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Enantioselective Conjugate Radical Addition to β-Acyloxy Acrylate Acceptors: An Approach to Acetate Aldol-Type Products

Mukund P. Sibi,* Jake Zimmerman, and Tara Rheault

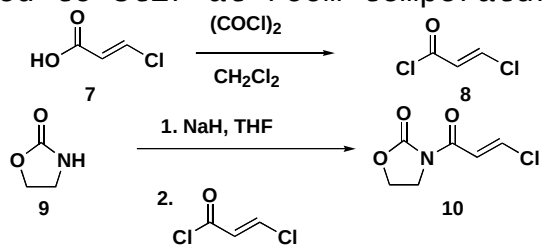
[*] Prof. M. P. Sibi, Mr. Jake Zimmerman, and Dr. Tara Rheault
Department of Chemistry
North Dakota State University
Fargo, ND 58105-5516 (USA)
E-mail: mukund.sibi@ndsu.nodak.edu
Fax: (+1)^701-231-1057

Experimental Procedures. Methylene chloride and THF were dried using Solv-tek solvent purification system prior to use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh). Melting points were determined using the Fisher-Johns melting point apparatus. All glassware was oven dried, assembled hot, and cooled under a stream of dry nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

^{1}H NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), a Varian Unity/Inova-400 NB (400 MHz), or a Varian Mercury-300 (300 MHz). Chemical shifts are reported in parts per million

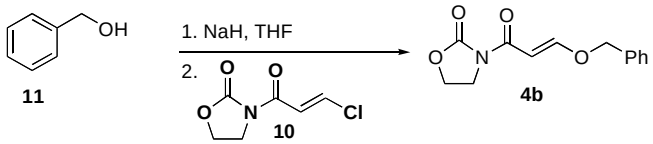
(ppm) down field from TMS, using residual $CDCl_3$ (7.27 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet, b = broad), coupling constant(s) and integration. ^{13}C NMR were recorded on a Varian Unity/Inova-500 NB (125 MHz), a Varian Unity/Inova-400 (100 MHz), or a Varian Mercury-300 (75 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of $CDCl_3$ (77.0 ppm) as an internal standard. HPLC analyses were carried out on a Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Millennium[32] workstation. Optical rotations were recorded on a JASCO-DIP-370 instrument. High-resolution mass spectra (FAB-HRMS) [EI+] were obtained at the Mass spectrometry Laboratory, Ohio State University, Columbus, OH.

General procedure for the preparation of oxazolidinone β-alkoxy(acyloxy) acrylate substrates (4a-i). Under N_2, to a flask containing 3-chloroacrylic acid (**7**) (3.55 g, 33 mmol), was added 5 mL of dry CH_2Cl_2 and oxalyl chloride (3.1 mL, 35 mmol) dropwise. After complete addition, 3-5 drops of DMF was added and the reaction was allowed to stir at room temperature for three hours.



To another flask containing 2-oxazolidinone (**9**) (3.5 g, 40 mmol) and THF (160 mL), was added NaH (60% in mineral oil, 1.8 g, 45 mmol) in portions at 0 °C under N_2. After complete addition, the solution was stirred for 0.5 hour at 0 °C and then for one hour at room temperature. A solution of 3-chloroacryloyl chloride (**8**) (taken directly from the previous reaction) was added via syringe at room temperature and the mixture stirred for 4 hours. The reaction was quenched with approximately 5 mL of water and the THF was removed using a rotary evaporator. The concentrated mixture was then extracted with EtOAc (3 x 60 mL). The extracts were combined, washed with water (2 x 20 mL) and 1 M NaOH (2 x 20 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica gel using hexane/EtOAc (3:1) as eluent to yield 4.05 g of **10** (70%) as a white solid; mp: 50-52 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.05 (t, *J* = 8.0 Hz, 2H), 4.43 (t, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 13.0 Hz, 1H), 7.78 (d, *J* = 13.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.7, 62.4, 123.6, 139.7, 153.4, 162.9.

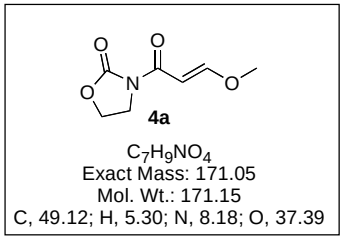
Synthesis of 4a and 4b



11 **10** **4b**

To a flask under N_2, benzyl alcohol **11** (0.35 g, 3.2 mmol) in THF (25 mL) was added followed by NaH (0.14 g, 3.5 mmol, 40 g/mol in oil). The solution was allowed to stir for 30 minutes at room temperature followed by the addition of **10** (0.55 g, 3.2 mmol)

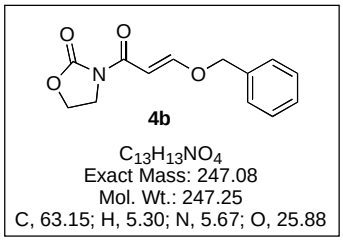
dissolved in 2 mL of THF via syringe. The reaction was stirred for 24h and then quenched with water. The reaction was then washed with water (2 x 10 mL) and 1 M NaOH (2 x 10 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica gel using hexane/EtOAc (3:1) as eluent. Substrate **4a** can be synthesized using the same procedure as in **4b** by simply substituting methanol for benzyl alcohol.



