# Efficient Synthesis of Enantiomerically Pure $\beta^{2}$-Ammino Acids via Chiral Isoxazolidinones 

Hee-Seung Lee, ${ }^{\dagger}$ Jin-Seong Park, ${ }^{\dagger}$ Byeong Moon Kim ${ }^{\ddagger}$ and Samuel H. Gellman ${ }^{\dagger}{ }^{\dagger}$
${ }^{\dagger}$ Department of Chemistry, University of Wisconsin, Madison, WI 53706-1396
${ }^{\ddagger}$ School of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea gellman@chem.wisc.edu

## Supporting Information

## EXPERIMENTAL SECTION



2-Acetyl-4-methyl-pentanoic Acid Benzyl Ester (1b) was prepared by a procedure analogous to that used for 1a. $t$-BuOK ( $3.57 \mathrm{~g}, 31.8 \mathrm{mmol}$ ), benzyl acetoacetate $(5.0 \mathrm{~mL}, 28.9 \mathrm{mmol})$ and isobutyl iodide ( 4.98 $\mathrm{mL}, 43.4 \mathrm{mmol}$ ) were used. The crude product was purified by silica gel column chromatography $($ EtOAc/hexanes $=1 / 30)$ to give $\mathbf{1 b}(6.31 \mathrm{~g})$ in $88 \%$ yield. $\mathrm{R}_{\mathrm{f}} 0.5(\mathrm{EtOAc} /$ hexanes $=1 / 10) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right.$, $300 \mathrm{MHz}) \delta 7.36-7.27(\mathrm{~m}, 5 \mathrm{H}), 5.21-5.12(\mathrm{~m}, 2 \mathrm{H}), 3.55\left(\mathrm{dd}, \mathrm{J}_{\mathrm{HH}}=8.4 \mathrm{~Hz}, \mathrm{~J}_{\mathrm{HH}}=6.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 2.16(\mathrm{~s}, 3 \mathrm{H})$, $1.87-1.78(\mathrm{~m}, 1 \mathrm{H}), 1.74-1.67(\mathrm{~m}, 1 \mathrm{H}), 1.56-1.47(\mathrm{~m}, 1 \mathrm{H}), 0.89\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=6.6 \mathrm{~Hz}, 6 \mathrm{H}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right.$, $75.4 \mathrm{MHz}) \delta 203.58,173.78,170.47,136.00,129.19,129.10,129.02,129.01,128.89,128.64,128.34$, $100.17,67.62,67.60,66.51,58.77,37.54,35.49,37.54,35.49,29.80,29.21,29.19,26.80,26.79,23.07$, 22.87, 22.71, 19.76; ESI-MS m/z; 271.1 ( $\mathrm{M}+\mathrm{Na}$, calcd 271.1), 519.2 ( $2 \mathrm{M}+\mathrm{Na}$, calcd 519.3).


2-Isopropyl-3-oxo-butyric Acid Benzyl Ester (1c) was prepared by a procedure analogous to that used for 1a. $t$-BuOK ( $7.15 \mathrm{~g}, 63.7 \mathrm{mmol}$ ), benzyl acetoacetate $(10.0 \mathrm{ml}, 57.9 \mathrm{mmol})$ and 2-iodopropane $(11.5 \mathrm{ml}$, $116 \mathrm{mmol})$ were used. The crude product was purified by silica gel column chromatography (EtOAc/hexanes $=$ $1 / 19)$ to give $\mathbf{1 c}(12.7 \mathrm{~g})$ in $94 \%$ yield. $\mathrm{R}_{\mathrm{f}} 0.5(\mathrm{EtOAc} /$ hexanes $=1 / 10) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.38$ $7.34(\mathrm{~m}, 5 \mathrm{H}), 5.17(\mathrm{~s}, 2 \mathrm{H}), 3.25\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=9.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 2.45(\mathrm{~m}, 1 \mathrm{H}), 2.20(\mathrm{~s}, 3 \mathrm{H}), 0.95\left(\mathrm{dd}, \mathrm{J}_{\mathrm{HH}}=7.8 \mathrm{~Hz}\right.$, $6.6 \mathrm{~Hz}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 202.88,169.01,135.37,128.55,128,37,128.26,67.50$, 66.86, 29.16, 28.69, 20.44, 20.37; ESI-MS m/z; 257.1 ( $\mathrm{M}+\mathrm{Na}$, calcd 257.1), 491.2 ( $2 \mathrm{M}+\mathrm{Na}$, calcd 491.2).


