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Diastereoselective Organocatalytic Addition of α-Angelica Lactone to β-Halo-α-ketoesters

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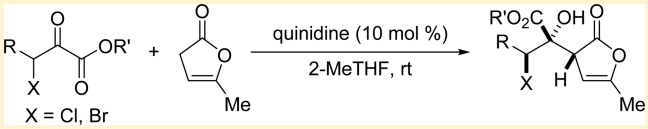
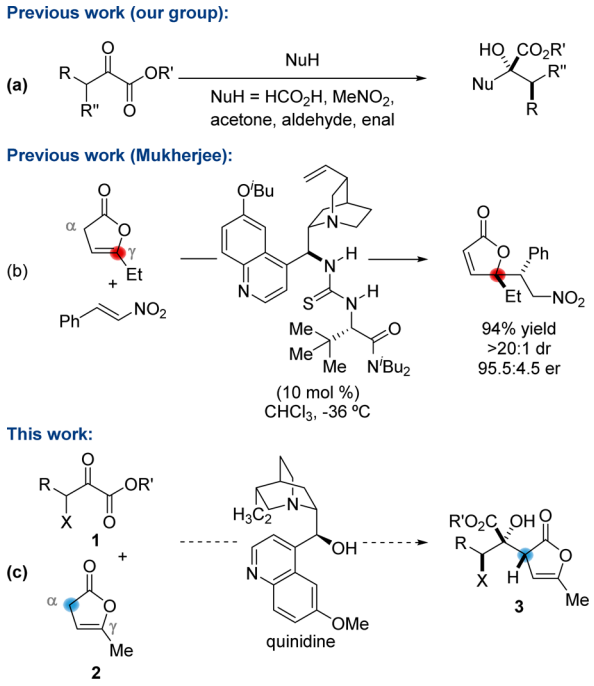
Supporting Information

ABSTRACT: A quinidine-catalyzed diastereoselective addition of α-angelica lactone to β-halo-α-ketoesters is reported. The α-angelica lactone displays unusual regioselectivity in this reaction, acting as a nucleophile at the α-position to provide fully substituted glycolic esters with three contiguous stereocenters. Subsequent diastereoselective hydrogenation provides an additional stereocenter within the lactone.



The construction of contiguous stereogenic polyads is an ongoing challenge in organic synthesis. In this context, β-stereogenic α-ketoesters (**1**) are molecules of interest due to their appreciable electrophilicity and their available functional handles for downstream transformations.[1] Previously, our group developed a number of methods for their synthesis[2] as well as their application in complexity-building transformations encompassing a variety of reaction manifolds (i.e., transfer hydrogenation, Henry reaction, acetone aldol, benzoin addition, and homoenolate addition; Scheme 1a).[3b−i] While these methods have provided access to a wide array of fully substituted glycolic acid scaffolds, there are few examples of the addition of prochiral nucleophiles.[3a,f,g] The application of α-angelica lactone (**2**) as a nucleophile presents an interesting opportunity to build more stereochemically complex products.

Scheme 1. Proposed Addition of α-Angelica Lactone to Stereogenic α-Ketoester



Unlike previously deployed pro-nucleophiles, lactone **2** poses additional challenges with respect to (1) reactivity due to the imposition of increased steric bulk, (2) regioselectivity (α- vs γ-nucleophilicity of the dienolate), and (3) stereoselectivity (eight stereoisomers are possible within the α-addition mode). This class of nucleophile has been studied in the stereoselective addition to nitrostyrenes and other prochiral electrophiles using cinchona alkaloid-derived thiourea organocatalysts (Scheme 1b).[4a] Other additions to nitrostyrenes,[4] aldimines,[5] enones,[6] enals,[7] and vinyl sulfones[8] have also been studied. In all of these cases, the α-angelica lactone exhibited electrophilic trapping at the γ-carbon. A rare example from Boukouvalas achieved α-trapping with α-angelica lactones via in situ generation of tin or boron dienolates for addition into aldehydes.[9] Herein, we describe initial studies toward the creation of complex stereotriads in the form of a quinidine-catalyzed diastereoselective aldol addition of **2** to **1** (Scheme 1c).