4a

$C_7H_9NO_4$
Exact Mass: 171.05
Mol. Wt.: 171.15
C, 49.12; H, 5.30; N, 8.18; O, 37.39

(4a): 3-(3-Methoxy-acryloyl)-oxazolidin-2-one: 79% yield; mp: 118-120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.74 (s, 3H), 3.76 (t, *J* = 8.0 Hz, 2H), 4.51 (t, *J* = 8.0 Hz, 2H), 5.13 (d, *J* = 14.4 Hz, 1H), 7.94 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.3, 51.7, 62.6, 100.3, 138.6, 153.9, 164.1.



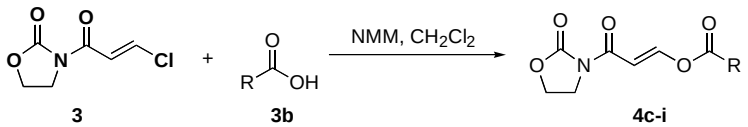
4b

$C_{13}H_{13}NO_4$
Exact Mass: 247.08
Mol. Wt.: 247.25
C, 63.15; H, 5.30; N, 5.67; O, 25.88

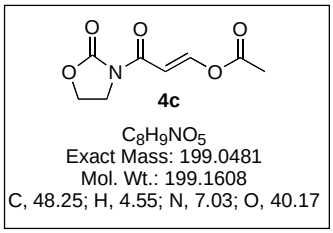
(4b): 3-(3-Benzyloxy-acryloyl)-oxazolidin-2-one: 60% yield; mp: 72-74 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.74 (t, *J* = 8.4 Hz, 2H), 4.49 (t, *J* = 8.4 Hz, 2H), 5.18 (s, 2H), 5.19 (d, *J* = 14.0 Hz, 1H), 7.28-7.38 (m, 5H), 7.97 (d, *J* = 14.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.3, 62.7, 66.4, 100.4, 128.5, 128.6, 128.8, 136.3,

138.8, 154.7, 166.5; HRMS Exact mass calcd for $C_8H_9NO_5Na$ $[M + Na]^+$: 270.0737; Found: 270.0732.

Synthesis of 4c-I

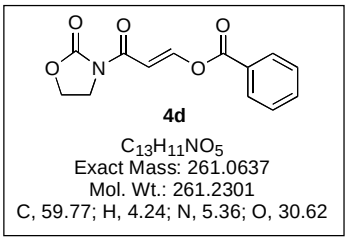


Under N_2, to a flask containing **3**[1] (1.04 g, 6.0 mmol) and benzoic acid (0.76 g, 6.2 mmol) in 45 mL of methylene chloride, was added N-methylmorpholine (NMM) (6.5 mL, 60 mmol) via syringe. The reaction was stirred for 24 hours at room temperature. The reaction was then washed with water (2 x 10 mL) and 1 M NaOH (2 x 10 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica gel using hexane/EtOAc (3:1) as eluent to yield all starting materials. Different acids can be used to yield the different β-oxygenated substrates. Their yields and characterization data are listed below.



(4c): Acetic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-propenyl ester: 88% yield; mp: 107-110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.23 (s, 3H), 4.08 (t, *J* = 8.0 Hz, 2H), 4.43 (t, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 12.0 Hz, 1H), 8.44 (d, *J* = 12.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8, 42.8, 62.3, 105.1, 151.1, 153.7, 164.9, 167.0;

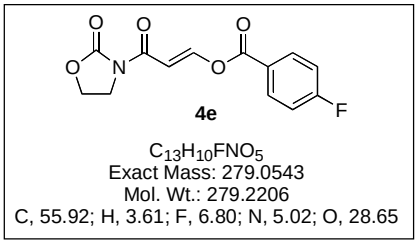
HRMS Exact mass calcd for $C_8H_9NO_5Na$ [M + Na]$^+$: 222.0373; Found: 222.0377.



4d

$C_{13}H_{11}NO_5$
Exact Mass: 261.0637
Mol. Wt.: 261.2301
C, 59.77; H, 4.24; N, 5.36; O, 30.62

(**4d): Benzoic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-propenyl ester:** 90% yield; mp: 152-155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.18 (t, *J* = 7.5 Hz, 2H), 4.45 (t, *J* = 7.8 Hz, 2H), 7.40 (d, *J* = 12.0 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 2H), 7.65 (t, *J* = 7.2 Hz, 1H), 8.15 (d, *J* = 9.6 Hz, 1H), 8.72 (d, *J* = 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.9, 62.3, 105.5, 127.8, 129.0, 130.7, 134.7, 151.6, 153.7, 162.7, 165.0; HRMS Exact mass calcd for $C_{13}H_{11}NO_5Na$ [M + Na]$^+$: 284.0529; Found: 284.0527.

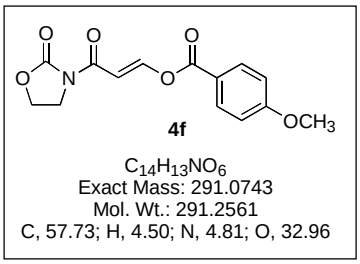


4e

$C_{13}H_{10}FNO_5$
Exact Mass: 279.0543
Mol. Wt.: 279.2206
C, 55.92; H, 3.61; F, 6.80; N, 5.02; O, 28.65

(4e): 4-Fluoro-benzoic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-propenyl ester: 90% yield; mp: 188-190 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (t, *J* = 8.0 Hz, 2H), 4.54 (t, *J* = 8.0 Hz, 2H), 7.18 (t, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 12.4 Hz, 1H), 8.17 (dd, *J* = 8.8 Hz and 5.2 Hz, 2H), 8.69 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.8, 62.3, 105.7, 116.3 (d, J = 22.0 Hz), 124.1, 133.3

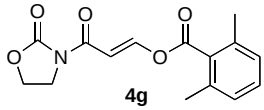
(d, J = 8.4 Hz), 151.4, 153.7, 161.8, 164.8, 166.8 (d, J = 255.1 Hz); HRMS Exact mass calcd for $C_{13}H_{10}FNO_5Na$ [M + Na]$^+$: 302.0435; Found: 302.0455.



