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Asymmetric Synthesis of Homocitric Acid Lactone

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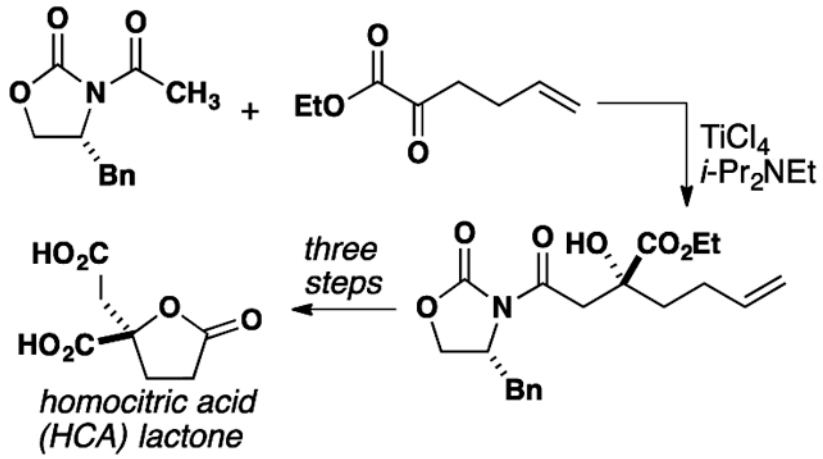
Abstract

A short, diastereoselective synthesis of homocitric acid lactone is described. The key step is a bioinspired aldol addition to set the stereogenic center in an intermediate that requires only modest oxidation state manipulation to complete the synthesis. This approach enables rapid generation of isotopomers in which carbon and hydrogen can be replaced by heavier nuclei at nearly every position.

Graphical Abstract



Introduction

Homocitric acid (HCA), which often occurs in its lactone form (**1**), is an important biosynthetic intermediate and a critical co-factor for nitrogenase.[1–5] The fleeting intermediacy of this compound makes it poorly available from natural sources and has resulted in many approaches to its synthesis from simple starting materials.[6–14] In order to enable the synthesis of isotopomers for spectroscopic studies of nitrogenase, we developed a stereoselective synthesis from diethyl oxalate.[15] Although this approach was reasonably streamlined, the number of steps makes this route cumbersome to larger scale throughput. HCA is made biosynthetically by an aldol addition of acetyl coenzyme A (CoASAc) to alpha ketoglutarate (Figure 1). Chen was able to capitalize on this approach synthetically in

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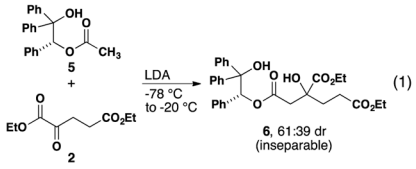
Supporting Information Available Copies of ^{1}H and ^{13}C NMR spectra and, X-ray data are available.

an extremely efficient synthesis of (±)-**1**.[16] Inspired by this result and its potential to offer an extremely short synthesis of (−)-**1**, we examined several approaches to absolute stereocontrol in the aldol addition, culminating in a four-step synthesis.

Results and Discussion

We first attempted to develop an auxiliary controlled variant of Chen's aldol reaction. Although there are few examples of ester-based chiral auxiliaries in aldol reactions, the work of Braun and Robin suggested that diastereocontrol was possible.[17,18] When the enolate derived from double deprotonation of the monoacetate of (+)-1,1,2-triphenylethanol (**5**) was treated with diethyl ketoglutarate (**2**), an appreciable amount of aldol product (69% conversion by NMR) was observed (eq 1). Selectivity was modest (61:39) and chromatographic separation proved to be prohibitively difficult.



(1)

We next turned our attention to the use of imide enolates, which offer reduced basicity and a broader array of substrates for controlling asymmetry. Although these enolates have been in use for nearly four decades, there are few examples of high levels of diastereocontrol from unsubstituted enolates derived from *N*-acetyl imides.[19–25] In addition, imide-based aldol additions rarely involve aldol additions to ketones[26–29] and there are only three cases using α-keto esters.[30–32] Mukaiyama reported that *N*-acetyl thiazolidinethione (**7**) would add to dimethyl ketoglutarate (**8**) with >90% enantiomeric excess (ee) when conducted with chiral amine **9** as a stoichiometric additive (Figure 2A).[30] Later, Chamberlin observed good yield in the addition of *N*-acetyl oxazolidinone (**11**) to benzyl lactate (**12**) with low diastereoselectivity (Figure 2B).[31] Finally, Zanda has reported that *N*-acetyl oxazolidinone (*ent*-**11**) will add to ethyl trifluorolactate (**14**) with diastereoselectivity nearly identical to Chamberlin's via the chlorotitanium enolate (Figure 2C).[32] Importantly, in both cases where the chiral imide-based aldol reactions lacked selectivity, the diastereomeric products were nearly separable by silica gel chromatography.

Armed with these examples, we set out to find the best aldol conditions for the synthesis of an intermediate leading to **1**. First we attempted to reproduce the Mukaiyama example, and no conversion to the desired aldol product was observed.[30] Next, following the other examples, attempted additions of the titanium enolates of both an oxazolidinone and a thiazolidinethione to dimethyl ketoglutarate were unsuccessful.

