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Tetrahedron Letters 48 (2007) 5976–5980
Tetrahedron Letters

A one-pot combination of amine and heterocyclic carbene catalysis: direct asymmetric synthesis of β-hydroxy and β-malonate esters from α,β-unsaturated aldehydes

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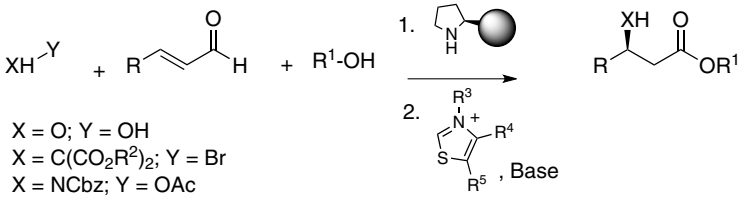
Received 17 May 2007; revised 11 June 2007; accepted 20 June 2007
Available online 26 June 2007

Abstract—The one-pot combination of amine and heterocyclic carbene catalysis (AHCC) enabled the synthesis of β-hydroxy, β-malonate and β-amino esters from α,β-unsaturated aldehydes with high enantioselectivity (91–97% ee).

Organocatalysis is a rapidly growing research field.[1] In particular, amine catalysis that relies on a catalytic cycle, which involves enamine and iminium intermediates has proven to be a powerful method for asymmetric reactions with carbonyl compounds.[2] For example, it has been successfully employed in the enantioselective syntheses of formyl functionalized epoxides,[3] cyclopropanes[4] and aziridines[5] using α,β-unsaturated aldehydes as acceptors. Another important method for the activation of unmodified carbonyl compounds is heterocyclic carbene catalysis.[6] This type of catalysis depends on the activation of aldehydes by forming hydroxy-enamine-type Breslow intermediates[7] with the heterocyclic carbene. In this context, Bode has recently shown that 2-epoxy and 2-cyclopropyl aldehydes can be converted into the corresponding acyclic esters under mild conditions.[8,9] Inspired by this research and our previous experience in amino catalysis,[10] we became interested in whether amine and heterocyclic carbene catalysis (AHCC) could be combined in one-pot for the biomimetic assembly of useful chiral molecules such as β-functionalized esters (Eq. 1, Scheme 1).



(1)

Thus, iminium activation of enals **1** followed by enantioselective conjugate addition of nucleophiles **2**, **3** and **4** followed by intramolecular 3-*exo*-*tet* cyclization by the in situ generated chiral enamine would furnish the corresponding 2-epoxy, 2-cyclopropyl and 2-aziridine aldehydes **5**, **6** and **7**, respectively (Scheme 1). Next, the base generated heterocyclic carbene catalysts would catalyze the C–O, C–C or C–N bond-cleavage ring opening followed by concomitant oxidation of the aldehyde and subsequent esterification. If successful, the one-pot AHCC process would be a highly enantioselective entry to β-functionalized esters **8**–**10**. Herein, we present the first novel one-pot combination of asymmetric AHCC that transforms widely available enals into