On the basis of the high levels of Felkin-Ahn diastereoselectivity observed α-keto ester with **1** previously,[3c,e−g] we selected this substrate class for our investigation. The results of aldol reactions using a panel of commercial and readily accessible Brønsted bases and conditions indicated that quinidine was an optimal catalyst for the diastereoselective addition. Quinidine provides a racemic product and, to date, the maximum enantioselectivity observed for the title reaction with any catalyst is 58:42 er (see the Supporting Information for full optimization and additional commentary).

Intriguingly, in all cases we studied, capture of the electrophile at the α-position of the lactone was the dominant mode of reactivity. We speculate that this divergence may arise from the more demanding steric environment imposed by the α-ketoester, as compared with those used in previous reports.[4−8] Additionally, for the most part, substitution at the

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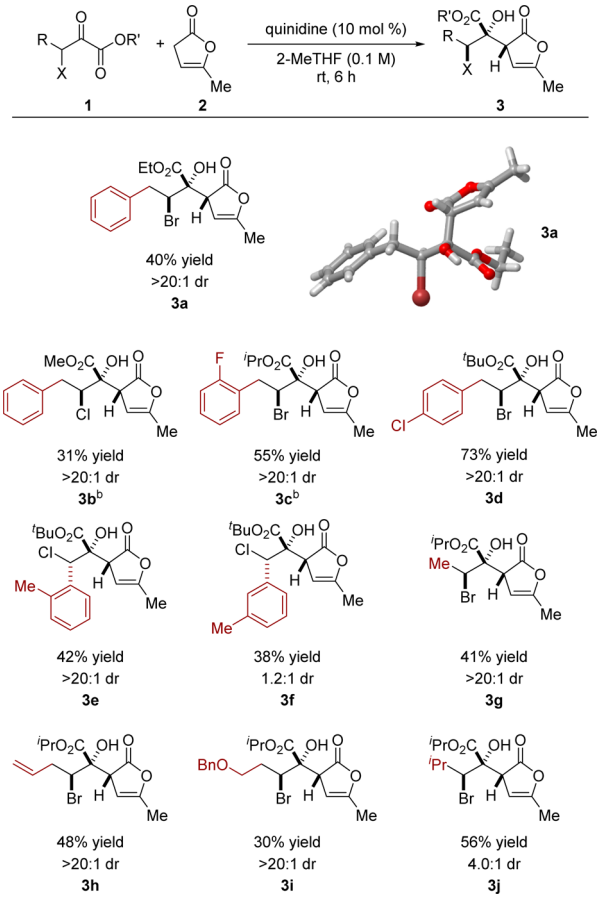
β-position of the α-ketoesters does not affect the intrinsically high diastereoselectivity of the reaction. Using β-halo-β-benzyl α-ketoesters, catalyzed addition of α-angelica lactone provided the aldol products **3a**−**3c** in modest yields in >20:1 dr (Scheme 2). By comparing β-bromo-substituted **3a** with β-chloro-

Scheme 2. Scope of the Reaction[a]

