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Regio- and Stereoselective Synthesis of (*E*)-Alkene *trans*-Xaa-Pro Dipeptide Mimetics Utilizing Organocopper-Mediated *Anti*-S_N2' Reactions

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Proline dipeptides (Xaa-Pro) exist as an equilibrium mixture of *cis*- and *trans*-rotamers, which depends on the energy barriers for imide isomerization. This conformation mixture contributes to both structure and function of proline-containing peptides and proteins. Structural motifs resembling these *cis*- or *trans*-conformers have served as useful tools for elucidating contributions of proline residues in the physicochemical and biological profiles of structures which contain them. Among such motifs are alkene dipeptide isosteres which mimic *cis*- or *trans*-imide using (*Z*)- or (*E*)-alkene, respectively. In this report, the first regio- and stereoselective syntheses of (*E*)-alkene dipeptide isosteres (**20**, **31**, and **35**) corresponding to *trans*-proline dipeptides are described. Key to the synthesis of these mimetics is the *anti*-S_N2' reaction of vinyl aziridines such as **15** or vinyl oxazolidinones such as **28** and **32** with organocopper reagents "RCu" (R = CH_2SiMe_2(O*i*-Pr)). Reaction of *cis*-vinylaziridine **15** derived from L-serine with organocopper reagent gave a precursor of the *trans*-L-Ser-D-Pro type alkene isosteres **20**, accompanied by an S_N2 side product. One limitation with the use of such aziridine-mediated methodology is formation of the corresponding *trans*-aziridine **22**, which leads to L−L type isosteres, that is unstable and obtainable only in low yield. On the other hand, both isomers of oxazolidinone derivatives can be easily obtained from *N*-Boc-protected amino alcohols. The reaction of *trans*- **28** or *cis*-oxazolidinone derivative **32** with organocopper reagents proceeds quantitatively with high regio- and diastereoselectivities in *anti*-S_N2' fashion. Subsequent oxidative treatment of the newly introduced isopropoxydimethylsilylmethyl group yields *trans*-L-Ser-L-Pro **31** or *trans*-L-Ser-D-Pro type isosteres **35**, respectively. Of note, synthesized isostere **31** can also be converted to *trans*-phosphoSer-Pro **42** and *trans*-Cys-Pro mimetics **44**. The present synthetic methodology affords *trans*-Xaa-Pro alkene-type dipeptide isosteres in high yield with relatively simple manipulation.

Introduction

Proline (Pro) exerts great influence on both the structure and function of peptides and proteins through *cis*-/*trans*-equilibrium of its associated peptide bonds (Xaa-Pro) (Figure 1).[1,2] Proline is the sole imino acid in naturally occurring mammalian proteins and forms imide bonds with amino acids *N*-terminal to the imino acid.

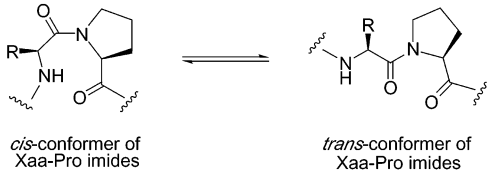

FIGURE 1. *Cis*- and *trans*-conformers of Xaa-Pro imides and their equilibrium.

Consequently, Xaa-Pro bonds exist in *cis*-/*trans*-equilibria having similar energy barriers[1] for imide isomerization.[2] Alternatively, other peptide bonds[3] favor *trans*-conformations with ca. 5.0 kcal/mol lower energy barriers for amide bond isomerization in *trans*- as compared to *cis*-conformations. Energetic similarity between *cis*- and *trans*-isomers of Xaa-Pro bonds may create multiple low

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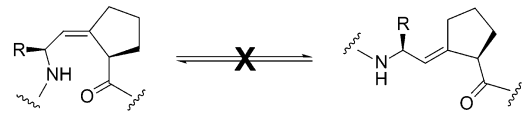

Xaa-ψ[(*Z*)-CH=C]-Pro (**1**) Xaa-ψ[(*E*)-CH=C]-Pro (**2**)

FIGURE 2. (*Z*)- or (*E*)-Alkene dipeptide isosteres corresponding to *cis*- or *trans*-proline peptide bonds, respectively.

energy conformers in Pro-containing proteins/peptides, which complicate understanding the relationship between Xaa-Pro geometry and biological activity. Although investigations of Xaa-Pro geometries of bioactive peptides using techniques such as X-ray and NMR spectroscopy have been extensively undertaken, it is difficult for such studies to define whether *cis*- or *trans*-geometries are involved with particular bioactive conformations.[4]

Restriction of Xaa-Pro imide conformations provides one promising means for studying relationships between imide bond geometry and biological activity of peptides. To control geometry, alkylproline analogues possessing substituents at the 2- or 5-positions of proline have been used to induce preference for *trans*- or *cis*-isomer populations, respectively.[5,6] Additionally, syntheses of dipeptide isosteres[7] corresponding to Xaa-Pro having *cis*- or *trans*-imide geometries have been made.[8,9] For example, cyclocystine,[8b] dipeptide lactams,[8c] and tetrazole derivatives[8e] have been incorporated as the *cis*-Pro mimetics into somatostatin, resulting in potent peptide mimetics.

Replacement of Xaa-Pro imide bonds with (*Z*)- or (*E*)-alkene units (**1** or **2** in Figure 2) represents a more straightforward method for mimicking proline imide backbone geometry. Dipeptide isosteres, including fluoroalkenes with *trans*-Pro geometry, have been nonstereoselectively synthesized by a strategy which relied on construction of alkene units using Peterson or Horner−Emmons olefination reactions of 2-substituted cyclopentanones, followed by derivatization of terminal functional groups.[9a,b] Etzkorn et al. have reported the first enantio- and regioselective synthesis of (*Z*)-alkene *cis*-proline mimetics (L-Ala-ψ[(*Z*)-CH=C]-L-Pro) corresponding to an L-Ala-L-Pro sequence.[9c] In this synthesis, a Still−Wittig [2,3]-sigmatoropic rearrangement[10] in THF was used for selective formation of trisubstituted (*Z*)-alkenes.[11] Subsequently, in the synthesis of Ser-Pro dipeptide alkene isosteres they found that a Still−Wittig reaction afforded opposite selectivities for (*Z*: *E*)-alkenes in THF (3:1) vs toluene (1:3).[9e] Extensive synthetic efforts toward (*E*)-alkene dipeptide isosteres **6** have been made by several groups, including us.[12−16] Organocopper-mediated reactions previously employed by us have converted either γ-mesyloxy-α,β-enoates **3**,[13] β-aziridinyl-α,β-enoates **4**,[12f−g,14] or β-(1,3-oxazolidin-2-on-5-yl)-α,β-enoates **5**[15] to α-substituted β,γ-enoates corresponding to **6** in highly regio- and stereoselective manners (Scheme 1).

Using our protocol, α-substituents corresponding to side chain functionality can be introduced into dipeptide mimetic backbones. However, in the case of Xaa-Pro dipeptides, which have cyclic structures that include peptide backbone, use of α,β-enoates as substrates (**3**−**5**) cannot be applied to the synthesis of corresponding mimetics. This fact prompted us to examine the feasibility of introducing "CO_2H" functionality included in the backbone in regio- and stereoselective fashion using organocopper-mediated reactions which would yield Xaa-Pro type alkene dipeptide isosteres. Regarding this point, Etzkorn et al. also utilized a strategy based on Still−Wittig [2,3]-rearrangements to introduce "CO_2H" units.[9c] Since hydroxyl functionality in serine residues can be converted to other functional groups, we selected Ser-Pro mimetics as synthetic targets. For introduction of the "CO_2H" moiety, we envisioned using isopropoxydimethylsilylmethyl groups,[17] which would be incorporated by

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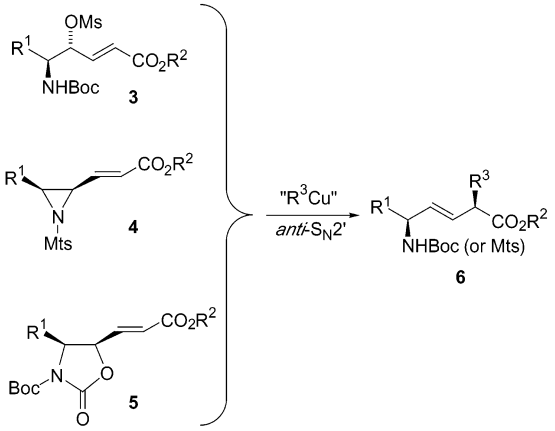
SCHEME 1. Synthesis of Nonproline Type (*E*)-Alkene Dipeptide Isosteres (6) via *Anti*-S_N2' Reaction of γ-Mesyoxy-α,β-enoates (3), β-Aziridinyl-α,β-enoates (4), or β-(1,3-Oxazolidin-2-on-5-yl)-α,β-enoates (5) with Organocopper Reagents