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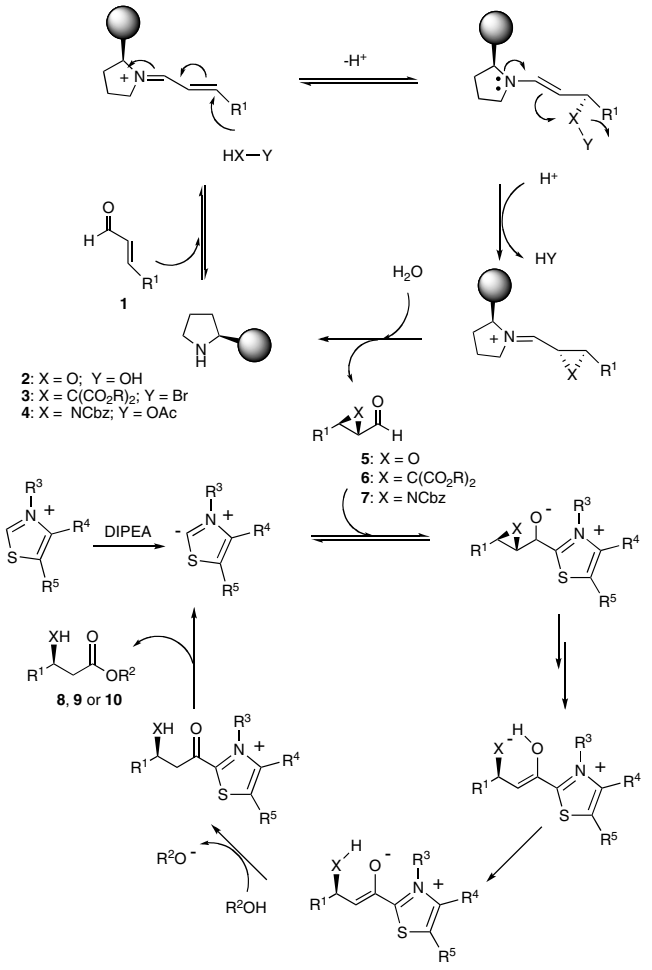
doi:10.1016/j.tetlet.2007.06.110



Scheme 1. One-pot combination of enantioselective AHCC catalysis.

β-functionalized esters, including acetate aldol adducts, in good to high yields and 91–97% ee under practical conditions.

After extensive screening of the one-pot asymmetric conversion of cinnamic aldehyde **1a** to β-hydroxy ester **8a** by AHCC, we found that the use of TMS protected diphenylprolinol **11**[11] and thiazolium precatalyst **12**[8] in $CHCl_3$ gave the best results with respect to the ee of **8a** (Eq. 2).

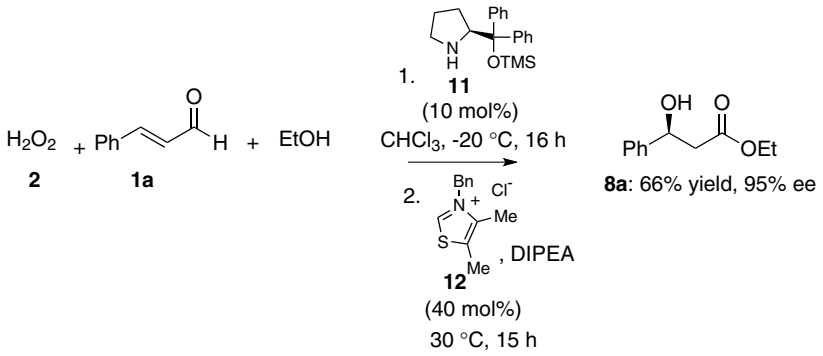
of **11** (10 mol %) in $CHCl_3$ (2 mL) and EtOH (1.5 mmol) at −20 °C. After 16 h the reaction was allowed to reach room temperature and **12** (40 mol %) and DIPEA (80 mol %) were added. Next, the reaction mixture was vigorously stirred for 15 h at 30 °C. Following work-up, β-hydroxy ester **8a** was isolated in 66% yield with 95% ee. Encouraged by this result we investigated this AHCC procedure for different enals **1** (Table 1).

We found that the reaction was general for a variety of enals **1** and alcohols. Thus EtOH and BnOH reacted with the in situ generated 2-epoxyaldehyde **5f** to form the corresponding β-hydroxy esters **8f** and **8g**, respectively, in good yields and high ee's (entries 5 and 6). In all the cases investigated, β-hydroxy esters **8** were isolated in good to high yields with 91–95% ee. Thus, this chemistry offers a valuable, highly enantioselective direct catalytic approach to β-hydroxy esters.[12] Notably, this class of compounds cannot be prepared by the otherwise successful amine-catalyzed direct asymmetric aldol methodology.[13] Moreover, **8a** can be readily transformed in high overall yield to *S*-Fluxoteine (Prozac®).[14]

We next embarked on the utilization of asymmetric AHCC for the conversion of enals **1** to β-malonate esters **9**. (Table 2).

