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Synthesis of (*Z*)-alkene-containing *cis*-proline dipeptide mimetics using samarium(II) diiodide (SmI_2)-mediated reductive alkylation reaction

Yoshikazu Sasaki,[a,b] Akira Shigenaga,[b] Nobutaka Fujii[a] and Akira Otaka[b,*]

[a]*Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan*
[b]*Graduate School of Pharmaceutical Sciences, The University of Tokushima, Tokushima 770-8505, Japan*

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Abstract—The amide bond between an amino acid and proline can take the *trans*- or *cis*-conformation. The conformation influences both the structure and function of peptides and proteins. Therefore, constrained mimetic, which corresponds to Pro-dipeptides whose amide bond is replaced with an (*E*)- or (*Z*)-alkene, is a useful bioprobe for elucidating the structure–function relationship of peptides and proteins. Herein, we report the synthesis of *cis*-(*Z*)-alkene-containing Pro-dipeptide mimetics via a samarium(II) diiodide (SmI_2)-mediated reductive alkylation reaction.

1. Introduction

Dipeptide mimetics represent attractive compounds for developing peptide-based drugs or bioprobes to analyze peptide and protein functions. Amino acyl prolines (Xaa–Pro), which are important dipeptide units, should be mimicked by a structural scaffold because the Xaa–Pro bonds can take either the *trans*- or *cis*-conformation (**1** or **2** in Fig. 1), and the conformation should influence the functions of a Pro-containing protein.[1] Therefore, constrained Pro-dipeptide mimetics, which correspond to *trans*- or *cis*-imides, have received increasing attention in the fields of organic, medicinal, and peptide/protein chemistry.[2] Much effort has focused on preparing constrained analogs, including alkene dipeptide mimetics that possess a replacement for the *trans*- or *cis*-imide with an (*E*)- or a (*Z*)-alkene, respectively (**3** or **4** in Fig. 1).[3–5]

In addition to other research groups, we have been engaged in preparing (*E*)- or (*Z*)-Xaa–Pro alkene mimetics.[4] Etzkorn et al. have reported the stereoselective syntheses of (*E*)- and (*Z*)-Pro mimetics using Still–Wittig [2,3]-sigmatropic and Ireland–Claisen [3,3]-sigmatropic rearrangements, respectively, as key transformations.[5] Alternatively, we have applied organocopper-mediated *anti*-S_N2' reactions to the stereoselective synthesis of *trans*-mimetics.[4a] Our synthesis of the trans derivative uses the *anti*-S_N2' reaction of a vinyl oxazolidinone derivative.

On the other hand, we envisioned that the construction of the five-membered ring corresponding to Pro moiety on an

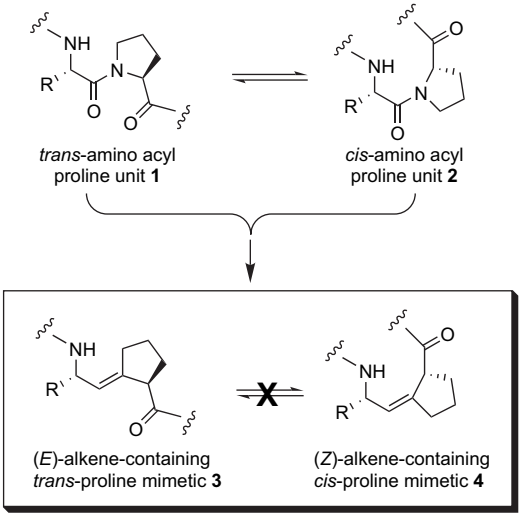

Figure 1. Amino acyl proline bonds can take a *trans*- or *cis*-conformation and the corresponding alkene-containing mimetics.

Keywords: Samarium diiodide; Reductive alkylation reaction; Dipeptide mimetic; Proline.
Abbreviations: Ns, 2-nitrobenzenesulfonyl; Bn, benzyl; TBS, *tert*-butyldimethylsilyl; DIBAL-H, diisobutylaluminumhydride; Tf_2NPh, *N*-phenylbis(trifluoromethanesulfonimide); TBAF, tetrabutylammonium fluoride; DMAP, 4-dimethylaminopyridine; TsCl, *p*-toluenesulfonylchloride; *o*-Tol, *o*-tolyl; TBSCl, *tert*-butyldimethylsilylchloride; HMPA, hexamethylphosphoramide; DMPU, *N,N′*-dimethylpropyleneurea; THP, tetrahydropyran.
* Corresponding author. Tel.: +81 88 633 7283; fax: +81 88 633 9505; e-mail: aotaka@ph.tokushima-u.ac.jp

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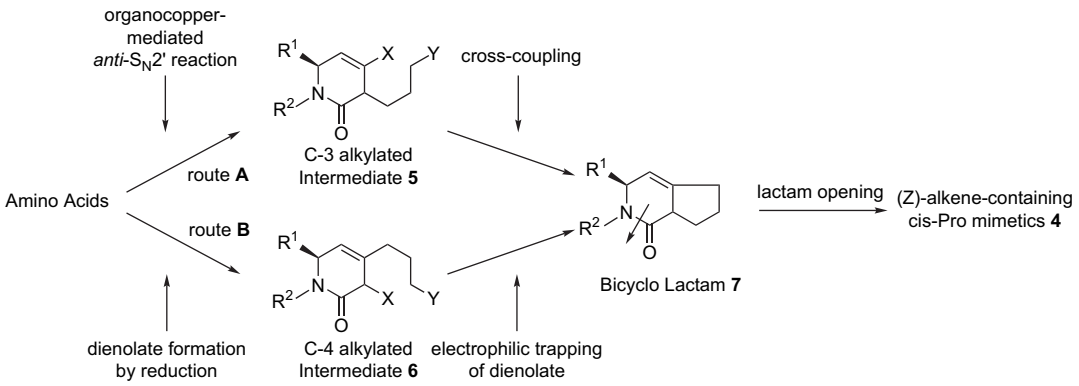


Scheme 1. Rational synthetic routes to (*Z*)-alkene-containing *cis*-Pro mimetic **4**.