4f

$C_{14}H_{13}NO_6$
Exact Mass: 291.0743
Mol. Wt.: 291.2561
C, 57.73; H, 4.50; N, 4.81; O, 32.96

(4f): 4-Methoxy-benzoic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-propenyl ester: 89% yield; mp: 164-166 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 3H), 4.11 (t, *J* = 7.8 Hz, 2H), 4.45 (t, *J* = 7.8 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2 H), 7.36 (d, *J* = 12.0 Hz, 1H), 8.10 (d, *J* = 8.7, 2H), 8.72 (d, *J* = 12.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.9, 55.8, 62.2, 104.9, 114.4, 119.9 133.0, 151.9, 153.8, 162.3, 165.0, 165.1; HRMS Exact mass calcd for $C_{14}H_{13}NO_6Na$ [M + Na]$^+$: 314.0635; Found: 314.0630.

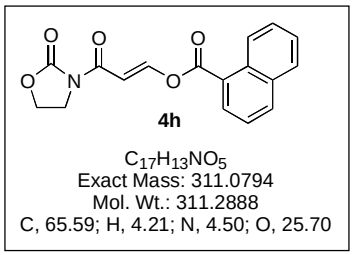


4g

$C_{15}H_{15}NO_5$
Exact Mass: 289.0950
Mol. Wt.: 289.2833
C, 62.28; H, 5.23; N, 4.84; O, 27.65

(4g): 2,6-Dimethyl-benzoic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-propenyl ester: 82% yield; mp: 145-147 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 6H), 4.10 (t, *J* = 7.5 Hz, 2H), 4.44 (t, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 7.24-7.33 (m, 2H), 8.71 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 42.8, 62.3,

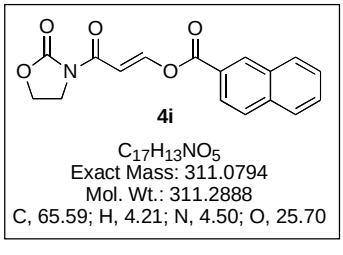
105.7, 128.3, 130.8, 130.9, 136.5, 151.2, 153.6, 164.9, 165.6; HRMS Exact mass calcd for $C_{15}H_{15}NO_5Na$ [M +Na]$^+$: 312.0842; Found: 312.0868.



4h

$C_{17}H_{13}NO_5$
Exact Mass: 311.0794
Mol. Wt.: 311.2888
C, 65.59; H, 4.21; N, 4.50; O, 25.70

(4h): Naphthalene-1-carboxylic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-propenyl ester: 87% yield; mp: 159-161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (t, *J* = 10.0 Hz, 2H), 4.46 (t, *J* = 10.0 Hz, 2H), 7.43 (d, *J* = 16 Hz, 1H), 7.59 (dt, *J* = 10.4 Hz and 1.6 Hz, 2H), 7.68 (dt, *J* = 11.2 Hz and 2.0 Hz, 1H), 7.93 (d, *J* = 9.6 Hz, 1H), 8.13 (d, *J* = 10.8 Hz, 1H), 8.43 (dd, *J* = 10.4 Hz and 2.0 Hz, 1H), 8.25 (d, *J* = 16.4 Hz, 1H), 9.02 (d, *J* = 11.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.9, 62.3, 105.2, 123.7, 124.7, 125.7, 126.9, 129.0, 129.1, 132.0, 132.4, 134.1, 135.7, 151.8, 153.7, 162.7, 165.1; HRMS Exact mass calcd for $C_{17}H_{13}NO_5Na$ [M + Na]$^+$: 334.0686; Found: 334.0706.



4i

$C_{17}H_{13}NO_5$
Exact Mass: 311.0794
Mol. Wt.: 311.2888
C, 65.59; H, 4.21; N, 4.50; O, 25.70

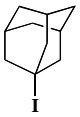
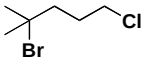
(4i): Naphthalene-2-carboxylic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-propenyl ester: 88% yield; mp: 171-174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.14 (t, *J* = 8.1 Hz, 2H), 4.47 (t, *J* = 8.1

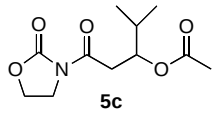
Hz, 2H), 7.47 (d, *J* = 12.6 Hz, 1H), 7.56-7.68 (m, 2H), 7.93 (t, *J* = 9.0 Hz, 2H), 8.01 (d, *J* = 7.8 Hz, 1H), 8.12 (dd, *J* = 8.7 Hz and 1.8 Hz, 1H), 8.75 (s, 1H), 8.80 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.9, 62.3, 105.5, 124.9, 125.4, 127.3, 128.1, 128.9, 129.4, 129.9, 132.6, 133.0, 136.4, 151.7, 153.8, 162.9, 164.9; HRMS Exact mass calcd for $C_{17}H_{13}NO_5Na$ $[M + Na]^+$: 334.0686; Found: 334.0712.

