JOC Notes

Enantioselective Synthetic Method for α-Alkylserine via Phase-Transfer Catalytic Alkylation of 2-Phenyl-2-oxazoline-4-carbonylcamphorsultam

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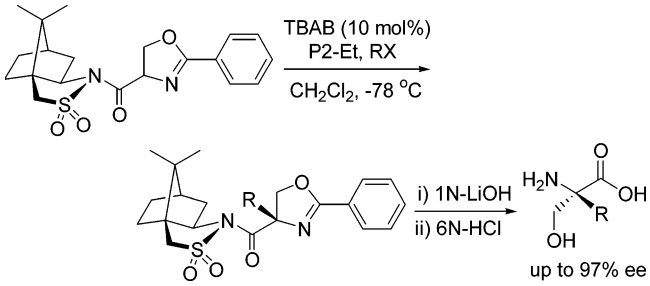
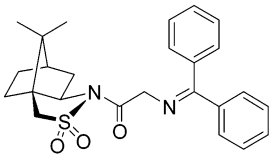


An enantioselective synthetic method for α-alkylserines by the phase-transfer catalytic alkylation of 2-phenyl-2-oxazoline-4-carbonylcamphorsultam (**4a**) was developed. The phase-transfer catalytic α-alkylation of **4a** using P2-Et at −78 °C gave α-alkylation (75∼99%, 90∼97% de), which could be easily hydrolyzed to α-alkylserines.

The enantioselective synthesis of chiral compounds is an extremely formidable challenge to the synthetic chemist. Chiral α-alkylserines have been regarded as important components in the fields of synthetic and medicinal chemistry.[1] As their quaternary carbon centers play an important role for their preferable conformations in peptide backbones,[2] chiral α-alkylserines have been frequently employed in the design of new peptidomimetic drugs.[3] In addition, several biologically active natural products have α-alkylserine moieties or the related structures.[4] A number of enantioselective synthetic methods have been reported for chiral α-alkylserines so far, but only a few are practical.[5]

Recently, we reported a new synthetic method for (±)-α-alkylserines by the selective α-alkylation of *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate (**1**) in phase-transfer catalytic conditions (Scheme 1).[6] As a successive study, the enantioselective version using chiral phase-transfer catalysts was also disclosed.[7] Both works showed that the phase-transfer catalytic condition is very efficient for the α-alkylation of the oxazoline-4-carboxylate system. In this note, we report a new enantioselective synthetic method for α-alkylserines via phase-transfer catalytic alkylation[8] of the oxazoline-4-carboxylate, possessing camphorsultam as a chiral auxiliary (**4a**).



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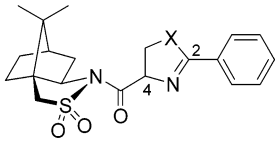

4a X = O
b X = S

The use of a chiral auxiliary, in conjunction with benzophenone imine glycine derivatives, has been studied by a number of groups.[9] Among them, Oppolzer's sultam was mostly employed for the enantioselective synthesis of α-amino acids (**3**).[9a−c] We adapted the camphorsultam as a chiral auxiliary to *tert*-butyl 2-phenyl-2-oxazoline-

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(1) (a) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (b) Cativiela, C.; Diaz-de-Villegas, M. D. T. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (c) Cativiela, C.; Diaz-de-Villegas, M. D. T. *Tetrahedron: Asymmetry* **2000**, *11*, 645.

(2) (a) Toniolo, C.; Crisma, M.; Formaggio, F.; Valle, G.; Cavicchioni, G.; Précigoux, G.; Aubry, A.; Kamphius, J. *Biopolymers* **1993**, *33*, 1061. (b) Karle, I. L.; Rao, R. B.; Prasad, S.; Kaul, R.; Balaram, P. *J. Am. Chem. Soc.* **1994**, *116*, 10355. (c) Formaggio, F.; Pantano, M.; Crisma, M.; Bonora, G. M.; Toniolo, C.; Kamphius, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1097. (d) Benedetti, E. *Biopolymers* **1996**, *40*, 3. (e) Karle, I. L.; Kaul, R.; Rao, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048.