unsaturated lactam as a (*Z*)-alkene precursor was a rational way for the preparation of the (*Z*)-alkene-containing Pro mimetics as shown in Scheme 1. This five-membered ring formation involves the use of C-3 alkylated intermediate **5** (route **A**) or C-4 alkylated intermediate **6** (route **B**). In the route **A** synthesis, an organocopper-mediated *anti*-S_N2' reaction yields the requisite intermediate **5** (X=I, Y=B(alkyl)$_2$), which then can be subjected to an intramolecular Suzuki coupling reaction to give bicyclo lactam **7** as a crucial precursor of the (*Z*)-Pro mimetic.[4b] In route **B**, intramolecular alkylation of a dienolate relevant to the intermediate **6** (X=metal, Y=halide or carbonyl) is likely to afford bicyclo lactam **7**. In terms of forming dienolates followed by α-substitution, we recently reported that reduction of γ-activated α,β-unsaturated enoates in a successive single electron transfer (SET) manner affords the corresponding dienolate, which then reacts with an appropriate electrophile at the α-position.[6] This reaction sequence has been successfully applied to the synthesis of (*E*)-alkene dipeptide mimetics, including fluoroalkene mimetics where organocopper[6a,b] or SmI_2[6c,d] is the reducing agent of choice. On the basis of these findings, we realized that route **B** synthesis would be possible using a reaction sequence that consists of reduction and subsequent α-alkylation of the resulting dienolate.

In this paper, we examined the feasibility of reductive alkylation with SmI_2[7,8] in the presence of alkyl halides to prepare (*Z*)-alkene-containing Pro mimetics, which correspond to the *cis*-Xaa–Pro conformation.

2. Results and discussion

As shown in Figure 2, we selected γ-acetoxy-β-substituted-α,β-unsaturated-δ-lactams (**8** and **9**) as requisite synthetic intermediates in the route **B** cyclization. The γ-acetoxy-α,β-unsaturated-δ-lactam moiety could be reduced by the action of SmI_2 to give the corresponding Sm-dienolate, which intramolecularly reacted with an alkyl halide or aldehyde unit in a one-pot manner.

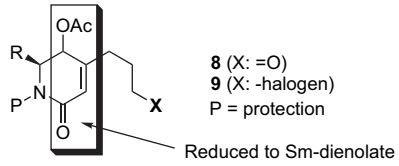
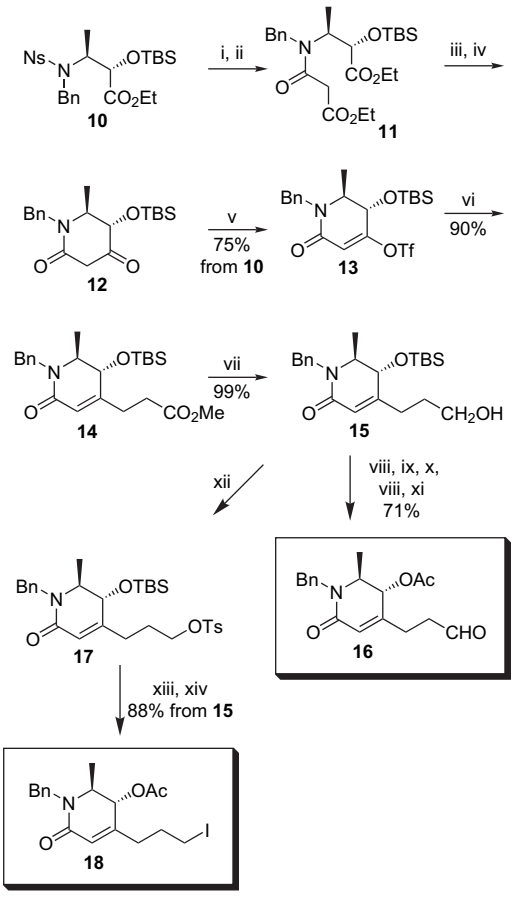


Figure 2. Requisite synthetic intermediates in route **B**.

Scheme 2 shows the synthetic route to the key intermediates. Starting from β-amino acid derivative **10**,[4b] a well-established sequence of reactions was applied to prepare α,β-unsaturated lactam **13**. A similar reaction sequence was also



Scheme 2. Synthetic route to key intermediates **16** and **18**. Reagents: (i) $HSCH_2CO_2H$, $LiOH\cdot H_2O$, DMF; (ii) $EtOCOCH_2COCl$, diisopropylethylamine (DIPEA), CH_2Cl_2; (iii) NaOEt, EtOH; (iv) H_2O, CH_3CN, reflux; (v) Tf_2NPh, Et_3N, CH_2Cl_2; (vi) $IZn(CH_2)_2CO_2Me$, $Pd[P(o\text{-}Tol)_3]_2Cl_2$; (vii) $NaBH_4$, MeOH, THF; (viii) TBAF, THF; (ix) TBSCl, imidazole, DMF; (x) Ac_2O, pyridine, DMAP, CH_2Cl_2; (xi) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2; (xii) TsCl, pyridine, CH_2Cl_2; (xiii) H_2SiF_6, MeOH, H_2O, CH_3CN, then Ac_2O, pyridine, DMAP, $CHCl_3$; (xiv) NaI, acetone.

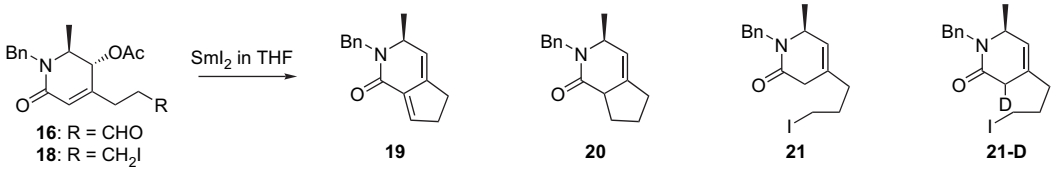
utilized to synthesize the corresponding *N*-dimethoxybenzyl derivative in the route **A** cyclization.[4b] The alkenyl triflate moiety in **13** was subjected to a palladium(0)-catalyzed cross-coupling reaction with a C3 unit. An organozinc reagent derived from methyl iodopropionate was utilized as the C3 unit. Among the examined Pd catalysts, $Pd[P(o\text{-}Tol)_3]_2Cl_2$ (20 mol %) afforded the best result as it yielded cross-coupling product **14** in 90% isolated yield. The ester function of the resulting coupling product **14** was reduced to give primary alcohol derivative **15**.[9] Selective *O*-TBS protection of the primary alcohol unit was achieved by the re-protection of TBAF-treated sample of **15** with TBSCl–imidazole in DMF to afford a secondary alcohol derivative, which was then subjected to O-acetylation followed by successive reactions, which consisted of *O*-TBS deprotection and Swern oxidation of the resulting primary alcohol to give potential precursor **16** for the route **B** cyclization. Alternatively, compound **15** also led to *O*-Ts derivative **17**. After converting the *O*-TBS to the *O*-Ac function, iodo derivative **18**, which is another key intermediate, was obtained by treating **17** with NaI in acetone. Having the precursors for the route **B** cyclization, we examined the bicyclo lactam formation by SmI_2.