After extensive screening, we found that enals **1** (0.3 mmol) were efficiently converted to the corresponding β-malonate esters **9** by reaction with 2-bromomalonate **3** (0.25 mmol) in the presence of catalyst **11** (20 mol %), precatalyst **12** (20 mol %) and DIPEA (40 mol %) in $CHCl_3$ (1 mL) and alcohol (0.75 mmol) solutions. TEA (0.25 mmol) was added as a proton sponge. Following work-up, esters **9** were isolated in good to high yields with excellent ee's (95–97% ee). For example, β-malonate ester **9d** was isolated in 68% overall yield with 96% ee (entry 4). Thus, the one-pot asymmetric AHCC was a practical method for the highly enantioselective synthesis of valuable β-malonate esters.[15]

The one-pot asymmetric AHCC was not only limited to the conversion of enals to β-hydroxy esters and

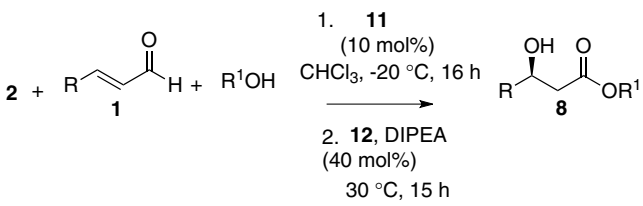


(2)

The optimized conditions involved addition of enal **1a** (0.5 mmol) and H_2O_2 (0.6 mmol) to a reaction mixture

β-malonate esters but also, for example, to the conversion of 2-heptenal **1g** to the corresponding β-amino acid

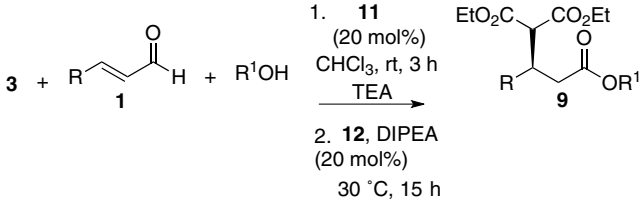
Table 1. One-pot catalytic tandem asymmetric epoxidation/esterification of various enals



Entry	R	R^1	Product	Yield[a] (%)	ee[b] (%)
1	Ph	Et	**8a**	66	95
2	4-ClC_6H_4	Et	**8b**	67	95
3	*n*-Bu	Et	**8c**	82[c]	91[c]
4	*n*-Pr	Et	**8d**	62	93
5	Me	Et	**8e**	59	93
6	CO_2Et	Et	**8f**	71[c]	94[c]
7	CO_2Et	Bn	**8g**	66[d]	91[d]

[a] Isolated yield of the pure product compound **8**.
[b] Determined by chiral-phase HPLC or GC analyses.
[c] Catalyst **12** and DIPEA were added after 6 h of reaction at 4 °C.
[d] BnOH was added together with **12**.

Table 2. Catalytic tandem asymmetric cyclopropanation/esterification of enals



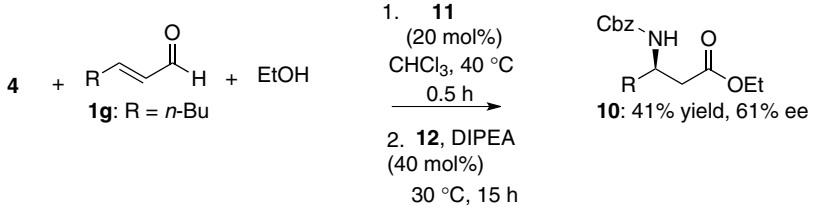
Entry	R	R^1	Product	Yield[a] (%)	ee[b] (%)
1	Ph	Et	**9a**	69	97
2	Ph	Me	**9b**	56 (74)[c]	97 (94)[c]
3	4-$NO_2C_6H_4$	Me	**9c**	66[d]	95
4	2-Naphth	Me	**9d**	68[e]	96

[a] Isolated yield of the pure product **9** after silica gel chromatography.
[b] Determined by chiral-phase HPLC analyses.
[c] 30 mol % **12**.
[d] Reaction first run for 1.5 h at rt followed by addition of **12**.
[e] Reaction first run for 6 h at 4 °C followed by addition of **12**.

ester **10** by reaction with *N*-Cbz protected amine **4** followed by subsequent esterification (Schemes 1 and 2).

