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Silylene transfer to α-keto esters and application to the synthesis of γ-lactones

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Abstract

Disubstituted α-hydroxy acids have been synthesized by metal-catalyzed silylene transfer to α-keto esters. A range of substituents are tolerated in the transformation with the exception of branched groups at the vinylic position. The α-hydroxy acid products can be converted into γ-lactones using a variety of lactonization conditions.

1. Introduction

α-Hydroxy acids are common structural motifs in nature.[1, 2] Several recent publications have featured natural products that incorporate this moiety into their synthesis, including thapsigarin, viridiofungin, zaragozic acid, and fukinolic acid (Scheme 1).[3-6] Given the prevalence of α-hydroxy acids in small molecules, new synthetic methods for their synthesis are desirable.[7-13] We recently reported the development of a method to obtain α-hydroxy acids from simple α-keto esters utilizing metal-catalyzed silylene transfer.[14] In this paper we report the expanded scope and utility of this methodology.

2. Results

The silylene-mediated conversion of α-hydroxy acids is general for a range of substrates (Table 1). The highest yields were obtained with linear α-keto esters (R^1 = Et, Me) and substrates featuring aromatic groups (Table 1, entry 5). The synthetic utility of the reaction could be enhanced by increasing the complexity of substituents at R^1. Incorporation of a protected oxygen atom is tolerated by the reaction conditions and provides an additional handle that can be elaborated in later synthetic steps (Scheme 2).[14]

The mechanism for the conversion of α-keto esters to α-hydroxy acids involves sequential pericyclic reactions. Initial generation of a silacarbonyl ylide intermediate (**7**) is followed by a 6π electrocyclization and tandem Ireland– Claisen rearrangement (Scheme 3), affording α-hydroxy acid products.[14-20]

Functionalization at R^2 (C4 of the Ireland–Claisen transition state, Scheme 3) provided direct transfer of stereochemical information to the two newly formed chiral centers in the Ireland–Claisen product (**9**). Substituents at this position have a preference for being pseudo-equatorial in the transition state to avoid steric congestion.[19] Initial investigations employed a methyl

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group at R^2 (**11**) as a single enantiomer; complete transfer of chirality was observed (Scheme 4).[14]

Extending the substrate scope to include protected hydroxyl groups at R^2 did not impede the transformation. Reactions of compounds **13** and **15** both led to enantiopure acids in good yields upon exposure to the reaction conditions (Scheme 5).

Employing substitutions at both R^1 and R^2 led to the formation of diastereomeric mixtures of α-hydroxy acid products (Scheme 6). The formation of diastereomers is likely due to competing interactions in the Ireland–Claisen transition state. Aligning the benzyloxy group of **17** anti to the incipient carbon–carbon bond in the transition state creates a *syn*-pentane like interaction between the methyl groups at positions C1 and C6 (**17a**).[21, 22] This interaction negates any favorable interactions gained by placing the ethyl group at C4 equatorial, leading to the observed mixture of diastereomers (**17b**).

Unfortunately, increasing the steric bulk at the C4 position (Et to *t*-Bu, **19**) does not improve the diastereomeric ratio of products formed. Submitting a diastereomeric mixture of α-keto esters to silylene transfer conditions (**19a** and **19b**) led to the formation of three products (**20a**, **20b**, and **20c**): two diastereomers of the mismatched substrate and a single diastereomer from the matched substrate, respectively (Scheme 8).[22] This result indicates that exocyclic stereocenters in the Ireland-Claisen transition state can influence the product distribution as effectively as stereocenters on the cyclic transition state.

Substitutions at R^3 are generally well tolerated (Table 2).[14] Substrates that feature branching at that position, however, do not give rearrangement products (Schemes 9, 10, and 11). α-Keto esters that did not give α-hydroxy acid products include terminally disubstituted allylic α-keto ester **25** and substrates that would require a dearomatization event (**21**). Branching at R^3 may not be tolerated because of the proximal silyl group in the Ireland–Claisen transition state. Of all the positions available for substitution on the various substrates, R^3 is the closest to the silyl functionality.

Ultimately, the silylene transfer products feature a homoallylic carboxylic acid that can be elaborated into γ-lactones by several different lactonization conditions. Traditional iodolactonization methods provided moderate to good yield of the desired lactone as a mixture of diastereomers (Table 3, entries 1-5).[23-26] Use of *N*-bromosuccinimide led to slightly improved diastereomeric ratios and decreased yield. Surprisingly, asymmetric dihydroxylation conditions yielded no product, but standard dihydroxylation conditions provided the requisite product **28c** as a single diastereomer.[27] It is conceivable that the catalyst-ligand complex in the asymmetric dihydroxylation is unable to accommodate the sterically congested α-hydroxy acid substrates.

Access to a variety of lactones with differing functionality provided an opportunity to synthesize a range of compounds. Several elaborations have led to differentiated products, including diol **29**, a potential precursor to the secondary marine metabolite (−)-delesserine (Scheme 13). Utilization of a slightly modified α-keto ester in the silylene transfer reaction could afford the natural product in a few additional steps.[28] Elaboration of the diol **29** to olefin **30** via reductive elimination provides a potential handle for ring-closing metathesis reactions (Scheme 13).[29]

3. Experimentals

3.1 General remarks

Melting points were obtained using a Büchi 510 melting point apparatus and are reported uncorrected. Analytical thin later chromatography was performed on EMD Silical Gel 60 F_{254} precoated plates. Liquid chromatography utilized force flow (flash chromatography) of the indicated solvent system on Silacycle Sila-P silica gel (SiO_2) 60Å pore size, 40-63 μm mesh. Infrared spectroscopy was performed on an Mattson Instruments FTIR, Galaxy System. High-resolution mass spectra were acquired on a Walters LCT Premier and were obtained by peak matching. Microanalyses were performed by Atlantic Microlabs, Atlanta, GA. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 400 and 100, and 500 and 125 MHz, respectively, using Bruker DRX 400 or DRX 500 spectrometers as indicated. These data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiciplity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Silacyclopropanes were stored and manipulated in an Innovative Technologies nitrogen-atmosphere dry box. All reactions were performed under an atmosphere of nitrogen or argon in glassware that had been flame-dried under vacuum prior to use. Solvents were distilled or filtered before use. Compounds **1–5**, **11**, **12**, **27a**, **27b**, and **27c**, were synthesized according to previously published reports.