The reaction of γ-acetoxy- or γ,γ-difluoro-α,β-enoates with SmI_2 in THF in the presence of an aldehyde as an electrophile proceeds efficiently to yield α-aldol compounds.[6c,d] On the basis of these findings, we speculated that treating **16** with SmI_2 in THF should give bicyclo lactams. To easily evaluate the reaction, the crude products were converted to dehydrated product **19**. However, the attempted cyclization proceeded with a low efficiency and yielded **19** in 9% isolated yield (Table 1, entry 1). Next, we investigated the synthetic utility of compound **18**, which possesses an alkyl halide moiety that serves the electrophilic part in SmI_2-mediated cyclization reactions. The reaction of **18** with SmI_2 (3 equiv) in THF at 0 °C for 30 min gave reductive alkylation product **20** and reduction product **21** in 35% and 22% yields, respectively. ^1H NMR analysis indicated that the alkylation reaction probably proceeds in a diastereoselective manner. The addition of HMPA or DMPU into the reaction mixture after 15 min treatment with SmI_2 was expected to enhance the nucleophilicity of the resulting dienolate, which would improve the cyclization yield. Although the chemical yield improved (43%), the reaction remained at an unsatisfactory level (Table 1, entries 3 and 4). In these attempted reactions, we were curious about the formation of reduction product **21** in the absence of a proton source such as an alcohol. In the case of SmI_2-mediated reduction of γ-activated-α,β-enoates, the presence of an alcohol as a proton source is crucial for a clean conversion.[6c] Because one possible origin of the proton in the reduction appears to be derived from the quenching procedure of the reaction, we attempted to quench the reaction with CD_3CO_2D (Table 1, entry 2). However, deuterated reduction product **21-D** was not observed.

These observations indicate that the hydrogen atom is likely incorporated at the α-position from THF in a radical mechanism (Fig. 3).[10–12] Compared to α,β-enoates, α,β-enamides (or unsaturated lactams) are less electrophilic due to the presence of the amide function. Successive SETs are involved in the formation of the anionic Sm-dienolate (e.g., **24**) from the enoates or enamides. Radical intermediates (**22** or **23**) produced through the first SET step are less electrophilic than the starting material. Therefore, the first SET step proceeds more rapidly than the second step. In conjunction with these considerations, we speculated that the SmI_2-mediated reduction of unsaturated lactam **18** would give a mixture that contains dienolates **24** and radicals **22** or **23** as reaction intermediates, whereas the enoates were susceptible to the successive SETs to form the dienolate intermediate. In the reduction of **18** with SmI_2 in THF, formed dienolate **24** and the radical intermediate **23** were likely to be involved in the reaction with the intramolecular electrophilic part and the hydrogen atom abstraction from THF, respectively. Therefore, we attempted to investigate the reaction conditions without the formation of **21** through the abstraction of hydrogen atom from THF.

The emphasis of our first attempt was to enhance the reduction potential of the Sm(II) reagent when the starting material should be reduced to the corresponding dienolate without accumulating radical intermediates. However, the reaction using $SmBr_2$ in THF,[13] which is known to have a superior reduction potential to SmI_2 in THF, did not afford

Table 1. Cyclization utilizing reductive-aldol or -alkylation reaction by SmI_2 in THF



Entry	Substrate	Reagents[a] in THF	Conditions	Products[f] (isolated yield %)
1	**16**	SmI_2[b]	rt, 1 h	**19** (9)
2	**18**	SmI_2[c]	0 °C, 30 min	**20** (35), **21** (22), **21-D** (0)
3	**18**	SmI_2, then HMPA[d] (12 equiv)	0 °C, 15 min[e]	**20** (43), **21** (42)
4	**18**	SmI_2, then DMPU[d] (12 equiv)	0 °C, 15 min[e]	**20** (43), **21** (39)

[a] Three equivalents of SmI_2 were used.
[b] Subsequent treatment with methanesulfonyl chloride (1.2 equiv) and Et_3N (5 equiv) in CH_2Cl_2.
[c] The reaction was quenched by the addition of CD_3CO_2D.
[d] After 15 min reaction with SmI_2 at 0 °C, HMPA or DMPU was added.
[e] After addition of HMPA or DMPU, the reaction mixture was stirred for 15 min at 0 °C and subsequently stirred for 18 h at room temperature.
[f] Compound **20** was obtained as a single diastereomer.

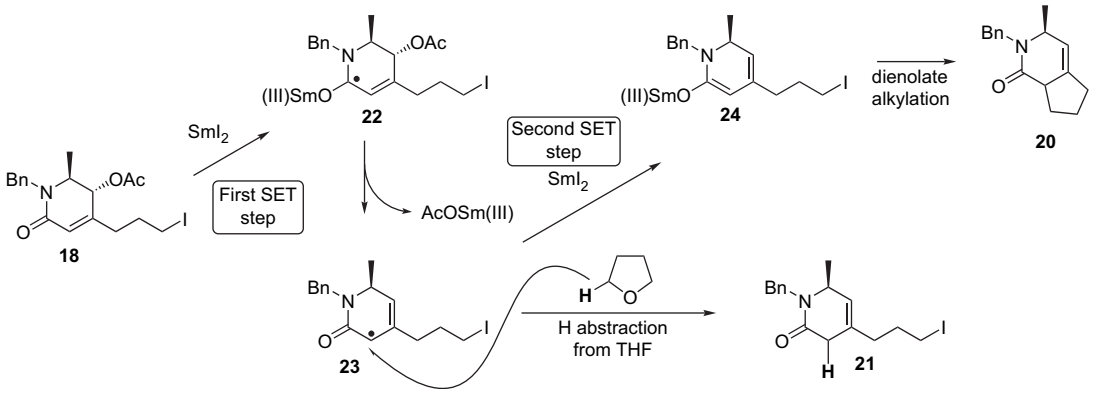


Figure 3. Plausible mechanism of the reaction with SmI_2 in THF.