Representative experimental procedure for chiral Lewis acid catalyzed conjugate addition of radicals to alkoxy enoates. Under N_2, a mixture of Lewis acid (0.10 mmol) and ligand (0.10 mmol) in CH_2Cl_2 (2 mL) was stirred at rt for 45 min. Oxazolidinone (**4c-i**) (0.10 mmol) (in 1 mL CH_2Cl_2) was added and the mixture was allowed to stir for an additional 30 min and then cooled to –78 °C. The reaction was then initiated by sequential addition of 2-iodo propane (or other radical precursors = RX, see Table below) (1 mmol), *n*-Bu_3SnH (0.5 mmol), Et_3B (0.5 mmol 1 M solution in hexanes) and oxygen (introduced via syringe). The reaction was monitored by TLC (50% EtOAc in hexane) and when judged complete was quenched with silica gel, concentrated, washed with hexanes and extracted with ether. The ether extract was concentrated over silica gel and purified by silica gel chromatography (hexane-ethyl acetate) to give the products (**5c-r**). The reaction procedure for standard racemic reactions is the same as above with the following modification. Racemic standards were prepared using $Yb(OTf)_3$ as a Lewis acid in the absence of a

chiral ligand and methylene chloride:tetrahydrofuran (2:1) as a solvent.

Table of radical precursors:

Radical Precursor (RX)	Product(s)	Radical Precursor (RX)	Product(s)
	5j		5m-n
	5k		5o-p
	5a-i		
	5l		5q-r

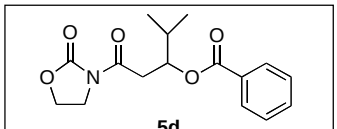


5c

$C_{11}H_{17}NO_5$
Exact Mass: 243.1107
Mol. Wt.: 243.2564
C, 54.31; H, 7.04; N, 5.76; O, 32.89

(5c): Acetic acid 2-methyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 20mg, 70 % yield (colorless oil); The enantiomeric purity was determined by HPLC (210 nm, 25 •C) t_R 15.8 min (major); t_R 25.6 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 89% ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 1.89-1.95 (m, 1H), 2.03 (s, 3H), 2.94 (dd, *J* = 15.5 Hz and 9.5 Hz, 1H), 3.33 (dd, *J* = 15.5 Hz and 2.5 Hz, 1H), 3.92-4.05 (m, 2H), 4.37-4.45 (m, 2H), 5.14-5.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.7, 18.5, 21.2, 32.1, 38.0,

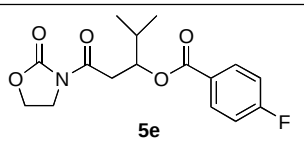
42.8, 62.4, 74.5, 153.9, 171.0, 171.2; HRMS Exact mass calcd for $C_{11}H_{17}NO_5Na$ $[M + Na]^+$: 266.0999; Found: 266.0994.



5d

$C_{16}H_{19}NO_5$
Exact Mass: 305.1263
Mol. Wt.: 305.3258
C, 62.94; H, 6.27; N, 4.59; O, 26.20

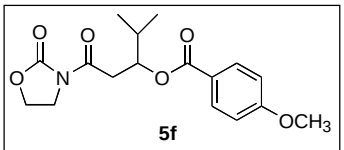
(5d): Benzoic acid 2-methyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 27 mg, 90% yield (colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 22.6 min (major); t_R 26.6 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 93% ee (*R* enantiomer). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, *J* = 2.4 Hz, 3H), 0.98 (d, *J* = 2.4 Hz, 3H), 2.00-2.05 (m, 1H), 3.14 (dd, *J* = 15.6 Hz and 9.2 Hz, 1H), 3.31 (dd, *J* = 15.6 Hz and 3.2 Hz, 1H), 3.86-3.92 (m, 2H), 4.24-4.38 (m, 2H), 5.38-5.43 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.7, 18.6, 32.3, 37.9, 42.8, 62.4, 75.1, 128.6, 129.8, 130.5, 133.1, 154.0, 166.4, 170.9; HRMS Exact mass calcd for $C_{16}H_{19}NO_5Na$ $[M + Na]^+$: 328.1155; Found: 328.1174.



5e

$C_{16}H_{18}FNO_5$
Exact Mass: 323.1169
Mol. Wt.: 323.3162
C, 59.44; H, 5.61; F, 5.88; N, 4.33; O, 24.74

(5e): 4-Fluoro-benzoic acid 2-methyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 30 mg, 94% yield (colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 25.3 min (major); t_R 30.6 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 62% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (d, *J* = 2.0 Hz, 3H), 1.03 (d, *J* = 2.0 Hz, 3H), 2.03-2.12 (m, 1H), 3.18 (dd, *J* = 15.6 Hz and 9.2 Hz, 1H), 3.37 (dd, *J* = 15.6 Hz and 3.2 Hz, 1H), 3.90-4.00 (m, 2H), 4.31-4.43 (m, 2H), 5.41-5.47 (m, 1H), 7.07-7.11 (m, 2H), 8.00-8.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 18.6, 32.3, 37.9, 42.8, 62.4, 75.3, 115.7 (d, J = 21.7 Hz), 126.6, 132.4 (d, J = 91. Hz), 153.9, 165.4, 169.0 (d, J = 234.8 Hz), 175.0; HRMS Exact mass calcd for $C_{16}H_{18}FNO_5Na$ $[M + Na]^+$: 346.1061; Found: 346.1073.