(3) (a) Barrett, G. C. *Amino Acids, Peptides and Proteins*; The Chemical Society: London, 1980; Vol. 13, p 1. (b) Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 55. (c) Richardson, J. S. *Biophysik. J.* **1992**, *63*, 1186. (d) Mickos, H.; Sundberg, K.; Luning, B. *Acta Chem. Scand.* **1992**, *46*, 989. (e) Gante, J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1699.

(4) (a) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Yoneta, M.; Chiba, K.; Hosino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 216. (b) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113. (c) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117. (d) Yamashita, T.; lijima, M.; Nakamura, H.; Isshiki, K.; Naganawa, H.; Hattori, S.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 557. (e) Kawatsu, M.; Yamashita, T.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 222.

(5) Previous synthetic methods of chiral α-alkylserines are cited in ref 7.

(6) Park, H.-g.; Lee, J.; Kang, M. J.; Lee, Y.-J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Jew, S.-s. *Tetrahedron* **2004**, *60*, 4243.

(7) Jew, S.-s.; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Ku, J.-M.; Park, H.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382.

(8) For our recent reports on the enantioselective phase-transfer catalytic alkylation, see: (a) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244. (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-K.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645. (c) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-K.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036. (d) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, I. Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245. (e) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497. (f) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Kim, T.-S.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1557.

(9) (a) Josien, H.; Martin, A.; Chassaing, G. *Tetrahedron Lett.* **1991**, *32*, 6547. (b) Josien, H.; Chassaing, G. *Tetrahedron: Asymmetry* **1992**, *3*, 1351. (c) Josien, H.; Lavielle, S.; Brunissen, A.; Saffroy, M.; Torrens, Y.; Beaujouan, J.-C.; Glowinski, J.; Chassaing, G. *J. Med. Chem.* **1994**, *37*, 1586. (d) Guillena, G.; Najera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 3935.

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SCHEME 1

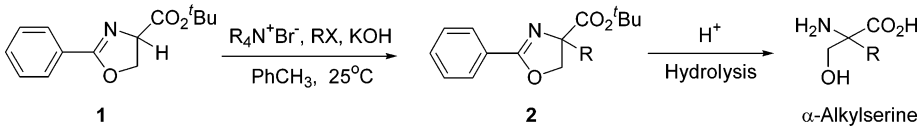
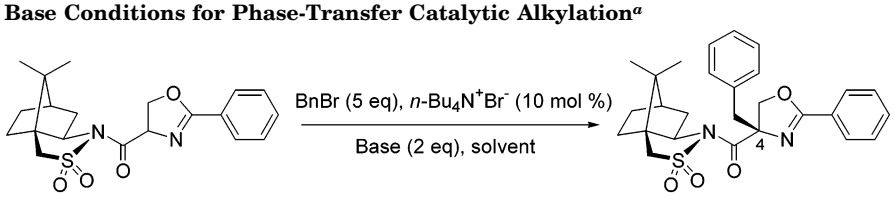


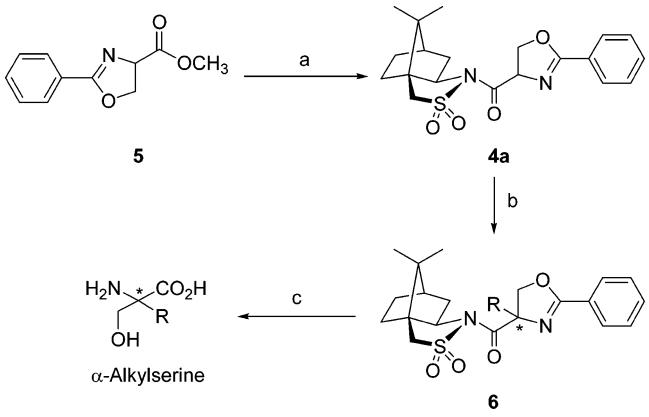
TABLE 1. Optimal Base Conditions for Phase-Transfer Catalytic Alkylation[a]