satisfactory results (Table 2, entry 1). Furthermore, dehalogenation was observed in the reduction using SmI_2–HMPA in THF.[14,15] Replacing THF as the reaction solvent with THP[11] or CH_3CN[12] has been reported to effectively suppress the radical-mediated side reaction involved in the SmI_2-mediated reduction. Unfortunately, using THP as the reaction solvent was unsatisfactory (Table 2, entry 2). Reduction with SmI_2 in CH_3CN did not yield reduced products, probably due to its low reduction potential (Table 2, entry 4). Additionally, the instability of SmI_2 in CH_3CN might be partly responsible for the result. DMPU as an additive to SmI_2 in the CH_3CN system is known to enhance both the stability and reduction potential of the reagent.[16] After surveying suitable reaction conditions, we found that the reaction of **18** with SmI_2–DMPU in CH_3CN at −18 °C for 3 min yielded the desired cyclized product **20** as a single diastereomer in 70% isolated yield without reduction product **21** (Table 2, entry 8). In this system, a long reaction time or an elevated temperature induced the isomerization of **20** to thermodynamically more stable α,β-enamide **25**.

The obtained cyclized product has a 3,6-trans relationship. This diastereoselectivity may be explained based on previous DFT calculations on the plausible oxa-π-allyllithium complex involved in the intermolecular alkylation of Li-dienolate with alkyl halides.[17] In this system, two oxa-π-allyllithium complexes **26** and **27** are possible where complex **27** is more stable than complex **26** (Fig. 4). The interaction between the cation (Li) and halide (alkyl halide) in the more stable complex **27** allows the alkyl halide to be located at the face opposite to the methyl group, which leads to the formation of the 3,6-trans product. Although other factors in the reaction cannot be excluded, this type of oxa-π-allylmetal complex may be the case for the Sm-dienolates and the more stable complex is probably the main contributor in the alkylation of the enolate.

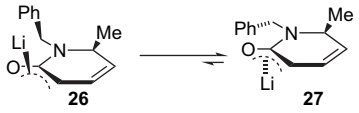
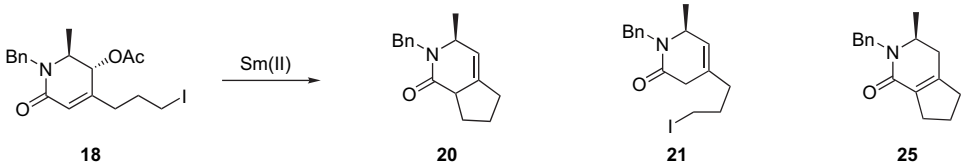


Figure 4. Plausible oxa-π-allyllithium complexes and their relative stability calculated by DFT.

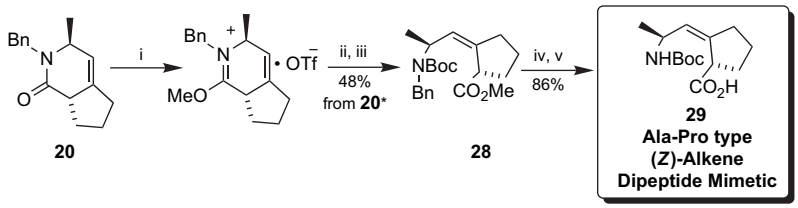
Conversion of lactam **20** to the corresponding Ala–Pro type (*Z*)-alkene dipeptide mimetic **29** was achieved by the reaction sequence shown in Scheme 3.[18] The reaction of **20** with MeOTf in dichloroethane effected the formation of the lactim ether. Without isolating the lactim ether, the obtained crude reaction mixture was subjected to hydrolysis in the presence of trifluoromethanesulfonic acid followed by *N*-Boc protection of the resulting secondary amino function to afford *N*-Boc-*N*-Bn-methyl ester **28** in 48% yield with

Table 2. Examination of reductive cyclization of **18** with Sm(II)



Entry	Reagent(s)	Conditions	Products[a] (isolated yield %)
1	$SmBr_2$ (3 equiv), THF	0 °C, 30 min	**20** (23), **21** (44)
2	SmI_2 (3 equiv), THP	0 °C, 30 min	**20** (10)
3	SmI_2 (3 equiv), HMPA (36 equiv), THP	0 °C, 30 min	**20** (23), **21** (33)[b]
4	SmI_2 (3 equiv), CH_3CN	0 °C, 30 min	—[b]
5	SmI_2 (3 equiv), DMPU (30 equiv), CH_3CN	0 °C, 3 h	**20** (41), **21** (5), **25** (6)[b]
6	SmI_2 (8 equiv), DMPU (80 equiv), CH_3CN	0 °C, 3 h	**20** (9), **25** (85)
7	SmI_2 (8 equiv), DMPU (80 equiv), CH_3CN	−18 °C, 1 min	**20** (50)
8	SmI_2 (8 equiv), DMPU (80 equiv), CH_3CN	−18 °C, 3 min	**20** (70)

[a] Compound **20** was obtained as a single isomer.
[b] Starting material was recovered.



Scheme 3. Conversion of lactam **20** to the corresponding Ala–Pro type (*Z*)-alkene dipeptide mimetic **29**. Reagents: (i) MeOTf, $ClCH_2CH_2Cl$; (ii) TfOH aq, THF; (iii) Boc_2O, DIPEA, DMF; (iv) 1 M KOH aq, THF; (v) Na-NH_3, THF. **Starting material **20** was partly recovered.*

recovery of starting material **20** (24%). Saponification of the resulting ester followed by a Birch reduction to remove the *N*-Bn group yielded dipeptide mimetic **29** in 86% isolated yield. The stereochemistry of the obtained compound was unambiguously established as the L–D mimetic by comparing to the literature.[5a] Formation of the L–D type is likely due to the preferential cyclization, which leads to the 3,6-trans bicyclo lactam as mentioned in the previous section.