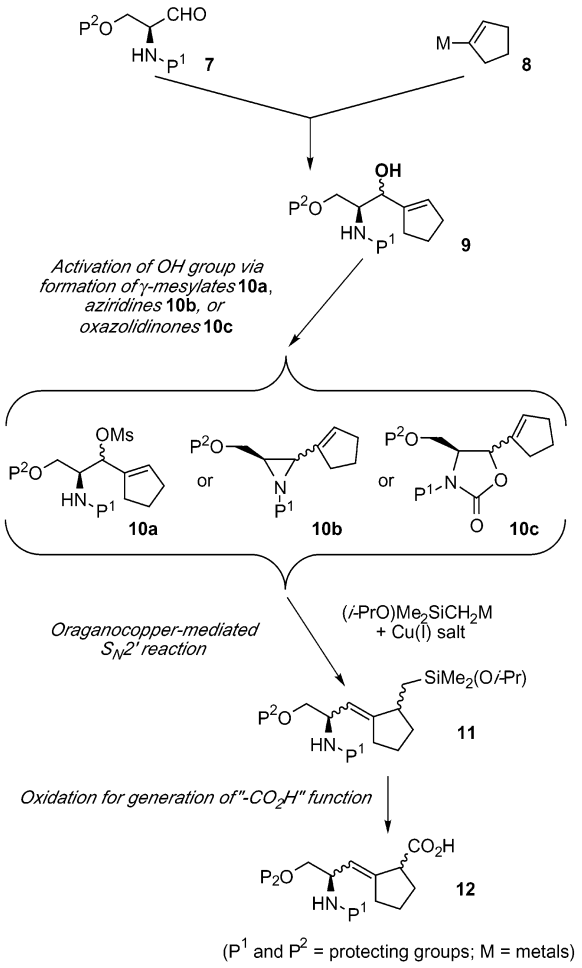
organocopper-mediated reactions and subsequently transformed to "CO_2H" groups by oxidative treatment. Accordingly, we report herein the regio- and stereoselective synthesis of (*E*)-alkene Ser-Pro dipeptide isosteres with *trans*-Xaa-Pro geometry using organocopper reagents. Additionally, conversion of Ser units to other amino acid residues is also investigated.

Results and Discussion

Our synthetic plan to Ser-Pro type alkene isosteres **12** is conceptually outlined in Scheme 2: (1) addition of metalated cyclopentenyl reagents **8**[18] to serinal derivatives **7**; (2) transformation of the resulting hydroxy group of **9** to a leaving group susceptible to organocopper reagents in an S_N2' manner; (3) incorporation of silylmethyl groups into **10** using organocopper-mediated S_N2' reactions; (4) conversion of the introduced silylmethyl group of **11** to a "CO_2H" moiety by oxidative treatment.

As shown in Scheme 3, we first selected aziridine moieties as the activating functionality for S_N2' reactions since our previous studies indicated that treatment of β-(*N*-activated-aziridinyl)-α,β-enoates **4** with organocopper reagents proceeded with high regio- and stereoselectivity to afford α-alkylated nonproline-type alkene dipeptide isosteres **6**. Herein *N*-benzenesulfonyl-type protecting groups (Mts, etc.) were preferably employed as *N*-activating groups since the use of these groups in the synthesis of alkene isosteres affords less undesired γ-alkylated product as compared with Boc groups.[12f,14] Additionally, requisite aziridines could be easily obtained by mild Mitsunobu reaction[19] of *N*-Mts-protected 1,2-amino alcohols. Reduction of the *N*-Mts-protected L-serine derivative (Mts-L-Ser(O*t*-Bu)-OMe **13**) with DIBAL in CH_2Cl_2-toluene at −78 °C, followed by addition of cyclopentenyllithium−$ZnCl_2$−LiCl in THF at −78 °C, exclusively afforded *syn*-1,2-amino alcohol **14**. The *syn* diastereoselectivity observed with NHMts aldehyde could be explained using a chelation-controlled Cram cyclic model.[20,21] Treatment of **14** with Ph_3P−DEAD in THF−

SCHEME 2. Synthetic Plan for Alkene-type Ser-Pro Dipeptide Isosteres



toluene gave *cis*-aziridine **15**. Relative configurations of aziridines (**15** and **22**), including *trans*-isomers later discussed, were determined by comparative NOE measurements (Scheme 3). Organocopper-mediated reaction[22] of resulting **15** with "lower-order" cyanocuprate, (*i*-PrO)-$Me_2SiCH_2Cu(CN)MgCl\cdot 2LiCl$ prepared from Grignard reagents[17] in THF at −78 °C for 2 h with additional stirring overnight at 0 °C, gave a mixture of *anti*-S_N2' product **16** and S_N2 product **17** in 83% combined yield (**16**:**17** = 3:1). Following flash chromatographic purification, the desired *anti*-S_N2' product **16** was subjected to oxidation in DMF using KF and 30% H_2O_2 to yield alcohol derivative **18** in 80% yield without affecting the alkene moiety. Following flash chromatographic purification, **18** was crystallized from Et_2O. X-ray analysis of **18** showed that it possessed (*E*)-alkene geometry and (*S*)-configuration of the introduced hydroxymethyl group. This indicated that the organocopper-mediated reaction proceeded in an *anti*-S_N2' manner with the resultant **18**

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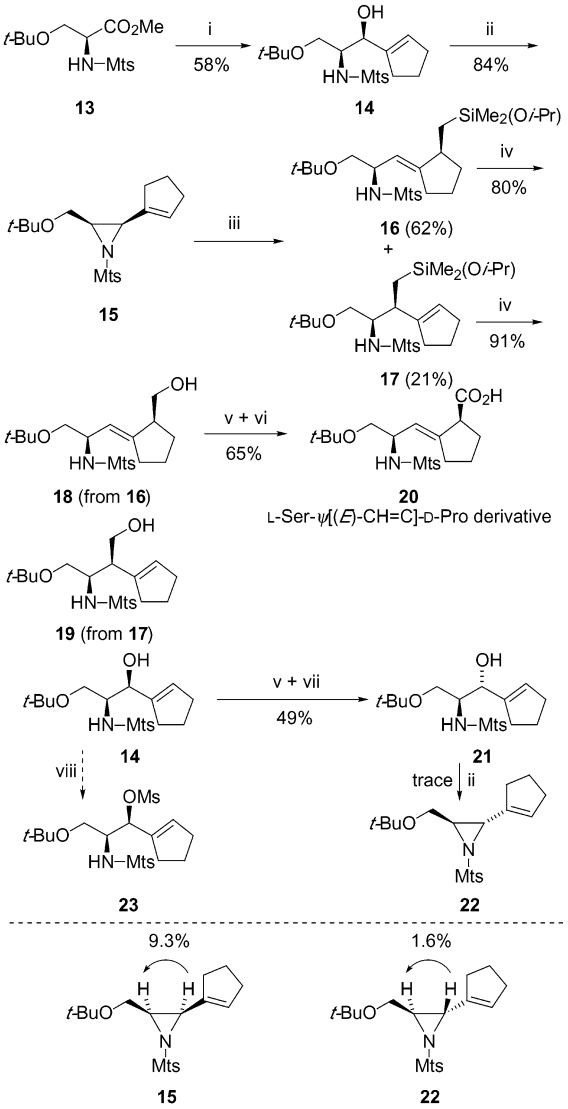
SCHEME 3. Synthesis of Ser-Pro Alkene Isosteres via Aziridines[a]



[a] Key: (i) DIBAL, CH_2Cl_2−toluene, and then cyclopentenyllithium, $ZnCl_2$, LiCl, THF; (ii) DEAD, Ph_3P, THF; (iii) (*i*-PrO)$Me_2SiCH_2Cu(CN)MgCl\cdot 2LiCl$, THF; (iv) 30% H_2O_2, KF, DMF; (v) Dess−Martin periodinane, $CHCl_3$; (vi) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, H_2O; (vii) $Zn(BH_4)_2$, Et_2O; (viii) MsCl, pyridine, $CHCl_3$.

representing a precursor of *trans*-L-Ser-D-Pro type alkene isosteres. Formation of this *anti*-S_N2' product can be explained in a fashion similar to the reported mechanism for the organocopper-mediated synthesis of **6** from **4**.[14,23] The structure of S_N2 product **17** was also ascertained by X-ray analysis of the corresponding alcohol derivative **19**. Alcohol derivative **18** was oxidized to carboxylic acid derivative **20** by a sequence of reactions, which included Dess−Martin periodinane[24] followed by $NaClO_2$-mediated reaction.[25] Flash chromatographic purification of crude material gave desired *N*-Mts-protected L-Ser-ψ[(*E*)-CH=C]-D-Pro **20** possessing *trans*-L-Ser-D-Pro configuration in 65% yield. During oxidative manipulations of **16** to **20**, no significant side reactions were observed.

Since application of organocopper reagents to *cis*-vinyl aziridine compound such as **15** constitutes a synthetic strategy for *trans*-L-Ser-D-Pro-type isosteres, we speculated that reaction of *trans*-vinyl aziridine derivative **22** with organocopper reagents would give *trans*-L-Ser-L-Pro-type alkene isosteres. To confirm this, we attempted the synthesis of *trans*-aziridine **22** from **14** by a sequence of reactions including oxidation/rereduction (inversion of hydroxy-configuration) followed by Mitsunobu reaction (aziridine formation). Oxidation of **14** with Dess−Martin periodinane followed by reduction with $Zn(BH_4)_2$ gave inverse *anti*-amino alcohol **21**. Subsequent Mitsunobu reaction of **21** with Ph_3P−DEAD proceeded quantitatively; however, flash chromatography over silica gel, even over Et_3N-pretreated gel, gave only a trace amount of desired *trans*-aziridine **22**. This may be attributed to the fact that *trans*-aziridine **22** was much less stable than *cis*-isomer **15**.[26] Additionally, attempted activation of **14** to **23** with MsCl as an approach toward L−L type isosteres also met with failure. Consequently, it was found that a synthetic strategy consisting of organocopper reagents and aziridine moieties as the activation devices could be applicable to the synthesis of *trans*-L-Ser-D-Pro (or *trans*-D-Ser-L-Pro) type alkene isosteres but not to that of *trans*-L−L (or *trans*-D−D) type. In addition to the limited use of aziridine-mediated techniques, removal of the *N*-Mts group requires harsher acidic conditions, such as 1 M TMSBr−thioanisole in TFA,[27] as compared to Boc-deprotection. When considering the use of the isosteres in peptide synthesis, more acid labile protecting groups such as Boc would be preferable for the *N*-protection.

