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Organocatalytic Enantioselective Michael Addition of α-Nitroacetate to α,β-Unsaturated Enones: A Route to Chiral γ-Nitro Ketones and δ-Keto Esters

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The catalytic enantioselective conjugate addition reaction of α-nitroacetate to α,β-unsaturated enones promoted by chiral bifunctional organocatalysts is described. The treatment of α-nitroacetate to α,β-unsaturated enones afforded the corresponding Michael adducts with high enantioselectivity. The conjugate addition adducts are easily converted to chiral γ-nitro ketones and δ-keto esters.

Key Words: Bifunctional organocatalysts, Asymmetric catalysis, Michael reaction, α-Nitroacetate, γ-Nitro ketones, δ-Keto esters

Introduction

The Michael addition reaction is widely recognized as one of the most important carbon-carbon bond-forming reactions in organic synthesis,[1] and the development of enantioselective catalytic conjugate addition reaction has been the subject of intensive research.[2] In addition to the great success catalyzed by metal complexes, the powerful and environmentally friendly organocatalyst-mediated asymmetric conjugate addition reaction has been explored intensively in recent years.[3,4] Enantioselective organocatalytic conjugate addition reaction of nitroalkanes to α,β-unsaturated carbonyl compounds represents a direct and most appealing approach to chiral nitroalkanes that are versatile intermediates in organic synthesis, which can be transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen, *etc*.[5] Although a number of catalytic enantioselective conjugate addition reaction of nitroalkanes to α,β-unsaturated enones have been reported,[6] up to now there are few examples of these reactions with α-nitroacetate using chiral organocatalysts.[7] However, an enantioselective conjugate addition of α-nitroacetate to α,β-unsaturated enones catalyzed by chiral primary amine organocatalysts remains elusive; although, if successfully promoted with a practically accessible chiral catalyst under mild conditions, it could provide a highly attractive, convergent approach toward optically active γ-nitro ketones and δ-keto esters. The δ-keto esters are valuable intermediates in organic synthesis.[8] A few synthetic methods for the catalytic asymmetric synthesis of δ-keto esters are now known. Some representatives examples include tandem Michael addition-decarboxylation of malonates to α,β-unsaturated enones,[9] chiral Lewis acid-catalyzed Mukaiyama-Michael reaction,[10] and Michael addition of chiral carbine complexes.[11] Recently, chiral primary amines have emerged as new and powerful catalysts for enantioselective organocatalytic reactions.[12] The development of enantioselective organocatalytic methodology in an aqueous medium has become the most desirable area of organic chemistry, due to the favorable features of water as an inexpensive, safe, and environmentally benign medium.[13]

As part of the research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[14] we recently reported asymmetric conjugate addition reaction of active methylenes and methines.[15] Herein, we wish to describe the enantioselective asymmetric conjugate addition of α-nitroacetate to α,β-unsaturated enones promoted by bifunctional organocatalysts containing chiral primary amines in more details.[16] The products resulted from a conjugate addition reaction will generate chiral γ-nitro ketones and δ-keto esters, which can be conveniently elaborated in organic synthesis.

Results and Discussion

The ogranocatalysts **I-VI** and **VIII-XI** were prepared according to the reported procedure (Fig. 1).[17]

Validation of the feasibility of the proposed Michael addition process started by evaluating a model reaction between α-nitro-

