 91%): ^{1}H NMR δ 0.86 (m, 3H), 1.29–1.34 (m, 4H), 1.84–1.90 (m, 2H), 3.19 (s, 3H), 6.19 (d, 1H, J = 5.8 Hz), 7.10 (d, 1H, J = 5.7 Hz); ^{13}C NMR δ 170.0, 153.9, 124.7, 111.3, 51.1, 36.7, 25.3, 22.6, 13.8; IR (thin film) ν 1770 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.57; H, 8.35. $[\alpha]^{25}_D$ = +40.7° (c = 0.405 in ether).

Benzyloxy Methyl Butenolide 3c. The lactone **3c** (126 mg, 0.34 mmol) and the TBAF solution (1.75 mL) were allowed to react together in the method described above. Flash column chromatography (1:4 ethyl acetate:hexanes) gave a clear oil (49 mg, 70%): ^{1}H NMR δ 1.71 (s, 3H), 4.33 (d, 1H, J = 11.2 Hz), 4.52 (d, 1H, J = 11.2 Hz), 6.17 (d, 1H, J = 5.6 Hz), 7.16 (d, 1H, J = 5.7 Hz), 7.24–7.35 (m, 5H); ^{13}C NMR δ 169.9, 154.5, 136.8, 128.5, 128.0, 127.7, 123.9, 108.9, 66.0, 23.9. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57, H, 5.92. Found: C, 70.32, H, 6.17. $[\alpha]^{25}_D$ = −77.5° (c = 0.120 in ether).

Methoxy Phenyl Butenolide 3d. The lactone **3d** (30 mg, 0.849 mmol) and the TBAF solution (1.5 mL) were allowed to react together in the method described above. Flash column chromatography (1:4 ethyl acetate:hexanes) gave a clear oil (79 mg, 49%): ^{1}H NMR δ 3.33 (s, 3H), 6.14 (d, 1H, J = 5.5 Hz), 7.30 (d, 1H, J = 5.5 Hz), 7.38–7.41 (m, 3H), 7.45–7.50 (m, 2H); ^{13}C NMR δ 170.6, 154.7, 135.4, 129.6, 128.8, 126.0, 121.9, 109.4, 52.1. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.55; H, 5.49. $[\alpha]^{25}_D$ = +31.6° (c = 0.342 in ether).

Nitrone Additions. The nitrones were made from the appropriate secondary amines using the procedure described by Murahashi and Shoita[31] and were used without further purification. The butenolide was dissolved in toluene in a two-neck round-bottom flask equipped with a condenser and brought to reflux. The crude nitrone in toluene was slowly added over 45 min. The solution was boiled 3 h more and then was cooled to rt and stirred for another 4 h. The reaction was poured into a mixture of water and ether, the water was extracted several times with ether, and the organic fractions were combined and dried over $MgSO_4$. The solvents were removed, and purification was accomplished by flash column chromatography in the proper eluent.

Ethoxy Butyl Isoxazolone 7a. The butenolide **4a** (75 mg, 0.407 mmol) was dissolved in 1 mL of toluene and heated to reflux. The crude nitrone **5** (approximately 2.75 mmol) was reacted with the butenolide in the manner described above. Purification by flash column chromatography (1:3 ethyl acetate:hexanes) gave 89 mg (89%) of a white solid: mp 83–85 °C; ^{1}H NMR δ 0.91 (t, 3H, J = 7.2 Hz), 1.13 (t, 3H, J = 7.0 Hz), 1.25–1.41 (m, 4H), 1.61 (m, 1H), 1.77 (m, 1H), 1.98–2.08 (m, 4H), 3.00 (m, 1H), 3.36 (m, 1H), 3.53–3.68 (m, 3H), 3.85 (t, 1H, J = 7.6 Hz), 4.43 (d, 1H, J = 6.3 Hz); ^{13}C NMR δ 176.0, 111.9, 80.7, 69.8, 57.8, 56.7, 55.7, 29.8, 28.9, 25.4, 24.2, 22.6, 15.2, 13.9. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.22; H, 8.48; N, 5.07. $[\alpha]^{25}_D$ = +105.9° (c = 0.205 in CH_2Cl_2).

Benzyloxy Methyl Isoxazolone 7c. The butenolide **4c** (75 mg, 0.367 mmol) was dissolved in 1 mL of toluene and heated to reflux. The crude nitrone **5** (approximately 4 mmol) was added, and the procedure above was followed. Flash chromatography (1:3 ethyl acetate:hexanes) gave 85 mg (80%) of a white solid: mp 63–64 °C; ^{1}H NMR δ 1.52–1.66 (m, 1H), 1.75 (s, 3H), 1.75–1.85 (m, 1H), 2.00–2.12 (m, 2H), 3.00 (m, 1H), 3.39 (m, 1H), 3.61 (d, 1H, J = 6.5 Hz), 3.86 (t, 1H, J = 7.7 Hz), 4.50 (d, 1H, J = 6.5 Hz), 4.64 (d, 1H, J = 17.7 Hz), 4.70 (d, 1H, J = 17.7 Hz), 7.24–7.35 (m, 5H); ^{13}C NMR δ 176.0, 137.4, 128.8, 128.3, 128.1, 110.8, 82.4, 70.6, 65.4, 57.0, 56.1, 30.0, 24.6, 17.3. Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.49; H, 6.53; N, 4.85. $[\alpha]^{25}_D$ = +91.4° (c = 0.152 in CH_2Cl_2).