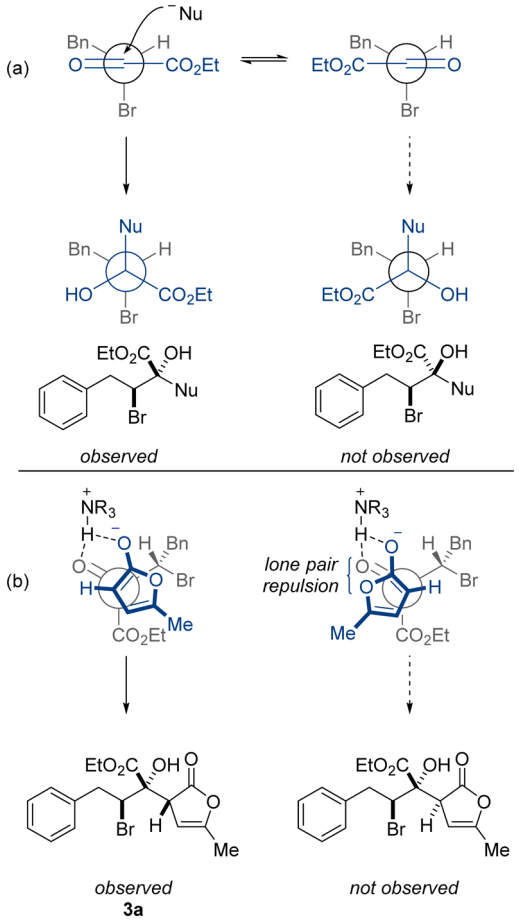


[a]Reaction was conducted on a 0.1 mmol scale using 2.0 equiv of α-angelica lactone. [b]Yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

substituted **3b**, we found that the identity of the halogen has no impact on diastereoselectivity. Benzyl-substituted substrates **3d** and **3e** gave >20:1 dr; however, while *para*-chlorophenyl-substituted **3d** gave an elevated 73% yield, *ortho*-fluoro-substituted **3c** gave 55% yield. Changing the *ortho*-tolyl group (**3e**) to a *meta*-tolyl group (**3f**) resulted in a dramatic loss of diastereoselectivity; the reason for this decrease in stereoselectivity is unclear. Aliphatic products **3g** and **3h** were formed diastereoselectively in 41 and 48% yield, respectively. While the branched product **3j** was formed in higher yield than other aliphatic substrates, a significantly lower diastereoselectivity was observed (4.0:1 dr). We found that the reaction to give **3i** was also diastereoselective, though low-yielding.

The relative stereochemistry afforded by the reaction was determined by an X-ray diffraction study performed on the lactone product **3a** (Scheme 2).[10] To rationalize the observed stereochemical outcome of the reaction, the Felkin-Anh (or Cornforth) model[11] for the approach of the nucleophile to the β-halo-α-ketoester can be used, whereby the nucleophile approaches *anti* to the large β-halo substituent (Scheme 3a).

Scheme 3. Stereochemical Model for Addition of Angelica Lactone to β-Halo-α-ketoesters



In this model, the angelica lactone attacks at the Bürgi-Dunitz angle over the smallest β-substituent while the carbonyl is orthogonal to the β-halo group, thereby controlling the relationship between secondary halogen-bearing stereocenter and the tertiary alcohol. Governance of the lactone stereocenter could arise from the trajectory of the α-angelica lactone that minimizes repulsion between the lone pairs on the furanyl oxygen and the carbonyl oxygen (Scheme 3b). We propose that hydrogen bonding with the catalyst facilitates this step, and the bifunctional nature of the catalyst may help explain its superior performance over Et_3N, although stereochemical transmission from the chiral catalyst is poor at our current level of optimization.[12]

Having developed conditions for the diastereoselective generation of **3**, we sought to extend our stereochemical arrays using downstream reduction of the dihydrofuranone. In the event, the resultant stereocenter was provided in >20:1 dr through catalytic hydrogenation (Scheme 4). A *syn* relationship between the lactone methine protons was determined through NOESY analysis, which is consistent with hydrogenation from the less hindered face of the lactone.

Drawing inspiration from prior work on α-angelica lactones and α-ketoesters, this work presents new opportunities for accessing glycolic acid scaffolds. This reaction proceeded diastereoselectively for a variety of α-ketoester derivatives. This method represents a convenient way to diastereoselectively produce three contiguous stereocenters using a commercial organocatalyst. Additionally, this method repre-