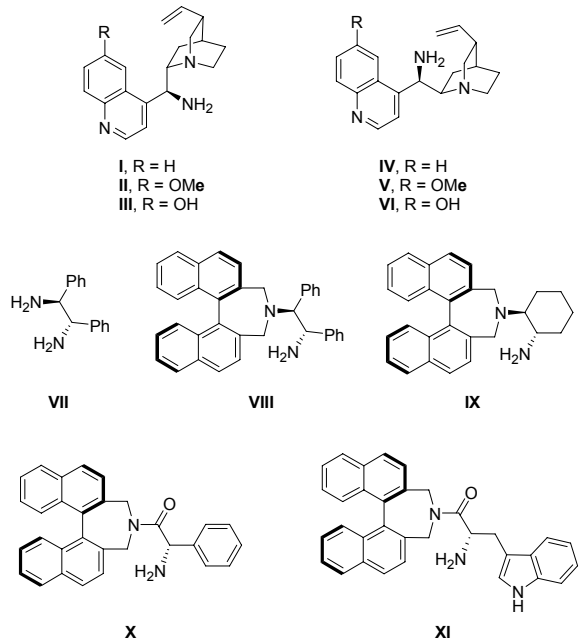
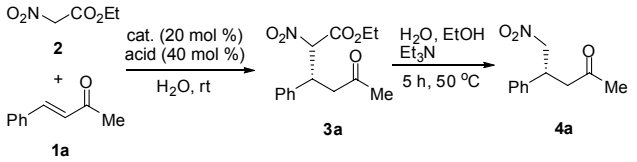


Figure 1. Structure of chiral primary amine catalysts.

Table 1. Optimization of the reaction conditions



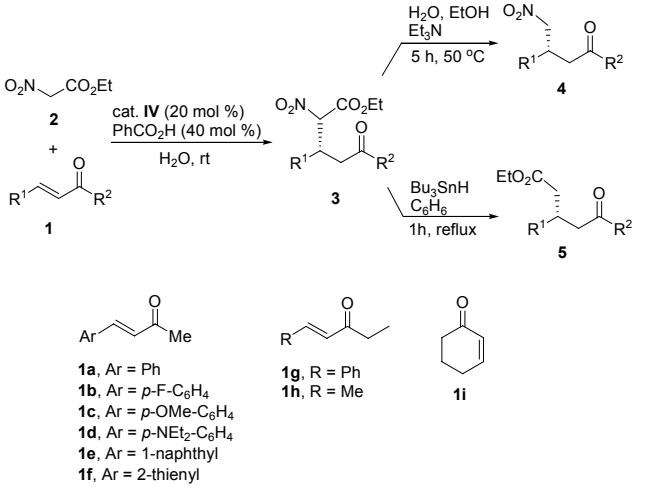
Entry	Cat.	Acid	Time (h)	Yield (%)[a]	ee (%)[b]
1	**I**	$PhCO_2H$	3	95	77 (*S*)
2	**II**	$PhCO_2H$	4	93	90 (*S*)
3	**III**	$PhCO_2H$	2	92	83 (*S*)
4	**IV**	$PhCO_2H$	2	98	93 (*R*)
5	**V**	$PhCO_2H$	3	97	77 (*R*)
6	**VI**	$PhCO_2H$	2	92	92 (*R*)
7	**VII**	$PhCO_2H$	10	89	39 (*S*)
8	**VIII**	$PhCO_2H$	13	71	59 (*S*)
9	**IX**	$PhCO_2H$	10	90	37 (*S*)
10	**X**	$PhCO_2H$	3	90	15 (*S*)
11	**XI**	$PhCO_2H$	3	98	39 (*S*)
12	**IV**	*m*-CN-$C_6H_4CO_2H$	5	93	93 (*R*)
13	**IV**	2-Cl-4,5-F_2-$C_6H_2CO_2H$	4	94	75 (*R*)
14	**IV**	*p*-NO_2-$C_6H_4CO_2H$	5	93	65 (*R*)
15	**IV**	*o*-SH-$C_6H_4CO_2H$	7	90	87 (*R*)
16	**IV**	Picolinic acid	7	87	89 (*R*)
17	**IV**	HCO_2H	13	83	67 (*R*)
18	**IV**	CF_3CO_2H	2	88	82 (*R*)
19	**IV**	$BrCH_2(CH_2)_4CO_2H$	12	89	61 (*R*)
20	**IV**	CH_3COCO_2H	2 d	28	65 (*R*)

[a]Isolated yield of **4a**. [b]Enantiomeric excess was determined by HPLC analysis using a Chiralpak AS column.