Ethoxy Butyl Isoxazolone 8a. The butenolide **4a** (40 mg, 0.217 mmol) was dissolved in 1 mL of toluene and was heated to reflux. The crude nitrone **6** (approximately 2.75 mmol) was reacted with the butenolide in the manner described above. Purification by flash column chromatography (3:1 hexanes: ethyl acetate) gave 48 mg (78%) of a white solid: mp 38–40 °C; ^{1}H NMR δ 0.90 (t, 3H, J = 7.0 Hz), 1.12 (t, 3H, J = 7.0 Hz), 1.22–1.59 (m, 9H), 1.70 (m, 2H), 1.96 (m, 2H), 2.93 (m, 1H), 3.29 (dd, 1H, J = 2.0, 6.8 Hz), 3.47–3.67 (m, 3H), 4.38

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(d, 1H, J = 6.8 Hz); ^{13}C NMR δ 176.5, 112.7, 80.2, 63.3, 57.8, 55.1, 50.1, 29.2, 25.4, 25.1, 22.7, 22.2, 19.1, 15.3, 13.9. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.58; H, 8.68; N, 4.92. $[\alpha]^{25}_D$ = +87.5° (c = 2.85 in ether).

Ethoxy Butyl Isoxazolone 10. The butenolide **4a** (50 mg, 0.271 mmol) was dissolved in 1 mL of toluene and was heated to reflux. The crude nitrone **9** (approximately 2.75 mmol) was reacted with the butenolide in the manner described above. Purification by flash column chromatography (6:1 hexanes: ethyl acetate) gave the product as a clear oil (78 mg, 87%): ^{1}H NMR δ 0.92 (t, 3H, J = 7.1 Hz), 1.13 (t, 3H, J = 7.0 Hz), 1.24–1.44 (m, 4H), 2.04 (m, 2H), 2.68 (dt, 1H, J = 5.0, 16.5 Hz), 3.06 (m, 1H), 3.22 (m, 1H), 3.38 (dt, 1H, J = 5.4, 11.8 Hz), 3.54–3.73 (m, 2H), 3.77 (dd, 1H, J = 3.0, 8.1 Hz), 4.45 (d, 1H, J = 6.6 Hz), 4.78 (d, 1H, J = 2.6 Hz), 7.09 (d, 1H, J = 7.2 Hz), 7.15–7.26 (m, 2H), 7.40 (d, 1H, J = 7.3 Hz); ^{13}C NMR δ 176.3, 133.5, 133.1, 128.4, 127.3, 127.1, 126.9, 111.8, 81.0, 66.1, 57.8, 57.4, 47.9, 29.1, 25.4, 24.5, 22.7, 15.2, 13.9. Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.71; H, 7.56; N, 4.02. $[\alpha]^{25}_D$ = +31.9° (c = 1.97 in CH_2Cl_2).

Ethoxy Butyl Alcohol 11. Palladium on carbon (32 mg, 0.0149 mmol) in ethyl acetate was pretreated with H_2 (50 psi) in a pressure tube with vigorous stirring for 1 h. The pressure was released, and isoxazolone **7a** (40 mg, 0.149 mmol) and di-*tert*-butyl dicarbonate (39 mg, 0.178 mmol) in 1 mL of ethyl acetate were added to the tube. H_2 (50 psi) was again, added and the reaction was stirred vigorously for 24 h. The H_2 was released, and the suspension was filtered through Celite. The filtrate solvent was removed, and the product was purified by flash column chromatography using 1:4 ethyl acetate:hexanes as the eluent. A clear oil (55 mg, 99%) was recovered: ^{1}H NMR δ 0.91 (t, 3H, J = 7.2 Hz), 1.14 (t, 3H, J = 7.0 Hz), 1.24–1.48 (m, 5H), 1.44 (s, 9H), 1.51 (s, 9H), 1.88–2.04 (m, 4H), 2.67 (m, 1H), 2.80 (dd, 1H, J = 3.6, 10.8 Hz), 3.32 (m, 2H), 3.60 (m, 2H), 3.98 (t, 1H, J = 2.6 Hz), 4.22 (dd, J = 7.2, 10.5 Hz, 1H), 6.25 (bs, 1H); ^{13}C NMR δ 174.7, 146.6, 110.5, 85.1, 80.9, 72.3, 57.7, 53.2, 49.5, 46.7, 28.3, 28.1, 27.3, 24.7, 23.1, 22.6 , 15.3, 13.9; IR (thin film) 3295, 1780, 1665 cm^{-1}. Anal. Calcd for $C_{19}H_{33}NO_6$: C, 61.43; H, 8.95; N, 3.77. Found: C, 61.53; H, 8.79; N, 3.58. $[\alpha]^{25}_D$ = +97.1° (c = 1.11 in CH_2Cl_2).

