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Stereoselective Synthesis of (*Z*)-Alkene-Containing Proline Dipeptide Mimetics

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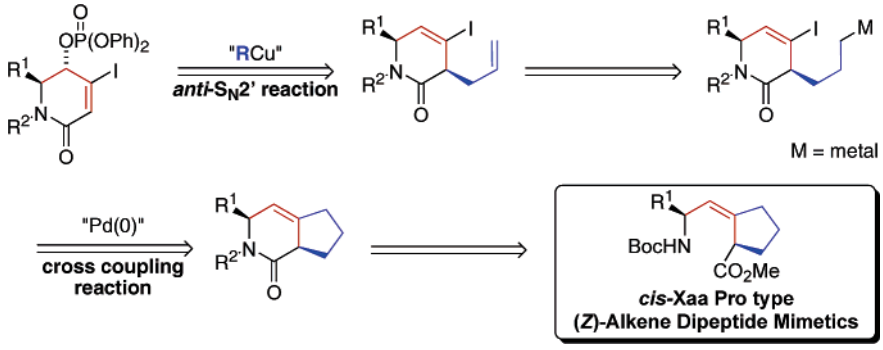
Received March 20, 2006



In peptides and proteins, the peptide bond between an amino acid and proline exists as an equilibrium mixture of the *cis*-imide and *trans*-imide due to the low energy barrier in their interconversion. This feature greatly influences the structure and function of the proline-containing peptides and proteins. Therefore, restricting the amide bond with an (*E*)- or (*Z*)-alkene should provide a promising method for elucidating the structure−activity relationships of the peptide and the proteins. In this report, the regio- and stereoselective synthesis of *cis*-alanylproline (Ala-Pro) type (*Z*)-alkene dipeptide mimetic is described. The key steps of this synthesis are to introduce a C3 unit onto a γ-phosphoryloxy-α,β-unsaturated-δ-lactam with an organocopper-mediated *anti*-S_N2' reaction and subsequently construct a five-membered proline-like cyclic structure with an intramolecular Suzuki coupling reaction. Hydrolysis of the amide bond in the resulting bicyclic lactam yields the desired *cis*-Ala-Pro type (*Z*)-alkene dipeptide isostere. The presented synthetic methodology should be applicable to the general syntheses of other *cis*-aminoacylproline type (*Z*)-alkene dipeptide mimetics.

Introduction

Proline (Pro) can form a *cis*- or *trans*-peptide bond through the acylation of the secondary amine with amino acids.[1] Low energy barriers in the cis/trans interconversion allow proline-containing peptides to exist in a trans or cis form, depending on the surrounding environments (Figure 1). These isomeric peptides (or proteins) show distinct biological functions, which differ from each other.[2−6] The genome sequence cannot deduce this kind of dynamic conformational change or the subsequent involvement in biological functions. Therefore, determining which conformer contributes to a biological function is an important task in peptide/protein chemistry. One potential method for this purpose is structural analysis of Pro-peptides with NMR or X-ray diffraction, but precise profiling of the conformer is difficult due to the facile interconversion between the cis and trans forms. Thus, use of synthetic equivalents which possess the fixed conformation for functional analysis of Pro-peptides represents a promising alternative to spectroscopic methods.[3,7] These include alkene-type dipeptide isosteres with

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10.1021/jo0606002 CCC: $33.50
Published on Web 05/18/2006

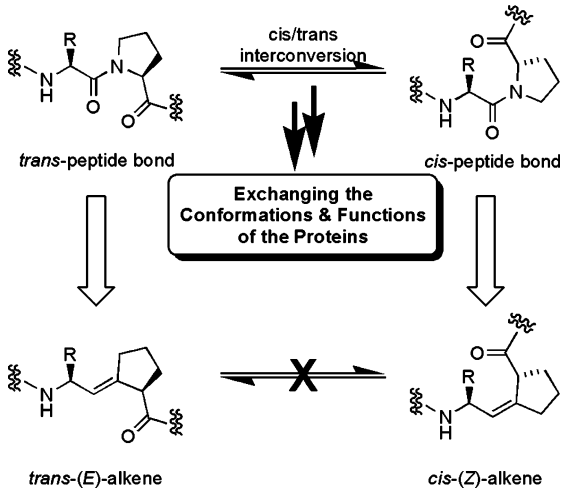
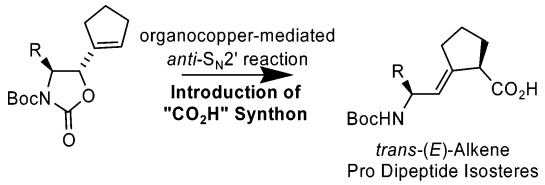


FIGURE 1. Cis/trans interconversion of peptide bond in proline dipeptide and *cis*-(*Z*)-alkene or *trans*-(*E*)-alkene dipeptide isosteres, which correspond to the *cis*- or *trans*-dipeptides.

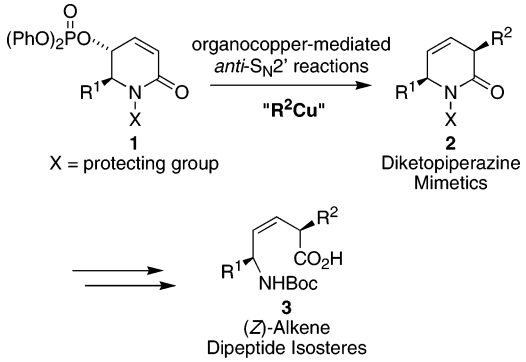
an (*E*)- or (*Z*)-olefin unit, which corresponds to the aminoacyl-proline bonds.

Therefore, many research groups, including ours, have been extensively engaged in the synthetic study on (*E*)- or (*Z*)-alkene-containing Pro dipeptide mimetics.[8−10] In terms of this issue, the efforts of Etzkorn's group have provided a practical route to alkene-containing Pro mimetics,[9] using Still−Wittig [2,3]-sigmatropic[9a,b,11] and Ireland−Claisen [3,3]-sigmatropic[9c,12] rearrangements as key transformations to prepare *cis*-Pro and *trans*-Pro mimetics, respectively. Alternatively, we have investigated using an organocopper-mediated *anti*-S_N2' reaction to synthesize alkene-type Pro mimetics, in which introduction of a "CO_2H" synthon using organocopper reagent into vinyl oxazolidinone derivatives led to the success in the development of a facile synthetic route to (*E*)-alkene-containing Pro dipeptide isosteres, which correspond to the *trans*-Pro dipeptides (Scheme 1).[10] In this synthetic protocol, the organocopper reagents derived from CuCN and (*i*-PrO)Me_2SiCH_2MgCl were utilized for "CO_2H" introduction, and the incorporated (*i*-PrO)Me_2SiCH_2 unit was oxidatively converted to "CO_2H".

SCHEME 1. Regio- and Stereoselective Synthesis of *trans*-(*E*)-Alkene Pro Dipeptide Isosteres, Using Organocopper Reagents



SCHEME 2. Regio- and Stereoselective *anti*-S_N2' Alkylation of γ-Phosphoryloxy-α,β-unsaturated Lactam 1 with Organocopper Reagents



However, attempts to prepare the *cis*-Pro mimetics with this protocol were unsuccessful since the "CO_2H" synthon was exclusively introduced into a preferable reactive conformer accessible to *trans*-(*E*)-alkene mimetics. Generally, only a few practical and efficient synthetic methods are available to synthesize (*Z*)-alkene-type dipeptide isosteres.[11b,13] Recently, we devised an efficient synthetic method for diketopiperazine mimetics, which possess one (*Z*)-alkene moiety per molecule, using organocopper reagents (Scheme 2).[14] These diketopiperazine mimetics[13,15,16] have potential as synthetic precursors for (*Z*)-alkene-type dipeptide isosteres. A careful examination of reaction conditions suitable to synthesize diketopiperazine mimetics indicated that utilizing highly stereo- and regioselective *anti*-S_N2' alkylation of a γ-phosphoryloxy-α,β-unsaturated lactam with organocopper reagents is crucial.[17] This result prompted

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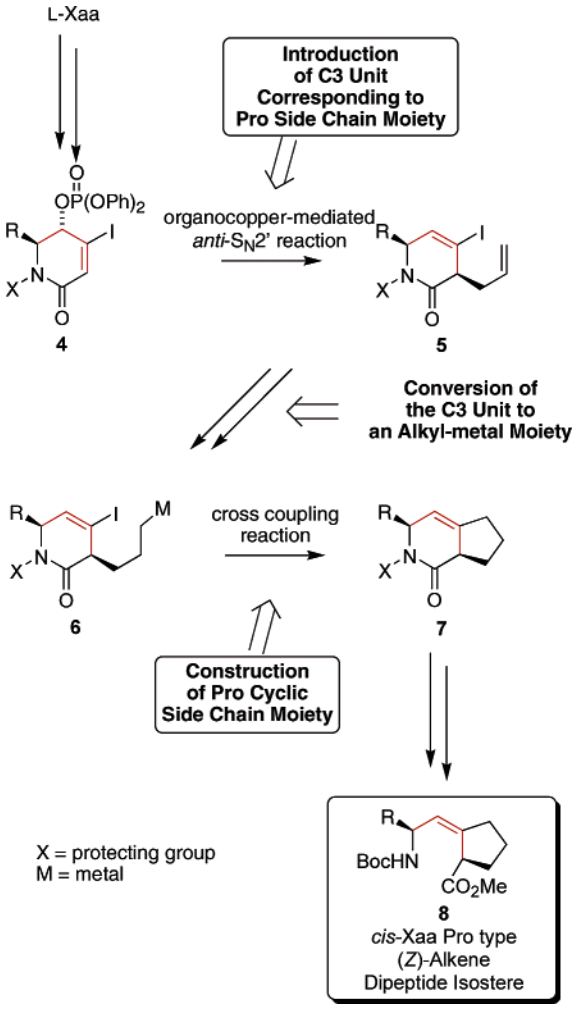
SCHEME 3. Synthetic Strategy for *cis*-Xaa-Pro Type (*Z*)-Alkene Dipeptide Isostere 8



us to explore synthetic protocols using organocopper reagents for (*Z*)-alkene-containing Pro dipeptide mimetics. Herein, we report the stereoselective synthesis of the (*Z*)-alkene mimetic, which corresponds to a *cis*-Pro dipeptide, using an organocopper-mediated *anti*-S_N2' reaction.