3.2 (*S*,*E*)-1-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pent-3-en-2-yl 2-oxopropanoate (13)

To a solution of (*S*,*E*)-1-(tert-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)pent-3-en-2-ol (0.520 g, 1.47 mmol) in benzene (30 mL) was added pyruvic acid (0.164 mL, 2.36 mmol), triethylamine (0.551 mL, 3.70 mmol), 4-dimethylaminopyridine (0.224 g, 1.84 mmol), and 2,4,6-trichlorobenzoylchloride (0.731 mL, 2.99 mmol). The reaction mixture was then stirred for 16 h, diluted with 5% aqueous citric acid, and extracted with EtOAc (3 × 25 mL). The organic layers were combined, dried with Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (10:1 hexanes:EtOAc) to provide **13** (0.617 g, 99%) as a yellow oil: $[\alpha]^{23}_{D}$ 8.2 (*c* 2.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, 2H), 6.93 (d, *J* = 8.6, 2H), 6.01 (dt, *J* = 15.6, 5.3, 1H), 5.81 (dd, *J* = 15.7, 6.9, 1H), 5.53 (dd, *J* = 12.1, 6.2, 1H), 4.52 (s, 2H), 4.07 (d, *J* = 5.0, 2H), 3.90 – 3.76 (m, 5H), 2.52 (d, *J* = 5.4, 2H), 0.91 (s, 9H), 0.10 (t, *J* = 4.2, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 167.3, 159.7, 132.9, 132.5, 130.2, 130.0, 114.3, 77.4, 72.5, 69.6, 64.9, 55.7, 27.2, 26.2, 18.7, -4.98; IR (thin film) 3021, 2933, 1733, 1216, 755 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{22}H_{34}NaO_6Si$ $(M + Na)^+$ 445.2022, found 445.2022.

3.3 (2*R*,3*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-3-((4-methoxybenzyloxy)methyl)-2-methylhex-4-enoic acid (14)

To **13** (0.318 g, 0.752 mmol) in toluene (10 mL) was added silacyclopropane **2** (0.215 g, 1.09 mmol) and the reaction mixture was then cooled to −25 °C. After stirring for 0.5 h, silver tosylate (0.021 g, 0.075 mmol) was added and the mixture was allowed to warm to room temperature. Upon stirring for 3 h, the solution was concentrated *in vacuo* and the resultant oil was purified by column chromatography (5:2 hexanes:EtOAc with 1% AcOH) to provide **14** (0.254 g, 80%) as a pale yellow oil: $[\alpha]^{23}_{D}$ − 12.7 (*c* 3.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6, 2H), 6.97 − 6.70 (m, 2H), 5.77 (t, *J* = 5.8, 2H), 4.42 (s, 2H), 4.23 (d, *J* = 3.5, 2H), 3.83 (d, *J* = 3.9, 3H), 3.61 (dd, *J* = 7.2, 5.5, 2H), 2.99 − 2.76 (m, 1H), 1.40 (s, 3H), 0.96 (d, *J* = 2.6, 9H), 0.18 − 0.09 (m, 6H).13C NMR (100 MHz, $CDCl_3$) δ 180.4, 159.7, 134.9, 129.9, 129.9, 129.9, 128.8, 126.1, 114.3, 76.3, 73.6, 71.4, 64.1, 55.6, 49.4, 27.7, 27.4, 26.4, 25.5, 18.8, -4.66, -4.68; IR (thin film) 3434, 3018, 2933, 2859, 1770, 1722 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{22}H_{36}NaO_6Si$ $(M + Na)^+$ 447.2179, found 447.2169.

3.4 (*R*,*E*)-5-(*tert*-Butyldiphenylsilyloxy)-1-(4-methoxybenzyloxy)pent-3-en-2-yl 2-oxopropanoate (15)

α-Keto ester **15** was isolated as a yellow oil (1.15g, 59%) using a procedure identical to the one outlined in **3.3**: $[\alpha]^{23}_{D}$ −17.1 (*c* 9.42, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 − 7.70 (m, 4H), 7.56 − 7.11 (m, 8H), 7.01 − 6.91 (m, 2H), 6.09 − 5.96 (m, 1H), 5.90 (ddt, *J* = 15.4, 7.0, 1.7, 1H), 5.77 − 5.65 (m, 1H), 4.62 (d, *J* = 5.0, 2H), 4.34 (ddd, *J* = 4.7, 3.8, 2.3, 2H), 3.88 (s, 3H), 3.71 (ddd, *J* = 14.7, 11.0, 5.7, 2H), 2.54 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 160.3, 159.6, 136.6, 135.8, 135.3, 133.6, 132.8, 130.1, 130.1, 129.8, 129.8, 129.7, 128.0, 128.4, 128.0, 128.0, 123.2, 114.2, 75.6, 73.2, 71.0, 63.6, 55.5, 27.1, 27.0, 19.50; IR (thin film) 3016, 2933, 2858, 1735, 1581, 1513 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{32}H_{38}NaO_6Si$ $(M + Na)^+$ 569.2335, found 569.2335.

3.5 (2*S*,3*S*,*E*)-3-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-6-(4-methoxybenzyloxy)-2-methylhex-4-enoic acid (16)

To **15** (0.188 g, 0.344 mmol) in toluene (5 mL) was added silacyclopropane **2** (0.095 g, 0.48 mmol) and the reaction mixture was cooled to −25 °C. After stirring for 0.5 h, silver tosylate (0.009 g, 0.03 mmol) was added and the mixture was allowed to warm to ambient temperature. After stirring for 2 h, the solution was concentrated *in vacuo* and the resultant oil was purified by column chromatography (5:2 hexanes:EtOAc with 1% AcOH) to provide **16** (0.099 g, 53%) as a pale yellow oil: $[\alpha]^{23}_{D}$ −0.7 (*c* 5.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.5, 4H), 7.54 −7.31 (m, 6H), 7.27 (d, *J* = 8.5, 2H), 6.89 (d, *J* = 8.5, 2H), 5.89 (dd, *J* = 15.5, 9.5, 1H), 5.74 (dt, *J* = 15.5, 5.8, 1H), 4.46 (s, 2H), 4.02 (d, *J* = 5.6, 2H), 3.97 − 3.66 (m, 6H), 2.77 (dt, *J* = 9.1, 4.4, 1H), 1.42 (s, 3H), 1.06 (s, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 159.5, 135.9, 135.8, 132.5, 132.4, 132.2, 130.5, 130.3, 129.7, 129.0, 128.1, 128.1, 114.1, 71.9, 70.3, 66.3, 55.5, 50.4, 27.0, 25.4, 19.3; IR (thin film) 3502, 2933, 2858, 1724, 1513 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{32}H_{40}NaO_6Si$ $(M + Na)^+$ 571.2492, found 571.2505.