Azomethine Ylide Additions. A catalytic amount of TFA (5 mol %) was added to a toluene solution of the azomethine ylide precursor **12** (306 mg, 1.36 mmol) and the butenolide **4a** (50 mg, 0.271 mmol). The tube was sealed, and the reaction was stirred at various temperatures for 3 h. The reaction was poured into a saturated aqueous $NaHCO_3$ solution and extracted several times with ether. The organics were dried over $MgSO_4$, the solvent was removed, and the products were purified by flash column chromatography (5% ether in CH_2Cl_2). The spectral assignments were made according to a HETCOR experiment. The major diastereomer **13a**: ^{1}H NMR δ 0.89 (t, 3H, J = 7.1 Hz, $CH_2CH_2CH_3$), 1.17 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.19–1.33 (m, 4H, $CH_2CH_2CH_3$), 1.63 (m, 1H, $CH_2CH_2CH_2$), 1.97 (m, 1H, $CH_2CH_2CH_2$), 2.14 (dd, 1H, J = 8.2, 9.8 Hz, CH_2N), 2.51 (dd, 1H, J = 7.2, 9.2 Hz, CH_2N), 2.87 (m, 1H, $CHCHC{=}O$), 3.13–3.22 (m, 2H, $O{=}CCH$ and $O{=}CCHCH_2N$), 3.30 (dd, 1H, J = 2.6, 9.8 Hz, CH_2N), 3.42 (d, 1H, J = 14.3 Hz, CH_2Ph), 3.58–3.71 (m, 1H, OCH_2CH_3), 3.73–3.80 (m, 2H, OCH_2CH_3 and CH_2Ph), 7.20–7.34 (m, 5H, Ph); ^{13}C NMR δ 177.5 ($C{=}O$), 138.6 (ipso), 128.3, 128.1, 126.9 (Ph), 109.9 (OCO), 59.2 (OCH_2CH_3), 58.8 (CH_2Ph), 57.3 (CH_2N), 53.6 (CH_2N), 46.7 ($CHC{=}O$), 46.4 ($OCCH$), 37.0 ($CH_2CH_2CH_2$), 25.2 ($CH_2CH_2CH_3$), 22.6 ($CH_2CH_2CH_3$), 15.3 (OCH_2CH_3), 13.9 ($CH_2CH_2CH_3$); IR (thin film) 1778 cm^{-1}; MS (EI) 317 (M$^+$), 91 (100); HRMS calcd 317.1991, found 317.1989; $[\alpha]^{25}_D$ = +17.5° (c = 0.200 in CH_2Cl_2). The minor diastereomer **13b**: mp 53–56 °C; ^{1}H NMR δ 0.81 (t, 3H, J = 6.9 Hz, $CH_2CH_2CH_3$), 1.13 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.19–1.38 (m, 4H, $CH_2CH_2CH_3$), 1.58 (m, 1H, $CH_2CH_2CH_2$), 2.05–2.18 (m, 1H, $CH_2CH_2CH_2$), 2.30 (t, 1H, J = 9.8 Hz, CH_2N), 2.46 (dd, 1H, J = 6.9, 9.0 Hz, CH_2N), 2.80 (m, 2H, $CHCHC{=}O$ and CH_2N), 3.18 (d, 1H, J = 9.2 Hz, CH_2N), 3.25 (t, 1H, J = 8.1 Hz, $O{=}CCH$), 3.41–3.60 (m, 2H, OCH_2CH_3 and CH_2Ph), 3.62–3.70 (m, 2H, OCH_2CH_3 and CH_2Ph), 7.21–7.29 (m, 5H, Ph); ^{13}C NMR δ 178.9 ($C{=}O$), 138.3 (ipso), 128.3, 128.2, 127.1 (Ph), 111.2 (OCO), 58.8 (OCH_2CH_3), 57.4 (CH_2Ph), 56.9 (CH_2N), 54.9 (CH_2N), 47.4 ($O{=}CCH$), 45.5 ($OCCH$), 30.8 ($CH_2CH_2CH_2$), 25.2 ($CH_2CH_2CH_3$), 22.4 ($CH_2CH_2CH_3$), 15.3 (OCH_2CH_3), 13.7 ($CH_2CH_2CH_3$); MS (EI) m/z 317 (M$^+$), 91 (100); HRMS calcd 317.1991, found 317.1991; $[\alpha]^{25}_D$ = +31.2° (c = 0.950 in ether).

