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Solid-phase synthesis of α-alkylserines via phase-transfer catalytic alkylation of polymer-supported 2-phenyl-2-oxazoline-4-carboxylate

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ABSTRACT

Described is the development of a new solid-phase synthetic method for α-alkylserines in which phase-transfer catalytic alkylation of polymer-supported 2-phenyl-2-oxazoline-4-carboxylate (**12**) is the key step. The easy preparation of the polymer-supported substrate **12**, the high chemical yield (up to 93%), and the mild cleavage conditions could make this method very practical for the synthesis of α-alkylserines.

1. Introduction

Since the pioneering work based on solid-supported resins by Merrifield in 1963, solid-phase synthesis has been popularly applied to various synthetic methods, especially peptide synthesis.[1] Ease of purification, fast synthetic processes, and automation have granted this method an important role in combinatorial chemistry and parallel synthesis for new drug development. A rapid growth of the synthetic method using a phase-transfer catalyst (PTC) for the preparation of unnatural α-amino acids in the last decade[2] has prompted many researchers to apply PTC-mediated-solution-phase reactions to solid-phase versions by using solid-supported-PTCs[3] or solid-supported substrates.[4] As representative works on the polymer-supported substrates (Fig. 1), O'Donnell and Scott developed efficient solid-phase synthetic methods for α-alkyl-α-amino acids and peptides by the phase-transfer alkylation of resin-bound *N*-(diphenylmethylene)glycine esters (*ester linkage*) **1**.[4] We recently reported solid-phase synthetic methods for nonnatural α-alkyl-α-amino acids using resin-bound *N*-(benzylidene)glycine esters (*imine linkage*) **2** under phase-transfer catalytic alkylation conditions.[5] In this article, we report a new solid-phase synthetic system for α-alkylserines using polymer-supported oxazoline-4-carboxylic acid derivatives.

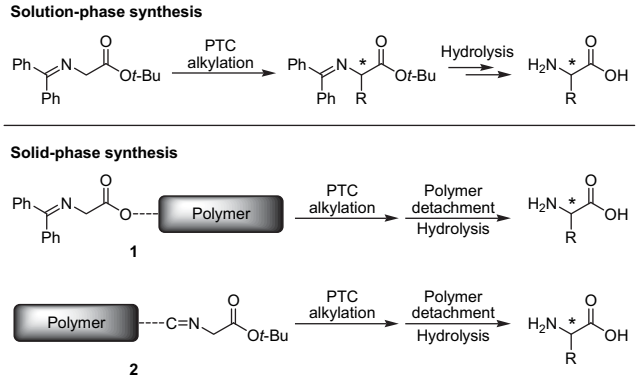
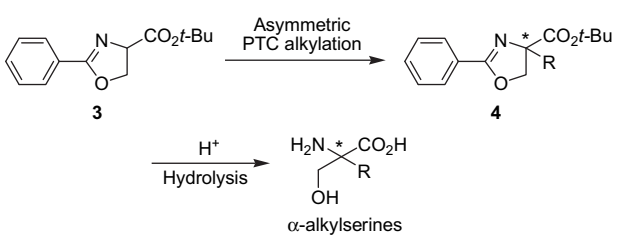


Figure 1. Phase-transfer catalytic synthesis of α-amino acids.

2. Results and discussion

We recently developed the efficient, novel substrate, 2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (**3**), for the catalytic enantioselective synthesis of α-serine derivatives under phase-transfer conditions (Scheme 1).[7]



Scheme 1. Synthesis of α-alkylserines via solution-phase PTC alkylation.