Results and Discussion

Scheme 3 depicts the envisioned synthetic outline to prepare (*Z*)-alkene-containing amino acid-proline (Xaa-Pro) dipeptide isosteres. On the basis of our previous synthetic study on diketopiperazine mimetics,[14] we selected β-iodo-γ-phosphoryloxy-α,β-unsaturated lactam **4**, which is derived from an amino acid, as a key synthetic intermediate. The planned transformations are as follows: (1) organocopper-mediated reaction to introduce a C3 unit (**4** to **5**); (2) conversion of the C3 unit to an alkyl−metal moiety (**5** to **6**); (3) an intramolecular cross-coupling reaction between the alkyl−metal and the vinyl iodide to construct a Pro cyclic structure (**6** to **7**); and (4) ring-opening of the resulting bicyclic lactam (**7** to **8**). The synthetic feasibility of this envisioned route was evaluated by synthesizing an Ala-Pro type (*Z*)-alkene isostere.

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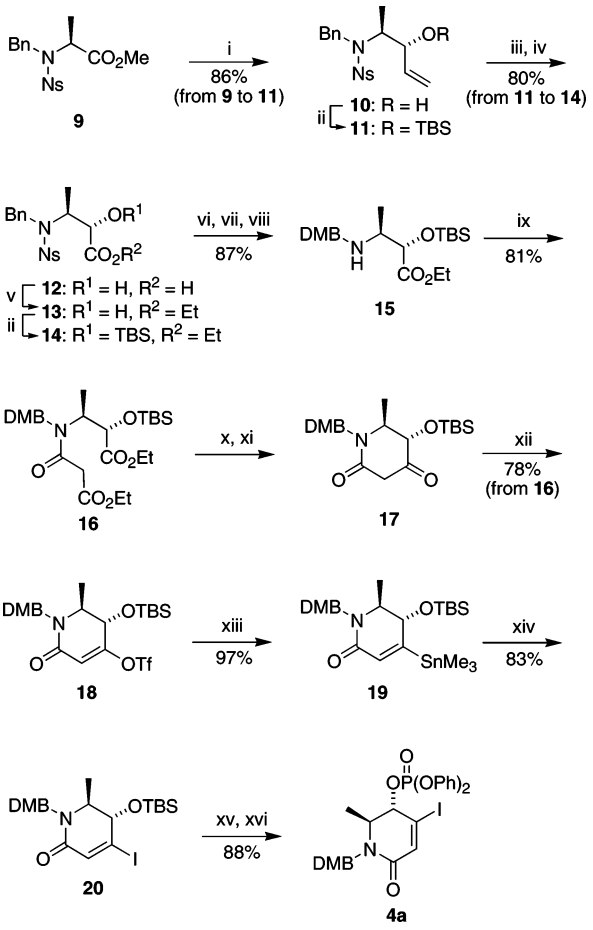
SCHEME 4. Synthesis of β-Iodo-γ-phosphoryloxy-α,β-unsaturated-δ-lactam 4a[a]



[a] Reagents and conditions: (i) DIBAL-H, toluene, CH_2Cl_2, then CH_2=$CHMgCl$, $ZnCl_2$, LiCl, THF; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2; (iii) O_3, EtOAc, then Me_2S; (iv) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH, H_2O; (v) $SOCl_2$, EtOH; (vi) $HSCH_2CO_2H$, $LiOH{\cdot}H_2O$, DMF; (vii) $Pd(OH)_2$, H_2, EtOH; (viii) 2,4-dimethoxybenzaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane; (ix) $EtOCOCH_2COCl$, diisopropylethylamine (DIPEA), CH_2Cl_2; (x) NaOEt, EtOH; (xi) H_2O, MeCN; (xii) Tf_2NPh, Et_3N, CH_2Cl_2; (xiii) $(Me_3Sn)_2$, $PdCl_2[P(o\text{-}Tol)_3]_2$, LiCl, THF; (xiv) I_2, CH_2Cl_2; (xv) TBAF, THF; (xvi) $(PhO)_2P(O)Cl$, pyridine.

Scheme 4 shows the preparation of key intermediate **4a** (R = Me, X = 2,4-dimethoxybenzyl; DMB), which is a prerequisite for the synthesis of the Ala-Pro type isostere. Activation of the γ-hydroxy group by formation of a γ-phosporyloxy compound is critical for the *anti*-S_N2' alkylation reactions[14,17] by organocopper reagents. The alkenyl iodide unit on lactam **4a** provides a scaffold for an intramolecular cross-coupling reaction, which is used to construct the proline cyclic structure.

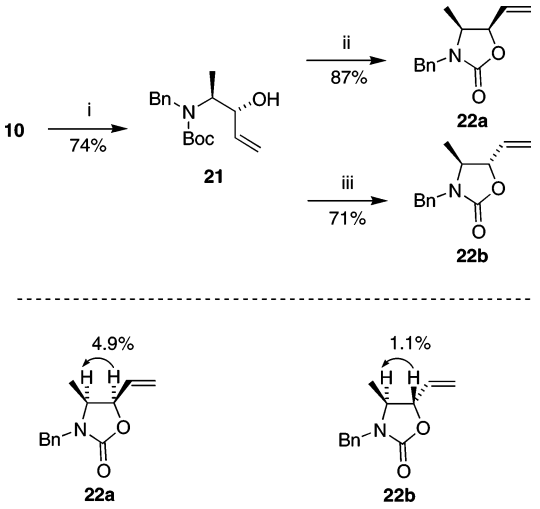
Reduction of *N*-2-nitrobenzensulfonyl-*N*-benzyl-protected L-alanine derivative **9** (2-nitrobenzensulfonyl = Ns) with DIBAL-H in CH_2Cl_2−toluene at −78 °C, and subsequent addition of vinyl Grignard reagent−$ZnCl_2$−LiCl in THF at −78 °C exclusively gave *anti*-1,2-amino alcohol **10**, which was purified by recrystallization from EtOAc−hexane. The resulting amino alcohol **10** was converted to protected allyl alcohol derivative **11** by *O*-*tert*-butyldimethylsilyl protection (*tert*-butyldimethylsilyl = TBS).[18] The Felkin−Anh model can explain the observed *anti*-diastereoselectivity.[19] Ozonolysis of the alkene moiety in compound **11** and subsequent oxidation with a $NaClO_2$-mediated reaction afforded α-hydroxy-β-amino acid derivative **12** where

the *O*-TBS protection on the hydroxy group was removed under acidic conditions in this oxidative treatment. Esterification of resulting carboxlic acid **12** with $SOCl_2$−EtOH yielded ester **13**. Treating **13** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)-2,6-lutidine in CH_2Cl_2 gave *O*-TBS-β-amino acid derivative **14** in 80% yield from **11**. After consecutive removal of the *N*-Ns[20] and *N*-benzyl groups on **14** with mercaptoacetic acid−LiOH·H_2O−DMF and hydrogenolysis with H_2/$Pd(OH)_2$, respectively, reductive alkylation of the resulting amino group with 2,4-dimethoxybenzaldehyde in the presence of $NaBH(OAc)_3$ afforded secondary amine derivative **15**. The secondary amino function of **15** was acylated with ethyl malonyl chloride to give malonylate **16** in 81% yield. Dieckmann condensation of the malonylate **16** with NaOEt−EtOH proceeded smoothly to give the corresponding cyclized tricarbonyl compound, which was then efficiently converted to the β-keto lactam **17** by a sequence of reactions including hydrolysis of the ethyl carboxylate and subsequent decarboxylation in H_2O−CH_3CN. Then, enol-trapping of β-keto lactam **17** was achieved by trifluoromethanesulfonylation with *N*-phenylbis(trifluoromethanesulfonimide) (Tf_2NPh)[21]−Et_3N in CH_2Cl_2 to give alkenyl triflate **18** in 78% yield from **16**. Palladium (0)-catalyzed stannylation of resulting triflate **18** with hexamethylditin afforded alkenyl tin compound **19** in 97% yield.[22] Exposing tin compound **19** to iodine in CH_2Cl_2 converted the alkenyl tin moiety on **19** to corresponding alkenyl iodide **20**, which is amenable to the intramolecular cross-coupling reactions to construct the proline cyclic side chain structure. After deprotection of the γ-*O*-TBS group on lactam **20** with tetrabutylammonium fluoride (TBAF) in THF, the resulting γ-hydroxy moiety was activated by $(PhO)_2P(O)Cl$ in pyridine to form key intermediate **4a** in 88% yield. This activation is suitable for organocopper-mediated *anti*-S_N2' alkylation reactions and allows the acyclic C3 unit corresponding to the proline moiety to be incorporated into the lactam.

To determine the relative configurations of the amino alcohol derivative with use of comparative NOE measurements, alcohol derivative **10** was converted to oxazolidinones **22** (Scheme 5). *N*-Boc amino alcohol **21**, which was derived from amino alcohol **10**, was converted to oxazolidinone **22a** by NaH in THF, while retaining the relative configuration. On the other hand, treatment of **21** under Mitsunobu condition afforded **22b** with inverted stereochemistry.[23] The comparative NOE measurements of oxazolidinones **22a** and **22b** support the *anti*-relative configuration of alcohol **10** (3*R*,4*S*).