(*S*)-α-Methylbenzylamine Azomethine Additions. A catalytic amount of TFA (5 mol %) was added to a 1 mL toluene solution of the butenolide **4a** (50 mg, 0.271 mmol) and the chiral azomethine precursor **14** (205 mg, 0.814 mmol), and the reaction was stirred at rt for 18 h. The reaction was poured into aqueous saturated $NaHCO_3$ solution and extracted with ether. The organics were dried over $MgSO_4$, the solvent was removed, and the products were purified by flash column chromatography (5% ether in CH_2Cl_2) to give 58 mg (65%) of the product (52% de). The major diastereomer **15a**: ^{1}H NMR δ 0.89 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.0 Hz), 1.25–1.30 (m, 4H), 1.32 (d, 3H, J = 6.5 Hz,), 1.62 (m, 1H), 1.99 (m, 1H), 2.22 (t, 1H, J = 3.0 Hz), 2.48 (m, 1H), 2.86 (m, 1H), 2.94 (dd, 1H, J = 2.6, 18.7 Hz), 3.11 (m, 1H), 3.21 (q, 1H, J = 6.5 Hz), 3.38 (dd, 1H, J = 3.2, 9.7 H), 3.60–3.71 (m, 1H), 3.76–3.86 (m, 1H), 7.18–7.27 (m, 5H); ^{13}C NMR δ 177.3, 145.0, 128.4, 128.2, 126.9, 110.0, 64.1, 59.2, 55.7 , 52.1, 46.5, 46.2, 37.1, 25.3, 22.9, 22.6, 15.3, 13.9; MS (EI) 331 (M$^+$), 316 (86), 105 (100), 91 (25); HRMS calcd 331.2147, found 331.2119; $[\alpha]^{25}_D$ = +62.1° (c = 1.11 in CH_2Cl_2). The minor diastereomer **15b**: ^{1}H NMR δ 0.71 (t, 3H, J = 7.1 Hz), 1.01–1.18 (m, 4H), 1.12 (t, 3H, J = 7.0 Hz), 1.32 (d, 3H, J = 6.6 Hz), 1.45 (m, 1H), 2.03 (m, 1H), 2.11 (dd, 1H, J = 8.4, 10.2 Hz), 2.35 (dd, 1H, J = 6.8, 8.8 Hz), 2.67 (m, 2H), 3.11 (dd, 1H, J = 10.3, 12.3 Hz), 3.24 (t, 1H, J = 7.5 Hz), 3.40–3.58 (m, 2H), 3.58–3.64 (m, 1H), 7.19–7.27 (m, 5H); ^{13}C NMR δ 179.3, 138.6, 128.7, 128.6, 127.4, 111.6, 59.2 , 57.7, 57.2, 55.3, 50.7, 47.8, 45.9, 31.2, 25.6 , 22.7, 15.7, 14.1; MS (EI) 331 (M$^+$), 316 (100), 105 (73), 91 (38); HRMS calcd 331.2147, found 331.2146; $[\alpha]^{25}_D$ = +14.1° (c = 0.085 in ether).

Addition of Lithium Thiolates to Butenolides. General Procedure. *n*-Butyllithium was slowly added to a −90 °C solution of benzyl mercaptan in THF. The solution was stirred at −90 °C for 0.5 h. A solution of the butenolide in THF was slowly added, and the solution was stirred for an additional 1.5 h at −90 °C. The reaction was warmed to −40 °C and stirred 3 h more. A saturated aqueous NH_4Cl solution was added, and the entire mixture was warmed to rt. The water layer was extracted with ether. The organics were combined and dried over Na_2SO_4. After removal of the solvent by rotary evaporation, the product was purified by flash column chromatography in the appropriate eluent.

Benzylthio Ethoxy Butyl Lactone 16a. *n*-Butyllithium (0.21 mL, 0.326 mmol) was added to the benzyl mercaptan (0.04 mL, 0.358 mmol) solution, and the reaction was stirred for the time indicated. The butenolide **4a** (60 mg, 0.326 mmol) in 2 mL of THF was added, and the procedure above was followed. The product was purified by flash column chromatography (1:5 ethyl acetate:hexanes) to give 75 mg of a clear oil (75%). ^{1}H NMR peaks were assigned on the basis of decoupling and NOE experiments: ^{1}H NMR δ 0.90 (t, 3H, J = 7.2 Hz, $CH_2CH_2CH_3$), 1.11 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.16–1.36 (m, 4H, $CH_2CH_2CH_3$), 1.87 (m, 1H, $CH_2CH_2CH_2$), 2.00 (m, 1H, $CH_2CH_2CH_2$), 2.50 (dd, 1H, J = 3.4, 17.5 Hz, $CH_2C{=}O$), 3.04 (dd, 1H, J = 7.3, 17.4 Hz, $CH_2C{=}O$), 3.24 (dd, 1H, J = 3.5, 7.3 Hz, CHS), 3.45–3.57 (m, 2H, OCH_2CH_3), 3.66 (d, 1H, J = 13.5 Hz, CH_2Ph), 3.78 (d, 1H, J = 13.5 Hz, CH_2Ph), 7.24–7.34 (m, 5H, Ph); ^{13}C NMR δ 174.4, 136.9, 128.8, 128.7, 127.5, 112.2, 58.3, 46.6, 37.3, 35.6, 31.4, 24.6, 22.5, 15.3, 13.9. Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84; S, 10.40. Found: C, 66.37; H, 7.72; S, 10.56. $[\alpha]^{25}_D$ = +127.9° (c = 0.870 in CH_2Cl_2).