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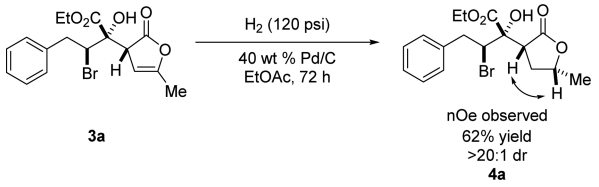
Scheme 4. Hydrogenation of Addition Product



sents a rare case where α-angelica lactone behaves as a regioselective α-nucleophile. Future directions for this work include investigations into the regioselectivty phenomenon and an expanded study of more complex α-angelica lactone nucleophiles.[13] Applications of this methodology and development of an asymmetric variant are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Comments. Nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR) were recorded at the following frequencies: ^{1}H NMR at 400 or 600 MHz, ^{13}C NMR at 101 or 151 MHz, ^{19}F NMR at 376 MHz, and ^{31}P NMR at 162 or 243 MHz with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm and ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br-s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a Finnigan linear trap quadrupole Fourier transform (LTQ-FT) spectrometer. TLC visualization was accomplished with UV light, phosphomolybdic acid in ethanol, or aqueous ceric ammonium molybdate solution. Yields refer to isolated yields after flash column chromatography; some samples contain residual minor diastereomers. Because all results are the averages of two trials, the stereoisomer ratios listed in the paper may not exactly match those represented in the NMR data below. 2-MeTHF and α-angelica lactone were purchased and used as received. β-Halo-α-ketoesters were prepared according to literature procedures.[3c,e−g] Commercially available quinidine was used as received. Because dr and % yield values reported in the paper reflect an average of two trials, they may not exactly match the isolated yields reported below.

General Procedure for Addition of α-Angelica Lactone to β-Halo-α-ketoester. A 1 dram vial was charged sequentially with β-halo-α-ketoester (0.1 mmol, 1.0 equiv), followed by 2-MeTHF (1.0 mL) and finally the α-angelica lactone (0.2 mmol, 2.0 equiv). The reaction was stirred at room temperature for one min. Quinidine (0.01 mmol, 10 mol %) was added in one portion. The reaction was stirred at room temperature for 6 h and then concentrated in vacuo. The crude materials thus obtained were purified using flash column chromatography with a gradient from 95:5 hexanes:EtOAc to 80:20 hexanes:EtOAc.

*(±)-Ethyl 3-Bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-4-phenylbutanoate (**3a**).* The title compound was prepared according to the general procedure; 18.1 mg (47%) was isolated. No minor diastereomer was observed. Light yellow solid, mp 114−116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H) 5.29 (s, 1H), 5.05 (dd, *J* = 11.4, 2.4 Hz, 1H), 4.35−4.30 (m, 1H), 4.26−4.21 (m, 1H), 3.98 (s, 1H), 3.91 (br, 1H), 3.61 (dd, *J* = 14.4, 2.4 Hz, 1H), 3.03 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.03 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.0, 171.2, 154.4, 137.9, 129.6, 128.4, 126.9, 100.7, 80.5, 63.4, 58.5, 50.3, 38.2, 14.1, 13.9; IR (thin film) ν 3433, 2359, 1794, 1747, 1647, 1541, 1456, 1237, 1122, 944, 777 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}BrNaO_5^+$ (M + Na$^+$): 405.0308, found 405.0296; TLC (1:5 EtOAc:hexanes) R_f = 0.51.

*(±)-Methyl 3-Chloro-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-4-phenylbutanoate (**3b**).* The title compound was prepared according to the general procedure; some impurities remained after repeated silica gel column chromatography. NMR yields were calculated using 1,3,5-trimethoxybenzene as an internal standard and using the signal of the desired product at δ 5.27 in the crude ^{1}H NMR spectrum. The product was obtained in 49% ^{1}H NMR yield. No minor diastereomer was observed. White solid, mp 70−72 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 5.27 (s, 1H), 4.88 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.92 (s, 1H), 3.90 (t, *J* = 2.4 Hz, 1H), 3.83 (s, 3H), 3.50 (dd, *J* = 13.8, 2.4 Hz), 3.89 (dd, *J* = 13.8, 2.4 Hz), 2.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.1, 171.7, 154.7, 137.2, 129.7, 128.4, 127.0, 100.2, 80.9, 64.5, 53.6, 50.5, 37.7, 14.0; IR (thin film) ν 3461, 1752, 1636, 1455, 1254, 1140, 1084, 703, 641, 523 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}ClNaO_5^+$ (M + Na$^+$): 347.0675, found 347.0648; TLC (1:5 EtOAc:hexanes) R_f = 0.10.