To examine the synthetic feasibility of introducing an acyclic C3 unit, which corresponds to the Pro side chain moiety by organocopper-mediated *anti*-S_N2' alkylation of β-iodo-γ-phosphoryloxy-α,β-unsaturated-δ-lactams, **4a** and **4b**[24] were subjected to reactions with several organocopper reagents as shown in Table 1. Here, we planned to transform the incorporated C3 unit into the corresponding C3 alkylborane moiety, which could be used in an intramolecular Suzuki coupling reaction with the alkenyl iodide. The C3 alkylborane unit could be formed by incorporating the allyl group and subsequent hydroboration of the terminal alkene. To introduce the allyl group by organocopper-mediated *anti*-S_N2'-alkylation, γ-phosphate **4a** was subjected to the treatment with an allyl copper reagent. However, the reaction with ClMgCu(CN)allyl·2LiCl gave a complex mixture including α-allyl product **23** and reductive product **24** (Table 1, entry 1). Thus, α-allylation with a stepwise transformation was conducted. Acyclic C3 units such as "$CH_2CH_2CO_2$-Me" or "$CH_2CH_2CH_2OR$" (R = Ac or TBS) were introduced by organocopper-mediated reactions. For alkylation with reagents that possess an ester function, organozinc-derived copper reagents were utilized.[25,26] Reaction of **4a** or **4b** with "lower order" cyanocuprates derived from zinc reagents, $IZnCu(CN)(CH_2)_2CO_2Me$·2LiCl and $IZnCu(CN)(CH_2)_3OAc$·2LiCl, in THF at 0 °C failed to complete the *anti*-S_N2' alkylation reactions due to the insufficient reactivity of these reagents (entries 2 and 4). On the other hand, applying a "higher order" counterpart, $(IZn)_2Cu(CN)[(CH_2)_2CO_2Me]_2$·2LiCl or $(IZn)_2Cu(CN)[(CH_2)_3OAc]_2$·2LiCl,[27] to the phosphates allowed the reactions to

SCHEME 5. Conversion of Allyl Alcohol 10 to Oxazolidinones 22 for NOE Analyses[a]



[a] Reagents and conditions: (i) $HSCH_2CO_2H$, LiOH·H_2O, DMF, then Boc_2O, Et_3N, THF; (ii) NaH, THF; (iii) PPh_3, diethyl azodicarboxylate, toluene, THF.

(18) Amino alcohol **10**, which was gradually decomposed at room temperature, was converted to more stable derivative **11** by *O*-TBS protection.

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(24) Phosphate **4b**, which was easily obtainable by synthetic manipulations similar to those of **4a**, was also used as a substrate in Table 1 to explore the suitable synthetic route to the desired isostere.

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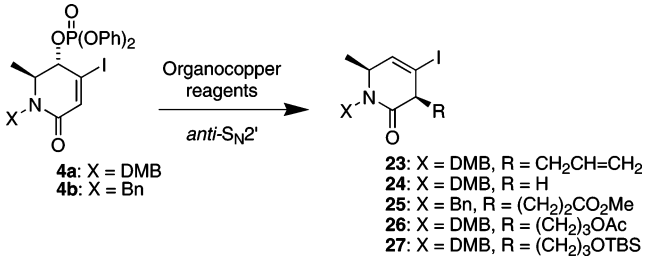
(27) The reactive structure of copper reagents prepared from CuCN and 2 equiv of organometallic reagents (RLi etc.) has been under discussion ($R_2Cu(CN)Li_2$ or R_2CuLi·LiCN). In this paper, the copper reagents derived from CuCN and 1 or 2 equiv of RZnX are referred to as "lower order" or "higher order" cyanocuprate ($RCu(CN)ZnX$ or $R_2Cu(CN)(ZnX)_2$), respectively, as a matter of convenience. For the discussion about the structure of the copper reagents, see: (a) Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031−4032. (b) Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem.*

TABLE 1. α-Alkylation of γ-Phosphoryloxy-α,β-unsaturated Lactam by Organocopper-Mediated *anti*-S_N2' Reactions



entry	substrate	reagent	conditions	products (isolated yield %)
1	**4a**	ClMgCu(CN)allyl·2LiCl	−78 °C/30 min	**23** (9), **24** (12)
2	**4b**	$IZnCu(CN)(CH_2)_2CO_2Me\cdot 2LiCl$[a]	0 °C/2 h	**25** (79)[b]
3	**4b**	$(IZn)_2Cu(CN)[(CH_2)_2CO_2Me]_2\cdot 2LiCl$[a]	0 °C/2 h	**25** (92)
4	**4a**	$IZnCu(CN)(CH_2)_3OAc\cdot 2LiCl$	−78 °C/30 min then 0 °C/30 min	**26** (85)
5	**4a**	$(IZn)_2Cu(CN)[(CH_2)_3OAc]_2\cdot 2LiCl$	−78 °C/30 min then 0 °C/30 min	**26** (96)
6	**4a**	$LiCu(CN)(CH_2)_3OTBS\cdot 2LiCl\cdot LiI$	−78 °C/30 min	**27** (93)

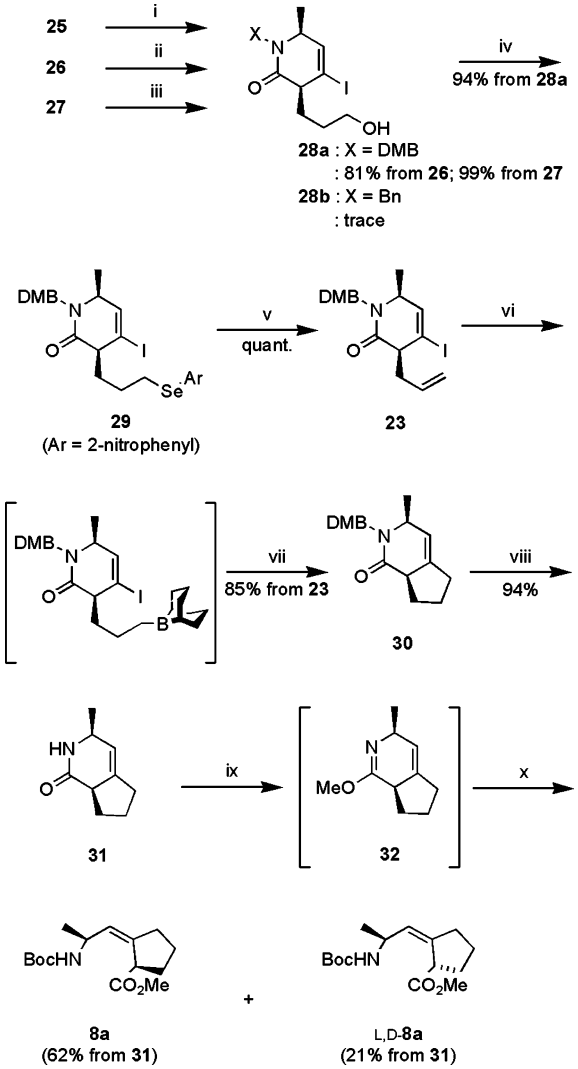
[a] Reagent was added at −78 °C. [b] Substrate **4b** (12%) was recovered.

proceed smoothly and produced the desired *anti*-S_N2' alkylated products in excellent yields (entries 3 and 5). Contrary to the organozinc-derived reagents, an organolithium[28]-derived "lower order" cyanocuprate, $LiCu(CN)(CH_2)_3OTBS\cdot 2LiCl\cdot LiI$, efficiently reacted with **4a** even at −78 °C with a high stereoselectivity to afford α-alkylated product **27** in good yield (entry 6). Organocopper reagents are known to react with β-iodo-α,β-unsaturated carbonyl compounds to give the corresponding β-substituted products.[29] On the other hand, in the case of substrates **4a** and **4b** (entries 2−6), the *anti*-S_N2' reactions preferentially proceeded without accompanying the β-substituted products.

Next, we attempted to convert the incorporated α-alkyl moieties in the resulting *anti*-S_N2' reaction products to alkylborane moieties, which are amenable to an intramolecular Suzuki coupling reaction, in order to construct the proline cyclic side chain unit. To this end, the resulting α-alkylated products were transformed to olefin **23**, which was subjected to 9-borabicyclo[3.3.1]nonane (9-BBN-H)-mediated hydroboration through the sequence of reactions shown in Scheme 6. First, we planned to convert methyl ester **25** to alcohol **28b** by reduction with $NaBH_4$ in MeOH−THF,[30] but the reduction of **25** gave a trace amount of the desired alcohol. Thus, we examined the conversion of other α-alkylated products to the alcohol. Therefore, acetate **26** was subjected to acid-catalyzed alcoholysis mediated by $Ti(Oi\text{-}Pr)_4$ in EtOH to give alcohol **28a** in 81% yield. Furthermore, treatment of *O*-TBS protected product **27** with H_2SiF_6 in H_2O−MeOH−MeCN afforded deprotected product **28a** in excellent yield.

Treatment of alcohol **28a** with 2-nitrophenylselenocyanate in pyridine at room temperature in the presence of tributylphos-

SCHEME 6. Conversion of α-Alkylated Products 26, 27 to *cis*-Ala-Pro Type (*Z*)-Alkene Dipeptide Isostere 8a[a]



[a] Reagents and conditions: (i) $NaBH_4$, MeOH, THF; (ii) $Ti(Oi\text{-}Pr)_4$, EtOH; (iii) H_2SiF_6, H_2O, CH_3CN, MeOH; (iv) 2-nitrophenylselenocyanate, PBu_3, pyridine; (v) H_2O_2, H_2O, THF; (vi) 9-BBN-H, THF; (vii) CsF, $PdCl_2$(dppf), DMF; (viii) H_2O, TFA; (ix) $Me_3O\cdot BF_4$, 2,6-di-*tert*-butylpyridine, CH_2Cl_2; (x) HCl, H_2O, THF, then Boc_2O, Et_3N.

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phine formed alkyl selenide **29** in 94% isolated yield.[31] This air-sensitive selenide **29** was immediately converted to the corresponding selenoxide, which underwent a facile elimination to form olefin **23** in quantitative yield. The resulting alkene **23** was hydroborated with 9-BBN-H in THF at room temperature to afford an alkylborane compound, which is a potential precursor for the intramolecular Suzuki coupling reaction to construct the proline cyclic side chain moiety. A survey of suitable conditions for intramolecular Suzuki coupling reactions[32] on this substrate revealed that treating the alkylborane with CsF in the presence of $PdCl_2$(dppf) (dppf = 1,1′-bis(diphenylphosphino)ferrocene) as a catalyst in THF−DMF at 50 °C formed the desired bicyclic lactam **30** in 85% yield from **23**. Use of K_3PO_4 or NaOH as a base, which is common in Suzuki coupling conditions, was also examined. However, the reaction with NaOH did not afford the desired lactam because the strong basicity formed the corresponding isomerized α,β-unsaturated bicyclic lactam and an α-epimerized product. The K_3PO_4 counterpart formed a complex mixture with little of the desired coupling product. Taken together, the use of CsF[33] was superior to that of K_3PO_4 or NaOH in this reaction. The superiority is probably due to the weak basic character of CsF and the facile formation of the borate complex caused by the high B−F affinity.