Inspired by the success of the Evans aldol reaction of benzyl lactate previously investigated by Chamberlin, we reasoned that ketoester **4** might be better behaved as the electrophile, perhaps because the extra ethoxycarbonyl group of **2** might be leading to unproductive modes of coordination to titanium. We first tried the reaction conditions of Chamberlin using LDA, but did not observe any aldol addition. We next turned to a titanium enolate reaction and were gratified to observe significant conversion to product (Table 1). Unfortunately, the

aldol addition products were accompanied by varying quantities of both unreacted acetyloxazolidinone and unsaturated ester **17** resulting from aldol condensation (Table 1, entry 1). The alkene configuration of **17** is assigned on the basis of chemical shift correlation with related compounds.[33] The configuration of the aldol products was deduced after conversion of the major isomer to homocitric acid (Scheme 1, *vide infra*) and confirmed that the modest preference for **16a** matched the results of Chamberlin (Figure 2). The alkene side product could be suppressed by conducting the reaction at lower temperature at the expense of conversion (Table 1, entry 2). Although the aldol product could be formed with little condensation by storing the reaction flask in a −80 °C freezer for 96 h (Table 1, entry 3), the time required and access to a −80 °C freezer made the method undesirable. The best results were obtained using conditions reported by Crimmins, in which N-methylpyrrolidinone (NMP) is used as a Lewis basic additive.[34] Under these conditions, yield is higher with shorter reaction times and elimination is suppressed at the expense of diastereoselectivity (Table 1 entries 4–7). Due to difficulties associated with obtaining the diastereomer ratio (dr) from NMR spectroscopy, dr was determined by isolation in most cases. The accuracy of the yield-based dr was established by direct comparison to the ratio determined by GCMS, which required the conversion of the aldol products to the corresponding TMS ethers to prevent decomposition by retro-aldol reaction during gas chromatography (Table 1, entry 6). When this result was repeated at a shorter reaction time (7.5 h), the isolated yield (41%; Table 1, entry 7) of aldol product 16a was comparable to the conversion observed by GCMS (46%, Table 1, entry 6), with slight variation in the dr. The best results, in terms of generating the largest amount of the major diastereomer, were realized at −40 °C with the use of excess enolate (Table 1, entry 8) or with excess ketoester (Table 1, entry 6). The ability to change the limiting reagent ensures minimum loss of starting materials in a synthesis involving isotopomers. Finally, the use of several oxazolidinone auxiliaries derived from *t*-leucinol, 1-amino-2- indanol, and β-amino-α,α-dimethyl-benzenepropanol (aka “superquat”) all resulted in poorer conversion (not shown).[22,25,35]

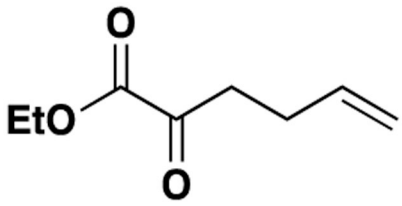
Aldol addition product **16a** could be easily converted into homocitric acid lactone (Scheme 1). Hydrolysis to the methyl ester was achieved in high yield using sodium methoxide. Although oxidative cleavage was variable, this transformation produced **19** in at least 50% yield. Final hydrolysis to HCA was achieved in 71% yield.

In conclusion, we have described a short asymmetric synthesis of homocitric acid lactone. This synthesis was inspired by the biosynthetic pathway that produces natural homocitric acid, and minimizes the use of protecting groups and oxidation state changes. Although the diastereoselectivity of the key step is modest, the ability to reisolate the unreacted oxazolidinone, paired with the small number of steps, makes carrying out the synthesis on gram scale attainable. Based on recent examples of multigram scale titanium-mediated aldol additions, accessing the aldol intermediate on a gram scale is feasible.[36,37] Importantly, the modularity of the starting materials enables the installation of heavy carbon at many points in the molecule to enable spectroscopy experiments that will discern the mechanistic role of this cofactor in nitrogen fixation by nitrogenase.[38]

Experimental Section

General Information and General Methods.

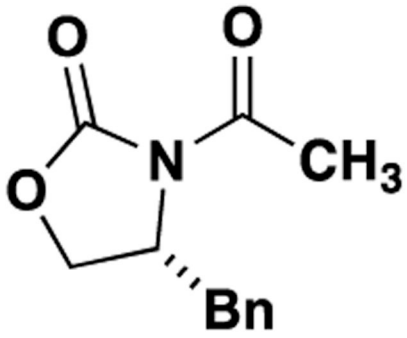
Unless otherwise specified, all commercially available reagents were used as received. All reactions using anhydrous solvents were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Anhydrous solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. Purification of reaction products was carried out by flash chromatography using silica gel F60 (230–400 mesh) or by automated chromatography with an UV/vis detector. Analytical thin layer chromatography was performed on 0.25 mm silica gel F-254 plates. Visualization was accomplished with UV light, $KMnO_4$, or bromocresol green followed by heating. Instrumentation. ^1H NMR spectra and proton-decoupled ^{13}C NMR spectra were obtained on a 400, 600, or 800 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to internal standard (TMS, 0.00 ppm) or residual solvent (CD_3OD, 3.31 ppm). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or combinations of these signals. Infrared spectra were taken on a FTIR spectrometer. Gas chromatography–mass spectrometry data was recorded on a spectrometer using electron impact ionization with an injection temperature of 250 °C and a temperature ramp of 50 to 300 °C (20 min) with a hold at 300 °C (15 min). The column used had a diameter of 0.25 mm and was 30.0 m long and 0.25 μm thick. For AMM analysis, samples were analyzed by flow-injection analysis into an orbitrap mass spectrometer operated in the centroided mode. Samples were injected into a mixture of 50% MeOH and 0.1% formic acid/H2O at a flow of 200 μL/min. Source parameters were 5 kV spray voltage, capillary temperature of 275 °C, and sheath gas setting of 20. Spectral data were acquired at a resolution setting of 100,000 fwhm with the lockmass feature, which typically results in a mass accuracy <2 ppm.