acetate (**2**) with (*E*)-4-phenylbut-3-en-2-one (**1a**) in the presence of 20 mol % bifunctional catalysts (Fig. 1) and 40 mol % of benzoic acid as additive in water at room temperature. As shown in Table 1, 9-amino-9-deoxyepicinchona alkaloids (**I-VI**) effectively promoted the addition in high yield and high enantioselectivity (entries 1-6). While (*S*,*S*)-diphenyl ethylendiamine (**VII**) and chiral primary amine organocatalysts (**VIII-XI**) bearing both central and axial chiral elements gave low ee values (entries 7-11). The best result has been obtained with 9-amino-9-deoxyepicinchonine (**IV**). Based on the exploratory studies, we decided to select catalyst **IV** for further optimization of reaction conditions. We examined our investigations by examining the reactivity and selectivity with organocatalyst **IV** in the presence of different acids, such as benzoic acid, substituted benzoic acids, picolinic acid, and aliphatic carboxylic acids as additives (entries 4 and 12-20). Among the additives probed, the best results (98% yield and 93% ee) were achieved when the reaction was conducted in benzoic acid (entry 4).

With optimal reaction conditions in hand, we then carried on evaluating the generality of this protocol. The results of a representative selection of α,β-unsaturated enones for the conjugate addition reaction are summarized in Table 2. As demonstrated, organocatalyst **IV**-catalyzed Michael addition of α-nitroacetate (**2**) to α,β-unsaturated enones **1** proved to be a general approach for the synthesis of versatile chiral δ-keto-α-nitroacetates **3** with diastereomeric ratios of 1:1 - 1:1.2. The conjugate addi-

Table 2. Enantioselective conjugate addition of α-nitroacetate to α,β -unsaturated ketones



Entry	**1**	Time (h)	Yield (%)[a]	ee (%)[b]	Yield (%)[a]	ee (%)[b]
1	**1a**	2	**4a**, 98	93	**5a**, 93	91
2[c]	**1b**	2.5	**4b**, 96	83	**5b**, 91	83
3[c]	**1c**	2	**4c**, 95	81	**5c**, 87	81
4	**1d**	2	**4d**, 97	65	-	-
5[c]	**1e**	2	**4e**, 95	77	**5e**, 90	80
6	**1f**	2.5	**4f**, 96	73	-	-
7	**1g**	2.2	**4g**, 97	89	**5g**, 92	91
8	**1h**	2.3	**4h**, 94	83	-	-
9	**1i**	2	**4i**, 93	85	-	-

[a]Isolated yield. [b]Enantiomeric excess was determined by HPLC analysis using chiral columns (Chiralpak AS for **4a**, AS-H for **4g**, IC for **4h**, AD-H for **4b-d**, **4f**, **4i** and Chiralcel OD-H for **4e**, Chiralpak IC for **5a-c**, **5g**, and Regis-whelk O1 for **5e**). [c]*m*-CN-$C_6H_4CO_2H$ was used as acid additive.

tion adducts **3** can be readily converted into the corresponding γ-nitro ketones **4** by decarboxylation.[7,14] Notably, good to high enantiomeric excess was obtained (up to 93% ee). The α,β-unsaturated ketones bearing substituted aryl, naphthyl, heteroaromatic, and methyl groups in β-position could effectively participate in the process (entries 1-8). Furthermore, cyclic system was also effective substrate for the process (entries 9). Absolute configuration was determined by comparison of the optical rotation and chiral HPLC data of the corresponding γ-nitro ketones **4**.[6,18] The conjugate addition adducts **3** can be readily converted into the corresponding δ-keto ester **5** by denitration.[19] The results of a representative selection of α,β-unsaturated enones for the conjugate addition reaction and denitration are summarized in Table 2. Good to high yields and enantiomeric excess (up to 91% ee for **5a** and **5g**) was obtained. Absolute configuration of δ-keto ester **5a** was determined by comparison of the optical rotation and chiral HPLC data with the published values of ref. 9.

Conclusion

In summary, we have developed organocatalytic enantio-

selective conjugate addition reaction of α-nitroacetate (**2**) to α,β-unsaturated enones **1** to afford synthetically useful chiral γ-nitro ketones **4** and δ-keto ester **5**. The process is efficiently catalyzed by a simple cinchona alkaloid derivative containing chiral primary amine. The significance of the approach is highlighted by its capability to introduce γ-nitro ketones **4** and δ-keto ester **5** with high enantioselectivity and yields under aqueous reaction conditions. Further details and application of this asymmetric Michael addition of nitroalkane nucleophiles will be presented in due course.