1d
2-Acetyl-6-tert-butoxycarbonylamino-hexanoic Acid Benzyl Ester (1d) was prepared by a procedure analogous to that used for $\mathbf{1 a} . t$ - $\mathrm{BuOK}(7.88 \mathrm{~g}, 70.2 \mathrm{mmol})$, benzyl acetoacetate $(11.0 \mathrm{ml}, 63.8 \mathrm{mmol})$ and ( $N$-Boc)-4-aminobutyl-1-bromide ${ }^{1}(13.4 \mathrm{~g}, 53.2 \mathrm{mmol})$ were used. The crude product was purified by silica gel column chromatography $(\mathrm{EtOAc} /$ hexanes $=1 / 5)$ to give $\mathbf{1 d}(16.4 \mathrm{~g})$ in $86 \%$ yield. $\mathrm{R}_{\mathrm{f}} 0.52(\mathrm{EtOAc} /$ hexanes $=1 / 2) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.39-7.32(\mathrm{~m}, 5 \mathrm{H}), 5.21(\mathrm{~s}, 2 \mathrm{H}), 4.56(\mathrm{br}, 1 \mathrm{H}), 3.45\left(\mathrm{t}, \mathrm{J}_{\mathrm{HH}}=7.2 \mathrm{~Hz}\right.$, $1 \mathrm{H}), 3.07(\mathrm{~m}, 2 \mathrm{H}), 2.18(\mathrm{~s}, 3 \mathrm{H}), 1.91-1.82(\mathrm{~m}, 2 \mathrm{H}), 1.49-1.35(\mathrm{~m}, 2 \mathrm{H}), 1.42(\mathrm{~s}, 9 \mathrm{H}), 1.32-1.22(\mathrm{~m}, 2 \mathrm{H})$; ${ }^{13} \mathrm{C}_{\mathrm{NMR}}\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 203.39,170.16,135.91,129.23,129.17,129.09,128.96,67.70,67.67$, 60.26, 40.74, 40.72, 30.38, 29.45, 29.01, 28.88, 28.84, 28.33, 25.15; ESI-MS m/z; 386.2 (M + Na, calcd 386.2), 749.4 ( $2 \mathrm{M}+\mathrm{Na}, 749.4$ ).


2-Isobutyl-acrylic Acid Benzyl Ester (2b) was prepared by a procedure analogous to that used for 2a. Compound $\mathbf{1 b}(6.31 \mathrm{~g}, 25.4 \mathrm{mmol})$, LiHMDS ( $27.9 \mathrm{~mL}, 27.9 \mathrm{mmol}$ ) and paraformaldehyde ( 3.5 g ) were used. The crude product was purified by column chromatography (EtOAc/hexanes $=1 / 50$ ) to give $\mathbf{2 b}(5.92 \mathrm{~g})$ in $94 \%$ yield. $\mathrm{R}_{\mathrm{f}} 0.50(\mathrm{EtOAc} /$ hexanes $=1 / 30) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.37-7.31(\mathrm{~m}, 5 \mathrm{H}), 6.21\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}\right.$ $=1.5 \mathrm{~Hz}, 1 \mathrm{H}), 5.51(\mathrm{~m}, 1 \mathrm{H}), 5.19(\mathrm{~s}, 2 \mathrm{H}), 2.20\left(\mathrm{dd}, \mathrm{J}_{\mathrm{HH}}=6.9 \mathrm{~Hz} \mathrm{~J}_{\mathrm{HH}}=1.2 \mathrm{~Hz}, 2 \mathrm{H}\right), 1.81(\mathrm{~m}, 1 \mathrm{H}), 0.88(\mathrm{~d}$, $\left.\mathrm{J}_{\mathrm{HH}}=6.6 \mathrm{~Hz}, 6 \mathrm{H}\right) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 167.18,139.62,136.13,128.46,128.03,127.89$, 126.03, 66.26, 41.27, 27.14, 22.21; ESI-MS m/z; 241.1 ( $\mathrm{M}+\mathrm{Na}$, calcd 241.1).