entry	base	solvent	temp (°C)	time	yield[b] (%)	de %[c] (configuration)[d]
1	KOH	$PhCH_3$	0	1 h	26	20 (4*S*)
2	50% KOH	$PhCH_3$	0	1 h	0	
3	BEMP	CH_2Cl_2	0	1 h	83	91 (4*S*)
4	BEMP	CH_2Cl_2	−20	3 h	87	92 (4*S*)
5	BEMP	CH_2Cl_2	−40	24 h	0[e]	
6	BTPP	CH_2Cl_2	0	1 h	82	93 (4*S*)
7	BTPP	CH_2Cl_2	−20	3 h	88	93 (4*S*)
8	BTPP	CH_2Cl_2	−40	24 h	0[e]	
9	P2-Et	CH_2Cl_2	0	5 min	75	65 (4*S*)
10	P2-Et	CH_2Cl_2	−20	5 min	80	82 (4*S*)
11	P2-Et	CH_2Cl_2	−40	5 min	85	93 (4*S*)
12	P2-Et	CH_2Cl_2	−78	5 min	95	97 (4*S*)

[a] Reaction was carried out with benzyl bromide (5 equiv), base (2 equiv), and tetrabutylammonium bromide (10 mol %) in toluene or methylene chloride. [b] Isolated yields. [c] Diastereoselectivity was determined by HPLC analysis of the benzylated oxazoline methyl ester from the hydrolysis of **6e** with 1 N LiOH, followed by methylation with excess diazomethane using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol (volume ratio = 99:1) as the eluent solvent; in this case, it was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] Absolute configuration for C(4) was determined by comparison of the optical rotation of α-benzylserine from the acidic hydrolysis of **6e** with the reported value.[7] [e] **4a** was recovered.

SCHEME 2[a]



[a] Reagents and conditions: (a) (1*S*)-(−)-2,10-camphorsultam, $Al(CH_3)_3$, $PhCH_3$, 60 °C, 30 h, 94%. (b) RX, *n*-$Bu_4N^+Br^-$ (10 mol %), base, toluene or CH_2Cl_2. (c) (i) 1 N LiOH, THF, rt, 10 min; (ii) 6 N HCl, EtOH, reflux, 12 h.

4-carboxylate (**1**) and investigated the optimal reaction conditions for the diastereoselective α-alkylation.

Substrate **4a** was easily prepared by the coupling of methyl 2-phenyl-2-oxazoline-4-carboxylate (**5**)[10] with (1*S*)-(−)-2,10-camphorsultam in the presence of trimethylaluminum in 94% yield (Scheme 2).[11] To determine the optimal alkylation conditions, the benzylation was performed using **4a** along with benzyl bromide (5.0 equiv) and various bases (2.0 equiv). During our investigation, the enantioselective synthesis of α-methylcysteine using 2-phenyl-2-thiazoline-4-carbonylcamphorsultam (**4b**) was independently reported by the Singh group.[12] The methylation of **4b** using *n*-BuLi and CH_3I at −78 °C in the presence of HMPA in tetrahydrofuran, followed by hydrolysis, provided α-methylcysteine (49%, 95% ee). However, in our oxazoline system (**4a**), *n*-BuLi or LDA in tetrahydrofuran at −78 °C gave no major product but many unidentifiable products, which were similarly obtained even in the presence of HMPA. The oxazoline-4-carboxylate moieties might be very sensitive to strong base conditions. Generally, strong base conditions gave *β*-elimination or substitution as major products in an oxazoline system,[6,4i,13] whereas both *t*-BuLi and *t*-BuOK in tetrahydrofuran at 0 °C gave no reaction, suggesting that their steric hindrance inhibits the α-hydrogen abstraction to form the corresponding enolate intermediate.

In the case of phase-transfer catalytic conditions (Table 1), 50% KOH in the presence of *n*-$Bu_4N^+Br^-$ led only to hydrolysis, affording 2-phenyl-2-oxazoline-4-carboxylic acid and (1*S*)-(−)-2,10-camphorsultam, but solid KOH provided α-benzylation (**6e**) in low chemical yield (26%) with poor diastereoselectivity (20% de[14]).