Experimental Section

General. All commercial reagents and solvents were used without purification. TLC analyses were carried out on precoated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light (254 nm), I_2, *p*-anisaldehyde, ninhydrin, and phosphomolybdic acid solution as an indicator. Purification of reaction products was carried out by flash chromatography using E. Merck silica gel 60 (230 - 400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz for ^{1}H, 50 MHz for ^{13}C) and a Bruker 500 MHz NMR (500 MHz for ^{1}H). Chemical shift values (δ) are reported in ppm relative to Me_4Si (δ 0.0 ppm). Optical rotations were measured on a JASCO-DIP-1000 digital polarimeter with a sodium lamp. The enantiomeric excesses (ee's) were determined by HPLC. HPLC analysis was performed on Younglin M930 Series and Younglin M720 Series, measured at 254 nm using the indicated chiral column.

General Procedure for Asymmetric Synthesis of γ-Nitro Ketones 4: A mixture of α,β-unsaturated ketones **1** (0.3 mmol), 9-amino-9-deoxyepiquinine (**IV**, 17.6 mg, 0.06 mmol) and benzoic acid (14.6 mg, 0.12 mmol) in 0.9 mL of H_2O was stirred at room temperature for 5 min. Ethyl 2-nitroacetate (**2**, 79.8 mg, 0.6 mmol) was added and the reaction mixture was stirred at room temperature for a specified reaction time period. EtOH (1.2 mL), H_2O (1.2 mL) and triethylamine (0.4 mL) was added into reaction mixture and resulting mixture was stirred at 50 °C. After being stirred for 5 h, the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc = 5:1 to give the desired product **4**.

(4*R*)-5-Nitro-4-phenylpentan-2-one (4a): $[\alpha]_D^{28}$ = −4.1 (*c* 1.00, $CHCl_3$, 93% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.26 (m, 3H), 7.23-7.20 (m, 2H), 4.64 (m, 2H), 4.00 (m, 1H), 2.91 (d, *J* = 6.9 Hz 2H), 2.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.4, 138.8, 127.9, 127.4, 79.5, 46.1, 39.1, 30.4; HPLC (65:35, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AS-H, t_R = 8.9 min (minor), t_R = 10.8 min (major).

(4*R*)-5-Nitro-4-(4-fluorophenyl)pentan-2-one (4b): $[\alpha]_D^{28}$ = +20.0 (*c* 0.55, $CHCl_3$, 83% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (m, 2H), 7.02 (m, 2H), 4.62 (m, 2H), 4.00 (m, 1H), 2.90 (d, *J* = 6.9 Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.1, 164.6, 134.5, 129.1, 128.9, 116.1, 79.4, 46.1, 38.2, 30.3; HPLC (90:10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 8.3 min (minor), t_R = 9.9 min (major).

(4*R*)-5-Nitro-4-(4-methoxylphenyl)pentan-2-one (4c): $[\alpha]_D^{28}$ = +2.2 (*c* 0.55, $CHCl_3$, 81% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.13 (d, *J* = 11.4 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.61 (m, 2H), 3.95 (m, 1H), 3.78 (s, 3H), 2.88 (d, *J* = 7.2 Hz, 2H), 2.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.5, 159.0, 130.6, 129.0, 114.4, 79.7, 55.2, 46.2, 38.3, 30.4; HPLC (90:10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 12.4 min (minor), t_R = 14.1 min (major).

5-Nitro-4-(4-diethylaminophenyl)pentan-2-one (4d): $[\alpha]_D^{22}$ = +9.0 (*c* 0.55, $CHCl_3$, 65% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.7 Hz, 2H), 4.58 (m, 2H), 3.88 (m, 1H), 3.31 (q, *J* = 6.9 Hz, 4H), 2.86 (d, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.13 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.0, 147.3, 128.2, 124.7, 111.9, 80.0, 49.0, 46.5, 44.3, 38.4, 30.5, 27.7, 12.6; HPLC (90:10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 8.4 min (minor), t_R = 9.2 min (major).