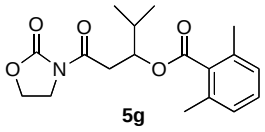


5f

$C_{17}H_{21}NO_6$
Exact Mass: 335.1369
Mol. Wt.: 335.3517
C, 60.89; H, 6.31; N, 4.18; O, 28.63

(5f): 4-Methoxy-benzoic acid 2-methyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 27 mg, 83% yield (colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 39.8 min (major); t_R 48.6 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 82% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (d, *J* = 2.8 Hz, 3H), 1.01(d, *J* = 2.8 Hz, 3H), 2.00-2.08 (m, 1H), 3.18

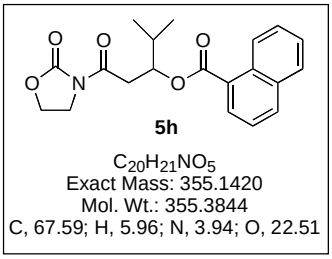
(dd, *J* = 15.2 Hz and 9.2 Hz, 1H), 3.33 (dd, *J* = 15.2 Hz and 3.2 Hz, 1H), 3.83 (s, 3H), 3.86-3.96 (m, 2H), 4.27-4.42 (m, 2H), 5.38-5.44 (m, 1H), 6.88 (dd, *J* = 6.8 Hz and 2.0 Hz, 2H), 7.95 (dd, *J* = 7.0 Hz and 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.7, 18.6, 32.4, 38.0, 42.8, 55.6, 62.3, 74.8, 113.8, 114.3, 131.8, 132.9, 151.9, 163.6, 170.9; HRMS Exact mass calcd for $C_{17}H_{21}NO_6Na$ $[M + Na]^+$: 358.1261; Found: 358.1272.



5g

$C_{18}H_{23}NO_5$
Exact Mass: 333.1576
Mol. Wt.: 333.3789
C, 64.85; H, 6.95; N, 4.20; O, 24.00

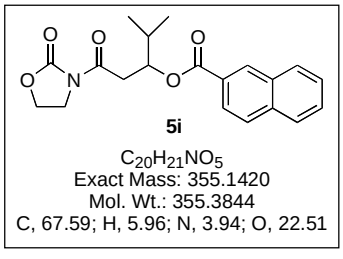
(5g): 2,6-Dimethyl-benzoic acid 2-methyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 27 mg, 82% yield (colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 19.0 min (minor); t_R 30.1 min (major) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 73% ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00 (d, *J* = 5.6 Hz, 3H), 1.01 (d, *J* = 5.6 Hz, 3H), 2.09-2.14 (m, 1H), 2.31 (s, 6H), 3.17 (dd, *J* = 16.4 Hz and 9.2 Hz, 1H), 3.26 (dd, *J* = 16.4 Hz and 3.2 Hz, 1H), 3.99 (t, *J* = 8.0 Hz, 2H), 4.35-4.44 (m, 2H), 5.47-5.52 (m, 1H), 6.99 (d, *J* = 7.6 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 18.0, 20.1, 31.9, 37.1, 42.8, 62.4, 75.6, 127.8, 129.4, 134.1, 135.2, 153.9, 169.9, 170.7; HRMS Exact mass calcd for $C_{18}H_{23}NO_5Na$ $[M + Na]^+$: 356.1468; Found: 356.1472.



5h

$C_{20}H_{21}NO_5$
Exact Mass: 355.1420
Mol. Wt.: 355.3844
C, 67.59; H, 5.96; N, 3.94; O, 22.51

(5h): Naphthalene-1-carboxylic acid 2-methyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 31 mg, 87% yield (colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 29.9 min (major); t_R 34.6 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 46% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (d, *J* = 7.2 Hz, 6H), 2.08-2.16 (m, 1H), 3.21 (dd, *J* = 15.6 and 9.6 Hz, 1H), 3.43 (dd, *J* = 15.6 Hz and 3.2 Hz, 1H), 3.95 (t, *J* = 8.4 Hz, 2H), 4.27-4.42 (m, 2H), 5.54-5.60 (m, 1H), 7.48-7.53 (m, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 8.84 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.9, 18.7, 32.4, 38.1, 42.8, 62.4, 75.2, 124.8, 126.0, 126.4, 127.7, 127.9, 128.7, 130.1, 131.6, 133.4, 134.0, 153.9, 167.3, 170.9; HRMS Exact mass calcd for $C_{20}H_{21}NO_5Na$ $[M + Na]^+$: 378.1312; Found: 378.1291.

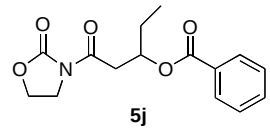


5i

$C_{20}H_{21}NO_5$
Exact Mass: 355.1420
Mol. Wt.: 355.3844
C, 67.59; H, 5.96; N, 3.94; O, 22.51

(5i): Naphthalene-2-carboxylic acid 2-methyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 28 mg, 79% yield

(colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 34.4 min (major); t_R 42.7 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 80% ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00 (d, *J* = 4.5 Hz, 3H), 1.01 (d, *J* = 4.5 Hz, 3H), 2.05-2.11 (m, 1H), 3.21 (dd, *J* = 15.5 Hz and 9.0 Hz, 1H), 3.33 (dd, *J* = 15.5 Hz and 3.0 Hz, 1H), 3.88 (t, *J* = 8.0 Hz, 2H), 4.25 (q, *J* = 8.0, 1H), 4.34 (q, *J* = 8.0 Hz, 1H), 5.45-5.49 (m, 1H), 7.45-7.53 (m, 2H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.97 (dd, *J* = 8.5 Hz and 1.5 Hz, 1H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.8, 18.7, 32.4, 38.0, 42.8, 62.4, 75.3, 125.5, 126.8, 127.7, 128.0, 128.4, 128.5, 129.6, 131.3, 132.7, 135.8, 154.0, 166.5, 170.9; HRMS Exact mass calcd for $C_{20}H_{21}NO_5Na$ $[M + Na]^+$: 378.1312; Found: 378.1339.