3.6 (*R*)-((*S*,*E*)-Hex-4-en-3-yl) 3-(benzyloxy)-2-oxobutanoate (17)

To (2*S*,3*R*)-((*S*,*E*)-hex-4-en-3-yl) 3-(benzyloxy)-2-hydroxybutanoate (0.152 g, 0.520 mmol) in CH_2Cl_2 (10 mL) was added pyridine (0.25 mL) followed by Dess-Martin periodinane (0.330 g, 0.779 mmol). The reaction mixture was stirred for 16 h and then diluted with saturated aqueous Na_2SO_3 and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were then combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude oil was purified by column chromatography (10:1 hexanes:EtOAc) to afford **17** (0.114 g, 76%) as a yellow oil: $[\alpha]^{23}_{D}$ 16.0 (*c* 1.66, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 − 7.26 (m, 5H), 5.86 (dq, *J* = 13.1, 6.5, 1H), 5.58 − 5.42 (m, 1H), 5.33 (q, *J* = 6.9, 1H), 4.73 (d, *J* = 11.5, 1H), 4.63 − 4.50 (m, 2H), 2.05 − 1.61 (m, 5H), 1.48 (d, *J* = 6.9, 3H), 0.95 (t, *J* = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 162.8, 137.7, 131.6, 128.9, 128.6, 128.4, 79.50, 77.9, 73.0, 27.8, 18.2, 17.0, 9.9; IR (thin film) 2971, 2939, 2879, 1726, 1214 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{17}H_{22}NaO_4$ $(M + Na)^+$ 313.1416, found 313.1415. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.14; H, 7.68.

3.7 1-(Benzyloxy)ethyl)-2-hydroxy-3-methylhept-4-enoic acid (18)

To **17** (0.150 g, 0.514 mmol) in toluene (5 mL) was added silacyclopropane **2** (0.147 g, 0.745 mmol) and the reaction mixture was cooled to −25 °C. After stirring for 0.5 h, silver tosylate (0.014 g, 0.05 mmol) was added and the mixture was allowed to warm to ambient temperature. Upon stirring for 2 h, the solution was concentrated *in vacuo* and the resultant oil was purified by column chromatography (5:2 hexanes:EtOAc with 1% AcOH) to provide a 1:1 mixture of diastereomers of **18** (0.108 g, 72%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 − 7.14 (m, 5H), 5.60 − 5.49 (m, 2H), 4.73 (dd, *J* = 11.3, 5.8, 2H), 4.11 − 3.88 (m, 1H), 3.00 − 2.70 (m, 1H), 2.18 − 1.97 (m, 2H), 1.34 (d, *J* = 5.9, 3H), 1.04 (m, 6H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 177.1, 138.4, 135.1, 128.9, 128.8, 128.7, 128.5, 128.2, 83.0, 78.8, 72.0, 41.9, 26.0, 16.5, 15.3, 14.1, 13.1; IR (thin film) 3020, 2973, 1756, 1708, 1216 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{17}H_{24}NaO_4$ (M + Na)+ 315.1572, found 315.1572.

3.8 (3*R*)-((*E*)-2,2-Dimethylhex-4-en-3-yl) 3-(benzyloxy)-2-oxobutanoate (19)

To (±)(2*S*,3*R*)-((*E*)-2,2-dimethylhex-4-en-3-yl) 3-(benzyloxy)-2-hydroxybutanoate (0.007 g, 0.02 mmol) in CH_2Cl_2 (1 mL) was added pyridine (0.2 mL) followed by Dess-Martin periodinane (0.014 g, 0.032 mmol). The reaction mixture was stirred for 16 h and then diluted with saturated aqueous Na_2SO_3, extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were then combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude oil was purified by column chromatography (10:1 hexanes:EtOAc) to afford **19** (0.069 g, 99%) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 − 7.32 (m, 5H), 5.91 − 5.79 (m, 1H), 5.61 − 5.46 (m, 1H), 5.15 (t, *J* = 8.1, 1H), 4.74 (d, *J* = 11.5, 1H), 4.65 − 4.45 (m, 2H), 1.79 − 1.71 (m, 2H), 1.67 − 1.56 (m, 1H), 1.50 (d, *J* = 4.0, 3H), 0.98 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 162.5, 137.2, 132.5, 128.5, 128.1, 128.0, 125.3, 84.9, 72.6, 34.5, 29.8, 25.8, 17.9, 16.7; IR (thin film) 3091, 3018, 2969, 1724, 1479 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{19}H_{26}NaO_4$ $(M + Na)^+$ 341.1729, found 347.1738.

3.9 1-(Benzyloxy)ethyl)-2-hydroxy-3,6,6-trimethylhept-4-enoic acid (20a-c)

To **19** (0.0623 g, 0.196 mmol) in toluene (2 mL) was added 1,1-di-tert-butyl-2,2-dimethylsilirane **2** (0.0587 g, 0.296 mmol) and the reaction mixture was cooled to −25 °C. After stirring for 0.5 h, silver tosylate (0.006 g, 0.02 mmol) was added and the mixture was allowed to warm to room temperature. After stirring for 12 h, HF·Pyr (0.20 mL, 1.75 mmol) was added to the solution. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$, the organic layer was rinsed with saturated aqueous $NaHCO_3$ (3 × 25 mL), the aqueous layers were then combined and acidified with 1M HCl (ca 100 mL) until pH 2. After the desired pH was reached, the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), the organic layers were combined, dried with Na_2SO_4, and concentrated to provide a 2:1:1 mixture of diastereomers of **20** (0.042 g, 67%) as a pale yellow oil. Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 − 7.28 (m, 5H), 5.70 − 5.58 (m, 1H), 5.33 (m, 1H), 4.81 − 4.65 (m, 2H), 4.59 − 4.45 (m, 2H), 4.05 − 3.92 (m, 1H), 2.82 − 2.74 (m, 1H), 1.32 −1.24 (m, 3H), 1.11 − 0.96 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 144.89, 137.2, 129.2, 128.8, 128.3, 124.7, 81.2, 77.1, 72.5, 41.5, 33.6, 30.2, 16.1, 14.1; IR (thin film) 3551, 3020, 2962, 2865, 1756, 1710 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{19}H_{28}NaO_4$ $(M + Na)^+$ 343.1885, found 343.1882.

3.10 Furan-2-ylmethyl 2-oxo-2-phenylacetate (21)

To a solution of benzoylformic acid (0.500 g, 3.33 mmol) in CH_2Cl_2 (25 mL) was added furfuryl alcohol (0.217 g, 2.22 mmol), *N*,*N*-dimethylaminopyridine (0.026 g, 0.22 mmol), and dicyclohexylcarbodiimide (0.687 g, 3.33 mmol). After stirring for 6 h, the solution was filtered, diluted with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried with Na_2SO_4, and concentrated *in vacuo*. The resultant oil was purified via column chromatography to give **21** (0.20 g, 45%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0, 2H), 7.69 (t, *J* = 7.4, 1H), 7.60 − 7.47 (m, 3H), 6.59 (d, *J* = 2.6, 1H), 6.45 (s, 1H), 5.42 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 163.8, 148.5, 144.2, 135.4, 132.8, 130.5, 129.3, 112.4, 111.2, 59.7; IR (thin film) 2955, 2877, 1736, 1689, 1451 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{10}NaO_4$ $(M + Na)^+$ 253.0477, found 253.0470.