(4*R*)-5-Nitro-4-(1-naphthalenyl)pentan-2-one (4e): $[\alpha]_D^{28}$ = −7.1 (*c* 0.55, $CHCl_3$, 77% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18-8.13 (d, *J* = 8.2 Hz, 1H), 7.89-7.75 (m, 2H), 7.62-7.24 (m, 4H), 4.93 (m, 1H), 4.76 (d, *J* = 6.9 Hz, 2H), 3.07 (d, *J* = 6.8 Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.6, 134.8, 134.2, 130.9, 129.3, 128.5, 127.0, 126.1, 125.3, 123.6, 122.3, 78.9, 46.0, 33.4, 30.3; HPLC (90:10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralcel OD-H, t_R = 44.3 min (minor), t_R = 51.0 min (major).

(4*R*)-5-Nitro-4-(2-thiophenyl)pentan-2-one (4f): $[\alpha]_D^{28}$ = +11.1 (*c* 0.55, $CHCl_3$, 73% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21 (d, *J* = 4.9 Hz, 2H), 6.95-6.90 (m, 2H), 4.67 (m, 2H), 4.32 (m, 1H), 2.97 (d, *J* = 6.8 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.5, 141.5, 127.1, 125.5, 124.7, 79.7, 46.8, 34.4, 30.3; HPLC (65:35, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 10.8 min (major), t_R = 12.0 min (minor).

(5*R*)-6-Nitro-5-phenylhexan-3-one (4g): $[\alpha]_D^{29}$ = −7.5 (*c* 1.00, $CHCl_3$, 89% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.31 (m, 3H), 7.23-7.21 (m, 2H), 4.70-4.62 (m, 2H), 4.05-4.01 (m, 1H), 2.89 (d, *J* = 7.2 Hz,2H), 2.40-2.36 (m, 2H), 1.01 (t, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.2, 138.9, 129.1, 127.9, 127.4, 79.5, 44.9, 39.1, 36.5, 7.6; HPLC (80:20, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AS-H, t_R = 11.6 min (minor), t_R = 14.7 min (major).

(5*R*)-6-Nitro-5-methylhexan-3-one (4h): $[\alpha]_D^{29}$ = +2.1 (*c* 1.00, $CHCl_3$, 83% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.47-4.29 (m, 2H), 4.05-4.01 (m, 1H), 2.89-2.82 (m, 1H), 2.64-2.38 (m, 4H), 1.10-1.05 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.0, 80.3, 45.2, 36.4, 28.2, 17.4, 7.6; HPLC (90:10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak IC, t_R = 10.9 min (minor), t_R = 11.4 min (major).

(3*R*)-3-(Nitromethyl)cyclohexanone (4i): $[\alpha]_D^{24}$ = −8.4 (*c* 0.55, $CHCl_3$, 85% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.49 (d, *J* = 6.7 Hz 2H), 2.76-2.56 (m, 1H), 2.52-1.96 (m, 6H), 1.69-1.85 (m, 1H), 1.43-1.67 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.1, 79.7, 44.0, 40.4, 36.8, 27.7, 24.1; HPLC (90:10, *n*-hexane : *i*-PrOH, 220 nm, 0.8 mL/min) Chiralpak AD-H, t_R = 17.3 min (major), t_R = 20.0 min (minor).

General Procedure for Asymmetric Synthesis of δ-Keto Esters 5: A mixture of α,β-Unsaturated ketones **1** (0.3 mmol), 9-amino-9-deoxyepiquinine (**IV**, 17.6 mg, 0.06 mmol) and benzoic acid

(14.6 mg, 0.12 mmol) in 0.9 mL of H_2O was stirred at room temperature for 5 min. Ethyl 2-nitroacetate (**2**, 79.8 mg, 0.6 mmol) was added and the reaction mixture was stirred at room temperature for a specified reaction time period. The reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was dissolved in 3 mL of benzene, and AIBN (4.9 mg, 0.03 mmol) and Bu_3SnH (261.9 mg, 0.9 mmol) were added, and the mixture was refluxed for 1 h. The reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel, eluted by hexane/EtOAc= 10:1 to give the desired product **5**.