2-Isopropyl-acrylic Acid Benzyl Ester (2c) was prepared by a procedure analogous to that used for 2a. Compound $\mathbf{1 c}(12.7 \mathrm{~g}, 54.4 \mathrm{mmol})$, LiHMDS ( $59.8 \mathrm{~mL}, 59.8 \mathrm{mmol}$ ) and paraformaldehyde ( 7.5 g ) were used. The crude product was purified by column chromatography (EtOAc/hexanes $=1 / 50$ ) to give $\mathbf{2 c}(10.0 \mathrm{~g})$ in $90 \%$ yield. $\mathrm{R}_{\mathrm{f}} 0.50(\mathrm{EtOAc} /$ hexanes $=1 / 30) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.38-7.25(\mathrm{~m}, 5 \mathrm{H}), 6.18(\mathrm{~m}$, $1 \mathrm{H}), 5.54(\mathrm{~m}, 1 \mathrm{H}), 5.20(\mathrm{~s}, 2 \mathrm{H}), 2.84(\mathrm{~m}, 1 \mathrm{H}), 1.09\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=6.9 \mathrm{~Hz}, 6 \mathrm{H}\right) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right)$ $\delta 167.14,47.05,136.14,128.50,128.06,127.98,122.06,66.26,29.32,21.80 ;$ ESI-MS m/z; $227.1(\mathrm{M}+$ Na, calcd 227.1).


2d
2-(4-tert-Butoxycarbonylamino-butyl)-acrylic Acid Benzyl Ester (2d) was prepared by a procedure analogous to that used for 2a. Compound $\mathbf{1 d}(16.4 \mathrm{~g}, 45.2 \mathrm{mmol})$, LiHMDS ( $49.7 \mathrm{~mL}, 49.7 \mathrm{mmol}$ ) and paraformaldehyde $(3.0 \mathrm{~g})$ were used. The crude product was purified by column chromatography $(\mathrm{EtOAc} /$ hexanes $=1 / 9)$ to give $\mathbf{2 d}(9.94 \mathrm{~g})$ in $66 \%$ yield. $\mathrm{R}_{\mathrm{f}} 0.40(\mathrm{EtOAc} /$ hexanes $=1 / 5) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right.$, $300 \mathrm{MHz}) \delta 7.39-7.35(\mathrm{~m}, 5 \mathrm{H}), 6.21(\mathrm{~m}, 1 \mathrm{H}), 5.57(\mathrm{~m}, 1 \mathrm{H}), 5.20\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=2.4 \mathrm{~Hz}, 2 \mathrm{H}\right), 4.52(\mathrm{br}, 1 \mathrm{H}), 3.12$ $(\mathrm{m}, 2 \mathrm{H}), 2.34(\mathrm{~m}, 2 \mathrm{H}), 1.53-1.47(\mathrm{~m}, 4 \mathrm{H}), 1.45(\mathrm{~s}, 9 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 167.37,156.48$, $140.81,136.57,129.02,129.01,128.62,128.49,125.69,66.83,40.77,31.98,30.09,28.92,26.10$; ESIMS m/z; 356.2 ( $\mathrm{M}+\mathrm{Na}$, calcd 356.2), 689.3 (2M+Na, calcd 689.4).