3.11 (*S*,*E*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)allyl 2-oxo-2-phenylacetate (23)

To a solution of benzoylformic acid (0.500 g, 3.33 mmol) in CH_2Cl_2 (25 mL) was added (*S*,*E*)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (0.351 g, 2.22 mmol), *N*,*N*-

dimethylaminopyridine (0.026 g, 0.22 mmol), and dicyclohexylcarbodiimide (0.687 g, 3.33 mmol). After stirring for 6 h, the solution was filtered, diluted with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried with $NaSO_4$, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (5:1 hexanes:EtOAc) to give **23** (0.25 g, 39%) as a yellow oil: $[\alpha]^{23}_D$ 15.2 (*c* 1.77, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (dt, *J* = 8.5, 1.5, 2H), 7.73 − 7.62 (m, 1H), 7.58 − 7.48 (m, 2H), 6.01 (ddd, *J* = 7.6, 6.3, 0.6, 1H), 5.92 (ddd, *J* = 15.5, 8.1, 3.8, 1H), 4.90 (d, *J* = 5.8, 2H), 4.58 (q, *J* = 6.8, 1H), 4.14 (dd, *J* = 8.2, 6.3, 1H), 3.64 (dd, *J* = 8.2, 7.4, 1H), 1.43 (d, *J* = 16.5, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 163.7, 135.4, 134.0, 130.4, 129.3, 126.4, 110.00, 109.99, 76.3, 69.6, 65.8, 27.0, 26.2; IR (thin film) 3020, 1739, 1691, 1527, 1220 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{16}H_{18}NaO_5$ $(M + Na)^+$ 313.1052, found 313.1046. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.41; H, 6.34.

3.12 3-Methylbut-2-enyl 2-oxo-2-phenylacetate (25)

To benzoylformic acid (0.500 g, 3.33 mmol) in CH_2Cl_2 (25 mL) was added 3-methyl-2-buten-1-ol (0.191 g, 2.22 mmol), *N*,*N*-dimethylaminopyridine (0.026 g, 0.22 mmol), and dicyclohexylcarbodiimide (0.687 g, 3.33 mmol). After stirring for 6 h, the solution was filtered, diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, dried with $NaSO_4$, and concentrated *in vacuo*. The resultant oil was purified by column chromatography to give **25** (0.516 g, 96%) as a yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.9, 2H), 7.67 (t, *J* = 7.4, 1H), 7.52 (t, *J* = 7.5, 2H), 5.49 (t, *J* = 6.9, 1H), 4.91 (d, *J* = 7.4, 2H), 1.81 (d, *J* = 6.1, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9, 164.3, 141.5, 135.3, 132.9, 130.4, 129.3, 117.8, 63.4, 26.2, 18.5; IR (thin film) 2973, 2936, 2859, 1912, 1747 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{14}NaO_3$ $(M + Na)^+$ 241.0841, found 241.0842. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.68; H, 6.64.

3.13 (±)-2-Ethyl-2-hydroxy-3-vinylheptanoic acid (27)

To (*E*)-oct-2-enyl 2-oxobutanoate (0.861 g, 4.34 mmol) in toluene (20 mL) was added silacyclopropane **2** (1.41 g, 6.30 mmol) and the reaction mixture was cooled to −25 °C. After stirring for 0.5 h, silver tosylate (0.121 g, 0.434 mmol) was added and the mixture was allowed to warm to room temperature. After stirring for 12 h, HF·Pyr (0.50 mL, 4.4 mmol) was added to the solution. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$, the organic layer was rinsed with saturated aqueous $NaHCO_3$ (3 × 45 mL), the aqueous layers were then combined and acidified with 1 M HCl (300 mL) until pH 2. After the desired pH was reached, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the organic layers were combined, dried with Na_2SO_4, and concentrated to provide **27** (0.519 g, 60%) as a white powder: mp 57 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 − 5.54 (m, 1H), 5.25 (d, *J* = 10.1, 1H), 5.14 (d, *J* = 17.1, 1H), 2.37 (t, *J* = 10.3, 1H), 2.13 − 1.70 (m, 2H), 1.59 − 1.11 (m, 6H), 0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 137.1, 119.2, 80.8, 52.2, 31.1, 29.8, 29.2, 22.8, 14.4, 8.16; IR (thin film) 3535, 3020, 2959, 1706, 1220 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{11}H_{20}NaO_3$ $(M + Na)^+$ 199.1334, found 199.1332. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.71; H, 9.96.

3.14 3-Hydroxy-5-(iodomethyl)-3-phenyldihydrofuran-2(3*H*)-one (28a)

To (±)-2-hydroxy-2-phenylpent-4-enoic acid (0.023 g, 0.12 mmol) in acetonitrile (3 mL) at 0 °C was added $NaHCO_3$ (0.030 g, 0.36 mmol) followed by iodine (0.091 g, 0.36 mmol). After stirring for 16 h the reaction mixture was diluted with water, and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were then combined, dried with Na_2SO_4, and concentrated *in vacuo*. The crude mixture was then purified via column chromatography (3:1 hexanes:EtOAc) to afford a 3:2 mix of diastereomers of **28a** (0.034 g, 91%) as a pale oil. Major diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.69 − 7.16 (m, 5H), 4.82 − 4.75 (m, 1H), 3.55

− 3.48 (m, 1H), 3.43 − 3.33 (m, 1H), 3.18 (s, 1H), 2.92 (m, 1H), 2.51 (dd, *J* = 13.1, 9.4, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 139.7, 129.3, 128.9, 125.4, 79.2, 76.1, 45.7, 6.3; IR (thin film) 3020, 2957, 1738, 1690 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{11}H_{11}INaO_3$ (M + Na)+ 340.9651, found 340.9651.

3.15 (3*S*,4*R*)-4-Butyl-3-hydroxy-5-(1-iodoethyl)-3-methyldihydrofuran-2(3*H*)-one (28b)

To (2*S*,3*R*)-2-hydroxy-2-methyl-3-((*E*)-prop-1-enyl)heptanoic acid (0.027 g, 0.14 mmol) in acetonitrile (3 mL) at 0 °C was added $NaHCO_3$ (0.034 g, 0.040 mmol) followed by iodine (0.101 g, 0.401 mmol). The reaction mixture was stirred for 10 h, diluted with H_2O (3 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were then combined, dried with Na_2SO_4, and concentrated *in vacuo*. The crude mixture was then purified by column chromatography (3:1 hexanes:EtOAc) to provide **28b** (0.021 g, 48%) as a 4:1 mixture of diastereomers. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (dq, *J* = 12.3, 6.2, 1H), 3.96 (t, *J* = 10.4, 1H), 3.10 (s, 1H), 2.41 (dt, *J* = 9.1, 4.5, 1H), 1.81 − 1.69 (m, 3H), 1.66 (s, 1H), 1.63 − 1.51 (m, 3H), 1.48 (s, 3H), 1.46 − 1.34 (m, 2H), 0.98 (t, *J* = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 81.9, 73.8, 50.6, 33.3, 32.2, 30.5, 23.3, 22.9, 21.4, 14.0; IR (thin film) 3020, 2958, 2876, 1734, 1690, 1215 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{11}H_{19}INaO_3$ (M + Na)$^+$ 349.0277, found 349.0269.

