Published in final edited form as:

J Org Chem. 2017 February 17; 82(4): 2276–2280. doi:10.1021/acs.joc.6b03059.

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

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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.

Graphical Abstract

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 has 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–3i} 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,3f, 3g} The application of α -angelica lactone (**2**) as a nucleophile presents an interesting opportunity to build more stereochemically complex products.

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The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

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

Optimization information and spectral data for all compounds (PDF)

Unlike previously deployed pro-nucleophiles, α -angelica 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 in 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 sulfones⁸ 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 α -angelica lactone (**2**) to β -halo- α -ketoesters (**1**) (Scheme 1c).

Based on the high levels of Felkin-Ahn diastereoselectivity observed with β -halo- α -ketoesters (**1**) previously,^{3b, 3d–3f} we selected this substrate class for our investigation. The results of aldol reactions using a panel of commercially, 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 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-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, *para*-chlorophenyl-substituted **3d** gave an elevated 73% yield while *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 relative to 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 In order to rationalize the observed stereochemical outcome of the reaction, the Felkin-Anh (or Cornforth) model¹¹ 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). 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 represents a rare case where α -angelica lactone behaves as a regioselective α -nucleophile. Future directions for this work include investigations into the regioselectivity 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 (^1H NMR, ^{13}C NMR, ^{19}F NMR and ^{31}P NMR) were recorded at the following frequencies: ^1H NMR at 400 MHz or 600 MHz, ^{13}C NMR at 101 MHz or 151 MHz, ^{19}F NMR at 376 MHz and ^{31}P NMR at 162 MHz or 243 MHz with solvent resonance as the internal standard (^1H NMR: CDCl_3 at 7.26 ppm and ^{13}C NMR: CDCl_3 at 77.0 ppm). ^1H 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 nitrate solution. Yields refer to isolated yields after flash column chromatography; some samples contain residual minor diastereomers. Since 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.^{3b-3e} Commercially available quinidine was used as received. Since d.r. 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, then concentrated *in vacuo*. The crude materials thusly obtained were purified using flash column chromatography, with a gradient from 95:5 hexanes/EtOAc to 80:20 hexanes/EtOAc.

($\pm$)-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; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{17}\text{H}_{19}\text{BrNaO}_5^+$ ($[\text{M}+\text{Na}^+]$): 405.0308, found 405.0296; **TLC** (1:5 EtOAc/hexanes): R_f = 0.51.

($\pm$)-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 calculating using 1,3,5-trimethoxybenzene as an internal standard and using the signal of the desired product at δ 5.27 in the crude $^1\text{H NMR}$ spectrum. The product was obtained in 49% $^1\text{H NMR}$ yield. No minor diastereomer was observed. White solid, mp 70–72 °C; $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{16}\text{H}_{17}\text{ClNaO}_5^+$ ($[\text{M}+\text{Na}^+]$): 347.0675, found 347.0648; **TLC** (1:5 EtOAc/hexanes): R_f = 0.10.

($\pm$)-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 calculating using 1,3,5-trimethoxybenzene as an internal standard and using the signal of the desired product at δ 5.29 in the crude $^1\text{H NMR}$ spectrum. The product was obtained in 57% $^1\text{H NMR}$ yield. No minor diastereomer was observed. White solid, mp 92–94 °C, $^1\text{H NMR}$ (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); $^{13}\text{C NMR}$ (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 $\text{C}_{18}\text{H}_{20}\text{BrFNaO}_5^+$ ($[\text{M}+\text{Na}^+]$): 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; 30.0 mg (70%) was isolated. No minor diastereomer was observed. Yellow solid, 117–120 °C; **^1H 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 $\text{C}_{18}\text{H}_{20}\text{BrClNaO}_5^+$ ($[\text{M}+\text{Na}^+]$): 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; 15.8 mg (43%) was isolated. No minor diastereomer was observed. White solid, mp 143–144 °C; **^1H 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 $\text{C}_{19}\text{H}_{23}\text{ClNaO}_5^+$ ($[\text{M}+\text{Na}^+]$): 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; 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 ^1H NMR spectrum, and were identified after separation by column chromatography. White solid, mp 133–135 °C; **^1H NMR** (600 MHz, CDCl_3) δ 7.32 (d, $J = 7.8$ Hz, 1H), 7.29 (s, 1H), 7.22 (t, $J = 7.8$ Hz, 1H), 7.14 (d, $J = 7.8$ 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 $\text{C}_{19}\text{H}_{23}\text{ClNaO}_5^+$ ($[\text{M}+\text{Na}^+]$): 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; 14.0 mg (44%) was isolated. No minor diastereomer was observed. White solid, mp 84–85 °C, **¹H NMR** (600 MHz, CDCl₃) 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); **¹³C NMR** (151 MHz, CDCl₃) 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 C₁₂H₁₇BrNaO₅⁺ ([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, **¹H NMR** (600 MHz, CDCl₃) 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); **¹³C NMR** (151 MHz, CDCl₃) 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 C₁₄H₁₉BrNaO₅⁺ ([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; 13.3 mg (30%) was isolated. No minor diastereomer was observed. Clear oil, **¹H NMR** (600 MHz, CDCl₃) 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); **¹³C NMR** (151 MHz, CDCl₃) 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 C₂₀H₂₅BrNaO₆⁺ ([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; 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, **¹H NMR** (600 MHz, CDCl₃) 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); **¹³C NMR** (151 MHz, CDCl₃) 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 $\text{C}_{14}\text{H}_{21}\text{BrNaO}_5^+$ ($[\text{M}+\text{Na}^+]$): 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 ethyl 3-bromo-2-hydroxy-2-(5-methyl-2-oxo-2,3-dihydrofuran-3-yl)-4-phenylbutanoate (**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, rinsing with ethyl acetate, and concentrated *in vacuo*. The crude materials thusly obtained were purified using flash column chromatography, with a gradient from 95:5 hexanes/EtOAc to 80:20 hexanes/EtOAc to yield 25.0mg (64%) desired product in >20:1 dr. Clear oil, **^1H 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 $\text{C}_{17}\text{H}_{21}\text{BrNaO}_5^+$ ($[\text{M}+\text{Na}^+]$): 407.0465, found 407.0454; **TLC** (1:5 EtOAc/hexanes): R_f = 0.24.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support was provided by Award R35 GM118055 from the National Institute of General Medical Sciences.