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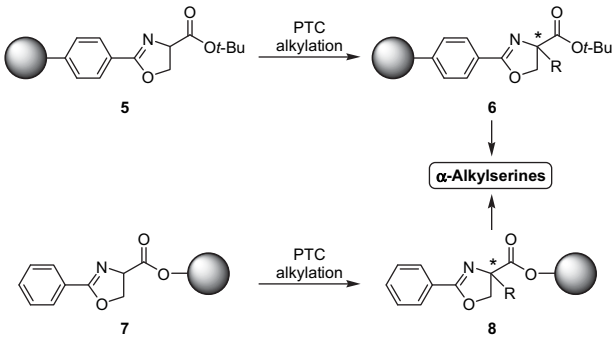
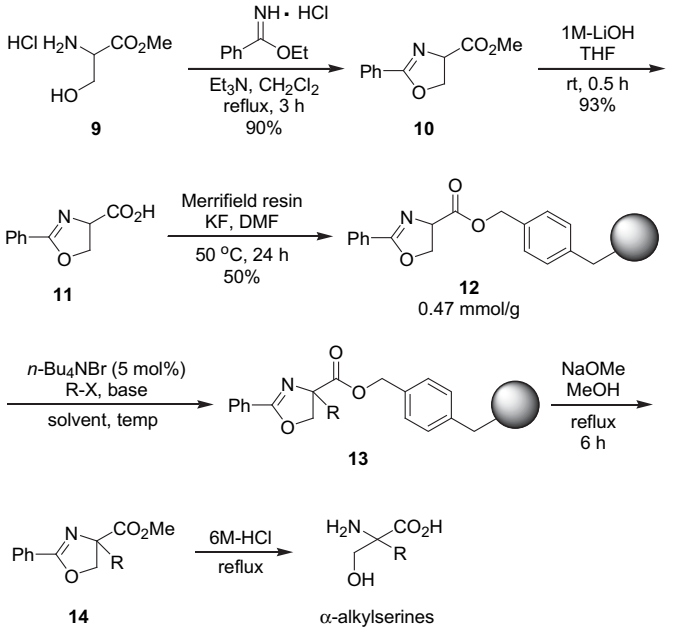
As part of our program for the conformational study of peptides containing α-alkylserines that can affect their conformations via intramolecular hydrogen bonding,[6] the solid-phase synthetic system was needed for practical preparation of various α-alkylserine derivatives. Based on our previous solid-phase synthetic approaches[5] and the O'Donnell and Scott's method,[4] both a 2-phenyl-2-oxazoline linkage **5** and ester linkage **7** were designed, respectively (Scheme 2).



Scheme 2. Solid-phase synthetic strategy of α-alkylserines.

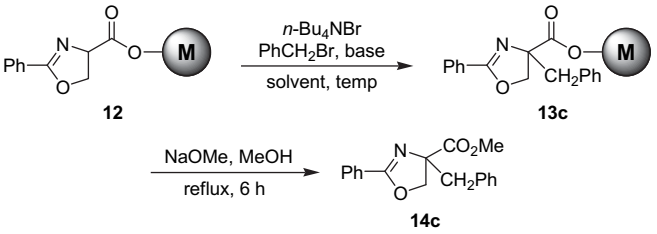
First, oxazoline-linked resin-bound substrate **5** was prepared from carboxypolystyrene resin (4.5 mmol/g) and serine *tert*-butyl ester by the reported methods.[7d] Coupling of the resin and serine *tert*-butyl ester using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), followed by cyclization with dimethylaminosulfur trifluoride (DAST), gave the corresponding resin-bound oxazoline *tert*-butyl ester **5**. For evaluation of its suitability as a substrate, catalytic benzylation of **5** under phase-transfer conditions in the presence of tetrabutylammonium bromide, a PTC, followed by hydrolysis with 6 M aq HCl was performed. However, unfortunately, only a trace amount of α-benzylserine was obtained in every trial with various conditions.

Next, our attention was turned toward the ester linkage as in **7**. The ester-linked polymer-supported substrate **12** was prepared from serine methyl ester HCl (**9**) in three steps with 42% overall yield (Scheme 3). Coupling of **9** with ethyl benzimidate hydrochloride, followed by hydrolysis with 1 M aq LiOH in THF gave 2-phenyl-2-



Scheme 3. Synthesis of α-alkylserines via solid-phase PTC alkylation.