Modification of the in situ catalytic esterification step by decreasing the temperature to −20 °C improved the ee of **10** to 83% but decreased the yield to 20%. Nevertheless, this result points to a broader scope for a one-pot combination of AHCC and offers a direct approach to β-amino acids.

Comparison with the literature revealed that the absolute configurations of **8a** and **9b** at C3 was *S* (**8a**: $[\alpha]_D^{25}$ −34.5 (*c* 1, $CHCl_3$)), lit. ($[\alpha]_D^{25}$ −52 (*c* 1, $CHCl_3$))[14] and *R* (**9b**: $[\alpha]_D^{25}$ −17.0 (*c* 1, $CHCl_3$)), lit. ($[\alpha]_D^{25}$ −29 (*c* 0.1,



Scheme 2. One-pot catalytic tandem asymmetric aziridination/esterification of **1g**.

$CHCl_3$)[16]), respectively. Thus, the stereochemistry of the AHCC reactions is directed by catalyst **11** as depicted in Scheme 1. This is in accordance with previous reactions catalyzed by chiral amine **11**.[5]

In summary, we report that asymmetric AHCC can be employed for the direct catalytic conversion of α,β-unsaturated aldehydes to valuable β-functionalized esters in good to high yields with up to 97% ee. The one-pot combination or linkage of amine and heterocyclic carbene catalysis opens up the possible biomimetic asymmetric assembly of highly functionalized optically active molecules from simple starting materials under mild conditions. Further expansion of AHCC to other reactions involving unmodified aldehydes and enals are ongoing in our laboratory.

Acknowledgements

We gratefully acknowledge the Swedish National Research Council and Carl-Trygger Foundation for financial support.