Ethyl 2-oxohex-5-enoate (4).

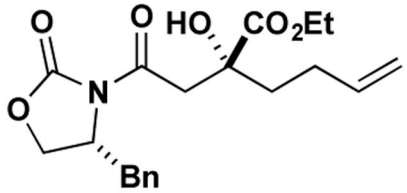
Compound **4** was prepared according to the previously reported procedure.[15] In a flask, magnesium turnings (1.230 g, 50.60 mmol) were stirred vigorously overnight under argon. A solution of 4-bromo-1-butene (2.20 mL, 21.7 mmol) in anhydrous THF (28 mL) was added in drop-wise aliquots over 15 min to the magnesium turnings under argon and stirred for 10 min. The rate of addition was slow enough that the THF did not boil. The solution was carefully drawn-up in a syringe leaving unreacted magnesium in the flask. The Grignard solution was added drop-wise to a flask at −78 °C containing diethyl oxalate (2.44 mL, 18.0 mmol) dissolved in anhydrous Et_2O (35 mL) and anhydrous THF (17.5) and allowed to stir for 4 h at −78 °C. The reaction was quenched with sat. aq. NH_4Cl (20 mL) at −78 °C. After quenching, EtOAc (20 mL) was added to the flask and the flask was allowed to warm to

room temperature. The two layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* with the rotary evaporator bath set to 40 °C and a vacuum that never pulled below 40 torr. The residue was purified by flash chromatography (0:100 to 5:95 EtOAc/hexanes) to give **4** as a slightly yellow oil (3.108 g, 89%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddt, J = 16.8, 10.3, 6.5 Hz, 1H), 5.07 (dd, J = 17.1, 1.6 Hz, 1H), 5.02 (dd, J = 10.3, 1.4 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 2.44 – 2.36 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.9, 161.1, 136.2, 116.0, 62.6, 38.5, 27.1, 14.1. ^{1}H and ^{13}C NMR is consistent with published data.[15]



(*R*)-3-Acetyl-4-benzyloxazolidin-2-one (11).

Compound **11** was prepared according to the previously reported procedure.[39] To a flask containing (*R*)-4-benzyloxazolidin-2-one (5.00 g, 28.2 mmol) and DMAP (0.079 g, 0.65 mmol) in THF (20 mL) was added Et_3N (3.93 mL, 28.2 mmol). The reaction mixture was cooled to 0 °C, and acetic anhydride (5.32 mL, 56.4 mmol) was added dropwise over a period of 5 min. The solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed with H_2O (2 × 20 mL) followed by brine (2 × 20 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (0:100 to 50:50 EtOAc/hexanes) to give **11** as white crystals (6.002 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 2H), 7.31–7.27 (m, 1H), 7.23–7.19 (m, 2H), 4.73–4.62 (m, 1H), 4.25–4.14 (m, 2H), 3.31 (dd, J = 13.4, 3.4 Hz, 1H), 2.78 (dd, J = 13.4, 9.6 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.4, 153.8, 135.4, 129.6, 129.1, 127.5, 66.3, 55.1, 38.0, 24.0; GCMS (EI) m/z calcd for $C_{12}H_{13}NO_3^{\bullet+}$ $[M]^{\bullet+}$ 219.1, found 219.1, t_R = 9.66 min. $[\alpha]_{365}^{23.1} = -194.20$ (c = 0.36, CH_3OH). NMR data matches reported literature values.[39]



Ethyl (*R*)-2-(2-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2-hydroxyhex-5-enoate (16a).

In a flame-dried flask under argon, $TiCl_4$ (1.05 mL of 1.0 M in CH_2Cl_2, 1.05 mmol) was added drop-wise to a solution of **11** (0.219 g, 1.00 mmol) in anhydrous CH_2Cl_2 (10 mL) at −40 °C, and was stirred for 15 min. *i*-Pr_2NEt (0.19 mL, 1.1 mmol) was added drop-wise to the $TiCl_4$ solution, which resulted in an instant color change to dark red. The reaction mixture was stirred for a further 40 min at −40 °C. *N*-Methyl-*2*-pyrrolidone (0.20 mL, 0.19 mmol) was added drop-wise to the solution and allowed to stir for 10 min at −40 °C followed by the addition of **4** (0.078 g, 0.50 mmol) drop-wise. The reaction was stirred for 7.5 h at −40 °C. The reaction was quenched drop-wise with sat. NH_4Cl in CH_3OH (10 mL) over 30 min at −40 °C and then allowed to warm to room temperature. The biphasic mixture was diluted with CH_2Cl_2 (20 mL) and H_2O (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude reaction mixture (or an aliquot) can be protected as a silyl ether using TMSCl (see Supporting Information) to determine the product ratio by GC/MS. The crude mixture was purified by flash chromatography (0:100 to 30:70 EtOAc:hexanes) to give **16a** as a clear oil (0.086 g, 46%).