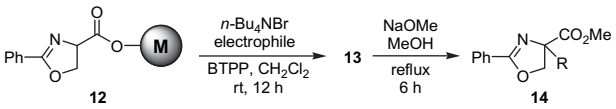
Table 1
Screening and optimization of reaction conditions for solid-phase alkylation via phase-transfer catalysis[a]

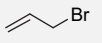
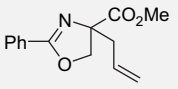
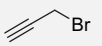
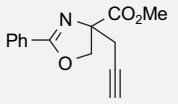
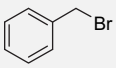
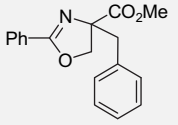
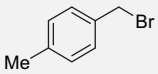
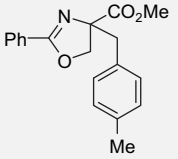
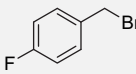
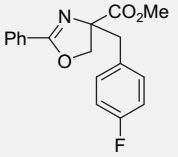
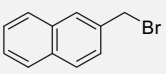
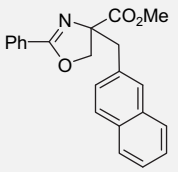
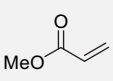
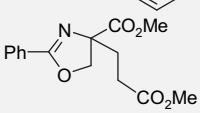


Entry	Base (equiv)	Solvent	Temp	Time (h)	Yield[b] (%)
1	Solid-KOH (5.0)	PhMe	rt	24	—[c]
2	50% KOH (5.0)	PhMe	rt	24	—[c]
3	50% CsOH (5.0)	PhMe	rt	24	—[c]
4	BTPP (2.0)	CH_2Cl_2	0 °C	24	92
5	BTPP (2.0)	CH_2Cl_2	rt	12	93

[a] Reaction was carried out with 5 equiv of benzyl bromide and 0.05 equiv of tetrabutylammonium bromide.
[b] Isolated yields for the two steps.
[c] Some of the substrate was hydrolyzed.

Table 2
Solid-phase catalytic alkylation of **12** under phase-transfer conditions[a]



Entry	Electrophile	Product		Yield[b] (%)
1			**14a**	85
2			**14b**	87
3			**14c**	93
4			**14d**	92
5			**14e**	92
6			**14f**	91
7			**14g**	90

[a] Reaction was carried out with 5 equiv of electrophile, 2 equiv of BTPP, and 0.05 equiv of tetrabutylammonium bromide.
[b] Isolated yields for the two steps.

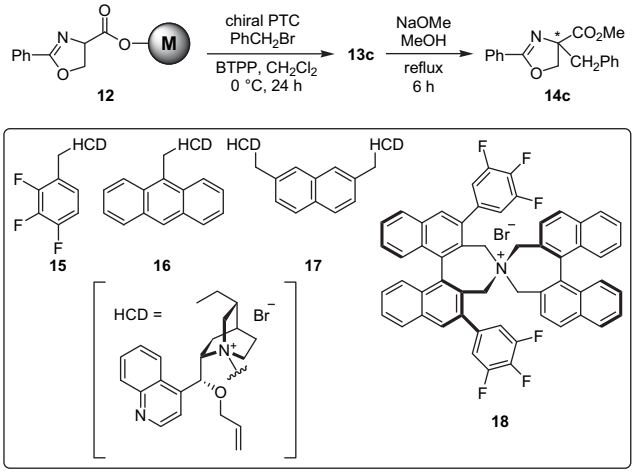
oxazoline-4-carboxylic acid (**11**). O-Alkylation of **11** with Merrifield resin using potassium fluoride base in DMF at 50 °C provided ester linkage substrate **12**.

Catalytic phase-transfer benzylations of **12** were performed using 5 mol % of tetrabutylammonium bromide, along with benzyl bromide (5 equiv) under various kinds of bases and solvent conditions (Table 1). Chemical yields were calculated with methyl 4-benzyl-2-phenyl-2-oxazoline-4-carboxylate (**14c**, R=CH_2Ph) released by the methanolysis of the benzylated product **13c** (R=CH_2Ph) with catalytic amount of sodium methoxide in methanol.

The catalytic phase-transfer benzylation was dramatically dependent on the base conditions. While none of the alkali bases employed in toluene led any benzylation (entries 1–3), *tert*-butyliminotris(pyrrolidino)phosphorane (BTPP),[7e] a strong non-metallic, non-ionic, and low-nucleophilic phosphazene base, gave high chemical yields (entry 4, 92% and entry 5, 93%) insensitive to reaction temperature. The benzylated product **14c** could be successfully hydrolyzed in 6 M aq HCl to give α-benzylserine in 98% yield. Further investigation for scope and limitation of this solid-phase synthetic system with several alkyl halides under optimal reaction conditions (entry 5 in Table 1) was performed. As shown in Table 2, high chemical yields (85–93%) were observed in allylic and benzylic halides, but less active aliphatic halides provided poor results (data not shown). The optimized solid-phase alkylation system was successively applied to the Michael addition as well (entry 7, 90%).