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12. *General one-pot reaction procedure for the preparation of* β-*hydroxy esters* **8**: A stirred solution of (*S*)-**11** (16 mg, 10 mol %) in $CHCl_3$ (2 mL) and EtOH (88 μL, 3.0 equiv) was cooled to −20 °C and to this solution, enal **1** (0.5 mmol) and H_2O_2 (0.6 mmol, 50% aqueous solution) were added sequentially. The reaction was vigorously stirred for 16 h at −20 °C. Next, the reaction mixture was allowed to reach room temperature and DIPEA (68 μL, 0.4 mmol) and thiazolium precatalyst **12** (48 mg, 0.2 mmol) were added. The temperature of the resulting yellow solution was increased to 30 °C and stirring continued for 15 h. Next, the reaction mixture was treated with satd aq NH_4Cl and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (pentane/ethyl acetate or pentane/Et_2O) to give the corresponding product **8**. *(S)-Ethyl 3-hydroxy-3-phenylpropanoate* **8a**:[14] $[\alpha]_D^{25}$ −34.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H), 7.30–7.26 (m, 1H), 5.13 (dd, *J* = 4.0, 8.8 Hz, 1H), 4.18 (q, *J* = 7.6 Hz, 2H), 3.31 (br s, 1H), 2.76 (dd, *J* = 8.8, 16.4 Hz, 1H), 2.70 (dd, *J* = 4.0, 16.4 Hz, 1H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 142.6, 128.7, 127.9, 125.8, 70.5, 61.0, 43.5, 14.3. The ee was determined by HPLC on Daicel Chiralpak OJ with *iso*-hexane/*i*-PrOH (94:6) as the eluent: minor isomer: t_R = 26.671 min; major isomer: t_R = 28.508 min; HRMS(ESI) the exact mass calculated for $[M+H]^+$ ($C_{11}H_{15}O_3$) requires *m*/*z* 195.1016, found *m*/*z* 195.1006.
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15. *One-pot reaction procedure for the synthesis of tri-carboxylate esters* **9a** *and* **9b** *from enal* **1a**: To a stirred solution of (*S*)-**11** (16 mg, 20 mol %) in $CHCl_3$ (1 mL), were added *trans*-cinnamic aldehyde **1a** (0.3 mmol), $BrCH(CO_2Et)_2$ (0.25 mmol), Et_3N (0.25 mmol) and EtOH or MeOH (3.0 equiv). The reaction was vigorously stirred at room temperature for 3 h. Next, DIPEA (40 mol %) and thiazolium precatalyst **12** (20 mol %) were added and the temperature was increased to 30 °C. After 15 h of stirring the reaction mixture was treated with satd aq NH_4Cl (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 6:1) to afford the corresponding esters **9a** or **9b**, respectively. *(R)-2-Ethoxycarbonyl-3-phenylpentanedioic acid diethyl ester* **9a**: $[\alpha]_D^{25}$ −8.4 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.21 (m, 5H), 4.21 (q, *J* = 7.2 Hz, 2H), 3.90–4.00 (m, 5H), 3.72 (d, *J* = 10.4 Hz, 1H), 2.84 (dd, *J* = 5.2, 15.6 Hz, 1H), 2.72 (dd, *J* = 10.0, 15.6 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 168.2, 167.7, 140.0, 128.5, 128.4, 127.4, 61.8, 61.5, 60.6, 57.5, 41.7, 38.9, 14.19, 14.15, 13.9; The ee of the product was determined by chiral