References

1. For a review, see: Eftekhari-Sis B, Zirak M. Chem Rev. 2015; 115:151–264. [PubMed: 25423283]
2. a) Steward KM, Johnson JS. Org Lett. 2010; 12:2864–2867. [PubMed: 20481613] b) Steward KM, Johnson JS. Org Lett. 2011; 13:2426–2429. [PubMed: 21486076]
3. a) Calter MA, Phillips RM, Flaschenriem C. J Am Chem Soc. 2005; 127:14566–14567. [PubMed: 16231897] b) Steward KM, Gentry EC, Johnson JS. J Am Chem Soc. 2012; 134:7329–7332. [PubMed: 22509806] c) Steward KM, Corbett MT, Goodman CG, Johnson JS. J Am Chem Soc. 2012; 134:20197–20206. [PubMed: 23186551] d) Goodman CG, Do DT, Johnson JS. Org Lett. 2013; 15:2446. [PubMed: 23631467] e) Corbett MT, Johnson JS. Angew Chem Int Ed. 2014; 53:255–259. f) Goodman CG, Johnson JS. J Am Chem Soc. 2014; 136:14698–14701. [PubMed: 25299730] g) Goodman CG, Walker MM, Johnson JS. J Am Chem Soc. 2015; 137:122–125. [PubMed: 25533016] h) Horwitz MA, Tanaka N, Yokosaka T, Uraguchi D, Johnson JS, Ooi T. Chem Sci. 2015; 6:6086–6090. [PubMed: 26508995] i) Horwitz MA, Zavesky BP, Martinez-Alvarado JJ, Johnson JA. Org Lett. 2016; 18:36–39. [PubMed: 26667068]
4. Examples of α -angelica lactone acting as a γ -nucleophile while adding to nitrostyrenes: Manna MS, Kumar V, Mukherjee S. Chem Commun. 2012; 48:5193–5195. Sekikawa T, Kitaguchi T, Kitaura H, Minami T, Hatanaka Y. Org Lett. 2016; 18:646–649. [PubMed: 26835718]
5. Examples of α -angelica lactone acting as a γ -nucleophile while adding to aldimines: Zhou L, Lin L, Ji J, Xie M, Liu X, Feng X. Org Lett. 2011; 13:3056–3059. [PubMed: 21595425]

6. Example of α -angelica lactone acting as a γ -nucleophile while adding to enones: Li X, Lu M, Dong Y, Wu W, Qian Q, Ye J, Dixon DJ. Nat Commun. 2014; doi: 10.1038/ncomms5479
7. Examples of α -angelica lactone acting as a γ -nucleophile while adding to enals: Quintard A, Lefranc A, Alexakis A. Org Lett. 2011; 13:1540–1543. [PubMed: 21319834]
8. Examples of α -angelica lactone acting as a γ -nucleophile while adding to vinyl sulfones: Simlandy AK, Mukherjee S. Org Biomol Chem. 2016; 14:5659–5664. [PubMed: 26646367]
9. Jefford CW, Jaggi D, Boukouvalas J. J Chem Soc, Chem Comm. 1988; 24:1595–1596.
10. CCDC1511793 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. a) Mengel A, Resier O. Chem Rev. 1999; 99:1191–1224. [PubMed: 11749444] b) Evans DA, Siska SJ, Cee VJ. Angew Chem Int Ed. 2003; 42:1761–1765. c) Cee VJ, Cramer CJ, Evans DA. J Am Chem Soc. 2006; 128:2920–2930. [PubMed: 16506771]
12. See Supporting Information for a full description of the attempted development of an asymmetric variant of this reaction.
13. Synthesis of more complex α -angelica lactone nucleophiles: Wu Y, Singh RP, Deng L. J Am Chem Soc. 2011; 133:12458–12461. [PubMed: 21766859]

Previous work (our group): **Previous work (Mukherjee):** **This work:** **Scheme 1.**Proposed addition of α -angelica lactone to stereogenic α -ketoester

Scheme 2. Scope of the reaction^a

^aReaction was conducted on 0.1 mmol scale, using 2.0 equiv of α -angelica lactone. ^bYield was determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 3.

Stereochemical model for addition of angelica lactone to β -halo α -ketoester

Scheme 4.
Hydrogenation of addition product^a