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# Application of samarium diiodide ($SmI_2$)-induced reduction of γ-acetoxy-α,β-enoates with α-specific kinetic electrophilic trapping for the synthesis of amino acid derivatives

**Akira Otaka,* Akira Yukimasa, Junko Watanabe, Yoshikazu Sasaki, Sinya Oishi, Hirokazu Tamamura and Nobutaka Fujii**

*Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: aotaka@pharm.kyoto-u.ac.jp; Fax: +81-75-753-4570; Tel: +81-75-753-4571*

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**γ-Acetoxy-α,β-enoates were easily reduced by samarium diiodide ($SmI_2$) in THF to generate samarium dienolates which were kinetically trapped with ease at their α-positions by electrophiles (proton, aldehydes or ketones) to yield (*E*)-alkene dipeptide isosteres or γ-amino acid derivatives in high chemical yields.**

Samarium diiodide ($SmI_2$) is a one-electron reducing agent which meets the demands of a wide range of chemical transformations.[1] During the course of our synthetic efforts directed at fluoroalkene dipeptide isosteres, we found that γ,γ-difluoro-α,β-enoates can be reduced to γ-fluoro-β,γ-enoates by $SmI_2$–$Bu^tOH$ in THF by two successive electron transfers.[2] This reaction appears to be classifiable into the same class of reaction where γ,δ-epoxy-α,β-enoates[3] or γ,δ-dihydroxy-α,β-enoate derivatives[4] undergo a reductive elimination by $SmI_2$ to yield δ-hydroxy-β,γ-enoates through the probable intermediary of dienolate species. These findings prompted us to examine the reductive formation by $SmI_2$ of dienolates **4** from γ-acetoxy-α,β-enoates[5] **1** with application of a kinetic electrophilic trap to the synthesis of amino acid derivatives including (*E*)-alkene dipeptide isosteres and γ-amino acids (Fig. 1).

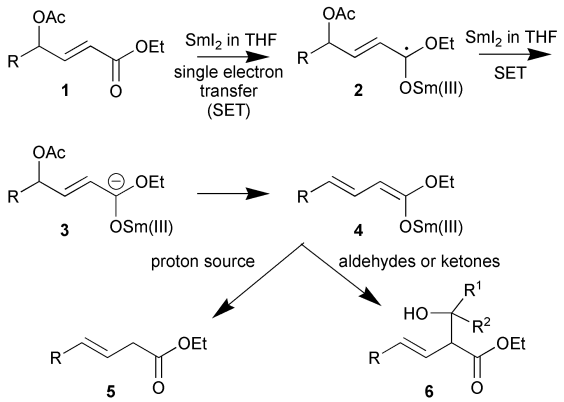
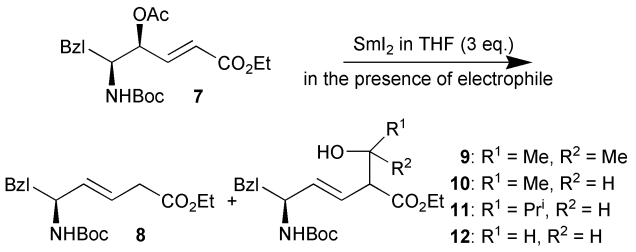



**Fig. 1** Plausible mechanism for $SmI_2$-induced formation of dienolates from γ-acetoxy-α,β-enoates and their trap with electrophiles.