Removing the *N*-dimethoxybenzyl group on bicyclic lactam **30** by TFA−H_2O afforded deprotected lactam **31** in 94% isolated yield. X-ray analysis of the recrystallized material indicated that lactam **31** represented a precursor of the L−L type Ala-Pro isostere, which demonstrates that organocopper-mediated introduction of the C3 unit unequivocally proceeds in an *anti*-S_N2' manner (X-ray analysis data are shown in the Supporting Information). Cleavage of the amide bond of **31** was achieved by formation of the lactim ether **32** with $Me_3O{\cdot}BF_4$[34]−2,6-di-*tert*-butylpyridine[35] in CH_2Cl_2 and subsequent HCl-mediated acid hydrolysis[13] in H_2O−THF. The addition of 2,6-di-*tert*-butylpyridine was critical to form the lactim ether smoothly. Without being isolated, the resulting methyl ester was treated with Boc_2O−Et_3N to furnish *cis*-Ala-Pro type (*Z*)-alkene isostere **8a**. The relative configuration of **8a** was established by X-ray analysis of the crystallized product (X-ray analysis data are shown in the Supporting Information). In this sequence of reactions, desired L−L type **8a** was obtained in 61% isolated yield, whereas corresponding epimerized product (L,D-**8a**) was co-generated in 21% yield. The observed epimerization likely occurs during the lactim ether formation step.[36] Although we extensively examined the reaction conditions for the ring-opening (*O*-alkylation reagents, reaction temperatures, and reaction solvents), the conditions have yet to be fully optimized. The stereochemistry of the obtained byproduct L,D-**8a** was tentatively assigned by comparative NMR measurements of **8a** and L,D-**8a**.

In conclusion, we have achieved a regio- and stereoselective synthesis of *cis*-Ala-Pro type (*Z*)-alkene dipeptide isostere. In this synthetic route, a five-membered proline cyclic structure was successfully constructed by incorporating the C3 unit, which corresponds to the proline cyclic side chain moiety onto γ-phosphoryloxy-α,β-unsaturated-δ-lactam with organocopper-mediated *anti*-S_N2' reactions and subsequent cyclization with palladium-catalyzed intramolecular cross-coupling reactions. This synthetic methodology may be applicable to the syntheses of other *cis*-proline type (*Z*)-alkene dipeptide isosteres. In addition to our previous synthetic study of *trans*-proline type (*E*)-alkene dipeptide isostere, our result should provide a useful method to probe the bioactivity−conformation relationships of proline-containing peptides and proteins.

Experimental Section

(2*S*)-2-[Benzyl-(2-nitrobenzenesulfonyl)amino]propionic Acid Methyl Ester (9) from L-Alanine. To methanol (120 mL) at −78 °C was added dropwise thionyl chloride (15.9 mL, 219 mmol), and the mixture was warmed to room temperature with stirring. To the mixture was added L-alanine (15.0 g, 168.4 mmol), and the reaction mixture was refluxed for 2 h. The recooled mixture was concentrated under reduced pressure to give oily residues. To a solution of the residues in 400 mL of CH_2Cl_2 were successively added nosyl chloride (39.2 g, 177 mmol) and DIPEA (64.5 mL, 371 mmol) at 0 °C. After additional stirring at room temperature for 2 h, the reaction mixture was quenched with 1 N HCl and extracted with EtOAc. The extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated in vacuo to give solid materials. To a solution of the materials in DMF (300 mL) at 0 °C were added K_2CO_3 (116 g, 842 mmol) and benzylbromide (21.0 mL, 177 mmol) with additional stirring at room temperature for 12 h. After removal of residual salts by centrifuge separation, 1 N HCl and EtOAc were added to the solution at 0 °C with stirring. The mixture was extracted with EtOAc, and the extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give solid products. Recrystallization of the products from EtOAc−*n*-hexane gave 56.3 g (88.4% yield) of the titled compound **9** as a colorless crystal: mp 84−85 °C; $[\alpha]^{20}_D$ −50.8 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J* = 7.2 Hz, 3H), 3.61 (s, 3H), 4.41 (d, *J* = 16.2 Hz, 1H), 4.79 (d, *J* = 16.2 Hz, 1H), 7.17−7.20 (m, 3H), 7.30 (m, 2H), 7.44 (m, 1H), 7.59 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 147.3, 136.2, 133.7, 133.1, 131.3, 130.9, 128.2, 127.5, 123.8, 56.1, 52.3, 49.5, 16.8. Anal. Calcd for $C_{17}H_{18}N_2O_6S$: C, 53.96; H, 4.79; N, 7.40. Found: C, 53.87; H, 4.72; N, 7.40.

(3*R*,4*S*)-4-[Benzyl-(2-nitrobenzenesulfonyl)amino]pent-1-en-3-ol (10) from 9. To a solution of dried $ZnCl_2$ (2.17 g, 15.9 mmol)−LiCl (672 mg, 15.9 mmol) in THF (30 mL) at −78 °C under argon was added vinylmagnesium chloride in THF (1.55 M, 10.2 mL, 15.9 mmol) with additional stirring for 30 min at 0 °C. To a solution of 2.00 g (5.29 mmol) of **9** in CH_2CH_2 (12 mL) was added dropwise 6.28 mL (6.34 mmol) of 1.01 M DIBAL-H in toluene at −78 °C under argon. After being stirred at −78 °C until disappearance of the starting material (ca 30 min), the solution of vinyl zinc reagent prepared above was added at −78 °C under argon with additional stirring for 2 h at 0 °C. 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 solution, water, saturated $NaHCO_3$, 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

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(36) Exposure of **8a** to the *N*-Boc protection reaction conditions induced no epimerization at the 4-position on the isostere.

EtOAc−*n*-hexane gave 1.76 g (88% yield) of the titled compound **10** as a colorless crystal: mp 90−92 °C; $[\alpha]^{24}_D$ −19.7 (*c* 1.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 7.2 Hz, 3H), 4.13 (m, 1H), 4.30 (m, 1H), 4.61 (d, J = 16.0 Hz, 1H), 4.73 (d, J = 16.0 Hz, 1H), 5.13 (d, J = 10.4 Hz, 1H), 5.18 (d, J = 17.2 Hz, 1H), 5.85 (ddd, J = 17.2, 10.4, 5.6 Hz, 1H), 7.19 (m, 3H), 7.31 (m, 2H), 7.42 (m, 1H), 7.57 (m, 2H), 7.67 (d, J = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 137.3 134.4, 133.1, 131.4, 131.3, 128.6, 128.5, 128.2, 127.5, 124.0, 116.2, 75.9, 58.1, 48.7, 12.4. Anal. Calcd for $C_{18}H_{20}N_2O_5S$: C, 57.43; H, 5.36; N, 7.44. Found: C, 57.19; H, 5.22; N, 7.36.

(3*R*,4*S*)-4-[Benzyl-(2-nitrobenzenesulfonyl)amino]-3-(*tert*-butyldimethylsilanyloxy)pent-1-en (11) from 10. To a solution of 11.0 g (29.2 mmol) of **10** in CH_2Cl_2 (50 mL) were added 2,6-lutidine (8.85 mL, 76.0 mmol) and TBSOTf (8.72 mL, 38.0 mmol) at 0 °C under argon. After being stirred at room temperature for 12 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$ solution at 0 °C. The mixture was extracted with EtOAc, and the extract was washed with saturated citric acid, brine, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give an oily product. Flash chromatographic purification of the crude material over silica gel with EtOAc−*n*-hexane (1:9) gave 14.3 g (100% yield) of the title compound **11** as a colorless oil: $[\alpha]^{24}_D$ 81.6 (*c* 0.686, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 1.29 (d, J = 4.8 Hz, 3H), 4.63 (m, 1H), 4.15 (m, 1H), 4.60 (d, J = 16.0 Hz, 1H), 4.66 (d, J = 16.0 Hz, 1H), 5.05 (d, J = 17.6 Hz, 1H), 5.06 (d, J = 10.4 Hz, 1H), 5.75 (ddd, J = 17.6, 10.4, 7.0 Hz, 1H), 7.14 (m, 3H), 7.23 (m, 2H), 7.34 (m, 1H), 7.55 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 136.9 134.8, 132.7, 131.2, 131.1, 128.4, 128.1, 127.3, 123.7, 116.7, 77.4, 59.4, 48.6, 25.9, 18.1, 14.4, −3.8, −4.7; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{35}N_2O_5SSi$ (MH^+) 491.2036, found 491.2029.

(2*S*,3*S*)-3-[Benzyl-(2-nitrobenzenesulfonyl)amino]-2-hydroxybutyric Acid Ethyl Ester (13) from 11. Ozone gas was bubbled through a stirring solution of **13** (14.5 g, 29.6 mmol) in EtOAc (200 mL) at −78 °C for 80 min. After removal of residual ozone by bubbling of N_2 gas for 10 min, Me_2S (2.18 mL, 296 mmol) was added to the solution with stirring at −78 °C for 15 min. The mixture was additionally stirred at 0 °C for 10 min, dried over $MgSO_4$, and concentrated in vacuo to give the crude aldehyde, which was subjected to the following reactions without further purification. To a stirring solution of the above crude material in *t*-BuOH (200 mL) and 2-methyl-2-butene (30 mL) were added an aqueous solution (45 mL) consisting of $NaH_2PO_4 \cdot 2H_2O$ (6.93 g, 44.4 mmol) and $NaClO_2$ (80%, 6.70 g, 59.3 mmol) at 0 °C. After being stirred at room temperature for 15 h, the reaction mixture was concentrated under reduced pressure to give residues. To the residues in EtOAc was added 1 N HCl (10 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude carboxylic acid **12**. After addition of $SOCl_2$ (2.49 mL, 34.1 mmol) to EtOH at −78 °C followed by warming the solution to room temperature, the crude **12** was added to the solution. The solution mixture was refluxed for 1 h and concentrated under reduced pressure. After flash chromatography over silica gel with EtOAc−*n*-hexane (1:4), the title compound **13** (87.9% yield) as a colorless oil was obtained: $[\alpha]^{24}_D$ 37.9 (*c* 0.870, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 2,99 (br, 1H), 4.28 (q, J = 7.2 Hz, 2H), 4.41 (d, J = 2.8 Hz, 1H), 4.62 (m, 1H), 4.73 (d, J = 16.0 Hz, 1H), 4.82 (d, J = 16.0 Hz, 1H), 7.15 (m, 3H), 7.28 (m, 2H), 7.36 (m, 1H), 7.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 137.2, 134.3 133.0, 131.3, 131.2, 128.1, 127.2, 123.9, 74.5, 62.6, 55.8, 48.8, 14.1, 13.3; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{23}N_2O_7S$ (MH^+) 423.1226, found 423.1224.