Therefore, we examined the susceptibility of *N*-Boc protected compounds to organocopper reagents for the synthesis of the isosteres, in which mesyloxy or 1,3-oxazolidin-2-on-5-yl moieties would be used as shown in Scheme 4. Reduction of starting *N*-Boc protected serine derivative **24** with DIBAL in CH_2Cl_2-toluene at −78 °C gave the corresponding aldehyde. Without isolation, the aldehyde was subsequently carried forward in a one-pot reaction using cyclopentenyllithium−$ZnCl_2$−LiCl in THF to yield a mixture of *syn*-**25** and *anti*-amino alcohols **26** (**25**:**26** = 87:13) in 48% combined yield. As described below, relative configurations of the amino alcohols were determined by comparative NOE measurements of corresponding oxazolidinone derivatives (**28** and **32** in Scheme 4). Attempted activation of the hydroxy group in **25** with MsCl−pyridine−DMAP in CH_2Cl_2 failed to give any corresponding activated product **27**.

Consequently, we planned to activate the hydroxy group by formation of 1,3-oxazolidin-2-one rings, where the hydroxy group would be protected and activated as a cyclic carbamate. Reaction of 5-vinyl-1,3-oxazolidin-2-one with organometallic reagents gave products resulting

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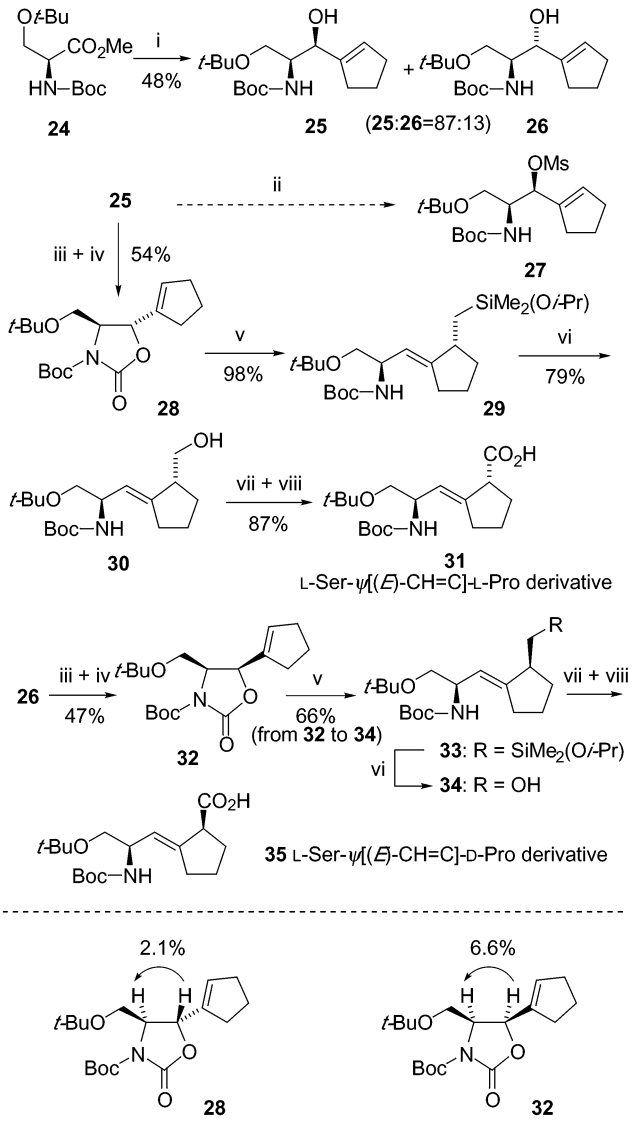
SCHEME 4. Synthesis of Ser-Pro Alkene Isosteres via Oxazolidinones[a]



[a] Key: (i) DIBAL, CH_2Cl_2–toluene, and then cyclopentenyllithium, $ZnCl_2$, LiCl, THF; (ii) MsCl, pyridine, $CHCl_3$; (iii) NaH, THF; (iv) $(Boc)_2O$, THF; (v) (*i*-PrO)$Me_2SiCH_2Cu(CN)MgCl\cdot 2LiCl$, THF; (vi) 30% H_2O_2, KF, DMF; (vii) Dess–Martin periodinane, $CHCl_3$; (viii) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, H_2O.

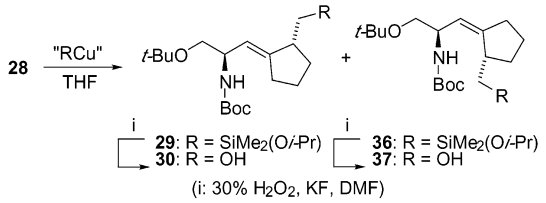
from ring-opening and decarboxylation.[28] Previously, we reported regio- and enantioselective synthesis of vinylglycine derivatives by alkylation of 5-vinyl-1,3-oxazolidin-2-ones with organocopper reagents.[28a] Additionally, we recently found that β-(*N*-Boc-1,3-oxazolidin-2-on-5-yl)-α,β-enoates are potential synthetic intermediates for the synthesis of alkene dipeptide isosteres using organocopper reagents (from **5** to **6** in Scheme 1).[15] Cyclization and *N*-Boc reprotection of **25** by treatment with NaH followed by $(Boc)_2O$ in THF gave *trans*-oxazolidinone derivative **28** in 54% yield. Organocopper-mediated reaction of the resulting oxazolidinone **28** with a "lower order complex" (*i*-PrO)$Me_2SiCH_2Cu(CN)MgCl\cdot 2LiCl$ in THF at −78 °C for 30 min, with additional stirring for 3 h at 0 °C, proceeded quantitatively with ring-opening and decarboxylation to give *anti*-S_N2' product **29** as the sole product.[29] Flash chromatographic purification gave pure **29** in 98% isolated yield. Note should be taken that retention of **29** in silica gel flash chromatography columns overnight can result in decomposition of the desired material to some extent. Oxidation of **29** with KF (4 equiv) and 30% H_2O_2 (12 equiv) in DMF gave alcohol derivative **30**. Use of 4-fold amounts of oxidants as compared to condition mentioned above allowed oxidation of unpurified **29** to **30**, thereby obviating the need for problematic purification of intermediate **29** over silica gel. Stepwise oxidation of purified **30** with Dess–Martin periodinane followed by $NaClO_2$ yielded desired *N*-Boc protected L-Ser-ψ[(*E*)-CH=C]-L-Pro **31**. Following flash chromatographic purification, the corresponding dicyclohexylamine (DCHA) salt of **31** was crystallized from Et_2O. X-ray analysis of the DCHA salt showed that it possessed a configuration corresponding to a *trans*-L-Ser-L-Pro type-alkene isostere. From this analysis, "lower order complexes" are likely to react with **28** in *anti*-S_N2' fashion. Next, to obtain *trans*-L-Ser-D-Pro-type alkene isosteres, *cis*-oxazolidinone derivative **32** was subjected to the "lower order complex" reagent. Requisite **32** was prepared from *anti*-amino alcohol **26** in a manner identical to protocols employed in the synthesis of **28**. Reaction of **32** with (*i*-PrO)$Me_2SiCH_2Cu(CN)MgCl\cdot 2LiCl$ in THF proceeded quantitatively to afford alkylated product **33**. Without flash chromatographic purification, crude **33** was oxidized to alcohol **34** with KF (16 equiv) and 30% H_2O_2 (48 equiv). Subsequent flash chromatographic purification provided pure **34** in 66% yield as calculated from **32**. Successive oxidation of **34** with Dess–Martin periodinane and $NaClO_2$ afforded desired L-Ser-ψ[(*E*)-CH=C]-D-Pro derivative **35**, corresponding to a *trans*-L-Ser-D-Pro dipeptide. The structure of **35** was assigned on the basis of conversion of precursor **34** to **18**, whose structure had been established already. This was acquired as follows: (1) selective removal of the Boc group of **34** using TMSOTf-2,6-lutidine in CH_2Cl_2[30]; (2) *N*-protection of Boc-deprotected product using MtsCl–Et_3N; (3) compounds obtained following reactions 1 and 2, showed identical NMR data and the same signs of optical rotation as compared to the established authentic compound **18**. On the basis of this, we concluded that reaction of *cis*-oxazolidinone **32** with the organocopper reagent proceeded in a fashion similar to the reaction of *trans*-oxazolidinone **28** (*anti*-S_N2' path) to give a precursor of *trans*-L-Ser-D-Pro alkene isostere **35**. These *anti*-S_N2' reactions were confirmed to proceed with high selectivity by comparison of NMR data of **30** and **34**. Additionally no *Z*-isomer contamination was observed by judging from a comparison of NMR data of **30** and **37** (discussed later).

Next, to examine the synthetic feasibility of *cis*-Ser-Pro isosteres, oxazolidinone **28** was subjected to reaction

(28) (a) Ibuka, T.; Suzuki, K.; Habashita, H.; Otaka, A.; Tamamura, H.; Mimura, N.; Miwa, Y.; Taga, T.; Fujii, N. *J. Chem. Soc. Chem. Commun.* **1994**, 2151. (b) Ibuka, T.; Mimura, N.; Aoyama, H.; Akaji, M.; Ohno, H.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 999. (c) Xin, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 6927. (d) Knight, J. G.; Ainge, S. W.; Harm, A. M.; Harwood: S. J.; Maughan, H. I.; Armour, D. R.; Hollinshead, D. M.; Jaxa-Chamiec, A. A. *J. Am. Chem. Soc.* **2000**, *122*, 2944.