(*E*)-Alkene dipeptide isosteres with substitution of *trans*-olefins for peptide bonds have recently become of great interest in medicinal or synthetic organic chemistry owing to their structural similarity to parent peptide bonds.[6] The δ-amino-γ-acetoxy-α,β-enoate[6] **7** was rapidly reduced with $SmI_2$–MeOH in THF to yield an L-Phe–Gly-type (*E*)-alkene dipeptide isostere **8** in 91% isolated yield (Table 1, run 2).† In this reaction, the presence of a proton source (MeOH) is necessary for clean conversion of **7** to **8** (in the absence of MeOH: 32%). Consecutive transfer of two electrons from $SmI_2$ into the π-electron system adjacent to an acetoxy group is likely to result in the formation of a dienolate species resulting from loss of the acetoxy group as shown in Fig. 1. Here, presence of a proton source leads to the kinetic trapping of the plausible dienolate intermediate to give an Xaa–Gly-type (*E*)-alkene isostere (Xaa = amino acid) (Fig. 1, **4** to **5**). Based on such a reaction mechanism, we expected that kinetic trapping of the dienolate with electrophiles such as aldehydes or ketones should give α-substituted (*E*)-alkene isosteres *via* aldol reactions at the α-carbon as shown in Fig. 1 (**4** to **6**). However, $SmI_2$-mediated reactions between aldehydes or ketones and electron deficient alkenes such as α,β-enoates have been reported to give γ-lactone derivatives through attack to the β-position of ketyls derived from the carbonyl compounds by reaction with $SmI_2$.[7] In our envisioned reaction system, α,β-enoates would be employed that have electron withdrawing leaving groups at the γ-position, which, in comparison with aldehydes or ketones, would allow the enoates to receive electrons more easily from $SmI_2$ to form dienolate intermediates. Indeed as shown in Table 1, reaction of **7** with $SmI_2$ in THF in the presence of aldehydes or ketones proceeded smoothly at 0 °C within 30 min to give α-hydroxyalkylated (*E*)-alkene isosteres (**9–11**) in reasonable chemical yields with accompanying small amounts of reduction product **8**. Such α-hydroxymethylation could be of great synthetic value since hydroxymethyl groups can be transformed to side chain functionalities of various amino acids. Trapping with formaldehyde under aprotic conditions of the dienolate resulting from $SmI_2$-mediated reduction should give the desired α-hydroxymethylated isostere. Treatment of **7** with $SmI_2$ in the presence of a stable reactive formaldehyde-complex, prepared from *s*-trioxane and methylaluminium bis(2,6-diphenylphenoxide),[8] gave the desired α-hydroxymethylated isostere **12** in an acceptable yield (Table 1, run 6). Observation of the α-specific kinetic trap can probably be rationalized by the fact that the π-electron density of a dienolate species is higher at the α-carbon

**Table 1** Synthesis of (*E*)-alkene dipeptide isosteres by $SmI_2$ in the presence of various electrophiles




| Run | Electrophile | Condition | Isolated yield (%)[a] |
|---|---|---|---|
| 1 | None | 0 °C, 10 min | **8** (32)[b] |
| 2 | MeOH[c] | 0 °C, 10 min | **8** (91) |
| 3 | Acetone[d] | 0 °C, 10 min | **9** (83), **8** (3) |
| 4 | Acetaldehyde[d] | 0 °C, 20 min | **10** (69)[e], **8** (2) |
| 5 | Isobutyraldehyde[d] | 0 °C, 15 min | **11** (86), **8** (3) |
| 6 | Formaldehyde[f] | 0 °C, 30 min | **12** (64), **8** (11) |

[a] Combined yield of diastereomers except for **8**. [b] Unidentified products were formed. [c] In THF : MeOH = 7 : 1. [d] 3 equiv. [e] (*Z*)-isomers (4%) were detected. [f] Formaldehyde complex was prepared from *s*-trioxane (2 equiv.), 2,6-diphenyl phenol (12 equiv.), and $Me_3Al$ (6 equiv.) in $CH_2Cl_2$–hexane.

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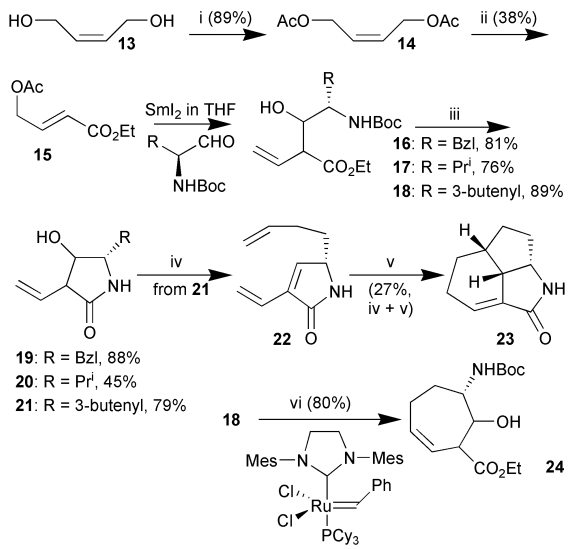
than the γ-carbon.[9] The use of alkyl halides such as methyl iodide as electrophiles did not give the desired α-alkylated products. It is worth noting that organocopper-mediated $S_N2'$ reactions used for the preparation of (*E*)-alkene dipeptide mimetics does not afford the α-hydroxyalkylated isosteres *via* single step manipulations.[10] As with enoate **7**, almost no stereoselectivity was noted for coupling reactions with the carbonyl compounds examined, making stereoselective introduction of carbonyl compounds an issue yet to be solved.