To enhance the diastereoselectivity, we finally attempted to use Schwesinger bases[15] (neutral nitrogen bases) for phase-transfer catalytic alkylation. Surprisingly, BEMP (entry 3, 91% de), BTPP (entry 6, 93% de), and P2-Et (entry 9, 65% de) all gave α-benzylated product

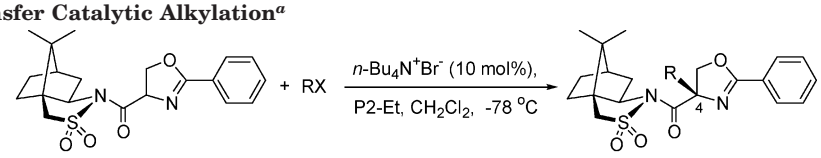
(10) Compound **5** was prepared from ethyl benzimidate and serine methyl ester on the basis of previous methods[6,7] (95%).

(11) (a) Basha, A.; Lipton, M.; Weinreb. S. M. *Tetrahedron Lett*. **1977**, *18*, 4171. (b) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett*. **1989**, *30*, 6009.

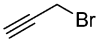
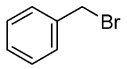
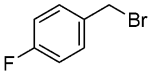
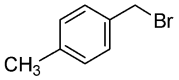
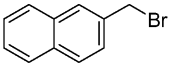
(12) Singh, S.; Rao, S. J.; Pennington, M. W. *J. Org. Chem*. **2004**, *69*, 4555.

(13) Blarer, S. J. *Tetrahedron Lett*. **1985**, *26*, 4055.

TABLE 2. Phase-Transfer Catalytic Alkylation[a]

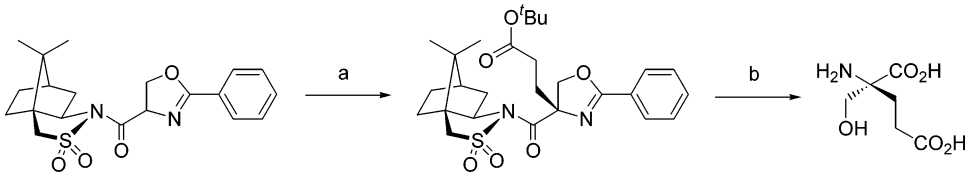


4a 6

entry	RX	yield[b](%)	de %[c] (Config.)[d]
a	CH_3I	75	90 (4*S*)
b		95	91 (4*S*)
c		95	90 (4*S*)
d		98	95 (4*S*)
e		95	97 (4*S*)
f		96	95 (4*S*)
g		98	94 (4*S*)
h		99	95 (4*S*)

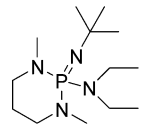
[a] Alkyl halides were varied using the conditions described in entry 12 of Table 1. [b] Isolated yields. [c] Diastereoselectivity was determined by HPLC analysis of the alkylated oxazoline methyl ester from the hydrolysis of **6** with 1 N LiOH, followed by methylation with excess diazomethane using a chiral column (DAICEL Chiralcel OD-H or AD-H) with hexane/2-propanol as the eluent solvent; in this case, it was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] Absolute configuration of C(4) was tentatively assigned to be 4*S* on the basis of the absolute configuration of **6e** (Table 1).[7]

SCHEME 3[a]

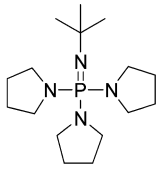


4a 9 10

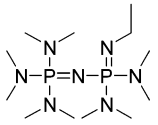
[a] Reagents and conditions: (a) *tert*-butyl acrylate, *n*-$Bu_4N^+Br^-$, P2-Et, CH_2Cl_2, −78 °C, 95%. (b) (i) 1 N LiOH, THF, rt; (ii) 6 N HCl, EtOH, reflux, 93% from **9**.



BEMP
pKa 27.6



BTPP
pKa 28.4



P2-Et
pKa 32.9

6e in high yields at 0 °C. When the reaction temperature was decreased, BEMP and BTPP did not show any significant increase of diastereoselectivity at −20 °C, and no reaction was observed at −40 °C. In contrast, P2-Et exhibited higher diastereoselectivities at lower reaction temperatures. The best results were obtained using P2-Et at −78 °C (entry 12, 95% yield, 97% de). The hydrolysis of **6e** (97% de) with 1 N LiOH gave 2-phenyl-2-oxazoline-4-benzyl-4-carboxylic acid (98%) along with (1*S*)-(−)-2,10-camphorsultam (94%), which could be recycled to prepare the substrate **4a**. The hydrolysis of 2-phenyl-2-oxazoline-4-benzyl-4-carboxylic acid with 6 N HCl, followed by purification using ion-exchange resin, afforded (*S*)-α-benzylserine in 95% yield.