(3*S*)-Ethyl-5-oxo-3-phenylhexanoate (5a): $[\alpha]_D^{25} = -10.6$ (*c* 1.00, $CHCl_3$, 91% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.15 (m, 5H), 4.08-4.01(m, 2H), 3.77-3.60 (m, 1H), 2.93-2.80 (m, 2H), 2.75-2.53 (m, 2H), 2.06 (s, 3H), 1.14-1.07 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.7, 171.6, 143.0, 128.5, 127.2, 126.7, 60.3, 49.3, 40.7, 37.3, 30.3, 14.0 ; HPLC (90:10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak IC, t_R = 28.9 min (major), t_R = 26.1 min (minor).

Ethyl-5-oxo-3- (4-fluorophenyl)hexanoate (5b): $[\alpha]_D^{26} = -16.0$ (*c* 3.00, $CHCl_3$, 83% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26-7.15 (m, 2H), 7.01-6.92 (m, 2H), 4.08-4.01 (m, 2H), 3.77-3.60 (m, 1H), 2.93-2.80 (m, 2H), 2.75-2.53 (m, 2H), 2.06 (s, 3H), 1.14-1.07 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.5, 171.5, 161.6 (*J* = 243.0 Hz), 138.6, 128.7, 115.5, 61.7, 49.4, 40.8, 36.5, 30.3, 14.0; HPLC (90:10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak IC, t_R = 19.8 min (major), t_R = 15.0 min (minor).

Ethyl-5-oxo-3-(4-methoxylphenyl)hexanoate (5c): $[\alpha]_D^{26}$ = +25.2 (*c* 0.10, $CHCl_3$, 81% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.15-7.11 (d, 2H), 6.84-6.79 (d, 2H), 4.08-4.01 (m, 2H), 3.77 (s, 3H), 3.77-3.60 (m, 1H), 2.93-2.80 (m, 2H), 2.75-2.53 (m, 2H), 2.06 (s, 3H), 1.14-1.07(m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.9, 171.7, 158.2, 134.9, 128.1, 113.8, 61.3, 55.0, 49.5, 40.9, 36.5, 30.2, 13.9: HPLC (90:10, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak IC, t_R = 25.3 min (major), t_R = 18.3 min (minor).

Ethyl-5-oxo-3-(1-naphthalenyl)hexanoate (5e): $[\alpha]_D^{27} = -20.0$ (*c* 1.00, $CHCl_3$, 80% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.27-8.19 (m, 1H), 7.81-7.76 (m, 2H), 7.59-7.32 (m, 4H) 4.14-4.95 (m, 2H), 3.00-2.95 (m, 2H), 2.80-2.77 (m, 2H), 2.09 (s, 3H), 1.12-1.05 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.9, 171.9, 134.8, 134.2, 130.9, 129.3, 128.5, 127.0, 126.1, 125.3, 123.6, 122.3, 60.4, 49.1, 40.3, 31.4, 30.2, 14.0; HPLC (80:20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiral HPLC Regis (s,s)-whelk O1 column, t_R = 18.0 min (major), t_R = 14.5 min (minor).

Ethyl-5-oxo-3-phenylhepanoate (5g): $[\alpha]_D^{27} = -12.5$ (*c* 1.00, $CHCl_3$, 91% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32-7.15 (m, 5H), 4.08-4.01 (m, 2H), 3.77-3.60 (m, 1H), 2.93-2.80 (m, 2H), 2.75-2.53 (m, 2H), 2.06 (s, 3H), 1.14-1.07 (m, 3H), 0.99-0.88 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.7, 171.6, 143.0, 128.5, 127.2, 126.7, 60.3, 48.2, 40.8, 37.4, 30.6, 14.0, 7.4; HPLC (80:20, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak IC, t_R = 14.6 min (major), t_R = 15.7 min (minor).

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