(29) No contamination of *syn*-S_N2' product, which corresponded to L-Ser-ψ[(*E*)-CH=C]-D-Pro, was confirmed by NMR analyses of **30** and **34**. The (Z)-iosomer **37** was easily separated over both TLC and flash chromatography from **30**.

TABLE 1. Treatment of Oxazolidinone 28 with Several Organocopper Reagents



run	reagent[a,b]	products (isolated yields %)
1	(*i*-PrO)$Me_2SiCH_2Cu(CN)MgCl\cdot 2LiCl$	**29** (98)
2	(*i*-PrO)$Me_2SiCH_2Cu(CN)MgCl\cdot BF_3\cdot 2LiCl$	**29** (95)
3	((*i*-PrO)$Me_2SiCH_2)_2Cu(CN)(MgCl)_2\cdot 2LiCl$	**29** (98)
4	((*i*-PrO)$Me_2SiCH_2)_2Cu(CN)(MgCl)_2\cdot BF_3\cdot 2LiCl$	**30**[c] (60), **37**[c] (33)

[a] 4 equiv of reagents was used. [b] Reaction at −78 °C for 30 min and then 0 °C for 3 h. [c] Obtained products were racemates.

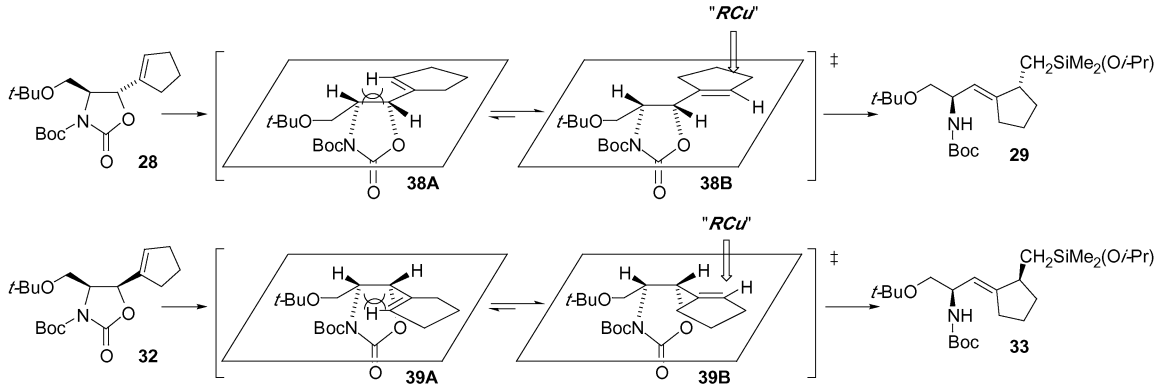


FIGURE 3. Plausible explanation for stereoselectivity in *anti*-S_N2' reaction using "lower-order" cyanocuprates.

with several organocopper reagents as shown in Table 1. Alkylation of **28** with either "lower-order" cyanocuprate−BF_3 complex,[31] (*i*-PrO)$Me_2SiCH_2Cu(CN)MgCl\cdot BF_3\cdot$ 2LiCl (run 2) or "higher-order" cyanocuprate complex, ((*i*-PrO)$Me_2SiCH_2)_2Cu(CN)(MgCl)_2\cdot$2LiCl (run 3) proceeded at −78 °C for 30 min then 0 °C for 3 h to give *anti*-S_N2' product **29** in quantitative yield. This was similar to what was observed using "lower-order" cyanocuprate, (*i*-PrO)-$Me_2SiCH_2Cu(CN)MgCl\cdot$2LiCl (run 1). In the case of run 1−3, treatment at 0 °C was necessary for complete consumption of starting material. In contrast, reaction of **28** with "higher-order" cyanocuprate-BF_3 complex, ((*i*-PrO)$Me_2SiCH_2)_2Cu(CN)(MgCl)_2\cdot BF_3\cdot$ 2LiCl (run 4), proceeded with near complete disappearance of **28** even at −78 °C to yield a mixture of *trans*- and *cis*-isomers (**29** and **36**). Since separation of each isomer using silica gel flash chromatography with prolonged times would cause decomposition, the mixture was oxidized and then subjected to flash chromatographic separation, to yield *trans*-alcohol **30** and *cis*-alcohol **37** (**30**:**37** = 1.8:1). Surprisingly, measurements of optical rotations of flash chromatographically purified samples showed that both alcohols were racemates. X-ray analysis of crystalline **37** supported that isolated material consisted of cocrystals possessing configurations corresponding to *cis*-L-Ser-D-Pro and its enantiomer.

As shown in Figure 3, a plausible mechanism for the regio- and stereoselective reaction with "lower-order" cyanocuprates was deduced based on analogy with γ-mesyloxy-α,β-enoates[13] or β-aziridinyl-α,β-enoates.[14] Copper-mediated substitution of acyclic allylic carbamates has been well documented to give *syn*-S_N2' products.[32] This is in contrast to the fact that other allylic derivatives typically undergo substitution *anti* to the leaving group.[23] Herein complexation of copper with the nitrogen in carbamates is likely to be responsible for *syn*-selectivity. In our cyclic carbamate system, a corresponding nitrogen lacks the ability to undergo complexation due to the presence of an *N*-Boc group. Therefore, reactive intermediates accounting for the organocopper-mediated *anti*-S_N2' reactions, conformer **38A** or **38B** for *trans*-oxazolidinone derivative **28** and conformer **39A** or **39B** for *cis*-oxazolidinone derivative **32**, could be envisioned. Therein, 1,3-allylic strain[33] may result in the preference for conformers **38B** and **39B**. Organocopper attack on preferred conformer **38B** or **39B** in *anti*-S_N2' manner should give **29** or **33** with the *trans*-proline geometry, respectively. This may be the case for both "lower-order" cyanocuprate-BF_3 complexes and "higher-order" cyanocuprates. Formation of enantiomerically pure *cis*-Xaa-Pro isosteres could be explained by the reaction of organocopper reagents via a path involved with unfavourable conformer **38A**. However, alkylation using "higher-order" cyanocuprate−BF_3 complexes afforded an

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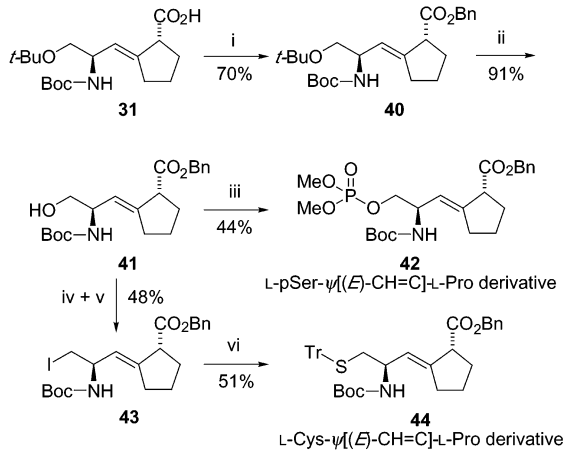
SCHEME 5. Synthesis of pSer-Pro and Cys-Pro Alkene Isosteres[a]



[a] Key: (i) BnBr, DCHA, DMF; (ii) TFA, CH_2Cl_2 then $(Boc)_2O$, Et_3N, THF; (iii) dimethyl *N*,*N*-diisopropylphosphoramidite, tetrazole, MeCN then H_2O_2; (iv) TsCl, pyridine, $CHCl_3$; (v) NaI, acetone; (vi) triphenylmethanethiol, Et_3N, DMF.

unprecedented racemic mixture of **29** and **36** (Table 1). Reaction mechanisms depicted in Figure 3 cannot provide an explanation for the formation of the racemic mixture. At this stage, reasons for the racemate formation still remains as a matter to be discussed further.

As shown in Scheme 5, we next examined the transformation of the hydroxy group corresponding to the Ser moiety. Amino acid sequences containing a Ser-Pro arrangement serve as kinase phosphorylation sites. Additionally, Pin 1, a phosphorylation-dependent peptidyl prolyl isomerase (PPIase), was recently found to regulate several intracellular signaling events involved in mitosis.[34] Synthesis of (*Z*)-alkene phosphoSer(pSer)-Pro isosteres has already been achieved by Etzkorn et al.[35] In conjunction with our recent studies on phosphopeptides,[36] we also carried out the synthesis of *trans*-L-pSer-L-Pro according to their protocol. Protection of carboxylic functionality in **31** gave benzyl ester **40**. Treatment of **40** with TFA followed by reprotection with $(Boc)_2O$ afforded alcohol derivative **41**. Phosphorylation of the resulting **41** with dimethyl phosphoramidite and tetrazole in acetonitrile,[37] followed by addition of 30% H_2O_2, gave protected L-pSer-ψ[(*E*)-CH=C]-L-Pro derivative **42** possessing *trans*-L-pSer-L-Pro geometry in 44% yield.

Conversion of Ser to Cys was also attempted. Compound **41** was activated as iodide **43** by a sequence of reactions consisting of tosylation with TsCl−pyridine in $CHCl_3$ followed by replacement with NaI in acetone. Reaction of **43** with triphenylmethanethiol in DMF, followed by flash chromatographic purification, gave *S*-protected *trans*-L-Cys-L-Pro type alkene isostere **44**.