Major diastereomer 16a:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.19 (d, *J* = 7.4 Hz, 2H), 5.80 (ddt, *J* = 16.9, 10.3, 6.5 Hz, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 4.69 – 4.63 (m, 1H), 4.35 – 4.25 (m, 2H), 4.22 (t, *J* = 8.4 Hz, 1H), 4.17 (dd, *J* = 9.2, 2.6 Hz, 1H), 3.70 (s, 1H), 3.48 (s, 2H), 3.22 (dd, *J* = 13.5, 2.9 Hz, 1H), 2.79 (dd, *J* = 13.5, 9.4 Hz, 1H), 2.31 – 2.23 (m, 1H), 2.05 – 1.96 (m, 1H), 1.89 – 1.80 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.2, 170.6, 153.2, 137.4, 134.9, 129.4, 129.0, 127.4, 115.1, 74.5, 66.3, 62.0, 55.0, 44.6, 38.5, 37.6, 27.3, 14.2; IR (thin film) 3514, 2929, 1782, 1737, 1700 cm^{-1}; AMM (ESI) *m* / *z* calcd for $C_{20}H_{26}NO_6^+$ $[M + H]^+$ 376.1755, found 376.1767. Diastereomer ratio from NMR calculated using the peaks at 3.22 and 3.25 corresponding to major and minor diastereomers respectively.

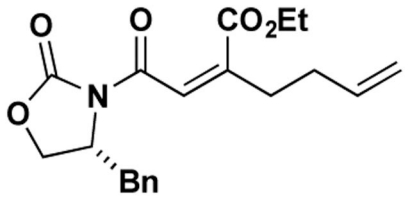
Minor diastereomer 16b:

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.24 (m, 1H), 7.19 (d, *J* = 7.4 Hz, 2H), 5.80 (ddt, *J* = 16.8, 10.4, 6.5 Hz, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 4.97 (d, *J* = 10.1 Hz, 1H), 4.69 – 4.63 (m, 1H), 4.32 – 4.23 (m, 2H), 4.21 (t, *J* = 8.5 Hz, 1H), 4.17 (dd, *J* = 9.1, 3.2 Hz, 1H), 3.78 (s, 1H), 3.52 (d, *J* = 18.0 Hz, 1H), 3.43 (d, *J* = 18.0 Hz, 1H), 3.25 (dd, *J* = 13.5, 3.0 Hz, 1H), 2.80 (dd, *J* = 13.5, 9.3 Hz, 1H), 2.33 – 2.24 (m, 1H), 2.03 – 1.95 (m, 1H), 1.89 – 1.79 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.3, 170.9, 153.4, 137.6, 135.0, 129.5, 129.1, 127.5, 115.2, 74.7, 66.4, 62.0, 54.9, 44.8, 38.6, 37.7, 27.5, 14.3; IR (thin film) 3525, 2981, 1782, 1737, 1700 cm^{-1}; AMM (ESI) *m* / *z* calcd for $C_{20}H_{26}NO_6^+$ $[M + H]^+$ 376.1755, found 376.1758.

TMS Ether of 16a.

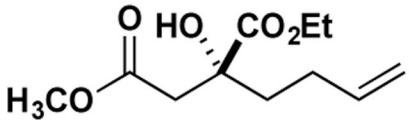
In a flame-dried flask under argon, imidazole (0.294 g, 4.32 mmol) was added to the crude reaction mixture (0.081 g) from the aldol reaction in CH_2Cl_2 (5.4 mL) followed by TMSCl (0.55 mL, 4.32 mmol) and stirred at room temperature for 24 h. The reaction was quenched

with saturated aq $NaHCO_3$ (8 mL). The resulting solution was extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was washed with brine (10 mL) and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (0:100 to 40:60 EtOAc:hexanes) to give the TMS ether of **16a** as a clear oil (0.038 g, 17% over two steps). GCMS of the crude reaction mixture gave a product ratio of (11:16a:16b = 26:46:28): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–7.31 (m, 2H), 7.29– 7.25 (m, 1H), 7.22–7.19 (m, 2H), 5.81 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.05 (dd, J = 17.2, 1.7 Hz, 1H), 4.98 (dd, J = 10.3, 1.6 Hz, 1H), 4.72–4.64 (m, 1H), 4.28–4.20 (m, 2H), 4.19 (d, J = 8.2 Hz, 1H), 4.15 (dd, J = 9.1, 3.2 Hz, 1H), 3.71 (d, J = 17.0 Hz, 1H), 3.29–3.21 (m, 2H), 2.82 (dd, J = 13.5, 9.1 Hz, 1H), 2.27–2.18 (m, 1H), 2.18–2.10 (m, 1H), 1.91–1.83 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.4, 169.8, 153.6, 137.9, 135.2, 129.7, 129.1, 127.5, 115.0, 77.8, 66.1, 61.3, 55.0, 44.6, 39.4, 37.7, 27.9, 14.3, 2.5; IR (thin film) 2981, 1782, 1752, 1707 cm–1 ; GCMS (EI) m/ z calcd for $C_{22}H_{30}NO_6Si^{\bullet+}$ $[M - CH_3]^{\bullet+}$ 432.2, found 432.3, t_R = 14.10 min; AMM (ESI) m/z calcd for $C_{23}H_{33}NO_6Si^+$ $[M + H]^+$ 448.2150, found 448.2149. $[\alpha]_{365}^{22.8} =$ – 247.72 (*c* = 0.80, CH_3OH).