3.16 4-Butyl-3-ethyl-3-hydroxy-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (28c)

To (±)-2-ethyl-2-hydroxy-3-vinylheptanoic acid (0.042 g, 0.19 mmol) in CH_2Cl_2 (5 mL) was added *N*-methylmorpholine-*N*-oxide (0.037 g, 0.24 mmol) followed by OsO_4 (2.5% in *t* -BuOH, 0.007 mL). The mixture was stirred for 56 h, diluted with Na_2SO_3, and extracted with EtOAc (3 × 10 mL). The organic layers were then combined, dried with Na_2SO_4, and concentrated *in vacuo*. The resulting viscous oil was then purified via column chromatography (1:1 hexanes:EtOAc) to provide **28c** (0.040 g, 73%) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (ddd, *J* = 9.7, 4.4, 2.2, 1H), 4.04 (d, *J* = 13.0, 1H), 3.72 (dd, *J* = 12.9, 4.2, 1H), 3.13 (s, 1H), 2.72 − 2.17 (m, 2H), 1.96 − 1.68 (m, 3H), 1.63 (d, *J* = 8.5, 1H), 1.55 − 1.34 (m, 4H), 1.07 (t, J = 7.5, 3H), 0.97 (t, *J* = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 82.9, 78.1, 62.8, 46.6, 29.9, 26.1, 25.8, 23.3, 14.3, 7.6; IR (thin film) 3434, 3020, 2935, 1772, 1214 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{11}H_20NaO_4$ (M + Na)$^+$ 239.1259, found 239.1266.

3.17 4-Butyl-3-ethyl-3-hydroxy-5-(iodomethyl)dihydrofuran-2(3*H*)-one (28d)

To a solution of (±)-2-ethyl-2-hydroxy-3-vinylheptanoic acid (0.020 g, 0.10 mmol) in THF (3 mL) at 0 °C was added *N*-iodosuccinimide (0.024 g, 0.11 mmol). After stirring for 0.5 h, the reaction mixture was concentrated *in vacuo* and the crude mixture was purified by column chromatography to give **28d** (0.029 g, 92%) as a 3:1 mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (ddd, *J* = 9.2, 5.9, 3.3, 1H), 3.65 (dd, *J* = 11.4, 3.3, 1H), 3.36 (dd, *J* = 11.4, 5.9, 1H), 2.82 (s, 1H), 2.38 (td, *J* = 8.8, 5.4, 1H), 1.90 − 1.32 (m, 7H), 1.12 (t, *J* = 7.4, 1H), 1.06 (t, *J* = 7.5, 3H), 0.98 (t, *J* = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 128.8, 80.5, 78.4, 52.2, 29.7, 26.0, 23.3, 14.3, 7.5, 6.6; IR (thin film) 3480, 2960, 2932, 2862, 1780 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{11}H_{19}INaO_3$ (M + Na)$^+$ 349.0277, found 349.0268.

3.18 5-(Bromomethyl)-4-butyl-3-ethyl-3-hydroxydihydrofuran-2(3*H*)-one (28e)

To a solution of (±)-2-ethyl-2-hydroxy-3-vinylheptanoic acid (0.020 g, 0.10 mmol) in THF (3 mL) at 0 °C was added *N*-bromosuccinimide (0.019 g, 0.11 mmol). After stirring for 0.5 h, the reaction mixture was concentrated and the crude mixture was purified by column chromatography (5:1 hexanes:EtOAc) to give **28e** (0.021 g, 76%) as a 5:1 mixture of diastereomers. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, *J* = 5.7, 1H), 3.80 (d, *J* = 11.7, 1H), 3.55 (dd, *J* = 11.6, 5.4, 1H), 2.90 (s, 1H), 2.49 (d, *J* = 5.8, 1H), 1.90 − 1.34

(m, 8H), 1.07 (t, *J* = 7.3, 3H), 0.98 (t, *J* = 6.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 128.6, 80.5, 78.2, 50.1, 33.1, 29.8, 26.0, 23.3, 14.2, 7.5; IR (thin film) 3471, 3020, 2960, 2933, 2873, 1778 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{11}H_{20}BrO_3$ $(M + H)^+$ 279.0596, found 279.0593.

3.19 (3*R*,4*S*)-5-(1,2-Dihydroxyethyl)-3-hydroxy-4-((4-methoxybenzyloxy)methyl)-3-methyldihydrofuran-2(3*H*)-one (29)

To (2*R*,3*R*,*E*)-2,6-dihydroxy-3-((4-methoxybenzyloxy)methyl)-2-methylhex-4-enoic acid (0.17 g, 0.53 mmol) in CH_2Cl_2 (10 mL) was added *N*-methylmorpholine-*N*-oxide (0.084 g, 0.72 mmol) followed by OsO_4 (2.5% in *t*-BuOH, 0.13 mL). The mixture was stirred for 16 h, diluted with saturated aqueous Na_2SO_3, and then extracted with $CHCl_3$:*i*-PrOH (3:1, 3 × 15 mL). The organic layers were combined, dried with $NaSO_4$, and concentrated *in vacuo*. The resultant oil was purified by column chromatography ($CHCl_3$:MeOH 10:1) to give a 5:1 mixture of diastereomers of **29** (0.086 g, 50%) as a pale yellow oil. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4, 2H), 6.91 (d, *J* = 8.5, 2H), 5.04 (s, 1H), 4.78 (s, 1H), 4.45 (d, *J* = 6.5, 2H), 4.33 (d, *J* = 6.7, 1H), 3.98 − 3.37 (m, 7H), 2.79 (d, *J* = 5.8, 1H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 159.8, 129.9, 128.8, 114.3, 80.5, 74.3, 73.5, 71.8, 67.2, 64.0, 55.7, 47.5, 19.4; IR (thin film) 3398, 3020, 2937, 1776, 1513 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{16}H_{22}NaO_7$ $(M + H)^+$ 349.1263, found 349.1267.

3.20 (3*R*,4*S*)-3-Hydroxy-4-((4-methoxybenzyloxy)methyl)-3-methyl-5-vinyldihydrofuran-2(3*H*)-one (30)

To a solution of **29** (0.19 g, 0.58 mmol) in THF (60 mL) was added triphenylphosphine (0.46 g, 1.8 mmol), imidazole (0.24 g, 3.5 mmol), and iodine (0.44 g, 1.8 mmol). The reaction mixture was heated to reflux for 2 h and then concentrated. The resultant oil was taken up in MTBE (20 mL) and washed with saturated aqueous $NaHCO_3$, saturated aqueous Na_2SO_3, and brine. The organic fraction was dried over Na_2SO_4 and concentrated *in vacuo* to provide a crude oil that was purified by column chromatography (1:1 hexanes:EtOAc) to give **30** as a yellow oil (0.17 g, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 − 7.11 (m, 2H), 6.90 (dd, *J* = 6.4, 4.9, 2H), 5.89 (ddd, *J* = 17.2, 10.4, 6.8, 1H), 5.40 (d, *J* = 17.1, 1H), 5.32 (d, *J* = 10.4, 1H), 4.58 (dd, *J* = 9.7, 7.0, 1H), 4.52 − 4.36 (m, 2H), 3.82 (s, 3H), 3.60 (d, *J* = 5.8, 2H), 2.81 (m, 1H), 2.51 (dt, *J* = 9.9, 5.8, 1H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 159.6, 134.5, 129.6, 119.6, 114.1, 79.7, 74.9, 73.4, 65.4, 55.5, 52.0, 20.3; IR (thin film) 3440, 3020, 2935, 1778, 1513 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{16}H_{20}NaO_5$ $(M + Na)^+$ 315.1208, found 315.1204.