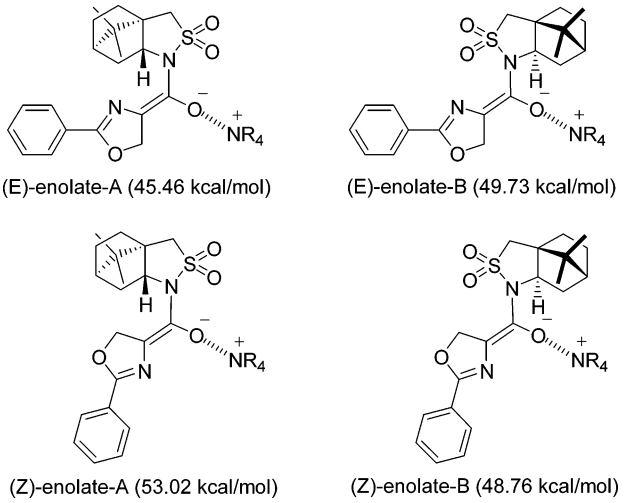
Further investigations of the phase-transfer catalytic alkylation with various alkyl halides were performed using the above optimal reaction conditions (entry 12, Table 1). As shown in Table 2, the active alkyl halides (entries b−h) gave α-alkylation in high chemical yields with high diastereoselectivities (90−97% de), but ali-

(14) Diastereomeric excess (de) of the alkylation products was determined by the chiral HPLC analysis of the corresponding methyl 2-phenyl-2-oxazoline-4-alkyl-carboxylates. Representative procedure for transformation to the methyl ester is explained in Supporting Information.

(15) (a) Schwesinger, R. *Chimia* **1985**, *39*, 269. (b) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed.* **1987**, *26*, 1167.

phatic halides provided no α-alkylation except methyl iodide (entry a), which might be due to the low reactivity. The high chemical yields and high diastereoselectivities indicated that the new synthetic method under phase-transfer catalytic conditions is very efficient for the asymmetric synthesis of α-alkylserines.

The optimized phase-transfer catalytic reaction was also successfully applied to the Michael reaction for the synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid (**10**), which is one of the most useful glutamate receptor ligands (Scheme 3).[16] The Michel addition of **4a** with *tert*-butyl acrylate using P2-Et in methylene chloride at −78 °C, followed by hydrolysis provided **10** (88% yield from **4a**, 85% de).



A plausible transition state in the catalytic alkylation is proposed in Figure 1. Molecular modeling studies of the enolate intermediates of **4a** revealed that the (*E*)-enolate-A (45.46 kcal/mol) is the most stable conformer among the four possible conformers.[17] Therefore, the (*E*)-enolate-A anion forms an ionic binding intermediate with the tetrabutylammonium cation, and the lower side of the intermediate is shielded by the camphor moiety. In consequence, electrophiles can only approach from above, affording the (4*S*)-**6** and (2*S*)-**10** in accord with the results.

In conclusion, we developed a new, efficient, asymmetric synthetic methodology for α-alkylserine by the diastereoselective phase-transfer catalytic alkylation of 2-phenyl-2-oxazoline-4-carbonylcamphorsultam (**4a**). The easy preparation of substrate **4a**, the high chemical yields and diastereoselectivities, and the efficient recovery of the chiral auxiliary could make this method very efficient for the synthesis of chiral α-alkylserines.

Experimental Section

General Procedure for the Enantioselective Phase-Transfer Catalytic Alkylation of 4a (Benzylation). To a methylene chloride solution (0.30 mL) of **4a** (50.0 mg, 0.129 mmol) and tetrabutylammonium bromide (4.16 mg, 0.013 mmol) was added benzyl bromide (0.077 mL, 0.644 mmol). After the reaction mixture was cooled to −78 °C, phosphazene base P2-Et (0.086 mL, 0.257 mmol) was added, and the reaction mixture was stirred at −78 °C until starting material had been consumed (5 min). The reaction mixture was quenched with saturated NH_4Cl solution, diluted with methylene chloride (20 mL), washed with water (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 10:1) to afford **6e** (58.5 mg, 95% yield) as a white foamy compound. The diastereoselectivity was determined by chiral HPLC analysis of the benzylated oxazoline methyl ester from the hydrolysis of **6e** with 1 N LiOH, followed by methylation with excess diazomethane (DAICEL Chiralcel OD-H, hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, 23 °C, λ = 254 nm, retention times; *S* (major) 18.0 min, *R* (minor) 37.5 min, 97% ee). The absolute configuration was determined by comparison of the optical rotation of α-benzylserine from the acid hydrolysis of **6e** with the reported value.[7]