Ethyl (*R*,*Z*)-2-(2-(4-benzyl-2-oxooxazolidin-3-yl)-2-oxoethylidene)hex-5-enoate (17).

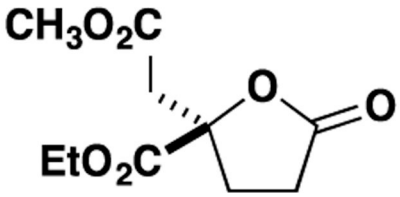
Recovered during aldol reactions with **4** and **11**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.27 (m, 1H), 7.22 (d, *J* = 7.4 Hz, 2H), 6.98 (t, *J* = 1.5 Hz, 1H), 5.83 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.10 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.04 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.74 – 4.68 (m, 1H), 4.36 – 4.25 (m, 2H), 4.25 – 4.20 (m, 1H), 4.18 (dd, *J* = 9.1, 2.9 Hz, 1H), 3.35 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.80 (dd, *J* = 13.5, 9.6 Hz, 1H), 2.57 – 2.50 (m, 2H), 2.37 – 2.29 (m, 2H), 1.33 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 168.7, 164.3, 153.4, 148.5, 136.60, 135.3, 129.6, 129.1, 129.1, 121.8, 116.1, 66.5, 61.5, 55.2, 37.8, 33.8, 31.4, 14.2; IR (thin film) 3029, 1782, 1730, 1689, 1640 cm^{-1}; AMM (ESI) *m / z* calcd for $C_{20}H_{24}NO_5^+$ $[M + H]^+$ 358.1649, found 358.1651.



1-Ethyl 4-methyl (*R*)-2-(but-3-en-1-yl)-2-hydroxysuccinate (18).

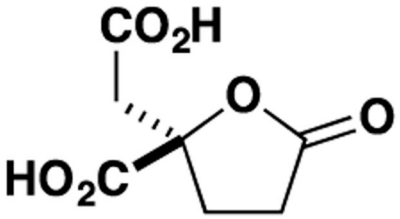
To a flame-dried flask under argon containing the major diastereomer (**16a**) (0.150 g, 0.400 mmol) in CH_3OH (6.0 mL) was added a solution of sodium methoxide (0.032 g, 0.592 mmol) in CH_3OH (4.0 mL) drop-wise at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and quenched with sat. aq. NH_4Cl (10 mL). The resulting solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (0:100 to 30:70

EtOAc:hexanes) to give **18** as a clear oil (0.092 g, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.02 (dd, *J* = 17.2, 1.5 Hz, 1H), 4.96 (dd, *J* = 10.1, 1.6 Hz, 1H), 4.32 – 4.23 (m, 2H), 3.71 (s, 1H), 3.68 (s, 3H), 2.94 (d, *J* = 16.1 Hz, 1H), 2.71 (d, *J* = 16.2 Hz, 1H), 2.28 – 2.19 (m, 1H), 1.99 – 1.90 (m, 1H), 1.84 – 1.74 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 174.8, 171.1, 137.4, 115.1, 74.7, 62.0, 51.8, 43.4, 38.3, 27.4, 14.1; IR (thin film) 3510, 2959, 1737, 1644 cm^{-1}; AMM (ESI) *m* / *z* calcd for $C_{11}H_{19}O_5^+$ $[M + H]^+$ 231.1227, found 231.1228.



Ethyl (*R*)-2-(2-methoxy-2-oxoethyl)-5-oxotetrahydrofuran-2-carboxylate (19).

To a flask containing **18** (0.167 g, 0.725 mmol) in EtOAc/CH_3CN/H_2O (5.3 mL, 2:2:3 by volume) was added $NaIO_4$ (0.826 g, 3.86 mmol) followed by ruthenium(III) chloride hydrate (4.4 mg, 0.021 mmol). The solution was stirred at room temperature for 1 h during which a light brown precipitate formed. The reaction was quenched with *i*-PrOH (20 mL) and filtered through Celite. The filter pellet was washed with additional *i*-PrOH (4 × 15 mL) and the filtrate was collected and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (10:90 to 100:0 EtOAc:hexanes) to give **19** as a clear oil (0.0926 g, 55%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.34 – 4.23 (m, 2H), 3.71 (s, 3H), 3.13 (d, *J* = 16.7 Hz, 1H), 2.98 (d, *J* = 16.8 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.65 – 2.53 (m, 2H), 2.40 – 2.32 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 175.5, 170.5, 169.1, 83.0, 62.6, 52.2, 41.4, 31.3, 27.9, 14.1; IR (thin film) 2959, 1789, 1737, 1164 cm^{-1}; AMM (ESI) *m* / *z* calcd for $C_{10}H_{15}O_6^+$ $[M + H]^+$ 231.0863, found 231.0863.