We then turned our attention toward asymmetric version by employing chiral PTCs instead of tetrabutylammonium bromide. Representative four kinds of quaternary ammonium salts (**15**,[8] **16**,[9] **17**,[10] **18**[11]) were employed as chiral PTCs for enantioselective phase-transfer catalytic benzylations of **12**. As shown in Table 3, relatively low enantioselectivity was obtained, even in the case of catalyst **18**, which gave quite high enantioselectivity in the corresponding solution-phase synthetic version (i.e., the benzylation of **3**).[7b] Only 42% enantiomeric excess was the highest one even with 1.0 equiv of the best PTC **18**. We speculate that the *tert*-butyl group of the oxazoline-4-carboxylate system in solution-phase system might be more sensitive compared to the *N*-(diphenylmethylene)glycinate regarding enantioselectivity.

Table 3
Asymmetric version of the solid-phase catalytic benzylation under phase-transfer conditions[a]



Entry	PTC (equiv)	Yield[b] (%)	ee[c] (%)	Config.[d]
1	**15** (0.1)	65	0	—
2	**16** (0.1)	84	4	*R*
3	**17** (0.1)	72	17	*R*
4	**18** (0.05)	85	20	*S*
5	**18** (1.0)	87	42	*S*

[a] Reaction condition was the same as Table 2, except catalyst and reaction temperature.
[b] Isolated yields for the two steps.
[c] Enantiopurity was determined by HPLC analysis of **14c** using a chiral column (Chiralcel OD) with hexanes/2-propanol as the eluent.
[d] Absolute configuration was assigned by comparison of the specific optical rotation of α-benzylserine from the hydrolysis of **14c** with the literature value.[7b]

3. Conclusion

An efficient, new solid-phase synthetic method for α-alkylserines was developed. Catalytic phase-transfer alkylation of the Merrifield resin-supported 2-phenyl-2-oxazoline-4-carboxylate (**12**) smoothly afforded the alkylated products in high chemical yields under mild reaction conditions. A phosphazene base, BTPP was found to be effective to make the alkylation possible, while alkali hydroxides were not. The ease in the preparation of the polymer-bound substrate, high chemical yields, and mild reaction conditions could make this method suitable for the combinatorial synthesis of α-alkylserines. In addition, preliminary attempt on the asymmetric alkylation of **12** with several representative chiral PTCs indicates that an intensive systematic investigation will be required to search the best-fit chiral catalyst for this solid-phase synthetic system.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR-300E and Perkin–Elmer 1710 FT spectrometer. Nuclear magnetic resonance (^1H NMR and ^{13}C NMR) spectra were measured on a JEOL JNM-LA 300 [300 MHz (^1H), 75 MHz (^{13}C)] spectrometer and JEOL JNM-GSX 400 [400 MHz (^1H), 100 MHz (^{13}C) spectrometer, using $CHCl_3$-*d* or CH_3OH-*d* or H_2O-*d* as a solvent, and were reported in parts per million relative to $CHCl_3$-*d* (δ 7.24) or CH_3OH-*d* (δ 4.87) or H_2O-*d* (δ 4.80) for ^1H NMR and relative to the $CHCl_3$-*d* (δ 77.23) or CH_3OH-*d* (δ 49.15) or H_2O-*d* (NA) resonance for ^{13}C NMR. Coupling constants (*J*) in ^1H NMR are in hertz. Low-resolution mass spectra (MS) were recorded on a VG Trio-2 GC–MS spectrometer. Melting points were measured on a Buchi B-540 melting point apparatus. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plate (silica gel 60 GF254, 0.25 mm) was used. For column chromatography, Merck Kieselgel 60 (70–230 mesh) was used.