In this work, we successfully synthesized (*Z*)-alkene-containing *cis*-proline dipeptide mimetics using a SmI_2-mediated reductive alkylation reaction. The reaction outcome is determined by the reaction solvent used in the reduction of the key intermediate such as **18** with SmI_2. The reductive alkylation in THF affords the desired cyclized product with concomitant formation of the reduction product where the hydrogen atom derived from THF is incorporated into the substrate via a radical mechanism. On the other hand, for the (*Z*)-alkene-containing *cis*-Pro mimetic, CH_3CN in the presence of DMPU is the solvent of choice for SmI_2-mediated reductive alkylation. The incorporation of the synthesized mimetics into peptides for biological evaluation is underway.

3. Experimental

3.1. General

^1H NMR spectra were recorded using JEOL-GSX-400 spectrometer at 400 MHz and ^{13}C NMR spectra were recorded using JEOL-GSX-400 spectrometer at 100 MHz or JEOL-JNM-AL300 spectrometer at 75 MHz. Tetrahydrofuran (THF) in every reaction conducted under argon was freshly distilled from sodium-benzophenone ketyl radical under argon. Melting points are uncorrected.

3.1.1. (2*S*,3*S*)-3-(Benzylethoxycarbonylacetylamino)-2-(*tert*-butyldimethylsilanyloxy)butyric acid ethyl ester (11) from 10. To a solution of **10** (4.00 g, 7.45 mmol) in CH_3CN were added Cs_2CO_3 (2.91 g, 8.94 mmol) and thiophenol (918 μL, 8.94 mmol) at 0 °C with stirring. After being stirred at room temperature for 12 h, the reaction mixture was filtered and the filtrate was diluted with EtOAc. Resulting organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give oily crude. To the crude in CH_2Cl_2 (70 mL) were added ethyl malonyl chloride (1.21 mL, 9.61 mmol) and DIPEA (1.67 mL, 9.61 mmol) at 0 °C under argon. After being stirred at room temperature for 10 h, the reaction mixture was quenched by addition of 1 M 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 residues. Column chromatography of the residues over silica gel with EtOAc–*n*-hexane (1:9) gave 2.87 g (85.6% yield) of the title compound **11** as colorless oil: $[\alpha]_D^{26}$ −32.4 (*c* 1.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) (mixture of rotamers, data for one isomer) δ 0.06 (s, 6H), 0.94 (s, 9H), 1.13 (d, *J*=7.2 Hz, 3H), 1.23–1.33 (m, 6H), 3.27 (d, *J*=15.2 Hz, 1H), 3.36 (d, *J*=15.2 Hz, 1H), 4.12–4.28 (m, 4H), 4.53 (d, *J*=18.4 Hz, 1H), 4.61 (d, *J*=4.8 Hz, 1H), 4.75 (d, *J*=18.4 Hz, 1H), 4.78 (br, 1H), 7.16–7.41 (m, 3H), 7.36 (t, *J*=7.6 Hz, 3H); HRMS (ESI-TOF) *m*/*z* calcd for $C_{24}H_{40}NO_6Si$ (MH^+) 466.2625; found 466.2646.

3.1.2. (5*S*,6*S*)-1-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-6-methyl-4-trifluoromethanesulfonyloxy-5,6-dihydro-1*H*-pyridin-2-one (13) from 11. To a solution of **11** (2.70 g, 5.80 mmol) in EtOH (14 mL) was added 14 mL (6.38 mmol) of freshly prepared NaOEt in EtOH (0.456 M) at 0 °C under argon, and the reaction mixture was stirred for 45 min and quenched with saturated citric acid solution. The mixture was extracted with EtOAc, and the extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give an oily material, which was used for following reactions without further purification. The mixture of the oil in 800 μL of H_2O and 160 mL of CH_3CN was refluxed for 2 h and concentrated under reduced pressure to give solid crude materials containing **12**. To a solution of the crude materials in CH_2Cl_2 (80 mL) were added *N*-phenylbis(trifluoromethanesulfonimide) (2.90 g, 8.12 mmol) and Et_3N (1.13 mL, 8.12 mmol) at 0 °C, and the mixture was stirred at room temperature for 10 h. The reaction mixture was quenched by the addition of H_2O and extracted with Et_2O. The organic phase was washed with H_2O 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 (5:95) gave the title compound **13** (2.41 g, 86.7% yield) as a white crystal: mp 70–72 °C; $[\alpha]_D^{27}$ −89.7 (*c* 0.61, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ −0.10 (s, 3H), 0.05 (s, 3H), 0.75 (s, 9H), 1.20 (d, *J*=6.8 Hz, 3H), 3.48 (q, *J*=6.8 Hz, 1H), 3.89 (d, *J*=15.1 Hz, 1H), 4.07 (s, 1H), 5.38 (d, *J*=15.1 Hz, 1H), 6.16 (s, 1H), 7.22–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, −5.0, 16.4, 17.9, 25.4, 47.3, 58.0, 70.2, 115.6, 127.5, 128.0, 128.6, 136.1, 156.6, 160.3. Anal. Calcd for $C_{20}H_{28}F_3NO_5SSi$: C, 50.09; H, 5.88; N, 2.92. Found: C, 49.82; H, 5.82; N, 3.02.

3.1.3. (2*S*,3*S*)-3-[1-Benzyl-3-(*tert*-butyldimethylsilanyloxy)-2-methyl-6-oxo-1,2,3,6-tetrahydropyridin-4-yl]propionic acid methyl ester (14) from 13. To a solution of **13** (2.41 g, 5.03 mmol) and $Pd[P(o\text{-}Tol)_3]_2Cl_2$ (198 mg,

0.251 mmol) in THF (30 mL) was added $IZnCH_2CH_2CO_2Me$[19] in THF (100 mL, 20.1 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 1 h and quenched with saturated $NaHCO_3$ solution. The mixture was extracted with Et_2O and the extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give residues. The residues were purified by silica gel column chromatography to give 1.90 g of the title compound **14** (4.56 mmol, 90.7% yield) as a white crystal: mp 78–80 °C; $[\alpha]_D^{27}$ −96.0 (*c* 0.18, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ −0.20 (s, 3H), 0.02 (s, 3H), 0.75 (s, 9H), 1.08 (d, *J*=6.8 Hz, 3H), 2.40–2.66 (m, 4H), 3.40 (q, *J*=6.8 Hz, 1H), 3.69 (s, 3H), 3.75 (s, 1H), 3.89 (d, *J*=15.2 Hz, 1H), 5.34 (d, *J*=15.2 Hz, 1H), 5.84 (s, 1H), 7.20–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −4.4, 16.3, 17.8, 25.5, 28.7, 31.2, 47.2, 51.7, 57.3, 70.5, 121.0, 127.0, 128.0, 128.3, 137.0, 148.8, 162.1, 172.3; LRMS (FAB) *m/z* 418 (MH^+), 360, 321 (base peak), 132, 91, 73; HRMS (FAB) *m/z* calcd for $C_{23}H_{36}O_4NSi$ (MH^+) 418.2414; found 418.2418.