Benzylthio Methoxy Butyl Lactone 16b. *n*-Butyllithium (1.3 M solution in hexanes, 0.35 mmol) was slowly added to the benzyl mercaptan solution (0.05 mL, 0.39 mmol). After the time mentioned above, a solution of the butenolide **4b** (60 mg, 0.35 mmol) in 5 mL of THF was added. The isolation procedure above was followed. The product was purified by flash column chromatography (1:5 ethyl acetate:hexanes) to give a clear oil (82 mg, 79%): ^{1}H NMR δ 0.87–0.93 (m, 3H), 1.24–1.36 (m, 4H), 1.87 (m, 1H), 2.00 (m, 1H), 2.51 (dd, 1H, J = 3.4, 17.5 Hz,), 3.03 (dd, 1H, J = 7.4, 17.5 Hz), 3.22 (dd, 1H, J = 3.5, 7.4 Hz), 3.24 (s, 3H), 3.67 (d, 1H, J = 13.5 Hz), 3.78

(d, 1H, J = 13.5 Hz), 7.24–7.32 (m, 5H); ^{13}C NMR δ 174.8, 137.2, 129.2, 129.1, 127.9, 112.6, 50.5, 46.6, 37.7, 36.0, 31.1, 24.8, 22.8, 14.2; IR (thin film) 1792 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53; S, 10.89. Found: C, 65.50; H, 7.54; S, 10.61. $[\alpha]^{25}_D$ = +105.3° (c = 0.300 in ether).

Phenylthio Ethoxy Butyl Lactone 17. Triethylamine (4 μL, 0.027 mmol) was added to a 0 °C CH_2Cl_2 solution of the butenolide **4a** (100 mg, 0.543 mmol) and thiophenol (56 μL, 0.543 mmol). After 15 min, the reaction was allowed to warm to rt over a 1.5 h period, the solvent was removed, and the product was purified by flash column chromatography (1:10 ethyl acetate:hexanes) giving 152 mg (95%) of the product as an oil: ^{1}H NMR δ 0.91 (t, 3H, J = 7.2 Hz), 1.14 (t, 3H, J = 7.0 Hz), 1.29–1.53 (m, 4H), 1.95 (m, 1H), 2.12 (m, 1H), 2.48 (dd, 1H, J = 1.9, 17.7 Hz), 3.13 (dd, 1H, J = 6.9, 17.7 Hz), 3.52–3.66 (m, 2H), 3.85 (dd, 1H, J = 1.9, 6.9 Hz), 7.24–7.34 (m, 5H); ^{13}C NMR δ 174.5, 132.6, 132.3, 129.3, 127.9, 111.6, 58.2, 50.4, 37.2, 30.9, 24.9 , 22.5, 15.2, 13.9; MS (FAB) 295 (M + 1), 249 (71); HRMS calcd 295.1368, found 295.1359; $[\alpha]^{25}_D$ = +8.6° (c = 0.348 in ether).

Epoxide 18. A 10% aqueous solution of NaOCl (0.271 mmol) was added at 0 °C to the butenolide **4a** (40 mg, 0.217 mmol) in 3 mL of ether and 3 mL of DMF. The reaction was stirred for 1 h. An aqueous saturated $Na_2S_2O_3$ solution was then added to the reaction, and the reaction was extracted several times with ether. The organics were dried over $MgSO_4$, the solvent was removed, and purification was accomplished by using radial chromatography (30:1 hexanes:ethyl acetate). Only 10 mg of the product (23%) was recovered: ^{1}H NMR δ 0.93 (t, 3H, J = 7.2 Hz), 1.19 (t, 3H, J = 7.0 Hz), 1.36–1.47 (m, 4H), 1.81 (m, 1H), 1.98 (m, 1H), 3.56–3.72 (m, 2H), 3.77 (d, 1H, J = 2.4 Hz), 3.94 (d, 1H, J = 2.4 Hz); ^{13}C NMR δ 169.6, 108.1, 58.7, 57.3, 50.0, 30.9 , 25.4, 22.6, 15.1, 13.9; $[\alpha]^{25}_D$ = +146.7° (c = 0.045 in CH_2Cl_2).