Isoxazolidinones $\mathbf{5 b} \mathbf{6} \mathbf{6}$. Compounds $\mathbf{5 b}$ and $\mathbf{6 b}$ were prepared by a procedure analogous to that used for 5a/6a. Compound 2b ( $5.90 \mathrm{~g}, 27.1 \mathrm{mmol}$ ), (S)-1-phenylethylhydroxylamine oxalate $\mathbf{3}(12.3 \mathrm{~g}, 54.2 \mathrm{mmol})$ and triethylamine ( 37.8 mL , 271 mmol ) were used for preparation of $\mathbf{4 b}\left(7.89 \mathrm{~g}, \mathrm{R}_{\mathrm{f}} 0.12\right.$, EtOAc/hexanes $=$ $1 / 10$ ), which was then treated with LiHMDS ( $24.4 \mathrm{~mL}, 24.4 \mathrm{mmol}$ ) to afford $\mathbf{5 b}$ and $\mathbf{6 b}$, each in diastereomerically pure form after silica gel column chromatography (EtOAc/hexanes $=1 / 19)$ in $78 \%$ overall yield from $\mathbf{2 b}$; $\mathrm{t}_{\mathrm{R}}=10.73 \mathrm{~min}(\mathbf{5 b})$ and $\mathrm{t}=17.15 \mathrm{~min}(\mathbf{6 b})(250 \mathrm{X} 4.6 \mathrm{~mm}$ Chiralcel OD column, isopropanol/hexanes $=2 / 98,1.0 \mathrm{~mL} / \mathrm{min})$.
(4S)-Isobutyl-2-((S)-1-phenylethyl)-isoxazolidin-5-one (5b): = 99\% de, $\mathrm{R}_{\mathrm{f}} 0.40(\mathrm{EtOAc} / \mathrm{hexanes}=$ $1 / 10) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.40-7.31(5 \mathrm{H}), 3.83(\mathrm{~m}, 1 \mathrm{H}), 3.36(\mathrm{~m}, 1 \mathrm{H}), 2.97(\mathrm{br}, 1 \mathrm{H}), 2.52(\mathrm{~m}$,
$1 \mathrm{H}), 1.79-1.71(\mathrm{~m}, 1 \mathrm{H}), 1.60(3 \mathrm{H}), 1.49(\mathrm{~m}, 1 \mathrm{H}), 1.33(\mathrm{~m}, 1 \mathrm{H}), 0.90-0.85(6 \mathrm{H})$; ESI-MS m/z; 270.1 ( $\mathrm{M}+\mathrm{Na}$, calcd 270.1).
(4R)-Isobutyl-2-((S)-1-phenylethyl)-isoxazolidin-5-one (6b): = 99\% de, $\mathrm{R}_{\mathrm{f}} 0.35$ (EtOAc/hexanes = $1 / 10) ;{ }^{1}{ }^{H}$ NMR $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.35-7.25(5 \mathrm{H}), 3.91\left(\mathrm{q}, \mathrm{J}_{\mathrm{HH}}=6.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 3.85(\mathrm{br}, 1 \mathrm{H}), 3.06(\mathrm{br}$, $1 \mathrm{H}), 2.73(\mathrm{br}, 1 \mathrm{H}), 1.82-1.20(\mathrm{br}, 6 \mathrm{H}), 0.95-0.84(6 \mathrm{H})$; ESI-MS m/z; 270.1 (M+Na, calcd 270.1).