3.1.4. (5*S*,6*S*)-1-Benzyl-5-(*tert*-butyldimethylsilanyloxy)-4-(3-hydroxypropyl)-6-methyl-5,6-dihydro-1*H*-pyridin-2-one (15) from 14. To a solution of **14** (4.19 g, 10.0 mmol) in MeOH (40 mL) and THF (40 mL) was added $NaBH_4$ (4.55 g, 121 mmol) in small portions over 12 h at 0 °C. After being stirred for 8 h at this temperature, the reaction mixture was quenched with 1 N HCl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give crude materials. Column chromatography purification of the crude over silica gel with EtOAc–*n*-hexane (2:1) gave **15** (3.85 g, 98.7% yield) as a white crystal: mp 85–87 °C; $[\alpha]_D^{26}$ −80.1 (*c* 0.84, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ −0.21 (s, 3H), 0.02 (s, 3H), 0.75 (s, 9H), 1.08 (d, *J*=7.2 Hz, 3H), 1.38 (t, *J*=4.8 Hz, 3H), 1.69–1.88 (m, 2H), 2.21–2.41 (m, 2H), 3.41 (qd, *J*=7.2 Hz, 1.2 Hz, 1H), 3.71 (m, 2H), 3.74 (d, *J*=1.2 Hz, 1H), 3.89 (d, *J*=15.4 Hz, 1H), 5.34 (d, *J*=15.4 Hz, 1H), 5.87 (s, 1H), 7.20–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.4, 16.3, 17.8, 25.6, 29.8, 30.1, 47.3, 57.3, 61.5, 70.1, 120.6, 127.0, 128.0, 128.3, 137.0, 150.7, 162.7. Anal. Calcd for $C_{22}H_{35}NO_3Si$: C, 67.82; H, 9.05; N, 3.60. Found: C, 67.58; H, 9.02; N, 3.58.

3.1.5. (2*S*,3*S*)-Acetic acid 1-benzyl-2-methyl-6-oxo-4-(3-oxopropyl)-1,2,3,6-tetrahydropyridin-3-yl ester (16) from 15. To a solution containing **15** (700 mg, 1.80 mmol) in THF (7 mL) was added 1 M TBAF in THF (1.98 mL, 1.98 mmol) at 0 °C. After being stirred for 4 h at room temperature, the mixture was quenched with 1 N HCl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give colorless oil. The solution of the above oil in 10 mL of DMF was mixed with TBSCl (325 mg, 2.16 mmol) and imidazole (281 mg, 4.13 mmol) at 0 °C, and stirred at this temperature for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ followed by extraction with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ followed by evaporation of solvent to give crude material. The crude in 10 mL of $CHCl_3$ was treated with Ac_2O (850 μL, 8.99 mmol), pyridine (722 μL, 8.99 mmol), and DMAP (22.0 mg, 0.180 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched with saturated NH_4Cl and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give oily crude. To a solution containing the crude in THF (10 mL) was added 1 M TBAF (1.98 mL, 1.98 mmol) at 0 °C. After being stirred at room temperature for 3 h, the mixture was quenched with 1 N HCl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give oily materials. To a solution of oxalylchloride (291 μL, 3.34 mmol) in CH_2Cl_2 (10 mL) was added DMSO (355 μL, 5.01 mmol) at −78 °C under argon. The mixture was stirred for 15 min at this temperature, followed by addition of the above oily materials in CH_2Cl_2 (10 mL) at −78 °C. After being stirred for 15 min at this temperature, the mixture was stirred for 1 h at −45 °C followed by addition of 2.18 mL of DIPEA (12.5 mmol) and 20 min stirring at 0 °C. The reaction mixture was quenched with 1 N HCl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give oily materials. After purification by column chromatography over silica gel with EtOAc–*n*-hexane (1:4), the title compound **16** was obtained as colorless oil (104 mg, 90.6% yield): $[\alpha]_D^{26}$ −84.9 (*c* 0.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J*=7.0 Hz, 3H), 1.79 (s, 3H), 2.45–2.60 (m, 2H), 2.64–2.79 (m, 2H), 3.50 (qd, *J*=7.0 Hz, 1.6 Hz, 1H), 3.73 (d, *J*=15.2 Hz, 1H), 4.93 (d, *J*=1.6 Hz, 1H), 5.47 (d, *J*=15.2 Hz, 1H), 6.01 (s, 1H), 7.22–7.34 (m, 5H), 9.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0, 20.7, 26.5, 40.6, 46.8, 53.7, 70.2, 124.6, 127.4, 128.0, 128.4, 136.9, 144.6, 161.7, 170.2; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{22}NO_4$ (MH^+) 316.1549; found 316.1534.

3.1.6. (2*S*,3*S*)-Acetic acid 1-benzyl-4-(3-iodo-propyl)-2-methyl-6-oxo-1,2,3,6-tetrahydropyridin-3-yl ester (18) from 15. A solution containing **15** (1.00 g, 2.57 mmol), DMAP (31.4 mg, 0.257 mmol), TsCl (735 mg, 3.85 mmol), and pyridine (620 μL, 7.71 mmol) in CH_2Cl_2 (5 mL) was stirred 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 crude materials containing **17**. To a stirred solution of the materials in CH_3CN (15 mL) and MeOH (1 mL) was added 3.9 mL of hexafluorosilicic acid solution (ca. 40%, ca. 11 mmol) at room temperature. The reaction mixture was heated to 40 °C and stirred for 3 h. After being cooled at 0 °C, the 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 residues. After column chromatography purification over silica gel with EtOAc–*n*-hexane (15:85), 884 mg of the title compound **18** (2.07 mmol, 88.4% yield) was obtained as colorless oil: $[\alpha]_D^{26}$ −87.8 (*c* 0.98, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, *J*=6.8 Hz, 3H), 1.80 (s, 3H), 1.93–2.08 (m, 2H), 2.30–2.37 (m, 2H), 3.14–3.26 (m, 2H), 3.49 (qd, *J*=6.8 Hz, 1.6 Hz, 1H), 3.73 (d, *J*=15.0 Hz, 1H), 4.91 (d, *J*=1.6 Hz, 1H), 3.48 (d, *J*=15.0 Hz, 1H), 6.07 (s, 1H), 7.20–7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.8, 16.0, 20.7, 30.1, 35.0, 46.7, 53.7, 70.0, 124.9, 127.3, 128.0, 128.3, 136.8, 144.4, 161.7, 170.1; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{23}NO_3I$ (MH^+) 428.0723; found 428.0717.