Ethoxy Butyl Diols 19a and 19b. Method A. $KMnO_4$ (89 mg, 0.565 mmol) was added to a −40 °C solution of the butenolide **4a** (80 mg, 0.434 mmol) and dicyclohexyl-18-crown-6-ether (16 mg, 0.043 mmol) in 10 mL of CH_2Cl_2. The reaction was stirred at −40 °C for 4 h and then warmed to 0 °C and stirred another 3 h. Solid $NaHSO_3$ and water were added to the reaction. A solution of 1 M H_2SO_4 was added until the purple color disappeared. The layers were separated, and the water layer was extracted several times with CH_2Cl_2. The organics were dried over Na_2SO_4, the solvent was removed, and the product was purified by flash column chromatography (1:1 ethyl acetate:hexanes) to give 65 mg of a white solid (66%, 86% versus recovered butenolide).

Method B. $RuCl_3{\cdot}H_2O$ (10 mg, 0.038 mmol) and $NaIO_4$ (174 mg, 0.814 mmol) in 1.5 mL of water were added to a 0 °C solution of the butenolide **4a** (100 mg, 0.543 mmol) in 4 mL of ethyl acetate and 4 mL of CH_3CN. The reaction was stirred vigorously for 3 min and was poured into an aqueous saturated $Na_2S_2O_3$ solution. The organics were extracted with ethyl acetate and combined. The organic solution was dried over Na_2SO_4, and the solvents were removed. Flash column chromatography using 1:4 ethyl acetate:hexanes gave 89 mg (75%) of two diols and 83 mg (70%) of the major diol diastereomer. The ^{1}H NMR peaks assignments for the two diastereomers were determined by decoupling and NOE experiments. The major diastereomer **19a**: mp 112–113 °C; ^{1}H NMR δ 0.92 (t, 3H, J = 6.8 Hz, $CH_2CH_2CH_3$), 1.14 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.23–1.55 (m, 4H, $CH_2CH_2CH_3$), 1.97 (m, 2H, $CH_2CH_2CH_2$), 2.82 (bs, 1H, OH), 3.19 (bs, 1H, OH), 3.61 (m, 2H, OCH_2CH_3), 4.15 (d, 1H, J = 4.5 Hz, CH(OH)CH), 4.71 (d, 1H, J = 4.2 Hz, CH(OH)C=O); ^{13}C NMR δ 176.7, 111.6, 71.9, 70.1, 58.2, 28.5, 24.6, 22.6, 15.2, 13.9. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 55.09; H, 8.17. $[\alpha]^{25}_D$ = +38.0° (c = 0.590 in ether). The minor diasteromer **19b**: ^{1}H NMR δ 0.91 (t, 3H, J = 6.9 Hz, $CH_2CH_2CH_3$), 1.25 (t, 3H, J = 7.0 Hz, OCH_2CH_3), 1.32–1.40 (m, 4H, $CH_2CH_2CH_3$), 1.60 (m, 1H, $CH_2CH_2CH_2$), 2.09 (m, 1H, $CH_2CH_2CH_2$), 3.10 (bs, 1H, OH), 3.27 (bs, 1H, OH), 3.69–3.87 (m, 2H, OCH_2CH_3), 4.20 (d, 1H, J = 4.7 Hz, CHCHC=O), 4.37 (m, 1H, CHC=O); IR (thin film) 3424, 1785 cm^{-1}.

Methoxy Phenyl Diol 20. $KMnO_4$ (96 mg, 0.607 mmol) was added to a −40 °C solution of the butenolide **4d** (72 mg, 0.379 mmol) and dicyclohexyl-18-crown-6-ether (17 mg, 0.0467 mmol) in 10 mL of CH_2Cl_2. The reaction was stirred at −40 °C for 3.5 h. It was then warmed to 0 °C and stirred for another 2 h. Solid $NaHSO_3$ and water were added to the reaction. A solution of 1 M H_2SO_4 was added until the purple color disappeared. The water layer was extracted several times with CH_2Cl_2, and the organics were dried over $NaSO_4$. The solvent was removed, and the product was purified by flash column chromatography (1:2 ethyl acetate:hexanes). This gave 35 mg of a white solid (41%). The ^{1}H NMR peaks were determined by NOE experiments: mp 130–131 °C; ^{1}H NMR (acetone-d_6) δ 2.80 (bs, 1H, OH), 2.82 (bs, 1H, OH), 3.13 (s, 3H, OCH_3), 4.38 (d, 1H, J = 4.1 Hz, CHCHC=O), 4.82 (d, 1H, J = 4.1 Hz, CHC=O), 7.40–7.47 (m, 5H, Ph); ^{13}C NMR (acetone-d_6) δ 175.1, 134.7, 129.0, 128.3, 127.4, 109.0, 75.0, 70.2, 50.5; MS (FAB) 225 (M + 1), 193 (49); HRMS calcd 225.0763, found 225.0759; $[\alpha]^{25}_D$ = +6.2° (c = 0.130 in CH_3OH).