Acknowledgments

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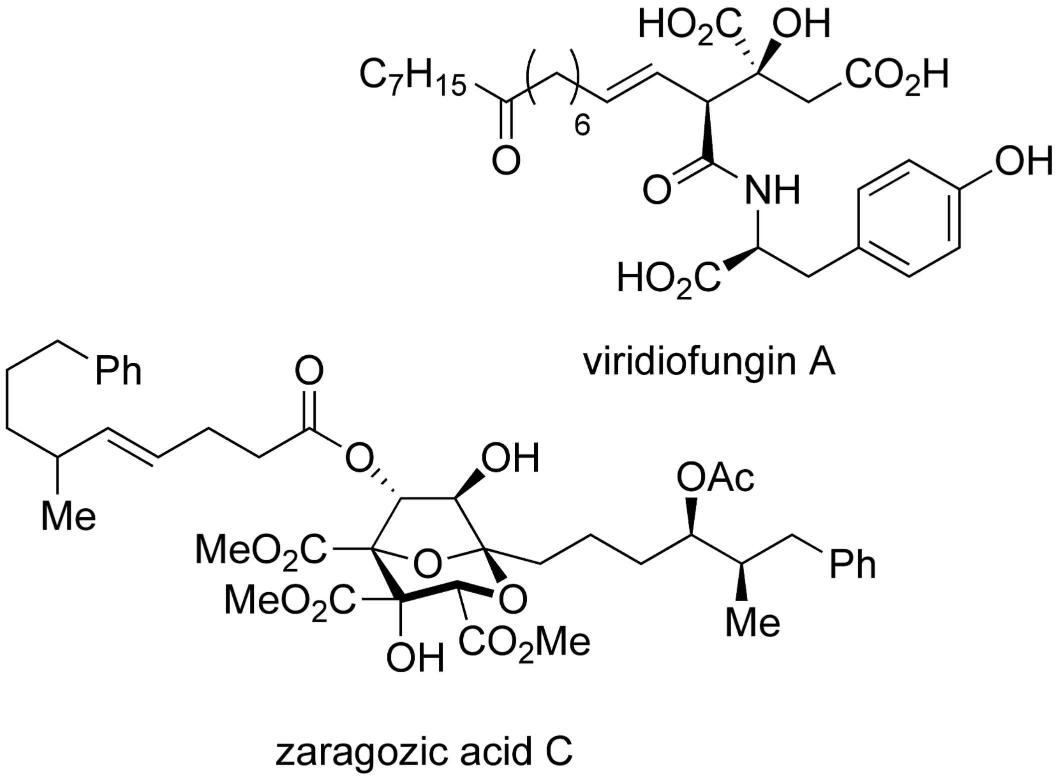
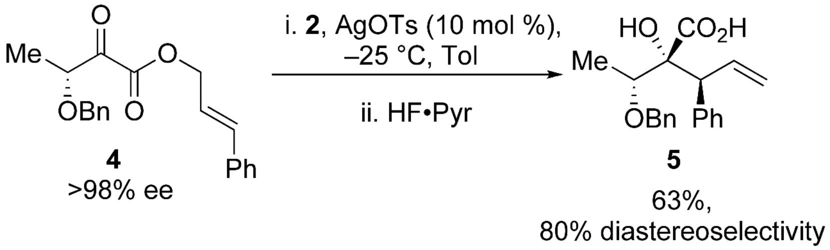
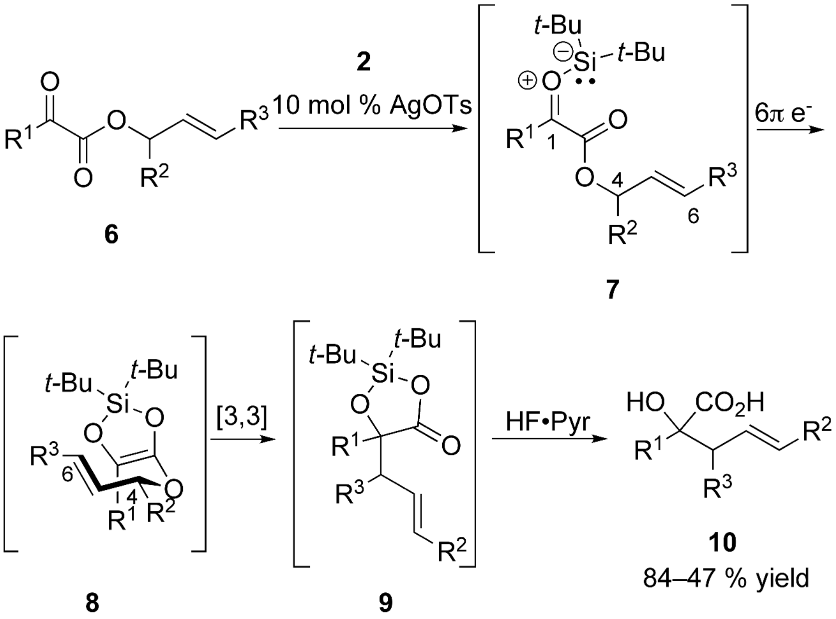


Scheme 1.
α-Hydroxy acid containing natural products.



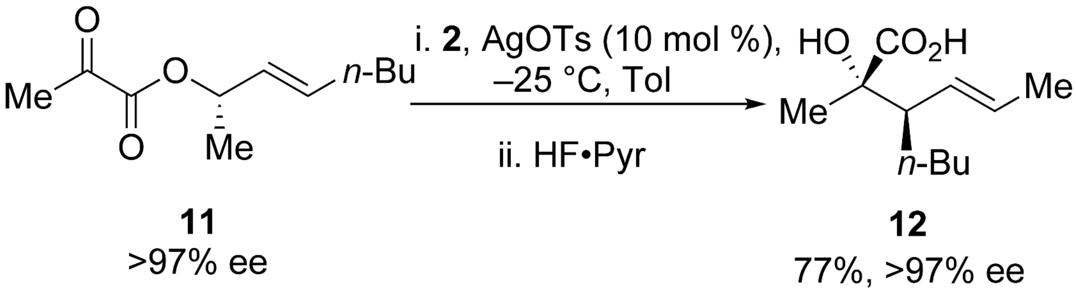
Scheme 2.