*(±)-Isopropyl 3-Bromo-4-(2-fluorophenyl)-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)butanoate (**3c**).* The title compound was prepared according to the general procedure; some impurities remained after repeated silica gel column chromatography. NMR yields were calculated using 1,3,5-trimethoxybenzene as an internal standard and using the signal of the desired product at δ 5.29 in the crude ^{1}H NMR spectrum. The product was obtained in 57% ^{1}H NMR yield. No minor diastereomer was observed. White solid, mp 92−94 °C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (t, *J* = 7.8 Hz, 1H), 7.30−7.26 (m, 1H), 7.17−1.15 (m, 1H), 7.09−7.06 (m, 1H), 5.29 (s, 1H), 5.12−5.08 (m, 2H), 4.00 (s, 1H), 3.88 (s, 1H), 3.46 (d, *J* = 14.4 Hz, 1H), 3.34 (dd, *J* = 14.4, 11.4 Hz, 1H), 2.02 (s, 3H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.9, 170.6, 162.1, 154.3, 131.5 (d, *J* = 4.1 Hz), 128.7 (d, *J* = 8.0 Hz), 125.0 (d, *J* = 15.3 Hz), 124.1 (d, *J* = 3.8 Hz), 115.4 (d, *J* = 22.2 Hz), 100.7, 79.9, 72.1, 56.5, 50.3, 31.0 (d, *J* = 2.1 Hz), 21.4, 21.3,14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.1; IR (thin film) ν 3853, 3750, 3649, 3437, 2349, 1653, 1558, 1507, 1457, 716, 578 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}BrFNaO_5^+$ (M + Na$^+$): 437.0370, found 437.0356; TLC (1:5 EtOAc:hexanes) R_f = 0.57.

*(±)-Isopropyl 3-Bromo-4-(4-chlorophenyl)-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)butanoate (**3d**).* The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography, and 30.0 mg (70%) was isolated. No minor diastereomer was observed. Yellow solid, 117−120 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 5.28 (s, 1H), 5.09 (m, 1H), 4.97 (s, 1H), 5.00 (dd, *J* = 11.4, 2.4 Hz, 1H), 3.98 (s, 1H), 3.86 (t, *J* = 2.4 Hz, 1H), 3.55 (dd, *J* = 14.4, 1.8 Hz), 3.02 (dd, *J* = 14.4, 2.4 Hz, 1H), 2.03 (s, 3H), 1.27 (dd, 12.6, 6.6 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.1, 170.6, 154.4, 136.4, 132.8, 131.1, 128.5, 100.7, 80.0, 72.1, 58.2, 50.2, 37.6, 21.4 (d, *J* = 8.9 Hz), 14.1; IR (thin film) ν 3421, 2359, 1794, 1741, 1635, 1495, 1102, 944, 813, 536 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}BrClNaO_5^+$ (M + Na$^+$): 453.0075, found 453.0068; TLC (1:5 EtOAc:hexanes) R_f = 0.30.

*(±)-tert-Butyl 3-Chloro-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-3-(o-tolyl)propanoate (**3e**).* The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography, and 15.8 mg (43%) was isolated. No minor diastereomer was observed. White solid, mp 143−144 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (br, 1H), 7.21−7.20 (m, 2H), 7.14 (m, 1H), 6.40 (s, 1H), 5.30 (s, 1H), 4.14 (s, 1H), 4.12 (t, *J* = 3.6 Hz, 1H), 2.49 (s, 3H), 2.02 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 169.5, 153.8, 136.1, 135.5, 103.2, 129.0, 128.9, 126.7, 100.4, 85.7, 80.3, 55.7, 51.3, 27.2, 19.6, 14.1; IR (thin film) ν 3853, 3839, 3734, 3649, 3446, 2390, 1653, 1558, 1540, 1507, 578, 508 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}ClNaO_5^+$ (M + Na$^+$): 389.1126, found 389.1114; TLC (1:5 EtOAc:hexanes) R_f = 0.57.