Tosylate 21a. The diol **19a** (38 mg, 0.174 mmol) and triethylamine (0.040 mL, 0.261 mmol) were combined in 1.5 mL of CH_2Cl_2 and cooled to 0 °C. The tosyl chloride (33 mg, 0.174 mmol) was added to the reaction in one portion, and the reaction was placed in the freezer for 18 h. The solution was diluted with more CH_2Cl_2, and the organics were washed with 1 N HCl aqueous solution, a saturated aqueous solution of $NaHCO_3$, and brine. The organics were dried over Na_2SO_4, and the solvent was removed. The crude product was purified by flash column chromatography using 1:3 ethyl acetate:hexanes as the eluent to give an oil (60 mg, 93%): ^{1}H NMR δ 0.92 (t, 3H, J = 7.2 Hz), 1.14 (t, 3H, J = 7.0 Hz), 1.24–1.47 (m, 4H), 1.98 (m, 2H), 2.45 (s, 3H), 2.65 (bs, 1H), 3.59 (q, 2H, J = 7.1 Hz,), 4.38 (d, 1H, J = 4.3 Hz), 5.32 (d, 1H, J = 4.3 Hz), 7.37 (d, 2H, J = 8.1 Hz), 7.86 (d, 2H, J = 6.6 Hz); ^{13}C NMR δ 169.1, 146.0, 131.9, 130.1, 128.3, 111.3, 75.5, 71.7, 58.4, 28.2, 24.5, 22.5, 21.7, 15.2, 13.8. Anal. Calcd for $C_{17}H_{24}O_7S$: C, 54.82; H, 6.50; S, 8.61. Found: C, 54.60; H, 6.42; S, 8.36. $[\alpha]^{25}_D$ = −22.1° (c = 2.75 in ether).

***p*-Nitrobenzenesulfonate 21b.** The diol **19a** (40 mg, 0.183 mmol) and triethylamine (28 mg, 0.275 mmol) were combined in 2 mL of CH_2Cl_2, and the solution was cooled to 0 °C. The *p*-nitrobenzenesulfonyl chloride (45 mg, 0.202 mmol) was added in one portion, and the reaction was placed in the freezer for 24 h. The reaction was then removed from the freezer, and the solvent was removed. The thick residue was dissolved in ethyl acetate and washed with a 1 N HCl aqueous solution and a saturated aqueous $NaHCO_3$ solution. The organics were dried over Na_2SO_4. The solvent was removed, and the crude material was purified by flash column chromatography using 1:3 ethyl acetate:hexanes as the eluent to give the product as a white solid (58 mg, 79%): mp 101–103 °C; ^{1}H NMR δ 0.92 (t, 3H, J = 6.8 Hz), 1.16 (t, 3H, J = 7.0 Hz), 1.29–1.48 (m, 4H), 1.98 (m, 2H), 2.75(bs, 1H), 3.60 (q, 2H, J = 7.1 Hz), 4.41 (d, 1H, J = 4.3 Hz), 5.48 (d, 1H, J = 4.3 Hz), 8.22 (d, 2H, J = 8.7 Hz), 8.42 (d, 2H, J = 8.7 Hz); ^{13}C NMR δ 169.0, 152.0, 141.1, 129.7, 124.5, 111.7, 76.6, 71.8, 58.6, 28.2 , 24.4, 22.5, 15.2, 13.8; $[\alpha]^{25}_D$ = +12.2° (c = 0.418 in CH_2Cl_2).

Acetonide 22. A few crystals of TsOH were added to a solution of the diol **19a** (81 mg, 0.371 mmol) and dimethoxypropane (1.15 mL, 9.28 mmol) in CH_2Cl_2. After 1.5 h at rt, the reaction was heated to reflux for 1.5 h. The reaction was cooled and diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4. The solvent was removed, and the product was purified by flash column chromatography using 1:20 and 1:2 ethyl acetate:hexanes as the eluent. The product was isolated as a clear oil (64 mg, 67% or 83% based on recovered diol): ^{1}H NMR δ 0.91 (t, 3H, J = 7.1 Hz), 1.12 (t, 3H, J = 7.0 Hz), 1.22–1.46 (m, 4H), 1.35 (s, 3H), 1.41 (s, 3H), 1.88 (m, 1H), 2.02 (m, 1H), 3.54–3.66 (m, 2H), 4.42 (d, 1H, J = 5.1 Hz), 4.83 (d, 1H, J = 5.1 Hz); ^{13}C δ 174.2, 114.3, 109.6, 79.6, 76.2, 58.0, 29.0, 26.9, 26.1, 24.9, 22.6, 15.2, 13.9. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.68; H, 8.64. $[\alpha]^{25}_D$ = +1.2° (c = 0.844 in ether).