Synthesis of α-hydroxy acids with branching at R^1.



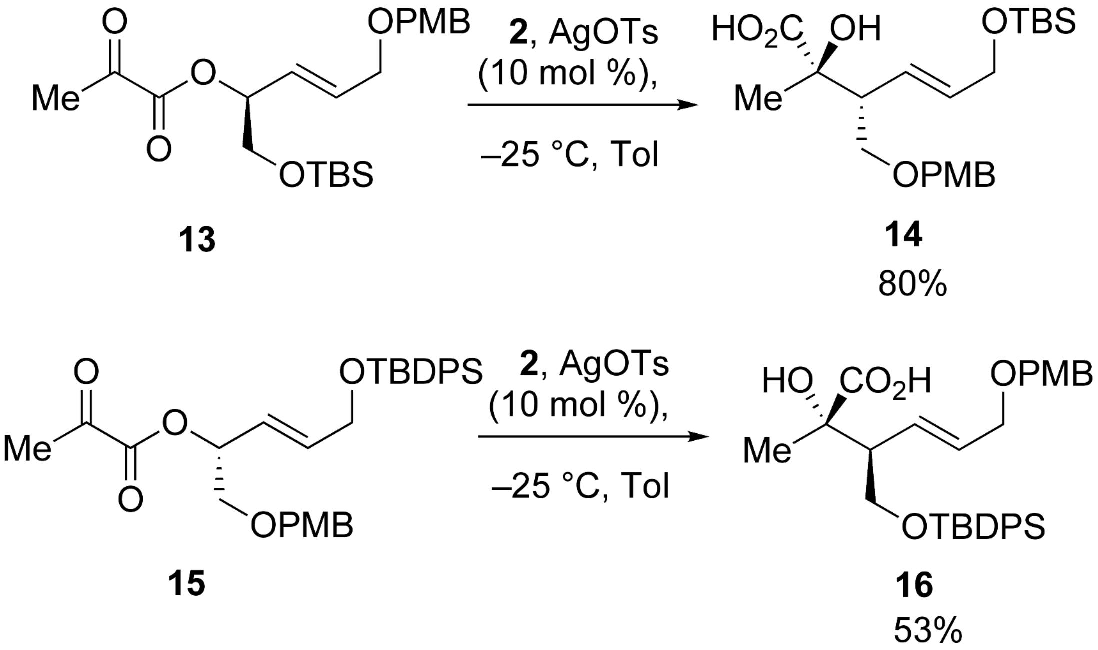
Scheme 3.

Postulated mechanism for the formation of α-hydroxy acids.

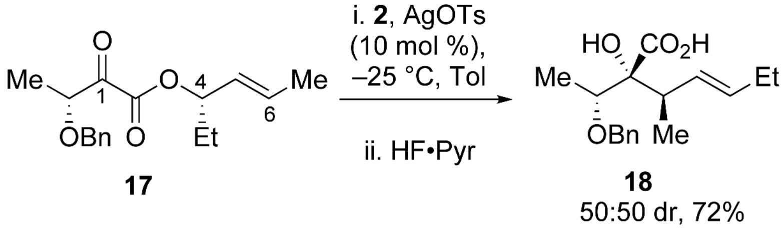


Scheme 4.

Enantiopure α-keto esters bearing a chiral substituent on the allylic ester at R^2 (C4).

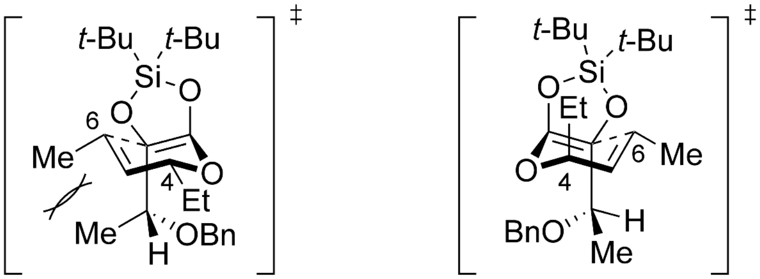


Scheme 5.
Synthesis of enantiopure α-hydroxy acids.



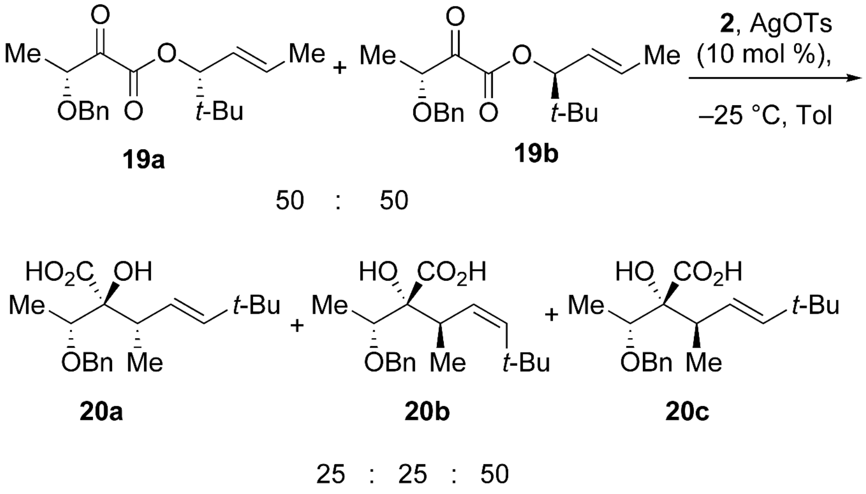
Scheme 6.

Competing chiral substituents at C1 and C4 lead to the formation of diastereomers.



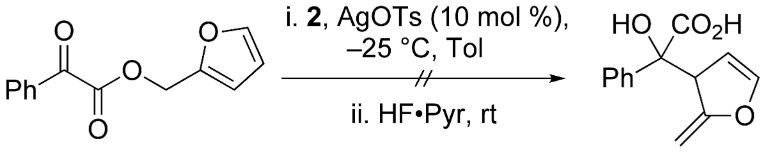
17a **17b**

Scheme 7.
Two potential transition states for compound **17**.



Scheme 8.

Incorporation of a *t*-butyl group at R^2 does not change diastereoselectivity



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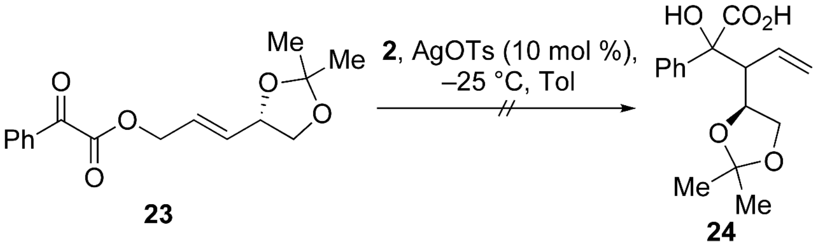
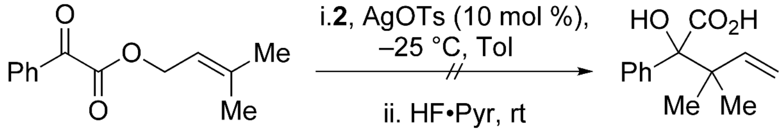
Scheme 9.