(*R*)-(−)-2-(carboxymethyl)-5-oxotetrahydrofuran-2-carboxylic acid ((−)-1) 19

(0.0449 g, 0.195 mmol) was dissolved in TFA/H_2O (2 mL, 1:1 by volume) and heated to reflux for 24 h. The reaction mixture was concentrated and left on the high vacuum (~ 1 torr) for 4 h. If necessary the product was purified on a short silica plug (0:100 to 40:60 acetone:hexanes) but generally no further purification was necessary to give (−)-**1** as an amorphous white solid (0.031 g, 85%). If a column was deemed necessary fractions were assayed for product by spotting on a TLC and staining with bromocresol green, any fractions containing acidic products were collected. ^{1}H NMR (600 MHz, CD_3OD) δ 3.16 (d, *J* = 17.1 Hz, 1H), 2.94 (d, *J* = 17.1 Hz, 1H), 2.70 – 2.56 (m, 2H), 2.54 – 2.46 (m, 1H), 2.43 – 2.34 (m,

1H); ^{13}C NMR (151 MHz, CD_3OD) δ 178.7, 174.1, 172.4, 84.7, 42.1, 32.3, 28.7. $[\alpha]_D^{20.2} = -6.01$. NMR data matches reported literature values.[15]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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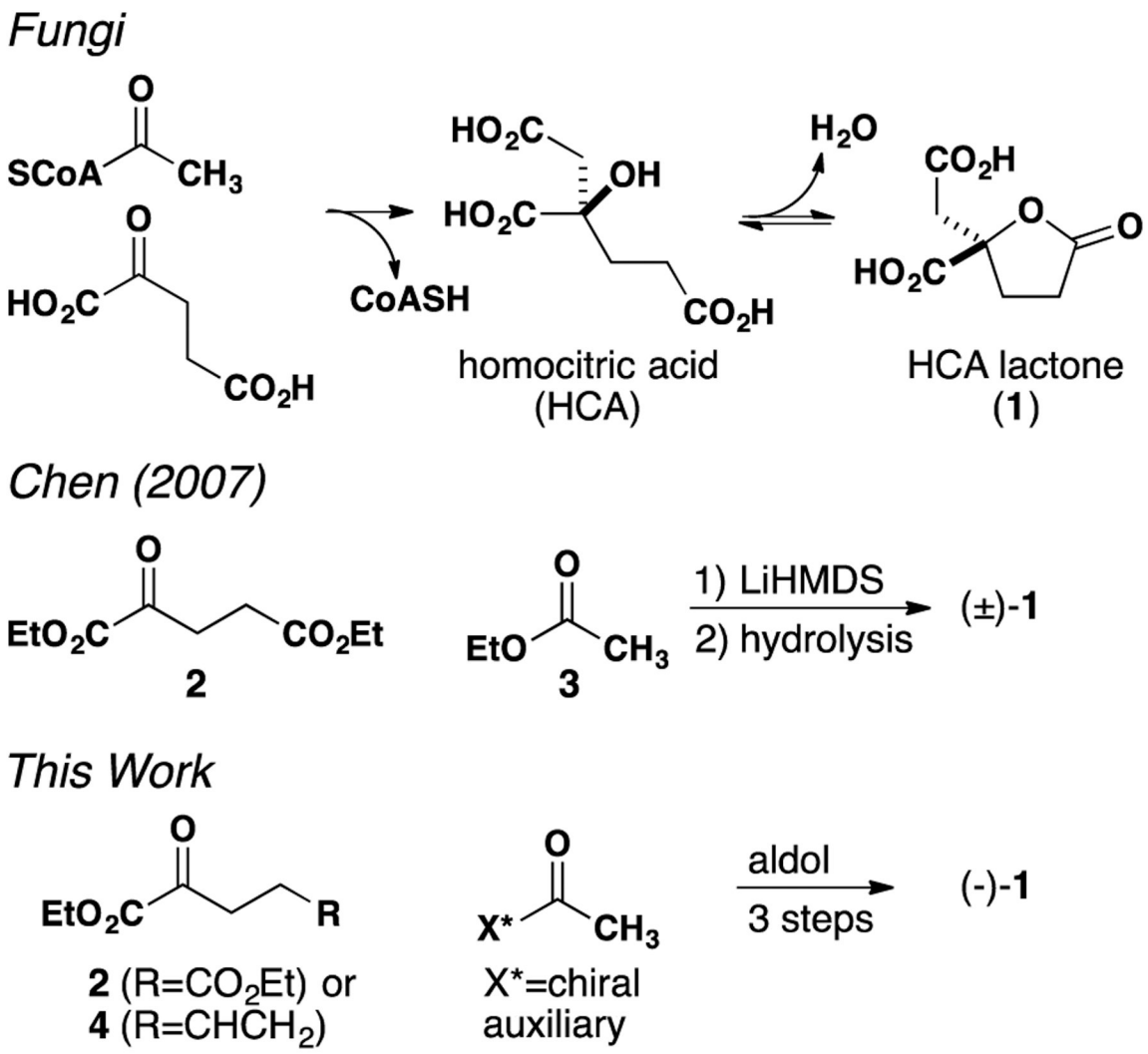


Figure 1.

Biosynthesis of **1** by fungi and the biomimetic approaches to the chemical synthesis of **1**.