*(±)-tert-Butyl 3-Chloro-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-3-(m-tolyl)propanoate (**3f**).* The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography, and 16.0 mg (44%) was isolated. The diastereoselectivity was determined by comparing the signals at δ 5.86 (major) and δ 5.81 (minor). Trace amounts of both diastereomers of the γ-addition product were also observed in the crude ^{1}H NMR spectrum and were identified after separation by column chromatography. White solid, mp 133−135 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.8 Hz, 1H), 7.29 (s, 1H),

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7.22 (t, J = 7.8 Hz, 1H), 7.14 (d, J = J = 7.8 Hz, 1H), 5.87 (s, 1H), 5.28 (s, 1H), 4.16 (t, J = 2.4 Hz, 1H), 3.82 (s, 1H), 2.35 (s, 3H), 2.02 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.2, 169.4, 153.6, 137.7, 135.9, 129.9, 129.7, 128.1, 126.2, 100.5, 85.8, 80.2, 62.1, 50.9, 27.5, 21.4, 14.1; IR (thin film) ν 3853, 3837, 3801, 3734, 3627, 2360, 2341, 1683, 1539, 1244, 791, 668 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}ClNaO_5^+$ (M + Na^+): 389.1126, found 389.1114; TLC (1:5 EtOAc:hexanes) R_f = 0.62.

*(±)-Isopropyl 3-Bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)butanoate (**3g**).* The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography, and 14.0 mg (44%) was isolated. No minor diastereomer was observed. White solid, mp 84−85 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.25 (s, 1H), 5.10 (m, 1H), 4.98 (q, 1H), 3.81 (s, 1H), 3.64 (t, 1H), 2.00 (s, 3H), 1.87 (d, J = 6.6 Hz, 1H), 1.28 (dd, J = 33.6, 6.0 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.9, 170.9, 154.1, 100.7, 79.9, 71.8, 50.7, 50.1, 21.5, 21.3,19.7, 14.0; IR (thin film) ν 3446, 2393, 1740, 1653, 1287, 1102, 782, 579, 519, 503 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}BrNaO_5^+$ (M + Na^+): 343.0152, found 343.0146; TLC (1:5 EtOAc:hexanes) R_f = 0.39.

*(±)-Isopropyl 3-Bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)hex-5-enoate (**3h**).* The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography; 18.0 mg (54%) was isolated. No minor diastereomer was observed. Clear oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.60−5.93 (m, 1H), 5.27−5.21 (m, 3H), 5.10 (quintet, J = 6.0 Hz, 1H), 4.83 (dd, J = 10.8, 3.0 Hz, 1H), 3.89 (s, 1H), 3.79 (br, 1H), 2.95−2.91 (m, 1H), 2.69−2.64 (m, 1H), 2.00 (s, 3H), 1.31 (d, J = 6.6 Hz, 3H), 1.26 (d, J = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.9, 170.6, 154.2, 134.6, 118.3, 100.6, 79.9, 72.0, 56.3, 50.2, 36.5, 21.5, 21.3, 14.1; IR (thin film) ν 3448, 1797, 1739, 1646, 1249, 1182, 1102, 945, 607, 505 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}BrNaO_5^+$ (M + Na^+): 369.0308, found 369.0297; TLC (1:5 EtOAc:hexanes) R_f = 0.35.