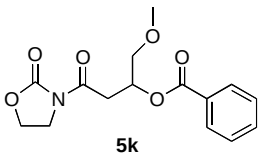


5j

$C_{15}H_{17}NO_5$
Exact Mass: 291.1107
Mol. Wt.: 291.2992
C, 61.85; H, 5.88; N, 4.81; O, 27.46

(5j): Benzoic acid 1-ethyl-3-oxo-3-(2-oxo-oxazolidin-3-yl)-propyl ester: 27 mg, 90% yield (colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 24.7 min (minor); t_R 27.6 min (major) [Chiralcel AD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 50% ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (t, *J* = 7.0 Hz, 3H), 1.80-1.85 (m, 2H), 3.27 (dd, *J* = 16.0 Hz and 8.5 Hz, 1H), 3.35 (dd, *J*

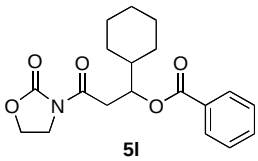
= 16.0 Hz and 4.0 Hz, 1H), 3.95-4.01 (m, 2H), 4.35-4.43 (m, 2H), 5.51-5.55 (m, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.7, 27.8, 40.1, 42.7, 62.4, 72.2, 128.6, 129.8, 130.5, 133.1, 153.9, 166.4, 170.4; HRMS Exact mass calcd for $C_{15}H_{17}NO_5Na$ [M + Na]$^+$: 314.0999; Found: 314.1008.



5k

$C_{15}H_{17}NO_6$
Exact Mass: 307.1056
Mol. Wt.: 307.2986
C, 58.63; H, 5.58; N, 4.56; O, 31.24

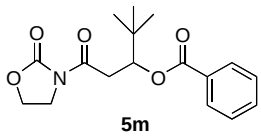
(5k): Benzoic acid 1-methoxymethyl-3-oxo-3-(2-oxo-oxazolidin-3-yl)-propyl ester: 27 mg, 77% yield (colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 40.8 min (minor); t_R 53.6 min (major) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 80% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.27-3.40 (m, 5H), 3.57 (dd, *J* = 10.8 Hz and 4.4 Hz, 1H), 3.66 (dd, *J* = 10.8 Hz and 4.8 Hz, 1H), 3.93 (t, *J* = 7.6 Hz, 2H), 4.31-4.38 (m, 2H), 5.64-5.67 (m, 1H), 7.36 (t, *J* = 7.6, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 8.0, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.1, 42.7, 59.5, 62.4, 69.6, 73.4, 128.5, 130.0, 130.1, 133.3, 153.9, 166.4, 171.0; HRMS Exact mass calcd for $C_{15}H_{17}NO_6Na$ [M + Na]$^+$: 330.0948; Found: 330.0917.



5l

$C_{19}H_{23}NO_5$
Exact Mass: 345.1576
Mol. Wt.: 345.3896
C, 66.07; H, 6.71; N, 4.06; O, 23.16

(5l): Benzoic acid 1-cyclohexyl-3-oxo-3-(2-oxo-oxazolidin-3-yl)-propyl ester: 27 mg, 75% yield (white solid); mp: 100-103 °C; The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 17.7 min (minor); t_R 21.0 min (major) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 84% ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.13-1.28 (m, 5H), 1.66-1.85 (m, 6H), 3.21 (dd, *J* = 15.5 Hz and 9.5 Hz, 1H), 3.40 (dd, *J* = 15.5 Hz and 3.5 Hz, 1H), 3.92-3.97 (m, 2H), 4.33 (q, *J* = 8.5 Hz, 1H), 4.40 (q, *J* = 7.5 Hz, 1H), 5.45-5.48 (m, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 26.2, 26.5, 28.2, 29.1, 38.1, 42.1, 42.8, 62.4, 74.6, 128.6, 129.9, 130.5, 133.1, 153.9, 166.3, 170.9; HRMS Exact mass calcd for $[M + Na]^+$: 368.1468; Found: 368.1460.

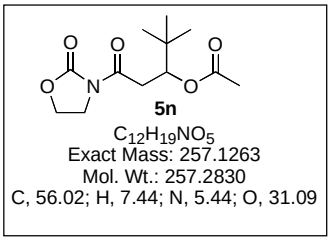


5m

$C_{17}H_{21}NO_5$
Exact Mass: 319.1420
Mol. Wt.: 319.3523
C, 63.94; H, 6.63; N, 4.39; O, 25.05

(5m): Benzoic acid 2,2-dimethyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 27 mg, 91% yield (colorless

oil); The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 12.1 min (minor); t_R 14.4 min (major) [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 89% ee (*R* enantiomer). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, 9H), 3.12 (dd, *J* = 15.0 Hz and 10.5 Hz, 1H), 3.47 (dd, *J* = 14.5 Hz and 2.0 Hz, 1H), 3.87-3.96 (m, 2H), 4.30 (q, *J* = 7.5 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 1H), 5.41 (dd, *J* = 10.5 Hz and 2.5 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 9.0 Hz, 1H), 8.02 (d, *J* = 9.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8, 26.1, 27.0, 36.8, 42.9, 62.4, 77.6, 128.6, 129.9, 130.2, 133.2, 166.4, 171.2; HRMS Exact mass calcd for $C_{17}H_{21}NO_5Na$ [M + Na]$^+$: 342.1312; Found: 342.1305.