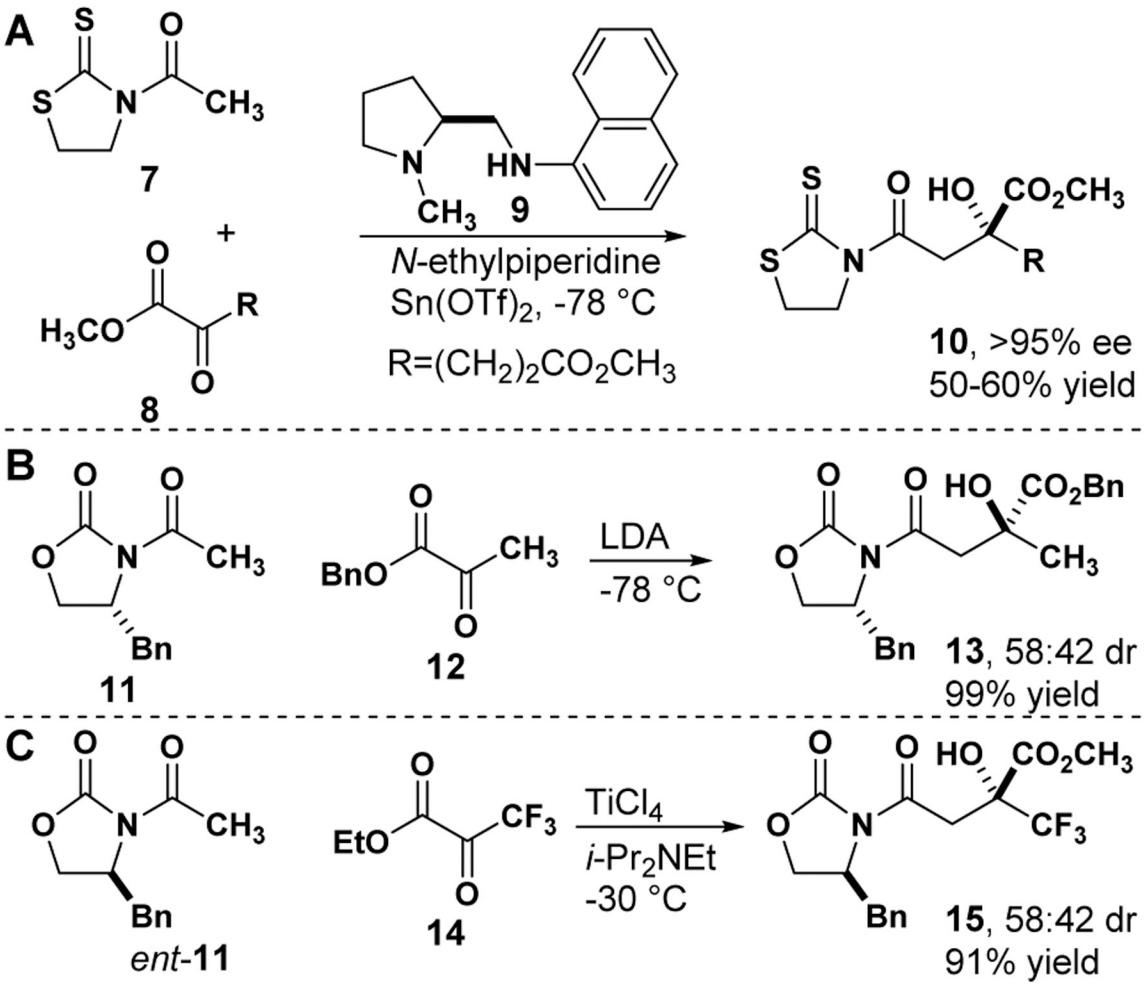
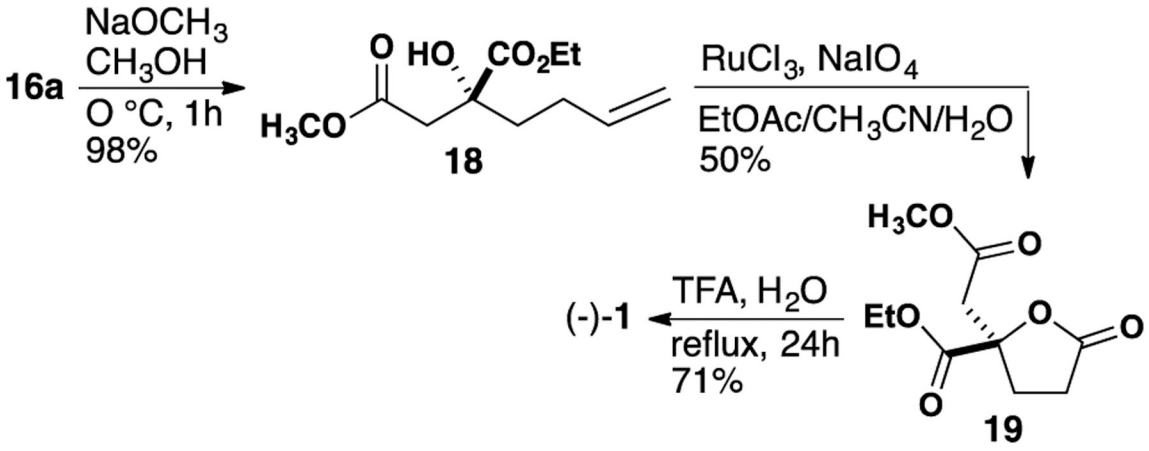


Figure 2.
Summary of acetate aldol reactions of α-keto esters.