3.1.7. Preparation of SmI_2 in THF solution. To a suspension of samarium (Kojundo Chemical Lab. Co., Ltd: 850 μm powder, 240 mg, 1.60 mmol) in THF (4 mL) was added CH_2I_2 (64.0 μL, 0.800 mmol) in THF (4 mL) at room temperature under argon. After 1 h stirring, 0.1 M of SmI_2 in THF solution (8 mL) was obtained.

3.1.8. (3*S*)-2-Benzyl-3-methyl-2,3,5,6-tetrahydro-[2]pyrindine-1-one (19) from 16 (Table 1, entry 1). To a solution containing **16** (75.0 mg, 0.238 mmol) in THF (3 mL) was added SmI_2 in THF (0.1 M, 7.13 mL, 0.713 mmol) at 0 °C under argon. After 1 h reaction, silica gel (300 mg) and *n*-hexane (3 mL) were added to the reaction mixture. The mixture was stirred for 5 min and filtrated. The resulting filtrate was diluted with EtOAc and washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated in vacuo to give crude materials. To a solution of the materials in CH_2Cl_2 (6 mL) was added MsCl (46.1 μL, 0.595 mmol) and Et_3N (247 μL, 1.78 mmol) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with 1 N HCl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give an oily crude. After purification of the crude over silica gel with EtOAc–*n*-hexane (5:95), the title compound **19** (5.10 mg, 8.96% yield) was obtained as a colorless oil: $[\alpha]_D^{26}$ −59.5 (*c* 0.19, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (m, 3H), 2.65 (m, 4H), 4.06 (m, 1H), 4.12 (d, *J*=15.3 Hz, 2H), 5.30 (s, 1H), 5.48 (d, *J*=15.3 Hz, 2H), 6.83 (s, 1H), 7.23–7.32 (m, 5H); LRMS (FAB) *m/z* 240 (MH^+), 240, 149, 91, 57 (base peak); HRMS (FAB) *m/z* calcd for $C_{16}H_{18}ON$ (MH^+) 240.1388; found 240.1392.

3.1.9. (3*S*,6*S*)-2-Benzyl-3-methyl-2,3,5,6,7,7a-hexahydro-[2]pyrindine-1-one (20) and (6*S*)-1-benzyl-4-(3-iodopropyl)-6-methyl-3,6-dihydro-1*H*-pyridin-2-one (21) from 18 (Table 1, entry 2). To a solution of 30.0 mg of **18** (0.0702 mmol) in THF (1 mL) was added SmI_2 in THF (0.1 M, 2.11 mL, 0.211 mmol) at 0 °C under argon. After being stirred for 30 min, acetic acid-d_4 (39.6 μL, 0.702 mmol) at this temperature was added to the reaction mixture. After being stirred for 30 min, the mixture was quenched by saturated NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give crude materials. After column chromatography purification over silica gel with EtOAc–*n*-hexane (from 15:85 to 1:4), the title compounds **20** (5.9 mg, 34.8% yield) and byproduct **21** (5.8 mg, 22.4% yield) were obtained as colorless oily materials. *Compound **20***: $[\alpha]_D^{26}$ −41.1 (*c* 0.88, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, *J*=6.6 Hz, 3H), 1.92–1.76 (m, 2H), 2.48–2.26 (m, 4H), 3.12–3.05 (m, 1H), 3.84–3.75 (m, 1H), 4.02 (d, *J*=14.9 Hz, 2H), 5.31 (d, *J*=15.2 Hz, 2H), 5.58–5.55 (m, 1H), 7.32–7.18 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 24.3, 29.0, 30.2, 45.1, 46.9, 53.8, 118.4, 127.1, 127.6, 128.4, 137.5, 142.0, 171.5; LRMS (FAB) *m/z* 242 (MH^+), 149, 91, 57 (base peak); HRMS (FAB) *m/z* calcd for $C_{16}H_{20}ON$ (MH^+) 242.1545; found 242.1552. *Compound **21***: $[\alpha]_D^{26}$ −25.7 (*c* 0.89, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J*=6.8 Hz, 3H), 1.95 (m, 2H), 2.15 (t, *J*=7.6 Hz, 2H), 2.91 (dd, *J*=20.8 Hz, 2.8 Hz, 1H), 3.01 (d, *J*=20.8 Hz, 1H), 3.17 (t, *J*=6.8 Hz, 2H), 3.85 (m, 1H), 4.06 (d, *J*=15.4 Hz, 1H), 5.39 (d, *J*=15.4 Hz, 1H), 5.47 (m, 1H), 7.22–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.7, 20.7, 30.3, 35.1, 36.0, 46.5, 52.6, 122.6, 127.2, 127.6, 128.5, 131.3, 137.0, 167.7; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{20}INONa$ (MNa^+) 392.0498; found 392.0487.

3.1.10. Reductive alkylation with SmI_2 and additive (HMPA or DMPU) in THF (Table 1, entries 3 and 4). To a solution of **18** (50.0 mg, 0.118 mmol) in THF (1.5 mL) was added SmI_2 in THF (0.100 M, 3.54 mL, 0.354 mmol) at 0 °C under argon. After 15 min, 4.24 mmol of HMPA or DMPU was added to the mixture, which was stirred for 18 h at room temperature. After addition of silica gel (300 mg) and *n*-hexane (3 mL), the mixture was filtrated and the filtrate was diluted with EtOAc followed by washing with saturated NH_4Cl and brine, and dried over $MgSO_4$. Concentration in vacuo gave crude materials. Column chromatography purification over silica gel with EtOAc–*n*-hexane (15:85) gave **20** (12.2 mg, 0.0506 mmol, 43.6% or 12.4 mg, 0.0514 mmol, 44.3% yield).