4.2. 2-Phenyl-2-oxazoline-4-carboxylic acid methyl ester (10)

To a CH_2Cl_2 solution (60 mL) of ethyl benzimidate·HCl (3.71 g, 20.0 mmol) and L-serine methyl ester HCl (3.11 g, 20.0 mmol) was added triethylamine (5.58 mL, 40.0 mmol), and the mixture was refluxed for 3 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL), washed with saturated $NaHCO_3$ solution (2×50 mL) and water (2×50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, hexane/EtOAc=9:1) to afford **9** (3.69 g, 90% yield) as colorless caramel. ^1H NMR (300 MHz, $CDCl_3$): δ 7.96 (d, *J*=7.3 Hz, 2H), 7.52–7.34 (m, 3H), 4.91 (t, *J*=14.6 Hz, 1H), 4.71–4.49 (m, 2H), 3.76 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 166.1, 131.7, 128.4, 128.2, 126.8, 69.4, 68.4, 52.6 ppm; IR (KBr) 2954, 1742, 1643, 1447, 1362, 1298, 1210, 1089, 972, 780, 698 cm^{-1}; MS (FAB) *m*/*z* 206 $[M+H]^+$; HRMS calculated for $C_{11}H_{11}NO_3$: 205.0739; found: 206.0811 $[M+H]^+$.

4.3. 2-Phenyl-2-oxazoline-4-carboxylic acid (11)

To a THF solution (60 mL) of 2-phenyl-2-oxazoline-4-carboxylate methyl ester (**10**) (3.69 g, 18.0 mmol) was added 1 M LiOH solution (60 mL, 60.0 mmol), and the mixture was stirred for 0.5 h at

room temperature. The reaction mixture was concentrated, acidified with 1 M HCl solution, extracted with EtOAc (4×200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford **11** as a white solid (3.20 g, 93% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.95–7.92 (m, 2H), 7.65–7.51 (m, 3H), 4.94–4.88 (m, 1H), 4.67–4.56 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.1, 169.0, 134.1, 131.7, 130.5, 130.4, 72.3, 70.0 ppm; IR (KBr) 3437, 2417, 1717, 1631, 1496, 1450, 1377, 1321, 1239, 1111, 1028, 955, 783, 701, 419 cm^{-1}; MS (FAB) *m*/*z* 192 $[M+H]^+$; HRMS calculated for $C_{10}H_9NO_3$: 191.0582; found: 192.0658 $[M+H]^+$.

4.4. Merrifield resin-supported 2-phenyl-2-oxazoline-4-carboxylate (12)

To a DMF solution (30 mL) of 2-phenyl-2-oxazoline-4-carboxylic acid (**11**) (1.35 g, 7.05 mmol) were added Merrifield resin (5.0 g, 0.94 mmol/g, purchased from BEADTECH in Korea) and potassium fluoride (0.82 g, 14.1 mmol). The reaction mixture was vigorously shaken at 50 °C for 24 h. The resin was then filtered and successively washed with DMF, 50% aq DMF solution, water, 50% aq MeOH, and finally MeOH. Pale yellow resin **12** was obtained after drying in vacuo (50%, 0.47 mmol/g). IR (KBr) 3435, 3024, 2919, 1638, 1491, 1448, 1024, 754, 697, 537 cm^{-1}.

4.5. General procedure for solid-phase alkylation of the solid-supported substrate 12

To a mixture of the Merrifield resin-supported 2-phenyl-2-oxazoline-4-carboxylate (**12**) (200 mg, 0.47 mmol/g) and tetrabutylammonium bromide (1.5 mg, 0.0047 mmol) in CH_2Cl_2 were added BTPP (0.057 mL, 0.188 mmol) and electrophile (0.47 mmol) at 25 °C. The reaction mixture was stirred for 12 h. The resin was then filtered and washed with a series of solvents: CH_2Cl_2, water, and methanol. Pale yellow alkylated resin **13** was obtained after drying in vacuo. A mixture of **13** and sodium methoxide (0.51 mg, 0.0094 mmol) in methanol was refluxed for 6 h. The reaction mixture was filtered and washed with MeOH and CH_2Cl_2. The filtrate was then concentrated. The residue was diluted with CH_2Cl_2 (50 mL), washed with water (2×10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexanes/EtOAc=10:1) to afford **14**.