(2*S*,3*S*)-3-[Benzyl-(2-nitrobenzenesulfonyl)amino]-2-(*tert*-butyldimethylsilanyloxy)butyric Acid Ethyl Ester (14) from 13. To a solution of **13** (7.50 g, 17.8 mmol) in CH_2Cl_2 (50 mL) were added 2,6-lutidine (3.31 mL, 28.4 mmol) and TBSOTf (6.52 mL, 28.4 mmol) at 0 °C under argon. After being stirred at room temperature for 12 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$ solution at 0 °C. The mixture was extracted with EtOAc, and the extract was washed with saturated citric acid, brine, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give solid materials. Recrystallization of the solid from EtOAc−*n*-hexane gave 8.29 g (87.1% yield) of the title compound **14** as a white crystal: mp 127−128 °C; $[\alpha]^{24}_D$ −112 (*c* 0.994, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.07 (s, 3H), 0.92 (s, 9H), 1.29 (d, J = 6.4 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 4.15 (q, J = 7.0 Hz, 2H), 4.32 (d, J = 4.8 Hz, 1H), 4.49 (m, 1H), 4.70 (s, 2H), 7.14 (m, 3H), 7.23 (m, 2H), 7.36 (m, 1H), 7.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 147.3, 136.8, 134.5 132.9, 131.5, 131.2, 128.2, 128.2, 127.3, 123.8, 75.8, 61.2, 56.9, 48.9, 25.8, 18.2, 14.5, 14.2, −4.9, −5.0. Anal. Calcd for $C_{26}H_{40}N_2O_7SSi$: C, 55.95; H, 6.76; N, 5.22. Found: C, 55.77; H, 6.72; N, 5.17.

(2*S*,3*S*)-2-(*tert*-Butyldimethylsilanyloxy)-3-(2,4-dimethoxybenzylamino)butyric Acid Ethyl Ester (15) from 14. To a solution of **14** (6.64 g, 12.4 mmol) in DMF (90 mL) were added $LiOH \cdot 2H_2O$ (5.19 g, 123 mmol) and mercaptoacetic acid (4.30 mL, 61.8 mmol) at 0 °C with stirring. The reaction mixture was stirred for 4 h followed by quenching with addition of H_2O. The mixture was extracted with EtOAc, and the extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily crude. After removal of the residual thiol reagent from the crude with silica pad filtration, the crude was used for the following reactions. To a solution of the crude in EtOH (100 mL) was added a drop of AcOH and 20% palladium hydroxide on carbon (2.00 g), and the suspension was stirred for 2 h under H_2 at room temperature. The mixture was filtrated through Celite pad and the filtrate was concentrated under reduced pressure to give an oily material. To a solution of the material in 1,2-dichloroethane (400 mL) were added 2,4-dimethoxybenzylaldehyde (2.00 g, 12.0 mmol) and $NaBH(OAc)_3$ (2.70 g, 12.0 mmol) at room temperature. The reaction mixture was stirred for 10 h, quenched with saturated $NaHCO_3$, and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated in vacuo to give oily residues. Purification of the residues with silica gel chromatography gave 4.43 g (87.0% yield) of the title compound **15** as a colorless oil: $[\alpha]^{24}_D$ −4.25 (*c* 0.638, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 1.06 (d, J = 6.4 Hz, 3H), 1.28 (t, J = 7.6 Hz, 3H), 1.99 (br, 1H), 3.02 (m, 1H), 3.73 (s, 2H), 3.80 (s, 6H), 4.18 (m, 2H), 4.31 (d, J = 4.0 Hz, 1H), 6.44 (m, 2H), 7.18 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 159.7, 158.3, 129.8, 121.1, 103.6, 98.4, 74.3, 60.6, 55.9, 55.4, 55.2, 45.7, 25.8, 18.3, 15.8, 14.3, −4.8, −5.2; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{38}NO_5Si$ (MH^+) 412.2519, found 412.2515.

(2*S*,3*S*)-2-(*tert*-Butyldimethylsilanyloxy)-3-[(2,4-dimethoxybenzyl)ethoxycarbonylacetylamino]butyric Acid Ethyl Ester (16) from 15. To a solution of **15** (545 mg, 1.32 mmol) in CH_2Cl_2 (15 mL) were added ethyl malonyl chloride (217 μL, 1.66 mmol) and DIPEA (300 μL, 1.72 mmol) at 0 °C under argon. After being stirred at room temperature for 10 h, the reaction mixture was quenched by addition of 1 N HCl at 0 °C. The mixture was extracted with EtOAc, and the extract was washed with 1 N HCl, brine, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the residues. Chromatograhy of the oil over silica gel EtOAc−*n*-hexane (1:4) gave 561 mg (80.1% yield) of the title compound **16** as a colorless oil: $[\alpha]^{24}_D$ −10.5 (*c* 0.300, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.95 (s, 9H), 1.07 (d, J = 7.2 Hz, 3H), 1.23−1.33 (m, 6H), 3.33 (d, J = 15.2 Hz, 1H), 3.41 (d, J = 15.2 Hz, 1H), 3.80 (s, 6), 4.11−4.27 (m, 4H), 4.31 (d, J = 18 Hz, 1H), 4.64 (d, J = 18 Hz, 1H), 4.65 (m, 1H), 6.45 (m, 2H), 7.02 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 167.6, 167.5, 160.1, 157.3, 127.3, 117.8, 103.6, 98.4, 73.7, 61.2, 60.9, 55.4, 55.1, 41.8, 25.7, 25.7, 18.1, 14.3,

14.2, 14.1, −5.0, −5.2; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{44}NO_8Si$ (MH^+) 526.2836, found 526.2844.

(5*S*,6*S*)-5-(*tert*-Butyldimethylsilanyloxy)-1-(2,4-dimethoxybenzyl)-6-methyl-4-trifluoromethanesulfonyloxy-5,6-dihydro-1*H*-pyridin-2-one (18) from 16. To a solution of **16** (560 mg, 1.07 mmol) in EtOH (2 mL) was added 6 mL (1.28 mmol) of freshly prepared NaOEt in EtOH (0.213 M) at 0 °C under argon, and the mixture was stirred for 30 min. After additional stirring at room temperature for 2 h, the reaction mixture was quenched with 1 N HCl at 0 °C. The mixture was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give an oil material, which was used for following reactions without further purification. A mixture of the oil in 150 μL of H_2O and 30 mL of CH_3CN was refluxed for 2 h and concentrated under reduced pressure to give solid crude materials. To a solution of the crude materials in CH_2Cl_2 (10 mL) were added *N*-phenylbis(trifluoromethanesulfonimide) (571 mg, 1.60 mmol) and Et_3N (443 μL, 3.20 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 h. The reaction mixture was quenched by the addition of 0.1 N HCl and extracted with Et_2O. The mixture was washed with 0.1 N HCl, brine, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give crude materials. Chromatographic purification of the crude materials over silica gel with EtOAc−*n*-hexane (1:9) gave the title compound **18** (448 mg, 78.0% yield) as a white crystal: mp 136−138 °C; $[\alpha]^{24}_D$ −103 (*c* 0.640, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H), 0.06 (s, 3H), 0.75 (s, 9H), 1.20 (d, J = 6.8 Hz, 3H), 3.54 (q, J = 6.8 Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 4.04 (s, 1H), 4.11 (d, J = 15.0 Hz, 1H), 5.10 (d, J = 15.0 Hz, 1H), 6.13 (s, 1H), 6.40−6.43 (m, 2H), 7.22 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 160.1, 158.2, 156.4, 130.4, 129.1, 116.5, 115.6, 104.4, 98.2, 70.1, 57.9, 55.2, 41.1, 25.3, 17.7, 16.5, −5.2, −5.3. Anal. Calcd for $C_{22}H_{32}F_3NO_7SSi$: C, 48.97; H, 5.98; N, 2.60. Found: C, 48.67; H, 5.78; N, 2.62.

(5*S*,6*S*)-5-(*tert*-Butyldimethylsilanyloxy)-1-(2,4-dimethoxybenzyl)-6-methyl-4-(trimethylstannanyl)-5,6-dihydro-1*H*-pyridin-2-one (19) from 18. To a suspension of dried LiCl (141 mg, 3.32 mmol) and $PdCl_2[P(o\text{-}Tol)_3]_2$ (65.3 mg, 0.0830 mmol) in THF (20 mL) was added a solution of **18** (448 mg, 0.830 mmol) in THF (5 mL) at 0 °C under argon, and the mixture was stirred at 50 °C for 20 min. The reaction mixture was quenched and extracted with saturated $NaHCO_3$ at 0 °C and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to leave solid residues. After chromatographic purification of the residues over silica gel with EtOAc−*n*-hexane (1:9), the title compound **19** (450 mg, 97.8% yield) was obtained as a white crystal: mp 143−145 °C; $[\alpha]^{24}_D$ −95.2 (*c* 0.039, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.16 (s, 3H), 0.24 (s, 3H), 0.75 (s, 9H), 1.07 (d, J = 6.8 Hz, 3H), 3.50 (m, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 4.03 (s, 1H), 4.24 (d, J = 14.8 Hz, 1H), 4.94 (d, J = 14.8 Hz, 1H), 6.27 (s, 1H), 6.42 (m, 2H), 7.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 160.0, 158.3, 154.2, 135.7, 130.8, 117.8, 104.4, 98.1, 70.8, 57.5, 55.3, 55.2, 41.4, 25.6, 17.6, 16.7, −4.2, −4.9, −9.5. Anal. Calcd for $C_{24}H_{41}NO_4SiSn$: C, 52.00; H, 7.45; N, 2.53. Found: C, 51.70; H, 7.44; N, 2.51.