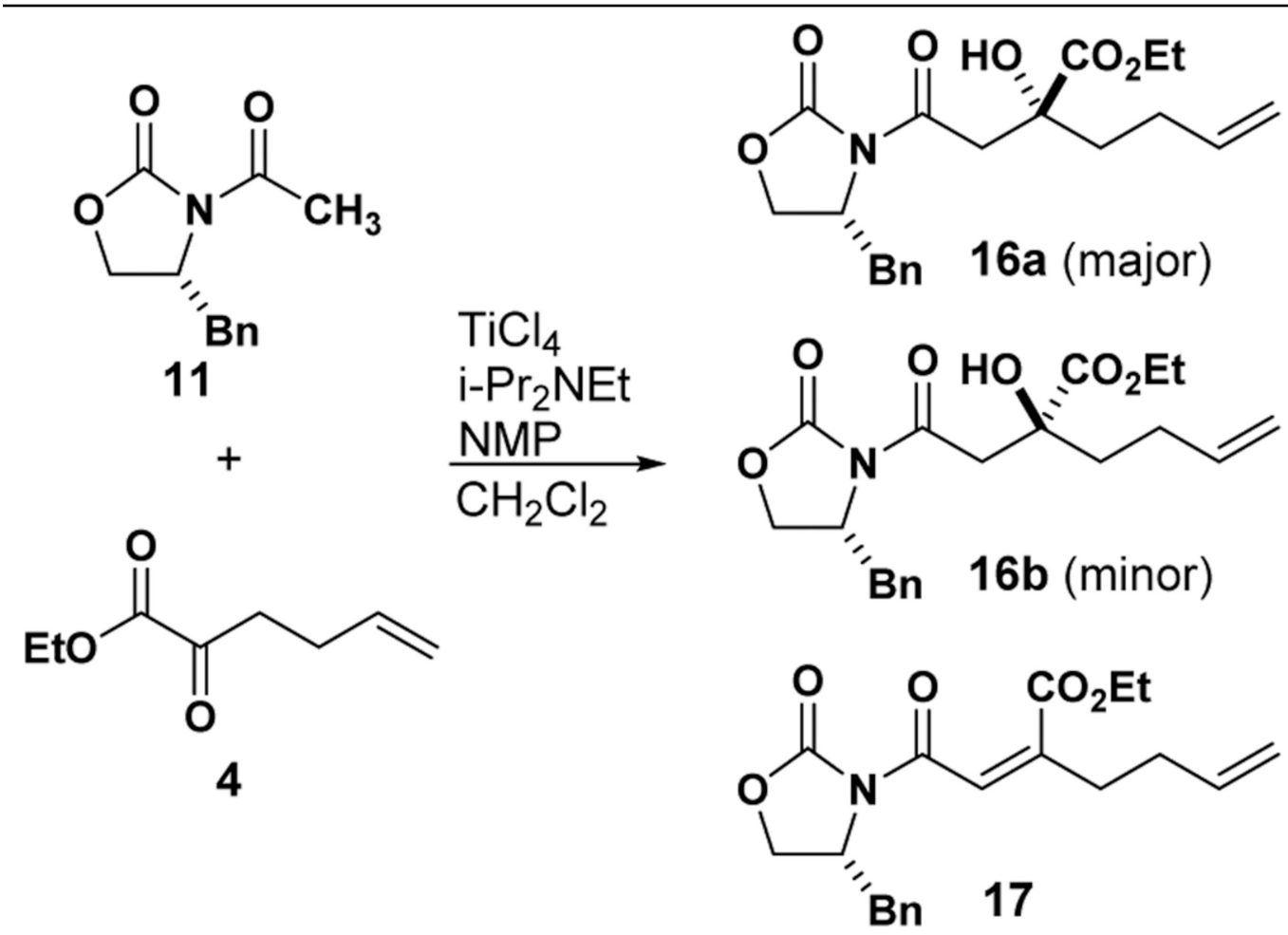


Scheme 1.

Conversion of aldol product **16a** to (−)-HCA (**1**).

Table 1.

Aldol addition reactions of 11+ 4.



entry[a]	temp.; time	NMP (equiv.)	conv. (%)[b]	aldol:elim[b] (16a +16b):17	dr[c] 16a:16b	yield of 16a (%)
1[d]	−78 to −60 °C; 5 h	0	60	79:21	51:49[b]	N/A
2[d]	−78 °C; 5 h	0	50	93:7	72:28	36
3	−78 °C; 96 h	0	77	83:17	71:29	42
4	−78 to 0 °C; 5 h	2.0	68	77:23	54:46	31
5	−78 to −40 °C; 8 h	2.0	75	93:7	63:37	34
6	−40 °C; 11 h	2.0	77	96:4	62:38[e]	46[e]
7	−40 °C; 7.5 h	20	73	95:5	56:44	41
8[f]	−40 °C: 7.5 h	20	88	95:5	53:47	46

[a] unless otherwise specified reactions were completed with 1 equiv. of **11** (orenf-**11**)to 1.1 equiv. of **4**.

[b] determined by integration in the ^{1}H NMR spectrum,

[c] determined based on isolated yield, unless otherwise noted. See experimental section for details,

[d] prepared with *ent*-**11**.

[e] determined by GCMS after converting to TMS ether. See supporting information,

[f] completed with 2 equiv. of **11** to **1** equiv. of **4**.