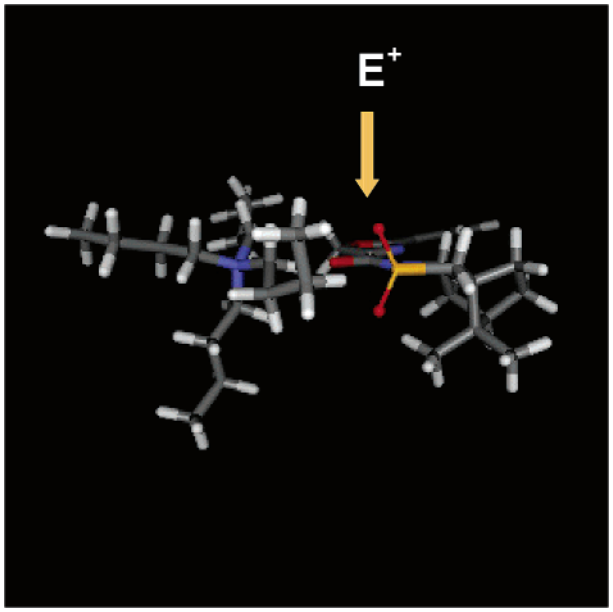


FIGURE 1. Plausible transition-state structure of a tetrabutylammonium (*E*)-enolate-A derived from **4a** and n-$Bu_4N^+Br^-$.

General Procedure for the Hydrolysis of 6e. To a tetrahydrofuran solution (2 mL) of 4-benzyl-2-phenyl-2-oxazoline-4-carbonylcamphorsultam **6e** (50.0 mg, 0.105 mmol) was added 1 N LiOH (2 mL), and the reaction mixture was stirred for 10 min. After tetrahydrofuran was removed in vacuo, the residue was extracted with EtOAc (5 mL). The removal of EtOAc in vacuo gave (1*S*)-(−)-2,10-camphorsultam (21.3 mg, 94%). The aqueous layer was acidified with 1 N HCl (2 mL) and extracted with EtOAc (15 mL). The removal of solvent in vacuo gave 4-benzyl-2-phenyl-2-oxazoline-4-carboxylic acid. To an ethanol solution (2 mL) of the acid was added 6 N HCl (2 mL), and the reaction solution was refluxed for 12 h. After solvent was removed in vacuo, the residue was purified by column chromatography (5% NH_4OH) using ion-exchange resin (Dowex 50WX8-100) to give (*S*)-(+)-α-benzylserine as a white solid (18.9 mg, 93% for two steps). $[\alpha]^{20}_D$ +16.0 (*c* 0.71, H_2O) [lit.[7] $[\alpha]^{20}_D$ +16.4 (*c* 0.81, H_2O)]. The physical and spectral properties were consistent with the literature values.[7]

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Supporting Information Available: Representative experimental procedures, as well as spectroscopic characterizations of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Zhang, J.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Org. Chem.* **2001**, *66*, 7555. (b) Choudhury, P. K.; Le Nguyen, B. K.; Laglois, N. *Tetrahedron Lett.* **2002**, *43*, 463. (c) Kawasaki, M.; Namba, K.; Tsujishima, H.; Sinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2003**, *44*, 1235.

(17) Calculations were done using the program SYBYL 6.5 from Tripos Software, Inc., St. Louis, MO. The four-enolate conformers were minimized using Tripos force field parameters and the conjugate gradient algorithm with a gradient convergence value of 0.005 kcal/mol Å. Partial atomic charges were calculated using the Gasteiger−Hückel method. The low-energy conformation was searched by the grid search method.