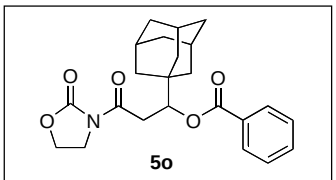


5n

$C_{12}H_{19}NO_5$
Exact Mass: 257.1263
Mol. Wt.: 257.2830
C, 56.02; H, 7.44; N, 5.44; O, 31.09

(5n): Acetic acid 2,2-dimethyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-propyl ester: 19 mg, 73% yield (oil); The enantiomeric purity was determined by HPLC (210 nm, 25 •C) t_R 12.9 min (major); t_R 29.5 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 95% ee . ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (s, 9H), 2.02 (s, 3H), 2.81 (dd, *J* = 14.5 Hz and 11.0 Hz, 1H), 3.43 (dd, *J* = 14.5 Hz and 1.5 Hz, 1H), 3.88-4.05 (m, 2H), 4.37-4.45 (m, 2H), 5.08 (dd, *J* = 10.5 Hz and 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

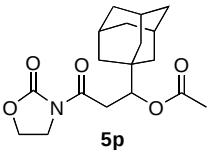
21.1, 25.9, 34.7, 36.7, 42.9, 62.4, 76.9, 153.9, 171.2, 171.4; HRMS Exact mass calcd for $C_{12}H_{19}NO_5Na$ $[M + Na]^+$: 280.1155; Found: 280.1149.



5o

$C_{23}H_{27}NO_5$
Exact Mass: 397.1889
Mol. Wt.: 397.4642
C, 69.50; H, 6.85; N, 3.52; O, 20.13

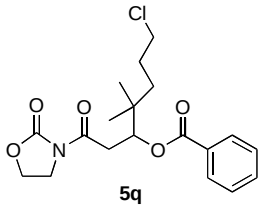
(5o): Benzoic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-1-tricyclo [3.3.1.10,0]dec-1-yl-propyl ester: 27 mg, 73% yield (white solid); mp: 169-173 •C The enantiomeric purity was determined by HPLC (254 nm, 25 •C) t_R 16.2 min (major); t_R 27.1 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 60% ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60-1.74 (m, 11H), 2.01-2.05 (m, 4H), 3.11 (dd, *J* = 14.5 Hz and 10.5 Hz, 1H), 3.47 (dd, *J* = 15.5 Hz and 2.5 Hz, 1H), 3.88-3.95 (m, 2H), 4.30 (q, *J* = 8.5 Hz, 1H), 4.38-4.43 (m, 1H), 5.27 (dd, *J* = 10.5 Hz and 2.0 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.2, 28.3, 35.3, 36.8, 36.9, 37.1, 38.2, 41.2, 42.9, 43.0, 62.2, 62.4, 77.8, 128.6, 129.9, 130.4, 133.1, 154.0, 161.2, 166.4, 171.5; HRMS Exact mass calcd for $C_{23}H_{27}NO_5Na$ $[M + Na]^+$: 420.1781; Found: 420.1755.



5p

$C_{18}H_{25}NO_5$
Exact Mass: 335.1733
Mol. Wt.: 335.3948
C, 64.46; H, 7.51; N, 4.18; O, 23.85

(5p): Acetic acid 3-oxo-3-(2-oxo-oxazolidin-3-yl)-1-tricyclo [3.3.1.10,0]dec-1-yl-propyl ester: 31 mg, 92% yield (white solid); mp: 138-140 °C; The enantiomeric purity was determined by HPLC (210 nm, 25 •C) t_R 14.3 min (major); t_R 33.0 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 57% ee. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.53-1.73 (m, 12H), 1.97-2.05 (m, 6H), 2.79 (dd, *J* = 11.6 Hz and 8.4 Hz, 1H), 3.45 (dd, *J* = 11.6 Hz and 1.6 Hz, 1H), 3.87-4.02 (m, 2H), 4.35-4.44 (m, 2H), 4.95 (dd, *J* = 8.8 Hz and 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 28.3, 35.4, 36.4, 37.1, 38.1, 42.9, 62.4, 73.5, 153.9, 171.2, 171.7; HRMS Exact mass calcd for $C_{18}H_{25}NO_5Na$ $[M + Na]^+$: 358.1625; Found: 358.1630.