Next, we examined the use of *N*-Boc protected α-aminal derivatives as trapping agents (Scheme 1). Reductive coupling between the aminal derivatives and the simple γ-acetoxy-α,β-enoate **15**, readily available from *cis*-2-butene-1,4-diol **13**, with $SmI_2$ provides unprecedented facile access to functionalized γ-amino acid derivatives that are useful for design of foldamers[11] or five-membered lactams. Generally, reaction of the Boc-protected aminal derivatives with organometallic reagents proceeds within a range of from poor to modest yields due to the enolizable nature of the aminals and the presence of NH hydrogens.[12] However $SmI_2$-mediated coupling reactions between γ-acetoxy-α,β-enoate **15** and aminal derivatives gave diastereomeric mixtures of γ-amino acid derivatives (**16–18**) in good yields although without diastereoselection.‡ These reactions occur under essentially neutral conditions, which could contribute to the observed high chemical yields. The resulting γ-amino acid derivatives possess functional groups amenable to further chemical transformation that could easily lead to additional structural units. For example, compound **18** was subjected to a further sequence of reactions composed of dehydration followed by an intramolecular Diels–Alder reaction to afford the tricyclic compound **23**,§ which represents a potential synthetic precursor of a lactam analogue of galiellalactone, an antagonist of IL-6 signalling.[13] Furthermore, conversion of **18** to a seven-membered cyclic γ-amino acid **24** was achieved using a second generation Grubbs' catalyst coordinated with the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ligand.[14]

In conclusion, as described herein, electrophilic γ-acetoxy-α,β-enoates **1** were easily reduced by $SmI_2$, potentially yielding Sm(III)-dienolate intermediates **4**. Subsequent α-specific kinetic proton trapping of this intermediate was utilized successfully for the synthesis of the Phe–Gly-type (*E*)-alkene dipeptide isostere **8**. Furthermore, the expected dienolates resulting from such $SmI_2$-mediated reduction were also efficiently trapped *in situ* by aldehydes and ketones, where the use of δ-amino-γ-acetoxy-α,β-enoates as substrates resulted in the formation of α-hydroxyalkylated (*E*)-alkene dipeptide isosteres (**9–12**). Combination of **15** with *N*-Boc-protected aminal derivatives in $SmI_2$-mediated reduction leads to a highly efficient coupling reaction that is applicable to the synthesis of a variety of γ-amino acid derivatives. To our knowledge, reductive dienolate formation using $SmI_2$ and its practical application to the preparation of compounds of synthetic and medicinal value have rarely been reported previously in the literature.[15] We believe that dienolate formation from readily available γ-acetoxy-α,β-enoates with $SmI_2$ under neutral conditions followed by kinetic trapping by electrophiles may be of significant synthetic value.




**Scheme 1** *Reagents*: (i) $Ac_2O$, pyridine, DMAP; (ii) $O_3$ gas then $Me_2S$, AcOEt, then $(EtO)_2P(O)CH_2CO_2Et$, LiCl, $Pr^i_2NEt$, $CH_3CN$; (iii) 4 mol $dm^{-3}$ HCl in dioxane then $NaHCO_3$ (aq) and extraction, then AcOH (2 equiv.), $CH_2Cl_2$; (iv) MsCl, $Et_3N$, $CH_2Cl_2$; (v) 110 °C, DMF; (vi) Grubbs' catalyst (second generation, 0.05 equiv.), reflux, $CH_2Cl_2$.

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## Notes and references

† Alkene dipeptide isosteres obtained in this study have alkene coupling constants ($^3J_{HH}$ = 15.5–16.1 Hz) which are consistent with those of alkenes possessing (*E*)-configurations.[6] For ease of determination of geometry of **9**, **10**, and **11**, a mixture of diastereomers was converted to the corresponding diens by treatment with MsCl–pyridine followed by treatment with DBU–$Et_3N$.

‡ To a mixture consisting of enoate **15** (500 mg, 2.90 mmol) and Boc-(*S*)-phenylalaninal (1.16 g, 4.64 mmol) in THF (12 $cm^3$) was added a solution of $SmI_2$ in THF (0.1 mol $dm^{-3}$, 87 $cm^3$) at 0 °C under argon. After being stirred at 0 °C for 30 min, the reaction was quenched by addition of saturated aqueous $NH_4Cl$ at this temperature. The whole was extracted with $Et_2O$, and the extract was washed with aqueous HCl (0.1 mol $dm^{-3}$) and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by flash chromatography gave the γ-amino acid derivative **16** (855.1 mg, 81% yield).

§ Relative configurations have yet to be completely assigned. However, the lactone counterpart (reverse configuration) of **22** was used for the preparation of a synthetic intermediate of galiellalactone. Therefore, relative configurations were tentatively assigned as shown in Scheme 1.

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