4.6. Spectroscopic characterization of the alkylated compounds 14

*4.6.1. 4-Allyl-2-phenyl-2-oxazoline-4-carboxylic acid methyl ester (**14a**).* Pale yellow oil (19.6 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97–7.94 (m, 2H), 7.50–7.36 (m, 3H), 5.75–5.61 (m, 1H), 5.19–5.12 (m, 2H), 4.76 (ABq, *J*=9.0 Hz, 1H), 4.30 (ABq, *J*=9.0 Hz, 1H), 3.79 (s, 3H), 2.75–2.29 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 164.9, 131.8, 131.5, 128.6, 128.3, 127.0, 120.0, 77.6, 73.0, 52.8, 42.3 ppm; IR (KBr): 2925, 2854, 1738, 1643, 1450, 1363, 1269, 1217, 1093, 1027, 980, 925, 698 cm^{-1}; MS (FAB^+): *m*/*z* 246 $[M+H]^+$; HRMS calculated for $C_{14}H_{16}NO_3$: 245.1052; found: 246.1130 $[M+H]^+$.

*4.6.2. 4-Propagyl-2-phenyl-2-oxazoline-4-carboxylic acid methyl ester (**14b**).* Pale yellow caramel (20.0 mg, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96–7.93 (m, 2H), 7.50–7.36 (m, 3H), 4.89 (ABq, *J*=9.2 Hz, 1H), 4.50 (ABq, *J*=9.2 Hz, 1H), 3.80 (s, 3H), 2.97 (ABq, *J*=16.7 Hz, 1H), 2.73 (ABq, *J*=16.7 Hz, 1H), 1.97 (t, *J*=3.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 165.8, 131.9, 128.7, 128.3, 126.8, 78.3, 77.2, 73.4, 71.3, 53.1, 28.0 ppm; IR (KBr): 3295, 2955, 1740, 1642, 1450, 1364, 1269, 1215, 1098, 1026, 980, 777, 696 cm^{-1}; MS (FAB^+): *m*/*z* 244 $[M+H]^+$; HRMS calculated for $C_{14}H_{14}NO_3$: 243.0895; found: 244.0974 $[M+H]^+$.

*4.6.3. 4-Benzyl-2-phenyl-2-oxazoline-4-carboxylic acid methyl ester (**14c**).* Pale yellow oil (25.9 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.97 (m, 2H), 7.53–7.12 (m, 8H), 4.76 (ABq, *J*=9.0 Hz, 1H), 4.41 (ABq, *J*=9.0 Hz, 1H), 3.78 (s, 3H), 3.36 (ABq, *J*=13.8 Hz, 1H), 3.21 (ABq, *J*=13.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 164.9, 134.9, 131.7, 130.2, 128.5, 128.3, 128.2, 127.0, 126.9, 78.5, 72.6, 52.7, 43.5 ppm; IR (KBr): 2923, 1737, 1644, 1496, 1451, 1362, 1268, 1213, 1094, 1027, 979, 698 cm^{-1}; MS (FAB^+): *m*/*z* 296 $[M+H]^+$; HRMS calculated for $C_{18}H_{18}NO_3$: 295.1208; found: 296.1287 $[M+H]^+$.

*4.6.4. 4-(4-Methylbenzyl)-2-phenyl-2-oxazoline-4-carboxylic acid methyl ester (**14d**).* Colorless caramel (26.9 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94–7.91 (m, 2H), 7.48–7.35 (m, 3H), 7.09–7.01 (m, 4H), 4.71 (ABq, *J*=9.0 Hz, 1H), 4.34 (ABq, *J*=9.0 Hz, 1H), 3.79 (s, 3H), 3.24 (s, 2H), 2.26 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 194.9, 136.6, 131.9, 131.7, 130.1, 129.0, 128.5, 128.2, 127.1, 78.8, 72.6, 52.7, 43.2, 21.0 ppm; IR (KBr): 2923, 1737, 1644, 1514, 1449, 1362, 1266, 1212, 1091, 1026, 979, 814, 777, 695 cm^{-1}; MS (FAB^+): *m*/*z* 310 $[M+H]^+$; HRMS calculated for $C_{19}H_{20}NO_3$: 309.1365; found: 310.1443 $[M+H]^+$.