In conclusion, we have achieved the first regio- and stereoselective synthesis of *trans*-Ser-Pro alkene dipeptide mimetics using an organocopper-mediated *anti*-S_N2' reaction onto key intermediate vinyl aziridines or vinyl oxazolidinones. Of note, the use of either *trans*- or *cis*-isomers of oxazolidinones in the *anti*-S_N2' reaction provides facile and efficient stereoselective access to *trans*-L−L (or D−D)- or *trans*-L−D (or D−L)-type proline dipeptide isosteres, respectively. Together with studies on *cis*-Xaa-Pro mimetics by Etzkorn et al., our results are of value in elucidating relationships between Xaa-Pro geometry in peptides and their biological activity. We are now examining the extension of combined oxazolidinone and organocopper chemistry to the synthesis of *cis*-proline alkene isosteres.

Experimental Section

(1*S*,2*S*)-{1-[(*tert*-Butoxy)methyl]-2-cyclopent-1-enyl-2-hydroxyethyl}[(2,4,6-trimethylphenyl)sulfonyl]amine (14) from 13. To a solution of 16.3 g (83.9 mmol) of 1-iodocyclopentene in THF (50 mL) at −78 °C under argon was added 53.8 mL (83.9 mmol) of 1.56 M *n*-BuLi in hexane with additional stirring for 30 min at this temperature. In another flask 11.4 g (83.9 mmol) of anhydrous $ZnCl_2$ and 3.6 g (83.9 mmol) of anhydrous LiCl were suspended in THF (80 mL) under argon. To the cooled suspension of $ZnCl_2$ and LiCl to −78 °C was added the above solution of cyclopentenyllithium in THF with additional stirring for 30 min at −78 °C. To a solution of 15.0 g (42 mmol) of **13** in CH_2Cl_2 (40 mL) was added dropwise 83.9 mL (83.9 mmol) of 1 M DIBAL in toluene at −78 °C under argon. After stirring the reaction at −78 °C until disappearance of the starting material (ca 1 h), the solution of metalated cyclopentenyl reagents prepared above was added at −78 °C under argon with additional stirring for 1 h at −78 °C. After being stirred at 0 °C for 4 h, the reaction was quenched with saturated citric acid solution at −78 °C and was allowed to warm to 0 °C. The mixture was extracted with EtOAc, and the extract was successively washed with saturated citric acid and brine, dried over $MgSO_4$, and concentrated under reduced pressure to leave residues. Addition of *n*-hexane to the residues gave solid materials. Recrystallization of the solid from EtOAc−*n*-hexane gave 9.7 g (58.0% yield) of the titled compound **14** as colorless crystals: mp 104−106 °C; $[\alpha]^{27}_D$ +54.6 (*c* = 1.01, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.93 (s, 2H), 5.60 (m, 1H), 5.30 (d, *J* = 7.9 Hz, 1H), 4.39 (s, 1H), 3.64 (s, 1H), 3.63 (dd, *J* = 9.2, 3.3 Hz, 1H), 3.51 (dd, *J* = 9.2, 2.3 Hz, 1H), 3.31 (m, 1H), 2.62 (s, 6H), 1.15 (s, 9H); Anal. Calcd for $C_{21}H_{33}NO_4S$: C, 63.77; H, 8.41; N, 3.54. Found: C, 63.48; H, 8.70; N, 3.47.

(2*S*,3*R*)-2-[(*tert*-Butoxy)methyl]-3-cyclopent-1-enyl-1-[(2,4,6-trimethylphenyl)sulfonyl]aziridine (15) from 14. To a solution of 2.0 g (7.6 mmol) of Ph_3P in THF (7 mL) were successively added 40% DEAD solution in toluene (3.4 mL, 7.6 mmol) and a solution of **14** (2.0 g, 5.1 mmol) in THF (5 mL) at 0 °C under argon. After being stirred at 0 °C for 1 h, the reaction mixture was purified by flash chromatography over silica gel with EtOAc−*n*-hexane (1:19) to give 1.6 g (84.0% yield) of the title compound **15** as a pale yellow oil: $[\alpha]^{26}_D$ −47.0 (*c* = 0.91, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 0.5 Hz, 2H), 5.61 (dd, *J* = 3.5, 2.0 Hz, 1H), 3.43 (dd, *J* = 7.0, 1.3 Hz, 1H), 3.33 (dd, *J* = 9.7, 5.6 Hz, 1H), 3.18 (dd, *J* = 9.7, 6.8 Hz, 1H), 3.05 (dt, *J* = 6.9, 5.7 Hz, 1H), 2.70 (s, 6H), 2.35−2.24 (m, 7H), 1.92−1.81 (m, 2H), 1.02 (s, 9H); Anal. Calcd for $C_{21}H_{31}NO_3S$: C, 66.81; H, 8.28; N, 3.71. Found: C, 66.55; H, 8.28; N, 3.54.

(1*R*,2′*S*,*E*)-(1-[(*tert*-Butoxy)methyl]-2-{2′-[2-methyl-2-(methylethoxy)-2-silapropyl]cyclopentylidene}ethyl)-

(34) (a) Yaffe, M. B.; Schutkowski, M.; Shen, M.; Zhou, X. Z.; Stukenberg, P. T.; Rahfeld, J. U.; Xu, J.; Kuang, J.; Kirschner, M. W.; Fischer. G.; Cantley, L. C.; Lu, K. P. *Science* **1997**, *278*, 1957. (b) Liou, Y. C.; Ryo, A.; Huang, H. K.; Lu, P. J.; Bronson, R.; Fujimori, F.; Uchida, T.; Hunter, T.; Lu, K. P. *Proc. Natl. Acad. Sci. U. S. A.* **2002**, *99*, 1335.

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[(2,4,6-trimethylphenyl)sulfonyl]amine (16) from 15. To a solution of LiCl (898 mg, 21.2 mmol) and CuCN (949 mg, 10.6 mmol) in THF (20 mL) was added 13.2 mL (10.6 mmol) of 0.8 M (*i*-PrO)Me_2SiCH_2MgCl in THF at −78 °C under argon with additional stirring for 5 min. The mixture was allowed to warm to 0 °C and then stirred for 10 min at this temperature. To recooled solution of the organocopper reagent to −78 °C was added a solution of 1.0 g (2.7 mmol) of **15** in THF (3 mL) at −78 °C under argon. The reaction was continued for 2 h at −78 °C and then overnight at 0 °C. The reaction was quenched at 0 °C by addition of saturated NH_4Cl−28% NH_4-OH solution (1:1, 20 mL) with additional stirring at room temperature. The mixture was extracted with Et_2O, and the extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give an oily product. Flash chromatographic purification of the crude material over silica gel with EtOAc−*n*-hexane (1:19) give 844 mg (62% yield) of the title compound **16** and 278 mg (21% yield) of S_N2-product **17** as colorless oils. **16**: $[\alpha]^{27}_D$ −0.8 (*c* = 1.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) *δ* 6.90 (d, *J* = 0.5 Hz, 2H), 5.20 (d, *J* = 3.5 Hz, 1H), 4.86 (ddd, *J* = 9.1, 4.9, 2.5 Hz, 1H), 3.95 (m, 1H), 3.89−3.81 (m, 1H), 3.27 (dd, *J* = 8.9, 4.0 Hz, 1H), 3.15 (dd, *J* = 8.9, 7.6 Hz, 1H), 2.60 (s, 6H), 2.28 (s, 3H), 2.11−1.97 (m, 3H), 1.91−1.82 (m, 1H), 1.69−1.59 (m, 1H), 1.50−1.34 (m, 1H), 1.57 (s, 9H), 1.15 (d, *J* = 1.8 Hz, 3H), 1.13 (d, *J* = 1.8 Hz, 3H), 0.93 (dd, *J* = 11.6, 7.0 Hz, 1H), 0.67 (dd, *J* = 14.9, 3.7 Hz, 1H), 0.84 (s, 3H), 0.76 (s, 3H); HRMS (FAB) *m*/*z* calcd for $C_{27}H_{46}NO_4SSi$ (MH^-) 508.2917, found 508.2908.

17: $[\alpha]^{21}_D$ +3.1 (*c* = 0.33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) *δ* 6.92 (d, *J* = 0.3 Hz, 2H), 5.38 (m, 1H), 5.17 (d, *J* = 9.2 Hz, 1H), 3.91 (m, 1H), 3.14−3.05 (m, 1H), 2.92 (dd, *J* = 8.4, 3.9 Hz, 1H), 2.72−2.67 (m, 1H), 2.65 (s, 6H), 2.27 (s, 3H), 2.22−2.12 (m, 3H), 2.03−1.93 (m, 1H), 1.80−1.69 (m, 2H), 1.13 (d, *J* = 1.7 Hz, 3H), 1.11 (d, *J* = 1.7 Hz, 3H), 1.02 (s, 9H), 0.46 (dd, *J* = 11.9, 14.9 Hz, 1H), 0.05−0.00 (m, 8H).

Conversion of S_N2 Product 17 to Corresponding Alcohol Derivative 19. By a procedure identical with that described for synthesis of **18** from **16** (next section), 178 mg (0.4 mmol) of **17** was oxidized to alcohol derivative **19** (130 mg, 91% yield). Recrystallization of **19** from Et_2O gave colorless crystals: mp 121−123 °C; $[\alpha]^{25}_D$ +6.9 (*c* = 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) *δ* 6.95 (s, 2H), 5.43 (m, 1H), 5.37 (d, *J* = 9.9 Hz, 1H), 3.96−3.88 (m, 1H), 3.69−3.61 (m, 1H), 3.45−3.38 (m, 1H), 3.13 (dd, *J* = 8.7, 1.6 Hz, 1H), 2.83 (dd, *J* = 8.8, 3.7 Hz, 1H), 2.77−2.72 (m, 1H), 2.65 (s, 6H), 2.30 (s, 3H), 2.27−2.10 (m, 2H), 1.81−1.71 (m, 2H), 1.55 (s, 9H); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{36}NO_4S$ (MH^+) 410.2365, found 410.2370. An X-ray structural analysis of **19** showed that the side reaction of **15** with the organocopper reagent proceeded via S_N2 path.