Isoxazolidinones $\mathbf{5 c} / \mathbf{6 c}$. Compounds $\mathbf{5 c}$ and $\mathbf{6 c}$ were prepared by a procedure analogous to that used for 5a/6a. Compound 2c (10.0 g, 49.0 mmol ), (S)- 1-phenylethylhydroxylamine oxalate $\mathbf{3}(22.3 \mathrm{~g}, 98.0 \mathrm{mmol}$ ) and triethylamine ( $68.3 \mathrm{~mL}, 490 \mathrm{mmol}$ ) were used for preparation of $\mathbf{4 c}\left(13.9 \mathrm{~g}, \mathrm{R}_{\mathrm{f}} 0.28\right.$, EtOAc/hexanes $\left.=1 / 10\right)$, which was then treated with LiHMDS $(44.8 \mathrm{~mL}, 44.8 \mathrm{mmol})$ to afford $\mathbf{5 c}$ and $\mathbf{6 c}$, each in diastereomerically pure form after silica gel column chromatography $(E t O A c /$ hexanes $=1 / 19)$ in $80 \%$ overall yield from $\mathbf{2 c} ; \mathrm{t}_{\mathrm{R}}=$ $7.12 \min (\mathbf{5 c})$ and $\mathrm{t}_{\mathrm{R}}=11.89 \mathrm{~min}(\mathbf{6 c})(250 \mathrm{X} 4.6 \mathrm{~mm}$ Chiralcel OD column, isopropanol/hexanes $=2 / 98,1.0$ $\mathrm{mL} / \mathrm{min}$ ).
(4S)-Isopropyl-2-((S)-1-phenylethyl)-isoxazolidin-5-one (5c): = 99\% de, $\mathrm{R}_{\mathrm{f}} 0.50(\mathrm{EtOAc} / \mathrm{hexanes}=$ $1 / 10) ;{ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.40-7.27(5 \mathrm{H}), 3.82\left(\mathrm{q}, \mathrm{J}_{\mathrm{HH}}=6.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 3.22\left(\mathrm{dd}, \mathrm{J}_{\mathrm{HH}}=9.2 \mathrm{~Hz}\right.$, $\left.\mathrm{J}_{\mathrm{HH}}=8.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 2.90-2.75(1 \mathrm{H}), 2.60-2,75(1 \mathrm{H}), 2.11(\mathrm{~m}, 1 \mathrm{H}), 1.58(3 \mathrm{H}), 1.02\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=7.2 \mathrm{~Hz}, 3 \mathrm{H}\right)$, $0.88(3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 175.12,139.99,128.77,128.22,127.59,69.87,56.58,48.72$, 26.56, 21.79, 20.50, 19.01; ESI-MS m/z; 256.1 ( $\mathrm{M}+\mathrm{Na}$, calcd 256.1), 489.2 ( $2 \mathrm{M}+\mathrm{Na}$, calcd 489.3).
(4R)-Isopropyl-2-((S)-1-phenylethyl)-isoxazolidin-5-one (6c): = 99\% de, $\mathrm{R}_{\mathrm{f}} 0.45(\mathrm{EtOAc} / \mathrm{hexanes}=$ $1 / 10) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.34-7.26(5 \mathrm{H}), 3.88\left(\mathrm{q}, \mathrm{J}_{\mathrm{HH}}=6.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 3.80-3.60(\mathrm{br}, 1 \mathrm{H}), 3.30-$ $2.50(\mathrm{br}, 2 \mathrm{H}), 2.13(\mathrm{~m}, 1 \mathrm{H}), 1.47(\mathrm{br}, 3 \mathrm{H}), 1.06\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=6.3 \mathrm{~Hz}, 3 \mathrm{H}\right), 0.95\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=6.9 \mathrm{~Hz}, 3 \mathrm{H}\right)$; ESI-MS m/z; 256.1 (M+Na, calcd 256.1), 489.2 (2M+Na, calcd 489.3).