(5*S*,6*S*)-5-(*tert*-Butyldimethylsilanyloxy)-1-(2,4-dimethoxybenzyl)-4-iodo-6-methyl-5,6-dihydro-1*H*-pyridin-2-one (20) from 19. To a solution of **19** (198 mg, 0.357 mmol) in CH_2Cl_2 (6 mL) was added iodine (136 mg, 0.536 mmol) at 0 °C under argon, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with a few drops of 28% NH_4OH and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give solid residues. Chromatography of the residues over silica gel with EtOAc−*n*-hexane (1:9) gave the title compound **21** (154 mg, 83.4%) as an amorphous powder: $[\alpha]^{24}_D$ −115 (*c* 0.686, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.11 (s, 3H), 0.13 (s, 3H), 0.77 (s, 9H), 1.18 (d, J = 6.8 Hz, 3H), 3.44 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.07 (s, 1H), 4.11 (d, J = 15.0 Hz, 1H), 5.01 (d, J = 15.0 Hz, 1H), 6.41 (m, 2H), 6.75 (s, 1H), 7.24 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 159.8, 158.3, 136.5, 130.8, 117.1, 111.1, 104.5, 98.3, 77.9, 57.9, 55.4, 41.1, 25.6, 18.0 16.9, −4.4, −4.6; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{33}INO_4Si$ (MH^+) 518.1224, found 518.1225.

(5*S*,6*S*)1-(2,4-Dimethoxybenzyl)-5-diphenylphosphoryloxy-4-iodo-6-methyl-5,6-dihydro-1*H*-pyridin-2-one (4a) from 20. To a solution of **20** (64.0 mg, 0.115 mmol) in THF (0.5 mL) was added 1 M TBAF in THF (121 μL, 0.121 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was quenched with 1 N HCl followed by extraction with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give crude materials, which were used in the following reaction without further purification. To a solution of the above materials in pyridine (2 mL) was added diphenylphosphoryl chloride (47.9 mg, 0.231 mmol) at 0 °C under argon with additional stirring at room temperature for 12 h. The reaction mixture was quenched with 1 N HCl and extracted with EtOAc. The extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily residues. After chromatographic purification of the residues over silica gel with EtOAc−*n*-hexane (1:9), the title compound **4a** (64.8 mg, 88.3% yield) was obtained as a colorless oil: $[\alpha]^{24}_D$ −204 (*c* 0.333, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.8 Hz, 3H), 3.66 (s, 3H), 3.75 (s, 3H), 3.83 (qd, J = 6.8, 1.6 Hz, 1H), 4.25 (d, J = 14.8 Hz, 1H), 4.74 (d, J = 14.8 Hz, 1H), 4.98 (dd, J = 8.4, 1.6 Hz, 1H), 6.31 (dd, J = 8.4, 2.4 Hz, 1H), 6.35 (d, J = 2.4 Hz, 1H), 6.93 (s, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.00 (m, 1H), 7.14−7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.3, 158.3, 150.2 (d, J = 7.1 Hz), 150.0 (d, J = 7.5 Hz), 130.9, 129.7 (d, J = 5.7 Hz), 125.4 (d, J = 7.4 Hz), 125.4, 120.1 (d, J = 5.0 Hz), 119.9 (d, J = 4.9 Hz), 116.5, 104.2, 102.7, 100.5, 98.2, 82.3 (d, J = 5.0 Hz), 60.3, 56.4 (d, J = 2.5 Hz), 55.3, 55.2, 42.2, 21.1, 17.0, 14.2; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{28}INO_7P$ (MH^+) 636.0648, found 636.0656.

(5*S*,6*S*)1-Benzyl-5-diphenylphosphoryloxy-4-iodo-6-methyl-5,6-dihydro-1*H*-pyridin-2-one (4b). By use of synthetic manipulations similar to those described for the preparation of **4a** from **14**, **4b** was obtained from **14** as a colorless oil: $[\alpha]^{20}_D$ −75.1 (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 6.8 Hz, 3H), 3.64 (qd, J = 6.8, 1.2 Hz, 1H), 4.15 (d, J = 15.2 Hz, 1H), 4.79 (d, J = 15.2 Hz, 1H), 4.98 (dd, J = 8.4, 1.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 7.15−7.35 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 150.1 (d, J = 7.4 Hz), 149.7 (d, J = 6.6 Hz), 139.3, 136.0, 129.6, 128.4, 127.9, 127.5, 125.4 (d, J = 7.4 Hz), 120.0 (d, J = 5.0 Hz), 119.8 (d, J = 4.2 Hz), 103.2 (d, J = 6.6 Hz), 81.9 (d, J = 5.0 Hz), 56.5 (d, J = 3.3 Hz), 48.0, 16.9; HRMS (ESI-TOF) *m*/*z* calcd for $C_{25}H_{24}INO_5P$ (MH^+) 576.0437, found 576.0439.

(3*R*,4*S*)-4-[Benzyl(*tert*-butoxycarbonyl)amino]pent-1-en-3-ol (21) from 10. To a solution of **10** (3.48 g, 9.25 mmol) in DMF (20 mL) were added mercaptacetic acid (1.29 mL, 18.5 mmol) and $LiOH\cdot H_2O$ (1.55 g, 37.0 mmol) at 0 °C, with additional stirring at room temperature for 14 h. The reaction mixture was quenched with saturated $NaHCO_3$ at 0 °C, followed by extraction with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily crude. To a solution of the crude in THF (30 mL) were added Boc_2O (2.42 g, 11.1 mmol) and Et_3N (1.55 mL, 11.1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 14 h, quenched with saturated citric acid, and extracted with EtOAc. The extract was washed with saturated citric acid, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to give residues. The residues were purified by column chromatography over silica gel with EtOAc−*n*-hexane (1:9) to give the title compound **21** (1.98 g, 73.6% yield) as a colorless oil: $[\alpha]^{24}_D$ 4.22 (*c* 0.946, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 7.2 Hz, 3H), 1.43 (br, 9H), 3.46 (d, J = 7.2 Hz, 1H), 3.50 (d, J = 7.2 Hz, 1H), 3.61 (br, 1H), 4.20−4.53 (m, 4H), 5.10 (d, J = 10.0 Hz, 1H), 5.20 (dt, J = 17.0, 1.6 Hz, 1H), 5.76 (ddd, J = 17.0, 10.0, 5.8 Hz, 1H), 7.20−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 139.0, 138.5,

128.3, 126.9, 115.5, 80.4, 75.9, 58.8, 51.3, 28.3, 11.7; HRMS (FAB) *m*/*z* calcd for $C_{17}H_{26}NO_3$ (MH^+) 292.1913, found 292.1914.

(4*S*,5*R*)-3-Benzyl-4-methyl-5-vinyloxazolidin-2-one (22a) from 21. To a solution of **21** (200 mg, 0.686 mmol) in THF (10 mL) was added 55% NaH (110 mg, 2.75 mmol) at −78 °C under argon. The reaction mixture was stirred at room temperature for 5 h, quenched with 1 N HCl at 0 °C, and extracted with EtOAc. The extract was washed with brine to give oily materials. After purification of the materials by chromatography over silica gel with EtOAc−*n*-hexane (1:9), the title compound **22a** (130 mg, 87.2% yield) was obtained as a colorless oil: $[\alpha]^{24}_D$ −5.90 (*c* 0.870, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, J = 6.8 Hz, 3H), 3.73 (td, J = 6.8, 6.8 Hz, 1H), 4.04 (d, J = 15.2 Hz, 1H), 4.83 (d, J = 15.2 Hz, 1H), 4.88 (t, J = 6.8 Hz, 1H), 5.37 (d, J = 10.6 Hz, 1H), 5.44 (d, J = 17.4 Hz, 1H), 5.83 (ddd, J = 17.4, 10.6, 6.8 Hz, 1H), 7.28−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 135.6, 130.8, 128.4, 127.6, 127.5, 119.6, 77.7, 52.9, 45.4, 13.5; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{16}NO_2$ (MH^+) 218.1181, found 218.1177.

(4*S*,5*S*)-3-Benzyl-4-methyl-5-vinyloxazolidin-2-one (22b) from 21. To a solution of 117 mg (0.446 mmol) of Ph_3P in THF (1 mL) were successively added a solution of **21** in THF (1 mL) and 40% azodicarboxylic acid diethyl ester solution in toluene (203 μL, 0.446 mmol) at 0 °C under argon. After being stirred at room temperature for 1 h, the reaction solvent was evaporated under reduced pressure to give oily residues. Purification of the residues by chromatography over silica gel with EtOAc−*n*-hexane (1:9) gave the title compound **22b** (53.0 mg, 71.1% yield) as a colorless oil: $[\alpha]^{24}_D$ −50.6 (*c* 0.209, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.1 Hz, 3H), 3.32 (qd, J = 7.3, 6.1 Hz, 1H), 4.12 (d, J = 15.2 Hz, 1H), 4.38 (t, 7.3 Hz, 1H), 4.76 (d, J = 15.2 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 5.40 (d, J = 17.0 Hz, 1H), 5.79 (ddd, J = 17.0, 10.4, 7.0 Hz, 1H), 7.26−7.36 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 135.8, 133.5, 128.7, 128.0, 127.8, 119.5, 81.8, 55.8, 45.8, 16.9; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{16}NO_2$ (MH^+) 218.1181, found 218.1186.