(1*R*,2′*S*,*E*)-{1-[(*tert*-Butoxy)methyl]-2-[2′-(hydroxymethyl)cyclopentylidene]ethyl}[(2,4,6-trimethylphenyl)sulfonyl]amine (18) from 16. To a solution of 500 mg (1.0 mmol) of **16** in DMF (5 mL) were successively added solid KF (228 mg, 3.9 mmol) and 30% H_2O_2 aqueous solution (1.3 g, 11.8 mmol) at room temperature. After being stirred at room temperature for 10 h, the reaction was diluted with H_2O, and extracted with Et_2O. The extract was successively washed with 1 M $Na_2S_2O_3$ solution and H_2O and dried over $MgSO_4$. The solvent was removed by evaporation, followed by flash chromatography over silica gel with EtOAc−*n*-hexane (1:4), to give 332 mg (80% yield) of the title compound **18**. Recrystallization of **18** from Et_2O gave colorless crystals: mp 111−112 °C; $[\alpha]^{26}_D$ −62.0 (*c* = 1.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) *δ* 6.96 (d, *J* = 0.5 Hz, 2H), 5.35 (d, *J* = 1.8 Hz, 1H), 5.24 (ddd, *J* = 9.0, 4.5, 2.4 Hz, 1H), 3.65−3.58 (m, 1H), 3.63 (dd, *J* = 11.4, 5.2 Hz, 1H), 3.42 (dd, *J* = 11.4, 6.3 Hz, 1H), 3.27−3.16 (m, 2H), 2.61 (s, 6H), 2.49 (m, 1H), 2.31 (s, 3H), 2.02−1.90 (m, 2H), 1.79−1.48 (m, 4H), 1.16 (s, 9H); Anal. Calcd for $C_{22}H_{35}NO_4S$: C, 64.51; H, 8.61; N, 3.42. Found: C, 64.24; H, 8.51; N, 3.33. An X-ray structural analysis of the crystals indicated that **18** possesses *trans*-L-Ser-D-Pro configuration.

(1*S*,2′*R*,*E*)-2-(3′-(*tert*-Butoxy)-2′-{[(2,4,6-trimethylphenyl)-sulfonyl]amino}propylidene)cyclopentanecarboxylic acid (L-Ser-*ψ*[(*E*)-CH=C]-D-Pro derivative 20) from 18. To a suspension of 621 mg (1.5 mmol) of Dess−Martin periodinane in $CHCl_3$ (2 mL) was added a solution of 300 mg (0.7 mmol) of **18** in $CHCl_3$ (1 mL) at 0 °C under argon. The reaction was continued for 1 h at room temperature and then quenched with 25% $Na_2S_2O_3$−saturated $NaHCO_3$ solution (1:1, 10 mL) at 0 °C. After being stirred at room temperature for 15 min, the mixture was extracted with Et_2O. The extract was successively washed with saturated $NaHCO_3$ solution and H_2O, dried over $MgSO_4$, and concentrated under reduced pressure to leave residues. The residues were redissolved with *t*-BuOH (2 mL). To the solution were successively added 2-methyl-2-butene (1.6 mL, 14.7 mmol) and an aqueous solution (1.5 mL) consisting of $NaClO_2$ (132 mg, 1.5 mmol) and NaH_2PO_4 (132 mg, 1.5 mmol) at room temperature. After being stirred for 15 h at room temperature, the reaction was concentrated under reduced pressure to give residues. To the residues was added 1 N HCl (2 mL), followed by extraction with EtOAc. The extract was successively washed with 1 M $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated to leave an oil. Flash chromatography of the oil over silica gel with EtOAc−*n*-hexane (1:2) gave 202 mg (65% yield) of the title compound **20** as a colorless oil: $[\alpha]^{26}_D$ −13.5 (*c* = 0.96, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) *δ* 6.93 (s, 2H), 5.49 (m, 1H), 5.31 (d, *J* = 4.3 Hz, 1H), 3.69 (m, 1H), 3.25 (m, 3H), 2.60 (s, 6H), 2.29 (s, 3H), 2.09−1.67 (m, 5H), 1.60−1.50 (m, 1H), 1.13 (s, 9H); HRMS (FAB) *m*/*z* calcd for $C_{22}H_{34}NO_5S$ (MH^+) 424.2158, found 424.2173.

(1*S*,2*R*)-{1-[(*tert*-Butoxy)methyl]-2-cyclopent-1-enyl-2-hydroxyethyl}[(2,4,6-trimethylphenyl)sulfonyl]amine (21) from 14. To a solution of 12.9 g (30.3 mmol) of Dess−Martin periodinane in $CHCl_3$ (10 mL) was added 6.0 g (15.2 mmol) of **14** in $CHCl_3$ (10 mL) at 0 °C with additional stirring for 1 h at room temperature. The reaction was quenched with saturated $Na_2S_2O_3$ and extracted with Et_2O. The extract was successively washed with saturated $NaHCO_3$ and H_2O, dried over $MgSO_4$, and concentrated to leave residue. The residue was dissolved with Et_2O (10 mL). To the solution was added 0.5 M $Zn(BH_4)_2$ in Et_2O (30 mL, 15.0 mmol) under argon at −78 °C. The reaction was continued at −78 °C for 30 min and then at 0 °C overnight and quenched with 1 N HCl at −78 °C. The mixture was allowed to warm to room temperature with stirring and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated to give crude materials. Flash chromatographic purification of the crude materials over silica gel with EtOAc−*n*-hexane (1:9) gave 2.9 g (49% yield) of the title compound **21** as a colorless oil: $[\alpha]^{23}_D$ −24.8 (*c* = 0.12, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) *δ* 6.95 (s, 2H), 5.66 (m, 1H), 5.52 (d, *J* = 8.6 Hz, 1H), 4.06 (s, 1H), 3.58 (d, *J* = 8.9 Hz, 1H), 3.51 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.43−3.36 (m, 1H), 3.34−3.30 (m, 1 H), 2.67 (s, 6H), 2.29−2.26 (m, 5H), 2.09−2.01 (m, 2H), 1.88−1.77 (m, 2H), 1.08 (s, 9H); HRMS (FAB) *m*/*z* calcd for $C_{21}H_{34}NO_4S$ (MH^+) 396.2208; found 396.2219. Attempted conversion of **21** to *anti*-aziridine derivative **22** by a procedure identical with that described for the synthesis of **15** from **14**, followed by flash chromatography, gave trace amount of corresponding aziridine **22** limited for NMR analysis. **22**: ^1H NMR (300 MHz, $CDCl_3$) *δ* 6.92 (d, *J* = 0.5 Hz, 2H), 5.73 (m, 1H), 3.88 (dd, *J* = 10.3, 5.0 Hz, 1H), 3.69 (dd, *J* = 10.3, 7.0 Hz, 1H), 3.46 (d, *J* = 3.9 Hz, 1H), 3.04−2.98 (m, 1H), 2.68 (s, 6H), 2.33−2.27 (m, 5H), 2.19−2.10 (m, 2H), 1.86−1.75 (m, 2H), 1.16 (s, 9H).

(1*S*,2*S*)-(*tert*-Butoxy)-*N*-{1-[(*tert*-butoxy)methyl]-2-cyclopent-1-enyl-2-hydroxyethyl}carboxamide (25) from 24. To a solution of 13.3 g (49.2 mmol) of **24** in CH_2Cl_2 (50 mL) was added dropwise 95.4 mL (96.3 mmol) of 1.01 M DIBAL in toluene at −78 °C under argon with additional stirring at −78 °C until disappearance of the starting material (ca. 1 h). To this solution was added cyclopentenyllithium−$ZnCl_2$−LiCl (96.3 mmol) in THF−hexane (1.7:1, 165 mL), prepared by a procedure identical with that described for the

synthesis of **14**, at −78 °C under argon. After being stirred for 2 h at −78 °C, followed by additional stirring at room-temperature overnight. The recooled reaction mixture to −78 °C was quenched with saturated citric acid, allowed to warm to 0 °C, and extracted with EtOAc. The extract was successively washed with saturated citric acid and brine, dried over $MgSO_4$, and concentrated to leave residues. Flash chromatographic purification of the residues over silica gel with EtOAc−*n*-hexane (1:9) gave 6.3 g of the title compound **25** and 0.9 g of *anti*-isomer **26** in 48% combined yield as colorless oils. **25**: $[\alpha]^{27}_D$ +15.3 (*c* = 1.90, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.68 (d, *J* = 2.0 Hz, 1H), 5.23 (d, *J* = 8.3 Hz, 1H), 4.51 (s, 1H), 3.78 (s, 1H), 3.69 (dd, *J* = 9.2, 3.0 Hz, 1H), 3.60 (dd, *J* = 9.2, 2.6 Hz, 1H), 2.40−2.17 (m, 4H), 1.87 (m, 2H), 1.43 (s, 9H), 1.20 (s, 9H); HRMS (FAB) *m*/*z* calcd for $C_{17}H_{32}NO_4$ (MH^+) 314.2331, found 314.2323. **26**: $[\alpha]^{28}_D$ +5.4 (*c* = 1.47, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.73 (d, *J* = 1.7 Hz, 1H), 5.44 (d, *J* = 7.8 Hz, 1H), 4.30 (s, 1H), 3.84−3.72 (m, 2H), 3.60 (dd, *J* = 9.1, 2.5 Hz, 1H), 3.51 (dd, *J* = 9.2, 2.5 Hz, 1H), 2.39−2.23 (m, 4H), 1.92 (m, 2H), 1.46 (s, 9H), 1.16 (s, 9H); HRMS (FAB) *m*/*z* calcd for $C_{17}H_{32}NO_4$ (MH^+) 314.2331, found 314.2337.