*(±)-Isopropyl 5-(Benzyloxy)-3-bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)pentanoate (**3i**).* The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography, and 13.3 mg (30%) was isolated. No minor diastereomer was observed. Clear oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41−7.28 (m, 5H), 5.25 (s, 1H), 5.14−5.09 (m, 1H), 4.98 (dd, J = 11.1, 2.4 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 11.1 Hz, 1H), 4.00 (s, 1H), 3.80−3.79 (m, 2H), 2.48−2.43 (m, 1H), 2.19−2.13 (m, 1H), 2.00 (s, 3H), 1.39−1.35 (m, 1H), 1.32 (d, J = 6.0 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.8, 170.7, 154.2, 138.3, 128.4, 127.7, 127.6, 100.6, 80.0, 72.9, 71.9, 68.0, 54.1, 50.4, 32.0, 21.5, 21.4, 14.1; IR (thin film) ν 3464, 2389, 1738, 1640, 1102, 788, 699, 607, 526^{-1}; HRMS (ESI) calcd for $C_{20}H_{25}BrNaO_6^+$ (M + Na^+): 463.0727, found 463.0708; TLC (1:5 EtOAc:hexanes) R_f = 0.27.

*(±)-Isopropyl 3-Bromo-2-hydroxy-4-methyl-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)pentanoate (**3j**).* The title compound was prepared according to the general procedure; the crude reaction mixture was purified using flash column chromatography, and 20.0 mg (57%) was isolated. The diastereoselectivity was determined by comparing the signals at δ 4.82 (major) and δ 5.04 (minor). White solid, mp 150−152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.25 (s, 1H), 5.08 (m, 1H), 4.82 (d, J = 1.8 Hz, 1H), 3.87 (s, 1H), 3.81 (t, J = 2.4 Hz, 1H), 2.37 (m, 1H), 2.0 (s, 3H), 1.28 (dd, J = 37.2, 6.0 Hz, 6H), 1.15 (dd, J = 26.4, 6.6 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.9, 171.2, 154.0, 100.9, 80.9, 71.9, 65.3, 50.7, 29.8, 23.2, 21.4, 21.3, 18.0, 14.0; IR (thin film) ν 3459, 2968, 1796, 1736, 1647, 1388, 1271, 1104, 942, 780 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{21}BrNaO_5^+$ (M + Na^+): 371.0465, found 371.0453; TLC (1:5 EtOAc:hexanes) R_f = 0.52.

*(±)-Ethyl 3-Bromo-2-hydroxy-2-(5-methyl-2-oxotetrahydrofuran-3-yl)-4-phenylbutanoate (**4a**).* A 1 dram vial was charged with 10% Pd/C (40 w/w %) and flushed with nitrogen. A solution of **3a** (0.1 mmol, 1.0 equiv) dissolved in EtOAc (1 mL) was added. The solution was sparged with H_2 for 5 min. The reaction was then allowed to stir for 72 h in a high-pressure reactor under 120 psi H_2. The reaction mixture then was filtered through a Celite plug, rinsed with ethyl acetate, and concentrated in vacuo. The crude materials thus obtained were purified using flash column chromatography, with a gradient from 95:5 hexanes:EtOAc to 80:20 hexanes:EtOAc to yield 25.0 mg (64%) of the desired product in >20:1 dr. Clear oil, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 4.59−4.55 (m, 1H), 4.46−4.42 (m, 3H), 4.04 (br, 1H), 3.77 (dd, J = 12.0, 9.0 Hz, 1H), 3.55 (d, J = 14.4 Hz, 1H), 2.70 (dd, J = 14.1, 12.0 Hz, 1H), 2.63−2.58 (m, 1H), 1.88−1.83 (m, 1H), 1.46 (d, J = 6.0 Hz, 3H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.5, 171.9, 138.0, 129.3, 128.4, 127.0, 78.4, 75.0, 63.4, 58.0, 48.1, 38.6, 32.2, 20.9, 14.2; IR (thin film) ν 3776, 3453, 2391, 2349, 1767, 1642, 1260, 749, 543 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{21}BrNaO_5^+$ (M + Na^+): 407.0465, found 407.0454; TLC (1:5 EtOAc:hexanes) R_f = 0.24.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b03059.

Crystallographic data for **2a** (CIF)

Optimization information and spectral data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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