Isoxazolidinones $\mathbf{5 d} / \mathbf{6 d}$. Compounds $\mathbf{5 d}$ and $\mathbf{6 d}$ were prepared by a procedure analogous to that used for 5a/6a. Compound $\mathbf{2 d}(9.94 \mathrm{~g}, 29.8 \mathrm{mmol})$, (S)-1-phenylethylhydroxylamine oxalate $\mathbf{3}(13.5 \mathrm{~g}, 59.6 \mathrm{mmol})$ and triethylamine ( $41.5 \mathrm{~mL}, 298 \mathrm{mmol}$ ) were used for preparation of $\mathbf{4 d}\left(12.3 \mathrm{~g}, \mathrm{R}_{\mathrm{f}} 0.50\right.$, EtOAc/hexanes $\left.=1 / 3\right)$, which was then treated with LiHMDS ( $28.8 \mathrm{~mL}, 28.8 \mathrm{mmol}$ ) to afford $\mathbf{5 d}$ and $\mathbf{6 d}$, each in diastereomerically pure form after silica gel column chromatography $(\mathrm{EtOAc} /$ hexanes $=1 / 3)$ in $84 \%$ overall yield from $\mathbf{2 d} ; \mathrm{t}_{\mathrm{R}}=$ $19.88 \mathrm{~min}(\mathbf{5 d})$ and $\mathrm{t}_{\mathrm{R}}=25.05 \mathrm{~min}(\mathbf{6 d})(250 \times 4.6 \mathrm{~mm}$ Chiralcel OD column, isopropanol/hexanes $=10 / 90$, $1.0 \mathrm{~mL} / \mathrm{min}$ ).
(4S)-[4’-(tert-Butoxycarbonylamino)butyl)]-2-((S)-1-phenylethyl)-isoxazolidin-5-one (5d): = 99\% de, $\mathrm{R}_{\mathrm{f}} 0.33$ (EtOAc/hexanes $=1 / 3$ ); This compound exists as a mixture of slowly interconverting rotamers according to NMR spectroscopy. ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.38-7.29(5 \mathrm{H}), 4.82(1 \mathrm{H}), 3.86-3.78$ $(1 \mathrm{H}), 3.36-3.31(1 \mathrm{H}), 3.11-3.00(2 \mathrm{H}), 3.00-2.80(1 \mathrm{H}), 2.60-2.51(1 \mathrm{H}), 1.88-1.80(1 \mathrm{H}), 1.58-1.55(3 \mathrm{H})$, $1.55-1,20(9 \mathrm{H}), 1.40(9 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 176.02,156.23,140.04,129.07,128.56$, 128.47, 127.86, 79.10, 77.08, 70.06, 60.36, 43.02, 40.28, 30.11, 28.63, 27.95, 24.73, 22.01; ESI-MS m/z; 385.2 ( $\mathrm{M}+\mathrm{Na}$, calcd 385.2), 747.3 ( $2 \mathrm{M}+\mathrm{Na}$, calcd 747.4).
(4R)-[4’-(tert-Butoxycarbonylamino)butyl)]-2-((S)-1-phenylethyl)-isoxazolidin-5-one (6d): = 99\% de, $\mathrm{R}_{\mathrm{f}} 0.27(\mathrm{EtOAc} /$ hexanes $=1 / 3)$; This compound exists as a mixture of slowly interconverting rotamers according to NMR spectroscopy. ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.37-7.27(5 \mathrm{H}), 4.58(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.90(\mathrm{q}$, $\left.\mathrm{J}_{\mathrm{HH}}=6.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 3.85(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 3.11-2.90(5 \mathrm{H}), 2.77(1 \mathrm{H}), 1.86-1.83(2 \mathrm{H}), 1.65-1.32(9 \mathrm{H}), 1.44(9 \mathrm{H}) ;$ ESI-MS m/z; 385.2 (M+Na, calcd 385.2), 747.3 (2M+Na, calcd 747.4).

(2S)-Isobutyl-3-(9H-fluoren-9-ylmethoxycarbonylamino)-propionic Acid (Fmoc-(S)- $\beta^{2}$ - $\mathrm{HL} \mathrm{Cu}-\mathrm{OH}$; 7b) was prepared from $\mathbf{5 b}$ by a procedure analogous to that used for $\mathbf{7 a}$ in $80 \%$ yield: $\mathrm{mp} 130-131{ }^{\circ} \mathrm{C} ;[\alpha]^{25}{ }_{\mathrm{D}}$ $=+10.8\left(\mathrm{c} 0.6, \mathrm{CHCl}_{3}\right),[\alpha]_{\mathrm{D}}^{\mathrm{tt}}=+10.8\left(7 \mathbf{b},{ }^{2} \mathrm{c} 0.6, \mathrm{CHCl}_{3}\right)$. This compound exists as a mixture of slowly interconverting rotamers according to NMR spectroscopy. ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}, 300 \mathrm{MHz}\right) \delta 7.75\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=7.2\right.$ $\mathrm{Hz}, 2 \mathrm{H}), 7.57\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=7.2 \mathrm{~Hz}, 2 \mathrm{H}\right), 7.41-7.28(\mathrm{~m}, 4 \mathrm{H}), 6.78$ and $5.26(\mathrm{~b}, 1 \mathrm{H}), 4.29-4.21(\mathrm{~m}, 3 \mathrm{H}), 3.46-$ $3.29(\mathrm{~m}, 2 \mathrm{H}), 2.81-2.59(\mathrm{~m}, 1 \mathrm{H}), 1.80-1.40(\mathrm{~m}, 2 \mathrm{H}), 1.40-1.20(\mathrm{~m}, 1 \mathrm{H}), 0.95-0.87(\mathrm{~m}, 6 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}, 75.4 \mathrm{MHz}\right) \delta 180.78$ (179.34), 156.48 (158.00), 143.81 (143.59), 141.25, 127.64, 127.00, 125.01 (124.79), 119.94, 66.84 ( 67.53 ), 47.14, 43.65 (44.03), 42.17 (42.92), 38.53 (38.97), 25.79, 22.34 (22.45); ESI-MS m/z; $144.1\left(\mathrm{M}-\mathrm{C}_{15} \mathrm{H}_{11} \mathrm{O}_{2}\right.$ (Fmoc), calcd 144.1025), 366.1 (M-H, calcd 366.2), 733.3 (2M-H, calcd 733.3).