*4.6.5. 4-(4-Fluorobenzyl)-2-phenyl-2-oxazoline-4-carboxylic acid methyl ester (**14e**).* Pale yellow caramel (27.2 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92–7.89 (m, 2H), 7.50–7.35 (m, 3H), 7.19–7.14 (m, 2H), 6.94–6.86 (m, 2H), 4.69 (ABq, *J*=9.0 Hz, 1H), 4.31 (ABq, *J*=9.0 Hz, 1H), 3.78 (s, 3H), 3.26 (d, *J*=13.7 Hz, 1H), 3.15 (d, *J*=13.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 165.1, 131.9, 131.8, 131.7, 130.8, 130.7, 128.5, 128.3, 126.9, 115.2, 115.0, 78.5, 72.7, 52.8, 42.7 ppm; IR (KBr): 2954, 1737, 1644, 1604, 1510, 1447, 1362, 1268, 1221, 1100, 1025, 980, 844, 783, 695 cm^{-1}; MS (FAB^+): *m*/*z* 314 $[M+H]^+$; HRMS calculated for $C_{18}H_{17}FNO_3$: 313.1114; found: 314.1192 $[M+H]^+$.

*4.6.6. 4-Naphthalen-2-ylmethyl-2-phenyl-2-oxazoline-4-carboxylic acid methyl ester (**14f**).* Pale yellow caramel (29.6 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93–7.90 (m, 2H), 7.77–7.65 (m, 4H), 7.49–7.33 (m, 6H), 4.75 (ABq, *J*=9.0 Hz, 1H), 4.41 (ABq, *J*=9.0 Hz, 1H), 3.80 (s, 3H), 3.45 (d, *J*=13.7 Hz, 1H), 3.39 (d, *J*=13.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 165.1, 133.3, 132.7, 132.4, 131.7, 129.1, 128.5, 128.4, 128.3, 127.8, 127.6, 127.5, 127.0, 126.0, 125.7, 78.8, 72.6, 52.8, 43.7 ppm; IR (KBr): 2924, 1736, 1643, 1446, 1362, 1265, 1214, 1092, 1025, 980, 822, 749, 696 cm^{-1}; MS (FAB^+): *m*/*z* 346 $[M+H]^+$; HRMS calculated for $C_{22}H_{20}NO_3$: 345.1365; found: 346.1443 $[M+H]^+$.

*4.6.7. 4-(2-Methoxycarbonyl-ethyl)-2-phenyl-2-oxazoline-4-carboxylic acid methyl ester (**14g**).* Pale yellow oil (24.6 mg, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97–7.93 (m, 2H), 7.51–7.36 (m, 3H), 4.73 (ABq, *J*=9.2 Hz, 1H), 4.26 (ABq, *J*=9.2 Hz, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 2.51–2.32 (m, 3H), 2.21–2.12 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 173.0, 165.3, 132.0, 129.6, 128.7, 128.3, 64.2, 68.6, 52.9, 51.8, 33.2, 28.8 ppm; IR (KBr): 2924, 2852, 1737, 1645, 1448, 1365, 1267, 1105, 1026, 981, 780, 698 cm^{-1}; MS (FAB^+): *m*/*z* 292 $[M+H]^+$; HRMS calculated for $C_{15}H_{18}NO_5$: 291.1107; found: 292.1185 $[M+H]^+$.

4.7. Hydrolysis of 14c: α-benzylserine

To an ethanol solution (1.5 mL) of 4-benzyl-2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **14c** (500 mg, 1.48 mmol) was added 6 M HCl (1.5 mL) and the reaction mixture was refluxed for 24 h. After the solvent was removed in vacuo, the residue was purified by column chromatography (5% aq NH_4OH) using ion-exchange resin (Dowex® 50WX8-100) to give (±)-α-benzylserine as a white solid (283 mg, 98%). Physical and spectral properties were consistent with the literature values.[7a] Chiral **14c** (42% ee, entry 5 in

Table 3) also was hydrolyzed by the same procedure to afford enantiomerically enriched (*S*)-(+)-α-benzylserine as a white solid. $[\alpha]_D^{20}$ +6.7 (*c* 0.50, H_2O) [lit.[7b] $[\alpha]_D^{20}$ +16.4 (*c* 0.81, H_2O)]. The physical and spectral properties were consistent with the literature values.[7b]

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