(4*S*,5*S*)-*tert*-Butyl 5-[(*tert*-Butoxy)methyl]-4-cycopent-1-enyl-2-oxo-3,1-oxazolidinecarboxylate (*trans*-oxazolidinone derivative 28) from 25. To a suspension of 777 mg (19.4 mmol) of 60% NaH in THF (20 mL) was added 1.5 g (4.9 mmol) of **25** in THF (5 mL) at room temperature under argon. The reaction was refluxed for 30 min and then cooled to 0 °C. To the reaction mixture was added $(Boc)_2O$ (2.1 g, 9.2 mmol). The reaction was stirred for 3 h at room temperature, quenched with saturated NH_4Cl solution, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give residues. The residues were purified by flash chromatography over silica gel with EtOAc−*n*-hexane (1:19) to yield 884 mg (54% yield) of the title compound **28** as a colorless oil: $[\alpha]^{26}_D$ −12.6 (*c* = 1.03, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80 (s, 1H), 4.96 (d, *J* = 2.3 Hz, 1H), 4.02 (m, 1H), 3.64 (dd, *J* = 9.2, 5.9 Hz, 1H), 3.52 (dd, *J* = 9.4, 2.8 Hz, 1H), 2.39−2.35 (m, 3H), 2.32−2.27 (m, 1H), 1.87 (m, 1H), 1.55 (s, 9H), 1.18 (s, 9H); Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.48; H, 8.74; N, 4.02.

(1*R*,2′*R*,*E*)-(*tert*-Butoxy)-*N*-(1-[(*tert*-butoxy)methyl]-2-{2′-[2-methyl-2-(methylethoxy)-2-silapropyl]cyclopentylidene}ethyl)carboxamide (29) from 28. To a solution of organocopper reagent (5.9 mmol) in THF (16 mL), prepared by a procedure identical with that described for the synthesis of **16**, was added 0.5 g (1.5 mmol) of **28** in THF (2 mL) at −78 °C under argon. The reaction was stirred at −78 °C for 30 min and then at 0 °C for 3 h, quenched with saturated NH_4Cl−28% NH_4OH (1:1, 10 mL) at 0 °C, and stirred at room temperature for 30 min. The mixture was extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated to give an oil. The oily material was purified by flash chromatography over silica gel with EtOAc−*n*-hexane (1:7) to yield 617 mg (98% yield) of the title compound **29** as a colorless oil: $[\alpha]^{27}_D$ −8.6 (*c* = 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.20 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.78 (s, 1H), 4.24 (m, 1H), 3.99 (dt, *J* = 12.2, 6.1 Hz, 1H), 3.39 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.27 (dd, *J* = 8.9, 4.8 Hz, 1H), 2.51 (q, *J* = 8.6 Hz, 1H), 2.37 (br, 1H), 2.16−2.07 (m, 1H), 1.96−1.88 (m, 1H), 1.80−1.71 (m, 1H), 1.64−1.46 (m, 1H), 1.43 (s, 9H), 1.16 (s, 9H), 1.15 (d, *J* = 6.7 Hz, 6H), 0.99 (dd, *J* = 14.8, 3.8 Hz, 1H), 0.53 (dd, *J* = 14.8, 10.7 Hz, 1H), 0.16−0.02 (m, 6H); HRMS (FAB) *m*/*z* calcd for $C_{23}H_{46}NO_4Si$ (MH^+) 428.3196, found 428.3182.

(1*R*,2′*R*,*E*)-2-{3′-(*tert*-Butoxy)-2′-[(*tert*-butoxy)carbonylamino]propylidene}cyclopentanecarboxylic acid (L-Ser-ψ[(*E*)-CH=C]-L-Pro derivative 31) from 29. By a procedure identical with that described for the synthesis of **18** from **16**, 538 mg (1.3 mmol) of **29** was converted to 325 mg (79% yield) of the corresponding alcohol derivative **30** as a colorless oil: $[\alpha]^{26}_D$ −27.4 (*c* = 1.42, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.27 (dd, *J* = 8.6, 2.0 Hz, 1H), 4.85 (d, *J* = 7.3 Hz, 1H), 4.29 (br, 1H), 3.57 (dd, *J* = 10.9, 6.6 Hz, 1H), 3.47 (dd, *J* = 10.9, 6.0 Hz, 1H), 3.41−3.30 (m, 2H), 2.64−2.45 (m, 2H), 2.27−2.21 (m, 2H), 1.88−1.52 (m, 4H), 1.44 (s, 9H), 1.16 (s, 9H); HRMS (FAB) *m*/*z* calcd for $C_{18}H_{34}NO_4$ (MH^+) 328.2488, found 328.2490. Compound **30** (273 mg, 0.8 mmol) was converted to 248 mg (87% yield) of the title compound **31** by a procedure identical with that described for the synthesis of **20** from **18**. **31**: colorless oil; $[\alpha]^{26}_D$ −32.8 (*c* = 1.10, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.55 (d, *J* = 7.2 Hz, 1H), 4.97 (s, 1H), 4.27 (s, 1H), 3.40−3.34 (m, 2H), 3.30 (dd, *J* = 8.6, 4.6 Hz, 1H), 2.56 (t, *J* = 8.4, 1H), 2.34 (q, *J* = 7.6 Hz, 1H), 2.04−1.97 (m, 1H), 1.96−1.86 (m, 2H), 1.70−1.63 (m, 1H), 1.44 (s, 9H), 1.14 (s, 9H); HRMS (FAB) *m*/*z* calcd for $C_{18}H_{30}NO_5$ (MH^-) 340.2123, found 340.2112.

DCHA Salt of 31. Treatment of a solution of 55 mg (0.2 mmol) of **31** in Et_2O (0.5 mL) with dicyclohexylamine (32 μL, 0.2 mmol), followed by standing at room temperature, afforded 84 mg (99% yield) of corresponding DCHA salt as colorless crystals: mp 141−144 °C; Anal. Calcd for $C_{30}H_{54}N_2O_5$: C, 68.93; H, 10.41; N, 5.36. Found: C, 68.63; H, 10.50; N, 5.14. An X-ray structural analysis of the crystals indicated that **31** possesses *trans*-L-Ser-L-Pro configuration.

"Lower-Order" Cyanocuprate−BF_3 Complex (Table 1, run 2). To a solution of "lower-order" cyanocuprate (0.6 mmol) in THF (2.4 mL) at −78 °C, which prepared by a procedure identical with that described for the synthesis of **16** from **15**, was added BF_3·Et_2O (72 μL, 0.6 mmol). After additional stirring for 5 min at −78 °C, 50 mg (0.14 mmol) of **28** was added at this temperature. The reaction was continued at −78 °C for 30 min and then at 0 °C for 3 h. Procedures identical to those described above gave 60 mg (95% yield) of **29**.

"Higher-Order" Cyanocuprate Complex (Table 1, run 3). To a solution of LiCl (50 mg, 1.2 mmol) and CuCN (53 mg, 0.6 mmol) in THF (1.5 mL) was added 1.7 mL (1.2 mmol) of 0.7 M (*i*-PrO)Me_2SiCH_2MgCl in THF at −78 °C under argon with additional stirring for 5 min. The mixture was allowed to warm to 0 °C and then stirred for 10 min at this temperature. To recooled solution of the organocopper reagent to −78 °C was added 50 mg (0.14 mmol) of **28** at this temperature. The reaction was continued at −78 °C for 30 min and then at 0 °C for 3 h. Procedures identical to those described above gave 62 mg (98% yield) of **29**.

"Higher-Order" Cyanocuprate−BF_3 Complex (Table 1, run 4). To a solution of "higher-order" reagent (0.6 mmol) described above at −78 °C was added BF_3·Et_2O (72 μL, 0.6 mmol). After additional stirring for 5 min at −78 °C, 50 mg (0.14 mmol) of **28** was added at this temperature. The reaction was continued at −78 °C for 30 min and then at 0 °C for 3 h. Procedures identical to those described above gave a crude mixture of **29** and **36**. The mixture was subjected to the oxidation identical with that described for the synthesis of **18** from **16** to yield 37 mg (60% yield) of **30** and 21 mg (33% yield) of **37** as racemates. Recrystallization of **37** from EtOAc−hexane gave colorless cocrystals of the racemate: mp 104−107 °C; $[\alpha]^{28}_D$ 0 (*c* = 0.30, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.21 (d, *J* = 7.9 Hz, 1H), 4.47 (s, 1H), 3.56−3.53 (m, 1H), 3.52−3.47 (m, 1H), 3.40−3.37 (m, 1H), 3.18 (t, *J* = 7.8 Hz, 1H), 2.98 (s, 1H), 2.37−2.31 (m, 1H), 2.27−2.21 (m, 1H), 1.90−1.83 (m, 1H), 1.70−1.63 (m, 1H), 1.57−1.47 (m, 2H), 1.44 (s, 9H), 1.18 (s, 9H); HRMS (FAB) *m*/*z* calcd for $C_{18}H_{34}NO_4$ (MH^+) 328.2488, found 328.2503. An X-ray structural analysis of the crystals indicated that **37** consists of racemate possessing relative configuration corresponding to *cis*-L-Ser-D-Pro.