Substrates requiring dearomatization are not tolerated.



Scheme 10.

α-Keto esters with bulky substituents at R^3 are not tolerated.



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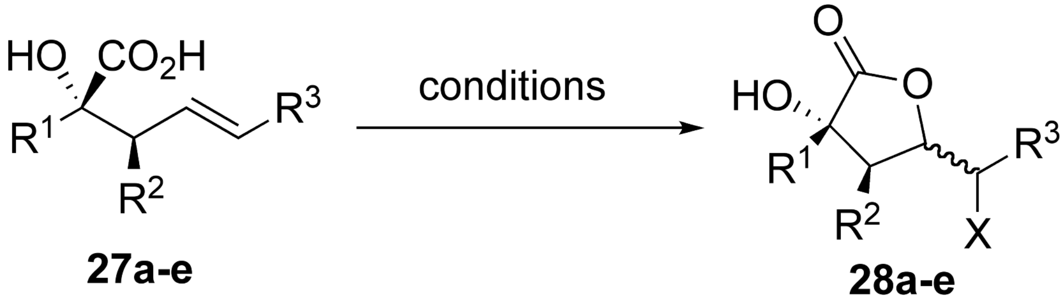
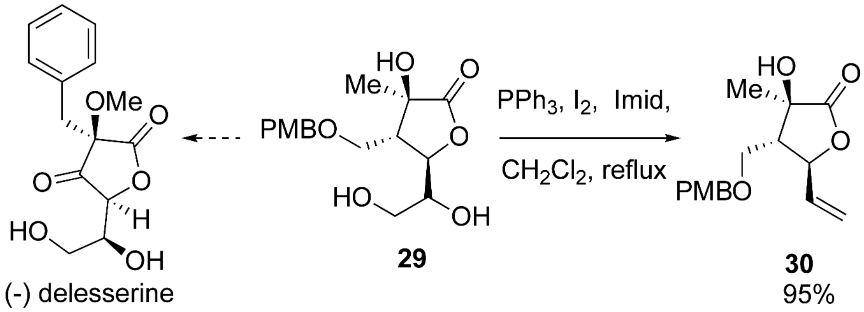
Scheme 11.

Terminally disubstituted alkenes are not tolerated.



Scheme 12.

Silylene transfer products can be converted to γ-lactones (Table 3).

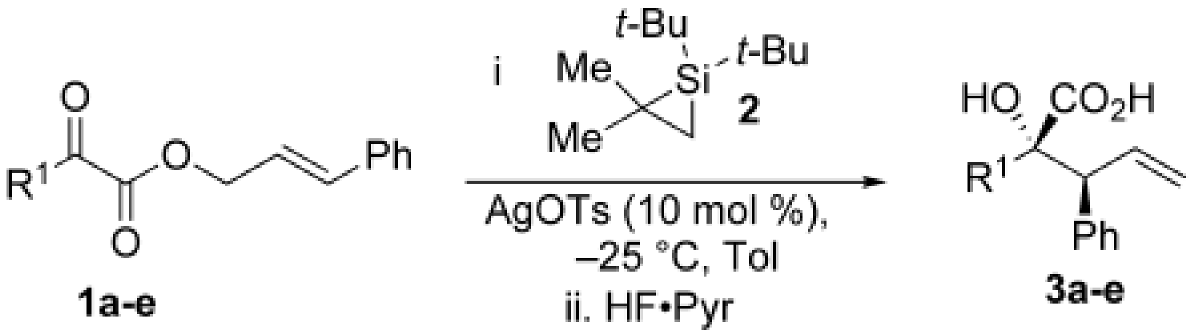


Scheme 13.

Elaboration of lactone products.

Table 1

Silylene transfer to α-keto esters with substitution at R^1

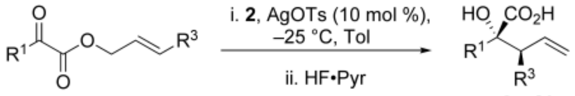


Entry	R^1	Product	% Yield	d.r.
1	Me	**3a**	70	≥97:3
2	Et	**3b**	84	≥97:3
3	*i*-Pr	**3c**	54	≥97:3
4	*t*-Bu	**3d**	47	≥97:3
5	Ph	**3e**	71	≥97:3

Conditions: α-keto ester (1.0 equiv), silacyclopropane **2** (1.5 equiv), AgOTs (0.10 equiv), toluene, −25 °C, 16 h. Then HF·Pyr (4.0 equiv), isolated yields.

Table 2

Silylene transfer to α-keto esters with substitution at R^3



1a, f-i → **2a, f-i**

Entry	R^1	R^3	Product	% Yield	d.r.
1	Me	Ph	**2a**	70	≥97:3
2	Ph	Me	**2f**	62	≥97:3
3	Ph	*n*-Bu	**2g**	72	≥97:3
4	Ph	$CH_2OTBDMS$	**2h**	71	≥97:3
5	Et	$(CH_2)_2OBn$	**2i**	75	≥97:3

Conditions: α-keto ester (1.0 equiv), silacyclopropane **2** (1.5 equiv), AgOTs (0.10 equiv), toluene, −25 °C, 16 h then, HF·Pyr (4.0 equiv), isolated yields.

Table 3

Lactonization conditions and results for the conversion of **27** to **28**

Entry	R^1	R^2	R^3	X	Conditions	Product	% Yield	d.r.
1	Ph	H	H	I	$NaHCO_3$, I_2, CH_3CN, 0 °C	**28a**	91	60:40
2	Me	*n*-Bu	Me	I	I_2, CH_3CN	**28b**	48	80:20
3	Me	*n*-Bu	Me	I	KI, I_2, THF, $NaHCO_3$	**28b**	34	80:20
4	Et	*n*-Bu	H	OH	H_2O, *t*-BuOH, AD mix	**28c**	-	-
5	Et	*n*-Bu	H	I	$NaHCO_3$, I_2, CH_3CN, 0 °C	**28d**	37	80:20
6	Et	*n*-Bu	H	Br	NBS, THF, 0 °C	**28e**	76	83:17
7	Et	*n*-Bu	H	I	NIS, THF 0 °C	**28d**	92	60:40
8	Et	*n*-Bu	H	I	Ti(O*i*-Pr)$_4$, NIS, CH_2Cl_2 −20 °C	**28d**	34	56:44
9	Et	*n*-Bu	H	OH	OsO_4, NMO, CH_2Cl_2	**28c**	73	100:0