HPLC analysis (Chiralpak Ad column, hexane/2-propanol = 95:5, 0.5 mL/min, 210 nm, t_R (major) = 24.714 min, t_R (minor) = 38.629 min); HRMS(ESI) the exact mass calculated for $[M+Na]^+$ ($C_{18}H_{24}O_6Na$) requires *m/z* 359.1465, found *m/z* 359.1476. *(R)-2-Ethoxycarbonyl-3-phenylpentanedioic acid 1-ethyl ester 5-methyl ester* **9b**: $[\alpha]_D^{25}$ −16.8 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.19 (m, 5H), 4.20 (q, $J = 7.2$ Hz, 2H), 3.92 (q, $J = 7.2$ Hz, 2H), 3.92–3.87 (m, 1H), 3.74 (d, $J = 7.2$ Hz, 1H), 3.52 (s, 3H), 2.86 (dd, $J = 4.5$, 15.6 Hz, 1H), 2.74 (dd, $J = 6.9$, 15.6 Hz, 1H), 1.26 (t, $J = 7.2$ Hz, 3H), 0.98 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.7, 168.1, 167.6, 140.0, 128.5, 128.2, 127.4, 61.8, 61.5, 57.4, 51.7, 41.6, 38.7, 14.2, 13.8. The ee of the product was determined by chiral HPLC analysis (Chiralpak ODH column, hexane/2-propanol = 97:3, 1.0 mL/min, 210 nm, t_R (minor) = 15.513 -min, t_R (major) = 18.297 min); HRMS(ESI) the exact mass calculated for $[M+Na]^+$ ($C_{17}H_{22}O_6Na$) requires *m/z* 345.1309, found *m/z* 345.1306. *One-pot reaction procedure for the synthesis of tri-carboxylate ester* **9c**: To a stirred solution of (*S*)-**11** (16 mg, 20 mol %) in $CHCl_3$ (1 mL), *trans*-4-nitro-cinnamic aldehyde (0.3 mmol), $BrCH(CO_2Et)_2$ (0.25 mmol), Et_3N (0.25 mmol) and MeOH (30 μL, 3.0 equiv) were added sequentially. The reaction mixture was vigorously stirred for 1.5 h at room temperature. Next, DIPEA (40 mol %) and thiazolium precatalyst **12**[8] (20 mol %) were added and the temperature was increased to 30 °C. After stirring for 15 h, the reaction mixture was treated with satd aq NH_4Cl (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 6:1) to afford the corresponding ester **9c**. *(R)-2-Ethoxycarbonyl-3-(4-nitrophenyl)-pentanedioic acid 1-ethyl ester 5-methyl ester* **9c**: $[\alpha]_D^{25}$ −20.4 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, $J = 8.8$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 4.22 (dq, $J = 1.2$, 7.2 Hz, 2H), 4.07–4.03 (m, 1H), 3.97 (dq, $J = 2.4$, 7.2 Hz, 2H), 3.76 (d, $J = 10.0$ Hz, 1H), 3.54 (s, 3H), 2.91 (dd, $J = 4.8$, 16.4 Hz, 1H), 2.78 (dd, $J = 10.0$, 16.4 Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.04 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 167.6, 167.2, 147.9, 147.3, 129.4, 123.8, 62.2, 61.9, 56.7, 52.0, 41.1, 38.1, 14.2, 14.0. The ee of the product was determined by chiral HPLC analysis (Chiralpak ODH column, *n*-hexane/2-propanol = 90:10, 0.5 mL/min, 210 nm, t_R (major) = 26.499 min, t_R (minor) = 32.644 min); HRMS (ESI) the exact mass calculated for $[M+Na]^+$ ($C_{17}H_{21}O_8NNa$) requires *m/z* 390.1159, found *m/z* 390.1150. One-pot reaction procedure for the synthesis of tri-carboxylate ester **9d**: To a stirred solution of (*S*)-**11** (16 mg, 20 mol %) in $CHCl_3$ (1 mL) at 4 °C, 3-(2-naphthyl)-2-propenal (0.3 mmol), $BrCH(CO_2Et)_2$ (0.25 mmol), Et_3N (0.25 mmol) and MeOH (30 μL, 3.0 equiv) were added sequentially. The resulting reaction mixture was vigorously stirred for 6 h at 4 °C. Next, DIPEA (40 mol %) and thiazolium precatalyst **12** (20 mol %) were added and the temperature was increased to 30 °C. After 15 h of stirring, the reaction mixture was treated with satd aq NH_4Cl (1 mL) and extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 6:1) to afford the corresponding ester **9d**. *(R)-2-Ethoxycarbonyl-3-(2-naphthyl)-pentanedioic acid 1-ethyl ester 5-methyl ester* **9d**: $[\alpha]_D^{25}$ −17.3 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79–7.76 (m, 3H), 7.70 (d, $J = 1.2$ Hz, 1H), 7.46–7.43 (m, 2H), 7.39 (dd, $J = 1.2$, 8.8 Hz, 1H), 4.23 (q, $J = 7.2$ Hz, 2H), 4.11 (ddd, $J = 4.8$, 10.0, 10.0 Hz, 1H), 3.92–3.85 (m, 3H), 3.50 (s, 3H), 2.95 (dd, $J = 4.8$, 15.6 Hz, 1H), 2.87 (dd, $J = 10.0$, 15.6 Hz, 1H), 1.27 (t, $J = 7.2$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 168.1, 167.6, 137.6, 133.4, 132.8, 128.3, 128.0, 127.7, 127.2, 126.22, 126.16, 125.9, 61.9, 61.5, 57.4, 51.7, 41.6, 38.6, 14.2, 13.8. The ee of the product was determined by chiral HPLC analysis (Chiralpak Ad column, *n*-hexane/2-propanol = 80:20, 0.5 mL/min, 210 nm, t_R (major) = 18.178 min, t_R (minor) = 28.392 min); HRMS (ESI) the exact mass calculated for $[M+Na]^+$ ($C_{21}H_{24}O_6Na$) requires *m/z* 395.1465, found *m/z* 395.1459.

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