Benzyl (1*R*,2′*R*,*E*)-2-{3′-(*tert*-Butoxy)-2′-[(*tert*-butoxy)-carbonylamino]propylidene}cyclopentanecarboxylate (40) from 31. To a solution of 231 mg (0.7 mmol) of **31** in DMF (1 mL) were successively added DCHA (97 μL, 0.7 mmol) and BnBr (97 μL, 0.8 mmol) at 0 °C. The reaction was stirred overnight at room temperature, diluted with H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated to leave residues. Flash chromatographic purification of the residues over silica gel with EtOAc−*n*-hexane (1:7) gave 203 mg (70% yield) of the title

compound **40** as a colorless oil: $[\alpha]^{19}_D$ −30.8 (c = 0.07, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 5.47 (dd, J = 8.7, 2.1 Hz, 1H), 5.11 (s, 2H), 4.84 (s, 1H), 4.24 (m, 1H), 3.43−3.29 (m, 2H), 3.19 (dd, J = 9.1, 4.8 Hz, 1H), 2.63−2.50 (m, 1H), 2.40−2.24 (m, 1H), 2.09−1.82 (m, 3H), 1.43 (s, 9H), 1.12 (s, 9H); HRMS (FAB) m/z calcd for $C_{25}H_{38}NO_5$ (MH^+) 432.2750, found 432.2737.

Benzyl (1*R*,2′*R*,*E*)-2-{2′-[(*tert*-Butoxy)carbonylamino]-3′-hydroxypropylidene}cyclopentanecarboxylate (41) from 40. To a solution of 191 mg (0.4 mmol) of **40** in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL) at 0 °C with additional stirring for 1 h at this temperature. After removal of TFA by N_2-stream, the residues were dissolved with THF (1 mL). The mixture was neutralized by Et_3N, followed by successive addition of Et_3N (56 μL, 0.4 mmol) and $(Boc)_2O$ (193 mg, 0.9 mmol). The reaction was stirred overnight at room temperature, extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give oily materials. Flash chromatographic purification of the oil over silica gel with EtOAc−n-hexane (1:4) yielded 152 mg (91% yield) of the title compound **41** as a colorless solid: $[\alpha]^{19}_D$ −44.9 (c = 0.09, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 5.26 (ddd, J = 8.9, 4.6, 2.7 Hz, 1H), 5.13 (dd, J = 26.1, 12.2 Hz, 2H), 4.65 (m, 1H), 4.27 (m, 1H), 3.46 (dd, J = 5.6 Hz, 2H), 3.42−3.34 (m, 1H), 2.58−2.46 (m, 1H), 2.42−2.25 (m, 1H), 2.11−1.82 (m, 3H), 1.54 (s, 9H); HRMS (FAB) m/z calcd for $C_{21}H_{30}NO_5$ (MH^+) 376.2124, found 376.2135.

Benzyl (1*R*,2′*R*,*E*)-2-{(3′-Bis(methoxy)phospharyloxy)-2′-[(*tert*-butoxy)carbonylamino]propylidene}cyclopentanecarboxylate (L-pSer-ψ[(*E*)-CH=C]-L-Pro Derivative 42) from 41. To a solution containing tetrazole (19 mg, 0.3 mmol) and **41** (50 mg, 0.1 mmol) in MeCN (0.5 mL) was added dimethyl N,N-diisopropylphosphramidite (19 mg, 0.2 mmol) in MeCN (0.5 mL) at 0 °C under argon. After the reaction was stirred at 0 °C for 1 h, 30% H_2O_2 solution (23 mg, 0.2 mmol) was added at 0 °C with additional stirring for 1 h. Then the mixture was diluted with H_2O and extracted with Et_2O. The extract was successively washed with 1 M $Na_2S_2O_3$, saturated $NaHCO_3$, and H_2O, dried over $MgSO_4$, and concentrated. After flash chromatography over silica gel with EtOAc−n-hexane (1:4), the title compound **42** (28 mg, 44% yield) as a colorless oil was obtained. **42**: $[\alpha]^{18}_D$ −17.5 (c = 0.11, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40−7.31 (m, 5H), 5.37 (dd, J = 8.6, 2.3 Hz, 1H), 5.12 (dd, J = 13.9, 12.5 Hz, 2H), 4.86 (s, 1H), 4.44 (s, 1H), 4.00−3.82 (m, 2H), 3.74 (dd, J = 11.0, 1.5 Hz, 6H), 3.38 (t, J = 7.3, 1H), 2.61−2.46 (m, 1H), 2.41−2.26 (m, 1H), 2.08−1.84 (m, 3H), 1.74−1.58 (m, 1H), 1.43 (s, 9H); HRMS (FAB) m/z calcd for $C_{23}H_{35}NO_8P$ (MH^+) 484.2100, found 484.2096.

Benzyl (1*R*,2′*R*,*E*)-2-{2′-[(*tert*-Butoxy)carbonylamino]-3′-iodopropylidene}cyclopentanecarboxylate (43) from 41. To a solution of 65 mg (0.2 mmol) of **41** in $CHCl_3$ (0.5 mL) were successively added pyridine (140 μL, 1.7 mmol) and TsCl (165 mg, 0.9 mmol) at 0 °C. The reaction was stirred for 30 min at 0 °C, diluted with H_2O, and extracted with EtOAc. The extract was successively washed with saturated citric acid and brine, dried over $MgSO_4$, and concentrated to give oily materials. After flash chromatography over silica gel with EtOAc−n-hexane (1:9), tosylated compound (65 mg, 71% yield) as a colorless oil was obtained. The tosylated compound: $[\alpha]^{24}_D$ −22.3 (c = 0.36, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.75 (d, J = 8.6 Hz, 2H), 7.39−7.29 (m, 7H), 5.35 (d, J = 6.6 Hz, 1H), 5.12 (dd, J = 15.0, 12.4 Hz, 2H), 4.61 (s, 1H), 4.39 (s, 1H), 3.97 (dd, J = 9.6, 3.6 Hz, 1H), 3.86 (dd, J = 9.9, 5.3 Hz, 1H), 3.45 (t, J = 7.3 Hz, 1H), 2.49−2.34 (m, 4H), 2.49−2.13 (m, 1H), 1.82−2.09 (m, 3H), 1.72−1.51 (m, 1H), 1.40 (s, 9H). Without further chracterization, the tosylated material (143 mg, 0.3 mmol) was converted to the title compound by the reaction with NaI (81 mg, 0.5 mmol) in acetone (1.5 mL) at room temperature. The reaction was stirred for 30 h at room temperature, diluted with H_2O, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated to leave residues. Flash chromatographic purification of the residues over silica gel with EtOAc−n-hexane (1:9) gave 61 mg (67% yield) of the title compound **43** as a colorless oil: $[\alpha]^{27}_D$ −30.8 (c = 0.07, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.39−7.32 (m, 5H), 5.35 (dd, J = 8.3, 2.3 Hz, 1H), 5.14 (dd, J = 17.5, 12.2 Hz, 2H), 4.62 (s, 1H), 4.18 (m, 1H), 3.37 (t, J = 7.1 Hz, 1H), 3.31−3.11 (m, 2H), 2.45−2.32 (m, 2H), 2.13−1.92 (m, 3H), 1.90−1.60 (m, 1H), 1.44 (s, 9H); HRMS (FAB) m/z calcd for $C_{21}H_{29}NO_4I$ (MH^+) 486.1143, found 486.1161.

Benzyl (1*R*,2′*R*,*E*)-2-{2′-[(*tert*-Butoxy)carbonylamino]-3′-(triphenylmethylthio)propylidene}cyclopentanecarboxylate (L-Cys-ψ[(*E*)-CH=C]-L-Pro derivative 44) from 43. To a solution of 5 mg (0.02 mmol) of triphenylmethanethiol in DMF (0.5 mL) was successively added **43** (8 mg, 0.02 mmol) in DMF (0.5 mL) and Et_3N (3 μL, 0.02 mL) at 0 °C. The reaction was continued for 10 h at room temperature, quenched with saturated NH_4Cl (1 mL), and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatographic purification (EtOAc−n-hexane = 1:9) of the crude materials gave 5 mg (51% yield) of the title compound **44** as a colorless oil: $[\alpha]^{26}_D$ −43.9 (c = 0.11, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.43−7.17 (m, 20H), 5.29 (dd, J = 8.6, 2.3 Hz, 1H), 5.02−5.14 (m, 2H), 4.42 (s, 1H), 4.16 (s, 1H), 3.32 (t, J = 7.3 Hz, 1H), 2.35−2.17 (m, 4H), 2.05−1.86 (m, 3H), 1.56 (m, 1H), 1.10 (s, 9H); HRMS (FAB) m/z calcd for $C_{40}H_{42}NO_4S$ (MH^-) 632.2834, found 632.2852.

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Supporting Information Available: Experimental procedures for the synthesis of **35** from **26**. ORTEP diagrams for **18**, **19**, **31**, and **37** and their CIF files. Copies of ^{1}H NMR spectra of compounds **15**, **22**, **28**, **31**, **32**, and **35** including NOE spectra for **15**, **22**, **28**, and **32**. Copies of ^{1}H NMR spectra in comparison between **30** and **34** or **30** and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

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