(3*S*,6*S*)-3-Allyl-1-(2,4-dimethoxybenzyl)-4-iodo-6-methyl-3,6-dihydro-1*H*-pyridin-2-one (23) from 4. To a solution of anhydrous LiCl (13.3 mg, 0.315 mmol) and CuCN (14.1 mg, 0.157 mmol) in THF (200 μL) was added 78.4 μL (0.157 mmol) of 2.0 M allylmagnesium chloride in THF at −78 °C under argon with stirring for 10 min. The mixture was allowed to warm to 0 °C and then stirred for 5 min at this temperature. To recooled solution of organocopper reagent to −78 °C was added a solution of **4a** (50 mg, 0.0786 mmol) in THF (1 mL). After being stirred at −78 °C for 30 min, the reaction mixture was quenched at 0 °C by addition of saturated NH_4Cl and 28% NH_4OH solution with additional stirring at room temperature. The mixture was extracted with Et_2O, and the extract was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give a crude mixture of **23** and **24**. Column chromatography purification of the crude materials over silica gel with EtOAc−*n*-hexane (1:9) gave **23** (4.0 mg, 9.5% yield) and **24** (3.7 mg, 12.2% yield) as colorless oily materials. **23**: $[\alpha]^{24}_D$ −63.1 (*c* 0.224, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.4 Hz, 3H), 2.62 (m, 1H), 2.83 (m, 1H), 3.31 (m, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.84 (m, 1H), 4.19 (d, J = 15.0 Hz, 1H), 5.08 (d, J = 15.0 Hz, 1H), 5.12 (d, J = 11.0 Hz, 1H), 5.20 (d, J = 16.8 Hz, 1H), 5.70 (m, 1H), 6.31 (d, J = 4.4 Hz, 1H), 6.44 (m, 2H), 7.19 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 159.9, 158.1, 137.7, 133.1, 130.3, 118.1, 117.1, 104.1, 98.1, 94.8, 55.2, 55.2, 54.8, 51.7, 40.5, 36.3, 21.1; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{23}INO_3$ (MH^+) 428.0723, found 428.0727. **24**: $[\alpha]^{20}_D$ −98.3 (*c* 0.204, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.8 Hz, 3H), 3.43 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 3.89 (m, 1H), 4.15 (d, J = 15.2 Hz, 1H), 5.15 (d, J = 15.2 Hz, 1H), 6.28 (m, 1H), 6.44 (m, 2H), 7.14 (d, J = 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 160.3, 158.5, 137.1, 130.4, 117.1, 104.3, 98.4, 86.5, 55.4, 54.9, 44.4, 40.6, 20.3; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{19}INO_3$ (MH^+) 388.0410, found 388.0405.

(3*S*,6*S*)-3-(1-Benzyl-4-iodo-6-methyl-2-oxo-1,2,3,6-tetrahydropyridin-3-yl)propionic Acid Methyl Ester (25) from 4b. To a suspension of activated zinc dust[25] (341 mg, 5.21 mmol) in THF (2 mL) was added 3-iodopropionic acid methyl ester (781 mg, 3.65 mmol) in THF (3 mL) at room temperature with additional stirring for 2 h. After further addition of THF (5 mL) to a solution of the zinc reagent, 2 mL of the reagent solution in THF was added to a solution of anhydrous Lick (58.8 mg, 1.39 mmol) and CuCN (62.3 mg, 0.695 mmol) in THF (4 mL) at −78 °C under argon, and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 10 min. To recooled solution of organocopper reagent to −78 °C was added **4b** (200 mg, 0.348 mmol) in THF (4 mL) at this temperature. The reaction mixture was stirred at 0 °C for 2 h, quenched with saturated NH_4Cl and 28% NH_4OH solution at 0 °C, followed by additional stirring at this temperature. The mixture was extracted with Et_2O, and the extract was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give residues. Column chromatography purification of the residues over silica gel with EtOAc−*n*-hexane (1:4) gave the title compound **25** (113 mg, 78.4% yield) as a colorless oil: $[\alpha]^{20}_D$ −85.5 (*c* 1.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, J = 6.4 Hz, 3H), 2.02 (m, 1H), 2.43 (m, 2H), 2.52 (m, 1H), 3.28 (m, 1H), 3.69 (s, 3H), 3.80 (m, 1H), 3.98 (d, J = 14.8 Hz, 1H), 5.38 (d, J = 14.8 Hz, 1H), 6.32 (d, J = 4.4 Hz, 1H), 7.21−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 166.7, 137.8, 136.3, 128.6, 127.9, 127.5, 94.9, 86.5, 54.5, 51.7, 51.4, 46.6, 20.7; HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{21}INNaO_3$ (Man^+) 436.0386, found 436.0381.

"Higher-Order" Cyanocuprate Complex (Table 1, entry 3) (25) from 4b. To a solution of anhydrous LiCl (58.8 mg, 1.39 mmol) and CuCN (62.3 mg, 0.695 mmol) in THF (4 mL) was added 4 mL of the zinc reagent prepared in the above Experimental Section at −78 °C under argon, and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 10 min. A procedure identical with those described above gave the tile compound **25** (132 mg, 91.6% yield).

Acetic Acid {3-[(3*S*,6*S*)-1-(2,4-Dimethoxybenzyl)-4-iodo-6-methyl-2-oxo-1,2,3,6-tetrahydropyridin-3-yl]propyl} Ester (26) from 4a. To a suspension of activated zinc dust[25] (154 mg, 2.36 mmol) in THF (1 mL) was added acetic acid 3-iodopropyl ester (337 mg, 1.57 mmol) in THF (2 mL) at room temperature with stirring for 2 h. After further addition of THF (2 mL) to the solution of zinc reagent, 0.5 mL of the reagent solution in THF was added to a solution of anhydrous LiCl (13.3 mg, 0.315 mmol) and CuCN (14.1 mg, 0.157 mmol) in THF (0.2 mL) at −78 °C under argon, and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 5 min. To recooled solution of organocopper reagent to −78 °C was added **4a** (50 mg, 0.0786 mmol) in THF (1 mL) at this temperature. The reaction mixture was stirred at −78 °C for 30 min and at 0 °C for 30 min, quenched with saturated NH_4Cl and 28% NH_4OH solution at this temperature, followed by additional stirring at this temperature. The mixture was extracted with Et_2O, and the extract was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily materials. Column chromatographic purification of the materials over silica gel with EtOAc−*n*-hexane (1:4) gave the title compound **26** (32.4 mg, 84.6% yield) as a colorless oil: $[\alpha]^{24}_D$ −91.1 (*c* 1.580, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 5.6 Hz, 3H), 1.61 (m, 1H), 1.72 (m, 1H), 1.82 (m, 1H), 2.07 (s, 3H), 2.14 (m, 1H), 3.25 (m, 1H), 3.79 (d, J = 1.2 Mz, 3H), 3.80 (d, J = 1.2 Mz, 3H), 3.88 (m, 1H), 4.12 (m, 1H), 4.17 (d, J = 14.8 Hz, 1H), 5.12 (d, J = 14.8 Hz, 1H), 6.32 (d, J = 4.4 Hz, 1H), 6.43−6.46 (m, 2H), 7.18 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 166.8, 160.2, 158.4, 138.0, 130.6, 117.1, 104.4, 98.3, 95.5, 64.0, 55.4, 55.4, 54.8, 51.4, 40.6, 29.2, 25.0, 21.1, 21.0; HRMS (ESI-TOF) *m*/*z* calcd for $C_{20}H_{27}INO_5$ (MH^+) 488.0934, found 488.0950.

"Higher-Order" Cyanocuprate Complex (Table 1, entry 5) (26) from 4a. To a suspension of activated zinc dust[25] (1.02 g, 15.6 mmol) in THF (6 mL) was added acetic acid 3-iodopropyl ester (2.22 g, 10.4 mmol) in THF (5 mL) at room temperature with stirring for 2 h. After further addition of THF (10 mL) to the solution of zinc reagent, 14 mL of the reagent solution in THF was added to a solution of anhydrous LiCl (310 mg, 3.46 mmol) and CuCN (293 mg, 6.92 mmol) in THF (5 mL) at −78 °C under argon, and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 10 min. To recooled solution of organocopper reagent to −78 °C was added **4** (1.10 g, 1.73 mmol) in THF (5 mL) at this temperature. The reaction mixture was stirred at −78 °C for 30 min and at 0 °C for 30 min, quenched with saturated NH_4Cl and 28% NH_4OH solution at this temperature, followed by additional stirring at this temperature. The mixture was extracted with Et_2O, and the extract was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily materials. Column chromatography purification of the materials over silica gel with EtOAc−*n*-hexane (1:4) gave the title compound **26** (806 mg, 95.5% yield) as a colorless oil.

(3*S*,6*S*)-3-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-1-(2,4-dimethoxybenzyl)-4-iodo-6-methyl-3,6-dihydro-1*H*-pyridin-2-one (27) from 4a. To a solution of *tert*-butyl-(3-iodopropoxy)-dimethylsilane (142 mg, 0.472 mmol) in Et_2O (1.5 mL) was added 621 μL (0.968 mmol) of 1.56 M *tert*-butyllithium in pentane at −78 °C under argon, with additional stirring for 30 min. In another flask CuCN (42.3 mg, 0.472 mmol) and anhydrous LiCl (40.0 mg, 0.944 mmol) were suspended in THF (3.5 mL) under argon. To the above solution of lithium reagent was added the recooled suspension of CuCN·2LiCl in THF to −78 °C at this temperature through cannular, followed by stirring at −78 °C for 45 min. To a cool solution of **4a** (150 mg, 0.235 mmol) in THF (10 mL) at −78 °C was added the organocopper reagent solution prepared above at −78 °C through cannular. After being stirred at this temperature for 30 min and at 0 °C for 15 min, the reaction mixture was quenched with saturated NH_4Cl and 28% NH_4OH solution at 0 °C followed by additional stirring at this temperature. The mixture was extracted with Et_2O, and the extract was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily materials. Column chromatography purification of the materials over silica gel with EtOAc−*n*-hexane (1:9) gave the title compound **27** (123 mg, 93.1% yield) as a colorless oil: $[\alpha]^{24}_D$ −59.0 (*c* 0.130, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.90 (s, 9H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.45 (m, 1H), 1.62 (m, 1H), 1.81 (m, 1H), 2.08 (m, 1H), 3.24 (m, 1H), 3.65 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 3.85 (m, 1H), 4.18 (d, *J* = 15.2 Hz, 1H), 5.10 (d, *J* = 15.2 Hz, 1H), 6.29 (d, *J* = 4.4 Hz, 1H), 6.43−6.46 (m, 2H), 7.18 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 160.1, 158.3, 137.5, 130.5, 117.2, 104.2, 98.2, 96.0, 62.7, 55.3, 54.8, 51.7, 40.5, 29.1, 29.0, 26.0, 20.8, 18.3, −5.2; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{38}INO_4Si$ (MH^+) 560.1693, found 560.1696.