(2R)-Isopropyl-3-(9H-fluoren-9-ylmethoxycarbonylamino)-propionic Acid (Fmoc-(R)- $\beta^{2}$ - $\mathbf{H V a l}-\mathrm{OH}$;
$\mathbf{8 c}$ ) was prepared from $\mathbf{6 c}$ by a procedure analogous to that used for $7 \mathbf{7 a}$ in $84 \%$ yield.; $[\alpha]^{25}=-12.1$ (c 0.97, $\left.\mathrm{CHCl}_{3}\right),[\alpha]_{\mathrm{D}}^{\mathrm{t}}=+11.5$ (enantiomer $7 \mathbf{c},{ }^{2} \mathrm{c} 0.97, \mathrm{CHCl}_{3}$ ). This compound exists as a mixture of slowly interconverting rotamers according to NMR spectroscopy. ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CD}_{3} \mathrm{OD}, 300 \mathrm{MHz}\right) \delta 7.71\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=7.2\right.$ $\mathrm{Hz}, 2 \mathrm{H}), 7.57\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=7.5 \mathrm{~Hz}, 2 \mathrm{H}\right), 7.34-7.22(\mathrm{~m}, 4 \mathrm{H}), 4.30-4.20(\mathrm{~m}, 2 \mathrm{H}), 4.11(\mathrm{~m}, 1 \mathrm{H}), 3.35-3.23(\mathrm{~m}$, $2 \mathrm{H}), 2.44-2.37(\mathrm{~m}, 1 \mathrm{H}), 1.87(\mathrm{~m}, 1 \mathrm{H}), 0.95\left(\mathrm{dd}, \mathrm{J}_{\mathrm{HH}}=6.9 \mathrm{~Hz}, \mathrm{~J}_{\mathrm{HH}}=8.3 \mathrm{~Hz}, 6 \mathrm{H}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CD}_{3} \mathrm{OD}, 75.4\right.$ MHz) $\delta 177.98,158.96,145.53,145.50,142.77,128.99,128.39,128.37,126.45,121.16,68.03,53.82$, 41.98, 30.01, 20.96, 20.64; ESI-MS m/z; 352.2 (M-H, calcd 352.2), 705.3 ( $2 \mathrm{M}-\mathrm{H}$, calcd 705.3).

The physical data for compound $\mathbf{8 c}$ prepared by the route in Scheme 4 in the main manuscript were identical to those of $\mathbf{8 c}$ prepared by the route in Scheme 3.