3.1.11. Preparation of SmI_2–DMPU in CH_3CN. Samarium powder (450 mg, 2.99 mmol: Aldrich—40 mesh, 99.9%) in a flask was dried in vacuo with stirring and heating for 30 min. Solid ICH_2CH_2I (423 mg, 1.50 mmol) was added to the above flask charged with argon. The mixture was dissolved in CH_3CN (13.2 mL: freshly distilled from CaH_2) at room temperature and stirred for 2 h at this temperature followed by addition of DMPU (1.81 mL, 15.0 mmol) to give purple solution of SmI_2–DMPU in CH_3CN.

3.1.12. Reductive alkylation with SmI_2–DMPU in CH_3CN. Compound **18** (50.0 mg, 0.117 mmol) in freshly distilled CH_3CN (500 μL) was treated with freshly prepared SmI_2–DMPU in CH_3CN (9.37 mL, 0.937 mmol) at −18 °C under argon followed by 3 min stirring. To the reaction mixture were added 200 mg of silica gel and 3 mL of *n*-hexane. After filtration of the mixture, the filtrate was diluted with EtOAc, washed with saturated NH_4Cl and brine, and dried over $MgSO_4$. Concentration under reduced pressure followed by column chromatography over silica gel with EtOAc–*n*-hexane (15:85) gave 19.8 mg of **20** (70.1% yield).

3.1.13. Physical data of (3*S*)-2-benzyl-3-methyl-2,3,4,5,6,7-hexahydro-[2]pyrindine-1-one (25). $[\alpha]_D^{26}$ −16.9 (*c* 0.24, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, *J*=6.6 Hz, 3H), 1.90–2.08 (m, 3H), 2.45–2.76 (m, 5H), 3.60 (m, 1H), 3.88 (d, *J*=15.3 Hz, 2H), 5.39 (d, *J*=15.3 Hz, 2H), 7.22–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 22.2, 30.3, 31.7, 36.7, 46.8, 50.7, 127.1, 127.8, 128.5, 131.5, 138.7, 150.0, 164.0; LRMS (FAB) *m/z* 242 (MH^+), 91 (base peak); HRMS (FAB) *m/z* calcd for $C_{16}H_{20}ON$ (MH^+) 242.1545; found 242.1548.

3.1.14. (1*S*)-2-[(2*S*)-2-(Benzyl-*tert*-butoxycarbonylamino)propylidene]cyclopentanecarboxylic acid methyl ester (28) from 20. Compound **20** (58.0 mg, 0.240 mmol) in 1,2-dichloroethane (1 mL) was treated with MeOTf (79.1 μL, 0.721 mmol) at 0 °C under argon. After being stirred for 3 h at room temperature, the reaction mixture was concentrated under vacuo to give an oily crude. To a solution containing the crude in THF (1.8 mL) was added 0.1% (w/w) TfOH aqueous solution (100 μL) and H_2O (100 μL) at room temperature. After 3 h, the mixture was dried with

$MgSO_4$ and filtrated. To a solution containing evaporated filtrate in DMF (2 mL) were added Boc_2O (105 mg, 0.481 mmol) and DIPEA (62.8 μL, 0.361 mmol) at room temperature. The reaction mixture was stirred for 2 h, quenched by 0.1 N HCl, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give crude materials. The materials were purified by column chromatography over silica gel with EtOAc–*n*-hexane (from 5:95 to 15:85) to give **28** (42.8 mg, 47.7% yield) as colorless oil and recovered **20** (13.8 mg, 23.8% yield): $[\alpha]_D^{26}$ 91.3 (*c* 1.29, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J=6.8 Hz, 3H), 1.44 (br, 9H), 1.72–1.86 (m, 2H), 1.90–2.02 (m, 2H), 2.03–2.18 (m, 1H), 2.23–2.39 (m, 1H), 3.65 (s, 9H), 4.70 (br, 1H), 4.37 (d, J=12.8 Hz, 1H), 4.41 (d, J=12.8 Hz, 1H), 5.47 (dd, J=1.6 Hz, 9.6 Hz, 1H), 7.15–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 24.6, 28.5, 30.9, 33.5, 39.3, 45.4, 47.6, 51.9, 79.6, 124.6, 126.5, 126.8, 128.0, 128.9, 140.0, 142.4, 174.8; HRMS (ESI-TOF) *m*/*z* calcd for $C_{22}H_{32}NO_4$ (MH^+) 374.2331; found 374.2324.

3.1.15. (1*S*)-2-[(2*S*)-2-*tert*-Butoxycarbonylaminopropylidene]cyclopentanecarboxylic acid 29 (Boc-L-Ala-Ψ[(*Z*)-CH=C]-D-Pro-OH) from 28. A solution containing **28** (12.0 mg, 0.0321 mmol) and 1 N KOH aqueous solution (32.0 μL, 0.0320 mmol) in THF (350 μL), H_2O (350 μL), and MeOH (100 μL) was stirred for 14 h at room temperature. The reaction mixture was quenched by 1 N HCl and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give an oily crude. To a flask containing THF (0.5 mL) and liquid NH_3 (1 mL) was added Na (10.0 mg, 0.412 mmol) at −78 °C. After 3 min, the crude was added with additional stirring for 20 min at −78 °C. The reaction mixture was quenched with solid NH_4Cl. After evaporation of NH_3 at room temperature, saturated NH_4Cl solution was added to the mixture, which was extracted with EtOAc. The extract was washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated to give oily materials. After purification by column chromatography over silica gel with EtOAc–*n*-hexane–AcOH (160:40:1), the title compound **29** was obtained (7.40 mg, 85.5% yield) as colorless oil: $[\alpha]_D^{28}$ 37.7 (*c* 0.11, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, J=6.6 Hz, 3H), 1.43 (s, 9H), 1.96–2.50 (m, 6H), 3.76 (br, 1H), 4.47 (br, 1H), 5.26 (dd, J=9.4 Hz, 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 24.7, 28.4, 31.0, 33.6, 45.5, 46.2, 79.3, 127.0, 141.4, 155.2, 180.1; LRMS (FAB) *m*/*z* 292 (MNa^+), 270 (MH^+), 214, 153, 152, 107 (base peak), 57; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{24}O_4N$ (MH^+) 270.1705; found 270.1712.

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