(3*S*,6*S*)-1-(2,4-Dimethoxybenzyl)-3-(3-hydroxypropyl)-4-iodo-6-methyl-3,6-dihydro-1*H*-pyridin-2-one (28a) from 26. To a solution of **26** (50 mg, 0.103 mmol) in EtOH (1 mL) was added titanium isopropoxide (60.1 μL, 0.205 mmol) at room temperature, and the mixture was refluxed 1 h. The reaction mixture was diluted with EtOAc at 0 °C, quenched with saturated $NaHCO_3$, and stirred at this temperature. After extraction of the mixture with EtOAc, the extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give residues. After column chromatographic purification of the residues over silica gel with EtOAc−*n*-hexane (1:1), the title compound **28a** (36.9 mg, 80.8% yield) was obtained as a colorless oil: $[\alpha]^{24}_D$ −25.1 (*c* 0.084, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, *J* = 7.6 Hz, 3H), 1.62 (m, 1H), 1.71 (m, 1H), 1.83 (m, 1H), 2.12 (m, 1H), 3.31 (m, 1H), 3.71 (t, *J* = 6.4 Hz, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 3.87 (m, 1H), 4.17 (d, *J* = 14.8 Hz, 1H), 5.11 (d, *J* = 14.8 Hz, 1H), 6.30 (d, *J* = 5.2 Hz, 1H), 6.43−6.46 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 160.1, 158.2, 137.5, 130.4, 116.8, 104.3, 98.2, 95.7, 62.1, 55.3, 55.3, 54.7, 51.3, 40.6, 29.6, 28.9, 20.8; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{25}INO_4$ (MH^+) 446.0828, found 446.0821.

28a from 27. To a solution of **27** (452 mg, 0.808 mmol) in CH_3CN (15 mL) was added 300 μL of 40% hexafluorosilicic acid at room temperature with additional stirring at this temperature for 40 min. The reaction mixture was quenched with saturated $NaHCO_3$ and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily materials. The materials were purified by column chromatography over silica gel with EtOAc−*n*-hexane (1:1) to give the title compound **28a** (355 mg, 98.6% yield).

(3*S*,6*S*)-1-(2,4-Dimethoxybenzyl)-4-iodo-6-methyl-3-[3-(2-nitrophenylselanyl)propyl]-3,6-dihydro-1*H*-pyridin-2-one (29) from 28a. To a solution of 2-nitorphenylselenocyanate (202 mg, 0.862 mmol) in pyridine were successively added **28a** (192 mg, 0.432 mmol) and tributylphosphine (214 μL, 0.862 mmol) at room temperature under argon. After being stirred at this temperature for 1.5 h, the reaction mixture was quenched by addition of 1 N HCl at 0 °C and extracted with EtOAc. The extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily products. Column chromatographic purification of the residues over silica gel with EtOAc−*n*-hexane (1:4) gave **29** (416 mg, 83.1% yield) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.4 Hz, 3H), 1.77 (m, 1H), 1.85 (m, 1H), 1.98 (m, 1H), 2.24 (m, 1H), 2.93 (m, 1H), 3.02 (m, 1H), 3.27 (m, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.86 (m, 1H), 4.16 (d, *J* = 15.0 Hz, 1H), 5.10 (d, *J* = 15.0 Hz, 1H), 6.30 (d, *J* = 4.4 Hz, 1H), 6.44 (m, 2H), 7.16 (d, *J* = 8.8 Hz, 1H), 7.32 (m, 1H), 7.55 (m, 2H), 8.29 (d, *J* = 8.0 Hz, 1H). Compound **29** was used for the next reaction without further analytical identification due to the air sensitivity.

23 from 29. To a solution of **29** (279 mg, 0.443 mmol) in THF (8 mL) was added 240 μL of 30% H_2O_2 at room temperature with additional stirring for 3 h. The reaction mixture was quenched with 1 N HCl at 0 °C and extracted with EtOAc. The extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated in vacuo to give residues. After purification of the residues by column chromatography over silica gel with EtOAc−*n*-hexane (1:9), the title compound **23** (189 mg, 99.9% yield) was obtained as a colorless oil.

(6*S*,3a*R*)-5-(2,4-Dimethoxybenzyl)-6-methyl-2,3,5,6,3a-pentahydro-5-azainden-4-one (30) from 23. The oily substrate **23** (280 mg, 0.655 mmol) was dried in vacuo with stirring at room temperature for 5 h. To the crude oil was added 4.91 mL (1.97 mmol) of 0.4 M 9-BBN-H in THF at room temperature under argon with additional stirring at this temperature for 7 h. To a suspension of dried CsF (299 mg, 1.97 mmol) and $PdCl_2$(dppf) (16.1 mg, 0.0197 mmol) in DMF (19.2 mL) was added the above alkyl borane solution at room temperature under argon. After being stirred at 50 °C for 3.5 h, the reaction mixture was quenched with addition of saturated $NaHCO_3$ at 0 °C and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily materials. Column chromatographic purification of the materials over silica gel with EtOAc−*n*-hexane (15:85) gave the title compound **30** (170 mg, 86.1% yield) as a colorless oil: $[\alpha]^{24}_D$ −62.5 (*c* 0.204, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, *J* = 6.8 Hz, 3H), 1.75 (m, 3H), 2.31 (m, 1H), 2.37 (m, 2H), 3.00 (m, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 4.04 (m, 1H), 4.35 (d, *J* = 15.4 Hz, 1H), 5.08 (d, *J* = 15.4 Hz, 1H), 5.30 (m, 1H), 6.40−6.44 (m, 2H), 7.06 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 159.4, 157.6, 140.1, 129.3, 118.3, 118.0, 103.9, 97.9, 55.1, 55.1, 52.8, 44.9, 40.2, 29.6, 29.1, 22.9, 21.2; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{23}NO_3$ (MH^+) 302.1756, found 302.1753.

(6*S*,3a*R*)-6-Methyl-2,3,5,6,3a-pentahydro-5-azainden-4-one (31) from 30. TFA (2.85 mL) and H_2O (150 μL) were added to **30** (90 mg, 0.299 mmol) at 0 °C with additional stirring at room temperature for 12 h. After residual TFA was blown away by N_2

gas, the reaction mixture was quenched by saturated $NaHCO_3$ at 0 °C and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give solid materials. After purification of the materials by column chromatography over silica gel with EtOAc−*n*-hexane (1:1), the title compound **31** (42.6 mg, 94.4% yield) was obtained as a colorless crystal: mp 138−140 °C; $[\alpha]^{24}_D$ 2.29 (*c* 0.250, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, J = 6.8 Hz, 3H), 1.70 (m, 1H), 1.78 (m, 2H), 2.21 (m, 1H), 2.38 (m, 2H), 2.95 (m, 1H), 4.17 (m, 1H), 5.41 (m, 1H), 5.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 142.3, 118.5, 48.9, 44.6, 30.0, 28.0, 23.8, 22.1. Anal. Calcd for $C_{18}H_{20}N_2O_5S$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.17; H, 8.83; N, 9.08.

(1*R*)-2-[(2*S*)-2-*tert*-Butoxycarbonylaminopropylidene]cyclopentanecarboxylic Acid Methyl Ester (Boc-L-Ala-Ψ[(*Z*)-CH=C]-L-Pro-OMe) (8a) from 31. To a solution of **31** (10 mg, 0.0661 mmol) and $Me_3O{\cdot}BF_4$ (29.4 mg, 0.199 mmol) in CH_2Cl_2 (500 μL) was added 2,6-*tert*-butylpyridine (17.6 μL, 0.0798 mmol) at room temperature under argon with additional stirring for 30 min at this temperature. To the recooled reaction mixture to 0 °C were successively added THF (0.5 mL), 0.6 N HCl (120 μL), and MeOH (200 μL). The homogeneous mixture was stirred at this temperature for 2 h and at room temperature for 5 h. To the solution were added Boc_2O (36.0 mg, 0.165 mmol) in THF (0.5 mL) and Et_3N (41.6 μL, 0.30 mmol) at 0 °C, and the reaction was continued at room temperature for 5 h. The reaction was quenched with addition of saturated $NaHCO_3$ and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give a crude mixture of **8a** and its epimer **L,D-8a**. Purification of the mixture by column chromatography over silica gel with EtOAc−*n*-hexane (1:9) gave the title compounds **8a** (11.6 mg, 61.9% yield) and its epimer **L,D-8a** (3.9 mg, 20.8% yield) as colorless oily materials. Keeping the oily material **8a** at −20 °C gave the crystal, which was brought to X-ray analysis. **8a**: mp 40−42 °C; $[\alpha]^{20}_D$ −74.9 (*c* 0.588, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.4 Hz, 3H), 1.43 (s, 9H), 1.59 (m, 1H), 1.84 (m, 1H), 1.99 (m, 2H), 2.28 (m, 1H), 2.43 (m, 1H), 3.50 (m, 1H), 3.69 (s, 3H), 4.26 (m, 1H), 4.46 (br, 1H), 5.33 (dd, J = 8.8, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 154.9, 143.3, 125.6, 77.2, 52.1, 46.2, 45.6, 34.0, 31.6, 28.4, 24.6, 22.2; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{25}NNaO_4$ (MNa^+) 306.1681, found 306.1671. **L,D-8a**: $[\alpha]^{20}_D$ 94.2 (*c* 0.234, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 6.0 Hz, 3 H), 1.43 (s, 9 H), 1.59 (m, 1 H), 1.84 (m, 1 H), 1.99 (m, 2 H), 2.28 (m, 1 H), 2.38 (m, 1 H), 3.67 (s, 3 H), 4.28−4.44 (m, 2 H), 5.23 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.2, 55.5, 51.9, 45.5, 33.7, 31.1, 28.4, 24.8, 21.1; HRMS (FAB) *m*/*z* calcd for $C_{15}H_{25}NO_4$ (MH^+) 284.1862, found 284.1852.

Acknowledgment. We thank Mr. K. Miyamoto, The University of Tokushima, for his support in X-ray analysis. This research was supported in part by the 21st Century COE Program "Knowledge Information Infrastructure for Genome Science", a Grand-in-Aid for Scientific Research (KAKENHI). Y.S. and A.N. are grateful for Research Fellowships from the JSPS for Young Scientists.

Supporting Information Available: ORTEP diagrams for **31** and **8a** and their CIF files; copies of ^{1}H and ^{13}C NMR spectra of **4a**, **4b**, **9**, **8a**, **L,D-8a**, **10**, **11**, **13**, **14**, **15**, **16**, **18**, **19**, **20**, **21**, **22a**, **22b**, **23**, **24**, **25**, **26**, **27**, **28**, **29**, **30**, **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0606002