Ethoxy Butyl Alcohol 23. Samarium(II) iodide in THF (7.08 mL, 0.708 mmol) was slowly added to a degassed solution of the acetonide **22** (61 mg, 0.236 mmol) and dry ethylene

glycol (0.16 mL, 2.83 mmol) in THF. The reaction was stirred at rt for 1 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, and ether was added. The organics were separated from the aqueous layer. The organic layer was then washed with a saturated aqueous solution of $Na_2S_2O_3$ and brine and dried over Na_2SO_4. The solvent was removed. The product was purified by flash column chromatography using 1:15 and 1:1 ethyl acetate:hexanes as the eluent to give the product as a clear oil (36 mg, 75% or 92% on the basis of recovered acetonide): ^{1}H NMR δ 0.91 (t, 3H, J = 7.0 Hz), 1.12 (t, 3H, J = 7.0 Hz), 1.29–1.39 (m, 4H), 1.97 (m, 2H), 2.36 (d, 1H, J = 17.7 Hz), 2.99 (dd, 1H, J = 5.3, 17.7 Hz), 3.51–3.65 (m, 2H), 4.19 (d, 1H, J = 5.3 Hz); ^{13}C NMR δ 176.1, 113.4, 71.7, 57.9, 38.3, 28.0, 24.9, 22.7, 15.3, 13.9. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 59.46; H, 8.77. $[\alpha]^{25}_D$ = +13.1° (c = 0.236 in ether).

Ethoxy Butyl Tetrahydrofuran 24. The acetonide **22** (44 mg, 0.170 mmol) and $Cp_2Ti(CH_3)_2$ (167 mg, 0.802 mmol) were combined in a pressure tube in 3 mL of THF. The tube was sealed and heated to 70 °C with stirring for 18 h. The reaction was cooled to rt. Acetone (0.12 mL, 1.6 mmol) was added, and the tube was sealed again. The reaction was heated to 50 °C for another 18 h. The reaction was transferred to a round-bottom flask, and the solvent was removed by rotary evaporation at 5 °C. The residue was treated with a 5:1 mixture of pentane:ether to precipitate the titanium salts. This mixture was filtered through basic Al_2O_3 and washed with pentanes. The solvent was removed in the fashion described above. A crude ^{1}H NMR spectrum showed a little impurity in the sample: ^{1}H NMR δ 0.91 (t, 3H, J = 6.9 Hz), 1.10 (t, 3H, J = 7.1 Hz), 1.22–1.42 (m, 4H), 1.33 (s, 3H), 1.44 (s, 3H), 1.79–1.92 (m, 2H), 3.42–3.56 (m, 2H), 4.30 (dd, 1H, J = 0.8, 1.9 Hz), 4.33 (d, 1H, J = 5.7 Hz), 4.48 (d, 1H, J = 1.3 Hz), 5.05 (d, 1H, J = 5.7 Hz); ^{13}C NMR δ 161.4 , 113.0, 111.2, 87.7, 82.3, 79.7, 56.5, 29.2, 26.8 , 26.0, 25.7, 22.8 , 15.3, 13.9.

Palladium on carbon (18 mg, 0.017 mmol) was placed in a pressure tube in dry ethyl acetate. The tube was purged with H_2 and pressured to 40 psi of H_2. The suspension was stirred vigorously at rt for 1 h. The H_2 was released from the tube, and the enol ether (0.170 mmol) produced from the reaction described above was added as a solution in ethyl acetate. The tube was sealed and pressured to 40 psi of H_2. The reaction stirred vigorously for 18 h. The H_2 pressure was released, and the reaction was filtered through Celite. The solvent was removed by rotary evaporation at 5 °C. The product was purified by flash chromatography using 20:1 pentanes:ether as the eluent. The two steps gave the tetrahydrofuran **24** as an oil (30 mg, 68%): ^{1}H NMR δ 0.86 (t, 3H, J = 7.1 Hz), 1.12 (t, 3H, J = 7.1 Hz), 1.19–1.39 (m, 4H), 1.25 (d, 1H, J = 6.4 Hz), 1.27 (s, 3H), 1.44 (s, 3H), 1.66–1.80 (m, 2H), 3.35–3.48 (m, 2H), 3.94 (dq, 1H, J = 3.9, 6.4 Hz), 4.36 (d, 1H, J = 6.0 Hz), 4.59 (dd, 1H, J = 3.9, 6.0 Hz); ^{13}C NMR δ 112.0, 109.2, 85.1, 81.6, 74.3, 55.2, 29.3, 26.2, 25.8, 25.1, 22.9, 22.3, 15.4, 13.9. Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 64.84; H, 9.86. $[\alpha]^{25}_D$ = +5.1° (c = 0.286 in ether).

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