(2R)-[4’-(tert-Butoxycarbonylamino)butyl)]-3-(9H-fluoren-9-ylmethoxycarbonylamino)-propionic
Acid (Fmoc- $(\boldsymbol{R})-\boldsymbol{\beta}^{\mathbf{2}}-(\boldsymbol{N}$-Boc)-HLys-OH; 8d) was prepared from $\mathbf{6 d}$ by a procedure analogous to that used for $7 \mathbf{a}$ in $78 \%$ yield. $\mathrm{mp} 139-140{ }^{\circ} \mathrm{C} ;[\alpha]^{25}=-4.6\left(\mathrm{c} 0.54, \mathrm{CHCl}_{3}\right),[\alpha]_{\mathrm{D}}^{\mathrm{tt}}=+4.8$ (enantiomer $7 \mathrm{~d},{ }^{3} \mathrm{c} 0.54$, $\mathrm{CHCl}_{3}$ ). This compound exists as a mixture of slowly interconverting rotamers according to NMR spectroscopy. ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CD}_{3} \mathrm{OD}, 300 \mathrm{MHz}\right) \delta 7.80\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=7.8 \mathrm{~Hz}, 2 \mathrm{H}\right), 7.65\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=7.5 \mathrm{~Hz}, 2 \mathrm{H}\right), 7.42-$ $7.29(\mathrm{~m}, 4 \mathrm{H}), 4.34\left(\mathrm{~d}, \mathrm{~J}_{\mathrm{HH}}=6.9 \mathrm{~Hz}, 2 \mathrm{H}\right), 4.2\left(\mathrm{t}, \mathrm{J}_{\mathrm{HH}}=6.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 3.36-3.28(\mathrm{~m}, 2 \mathrm{H}), 3.04\left(\mathrm{t}, \mathrm{J}_{\mathrm{HH}}=6.9 \mathrm{~Hz}\right.$, $2 \mathrm{H}), 2.61(\mathrm{~m}, 1 \mathrm{H}), 1.60-1.34(\mathrm{~m}, 6 \mathrm{H}), 1.45(\mathrm{~s}, 9 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CD}_{3} \mathrm{OD}, 75.4 \mathrm{MHz}\right) \delta 178.49,159.07$, $145.55,142.82,129.03,128.41,126.47,121.19,80.10,68.03,68.00,47.27,43.68,43.66,41.35,31.15$, 30.67, 29.09, 25.61; ESI-MS m/z; 259.2 ( $\mathrm{M}_{-\mathrm{C}}^{15} \mathrm{H}_{11} \mathrm{O}_{2}$ (Fmoc), calcd 259.2), 481.2 (M-H, calcd 481.2).

## REFERENCES

(1) Ina, H.; Ito, M.; Kibayashi, C. J. Chem. Soc., Chem. Commun., 1995, 1015.
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(3) Gademann, K.; Kimmerlin, T.; Hoyer, D.; Seebach, D. J. Med. Chem. 2001, 44, 2460.

oIS


128.540
126.639
110.127
110.099


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Lee 3442


## Lee 3442 <br> 020828_08 39 (0.715) Cm (28:62-149:167)

TOF MS ES+




Lee 2799


Lee 2799




Park 3014






Lee 3443



020828_09 39 (0.725) Cm (28:51-116:139)

ヶ2s


Park 3015
(20730_03 42 (0.778) Cm (28:52-87:104)


Wdd

Park 3042
(020731_05 43 (0.790) Cm (30:52-88:106)





Lee 2275


Lee 2275
020618_31 $34(0.625) \mathrm{Cm}(30: 37-142: 151) \quad 270.1 \quad$ TOF MS ES +



s६s


(




$07 S$


Park 612



${ }^{\text {qr }}$


—— 29.320

## Park 613



## Park 613



$9 \vdash$ S



Park 1018
020322 _04 33 ( 0.607 ) Cm (22:49)


fo unגџəəds tyNN H


.978




Park 1103

zss



## Park 728

020307_03 $34(0.624) \mathrm{Cm}(24: 52)$
100 $\quad 223.1 \quad$ TOF MS ES +


Park 784
020308_11 33 (0.605) Cm (26:44)
TOF MS ES +
(100)

## Park 784





Park 1489



Z9S





## Park 944







$-167.374$

## $\longrightarrow \quad 156.483$



66.831


$=30.085$
$\square$
$\square$

Park 946

-
89S
Wdd







Park 1476