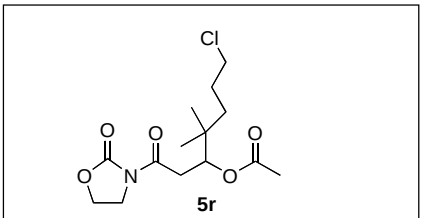


5q

$C_{19}H_{24}ClNO_5$
Exact Mass: 381.1343
Mol. Wt.: 381.8506
C, 59.76; H, 6.34; Cl, 9.28; N, 3.67; O, 20.95

(5q): Benzoic acid 5-chloro-2,2-dimethyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-pentyl ester: 30 mg, 76% yield (colorless oil); The enantiomeric purity was determined by HPLC (254 nm, 25

•C) t_R 22.4 min (minor); t_R 27.1 min (major) [Chiralcel AD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 50% ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (d, *J* = 4.0 Hz, 6H), 1.42-1.49 (m, 1H), 1.51-1.57 (m, 1H), 1.81-1.89 (m, 2H), 3.14 (dd, *J* = 15.0 Hz and 10.0 Hz, 1H), 3.46 (dd, *J* = 15.0 Hz and 2.5 Hz, 1H), 3.51 (t, *J* = 6.5 Hz, 2H), 3.88-3.96 (m, 2H), 4.30 (q, *J* = 9.0 Hz, 1H), 4.41 (q, *J* = 9.0 Hz, 1H), 5.47 (dd, *J* = 10.0 Hz and 2.5 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.3, 23.6, 27.4, 36.2, 36.5, 37.5, 42.9, 45.9, 62.4, 76.5, 128.7, 129.9, 130.2, 133.3, 153.9, 166.3, 171.0; HRMS Exact mass calcd for $C_{19}H_{24}ClNO_5Na$ $[M + Na]^+$: 404.1235; Found: 404.1216.



5r

$C_{14}H_{22}ClNO_5$
Exact Mass: 319.1187
Mol. Wt.: 319.7812
C, 52.58; H, 6.93; Cl, 11.09; N, 4.38; O, 25.02

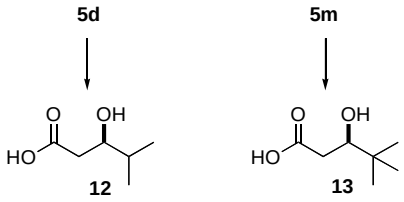
(5r): Acetic acid 5-chloro-2,2-dimethyl-1-[2-oxo-2-(2-oxo-oxazolidin-3-yl)-ethyl]-pentyl ester: 21 mg, 70 % yield (white solid); The enantiomeric purity was determined by HPLC (210 nm, 25 •C) t_R 16.4 min (major); t_R 32.7 min (minor) [Chiralcel OD (0.46 cm x 25 cm)(from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 90/10, 1.0 mL/min] as 88 % ee. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (m, 6H), 1.30-1.38 (m, 2H), 1.73-1.80 (m, 2H), 2.03 (s, 3H), 2.83 (dd, *J* = 14.5 Hz and 10.0 Hz, 1H), 3.43 (dd, *J* = 14.5 Hz and 2.0

Hz, 1H), 3.49-3.53 (m, 2H), 3.89-4.05 (m, 2H), 4.36-4.45 (m, 2H), 5.14 (dd, *J* = 10.0 Hz and 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 23.2, 23.4, 27.3, 36.1, 36.5, 42.8, 42.9, 45.9, 62.4, 75.9, 153.9, 171.2, 171.3; HRMS Exact mass calcd for $C_{14}H_{22}ClNO_5Na$ [M + Na]$^+$: 342.1079; Found: 342.1093.

Stereochemical analysis for products 5d and 5m.

Hydrolysis of 5d and 5m to 12 and 13.

To a 25 mL round bottom flask was added **5m** (95 mg, 0.30 mmol) (starting with 89% ee) containing a solution of dry MeOH (10 mL) and magnesium bromide etherate (155 mg, 0.60 mmol). The resulting mixture was heated to 70 •C and stirred under N_2 for 2 hours. The reaction was allowed to cool, diluted in ethyl acetate, washed with water (15 mL x 3), dried over $MgSO_4$ and concentrated. The corresponding crude methyl ester was directly taken to the next hydrolysis step. The methyl ester (70 mg, 0.28 mmol) was added to a solution of 1 M NaOH (10 mL) and THF (5 mL) and the mixture stirred vigorously for 5 hours. The reaction mixture was then acidified using 1 M HCl, extracted with methylene chloride, dried over $MgSO_4$ and concentrated to yield pure **13** (20 mg, 50%) after column chromatography. Compound **5d** (starting from 93% ee) was converted to **12** following the same procedure. The NMR data of **12** and **13** was compared to literature data and found to be identical.[1]



Compounds **12-13** were characterized according to literature data.[2] Stereochemical assignment for **12-13** is as follows: **12** $[\alpha]_D^{25}$ +25.8 (*c* 0.40, $CHCl_3$) {lit. $[\alpha]_D^{25}$ + 40.5 (*c* 0.60, $CHCl_3$) for (*R*)-enantiomer}[2]; **13** $[\alpha]_D^{25}$ +20.1 (*c* 0.75, $CHCl_3$) {lit. $[\alpha]_D^{25}$ + 53.2 (*c* 1.0, $CHCl_3$) for (*R*)-enantiomer}.[2] It should be noted that some racemization is thought to have occurred during the hydrolysis since there is some discrepancy between experimental and literature rotation data.

References

1. This is a known compound. For other preparations of this compound see: a) D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, *J. Am. Chem. Soc.* **1999**, *121*, 7559-7573; b) D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross, S. J. Miller, *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 798-800.

2. C. Palomo, M. Oiarbide, J. M. Aizpurua, A. González, J. M. García, C. Landa, I. Odriozola, A. Linden, *J. Org. Chem*. **1999**, *64*, 8193-8200.