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Synthesis of optically active α-(allenyl)- and α-substituted-α-(allenyl)glycines

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ABSTRACT

The synthesis of various types of optically active α-(allenylsilane-containing)glycines via a chirality-transferring ester-enolate Claisen rearrangement of α-acyloxy-α-alkynylsilanes is described. The conversion of the rearranged products into the optically active silicon-free α-(allenyl)- and α-substituted-α-(allenyl)glycines was achieved by the removal of the Me_2PhSi- or TMS group from the allene terminus.

Amino acids possessing an allenyl side chain have attracted significant attention due to their inhibitory activities to certain enzymes as irreversible inhibitors, so-called suicide or mechanism-based inhibitors.[1] γ-Allenyl-γ-aminobutyric acid (**1**) and α-allenyl DOPA (**2**) are the representative examples, that is, **1** is known to be an inhibitor of GABA transaminase[2] and **2** exhibits a potent inhibitory activity against porcine kidney aromatic group amino acid decarboxylase (Fig. 1).[3] Therefore, α-allenyl amino acids are attractive candidates for the development of mechanism-based enzyme inhibitors. However, only a limited number of reports for their syntheses including the enantioselective versions have appeared.[4] Herein, we describe the enantio- and diastereoselective synthesis of α-substituted-α-(allenyl)glycines **3** and **4**, and α-(allenyl)glycine **5** using the ester-enolate Claisen rearrangement of α-acyloxy-α-alkynylsilanes.

(1)

(2)

We recently reported the ester-enolate Claisen rearrangement of α-acyloxy-α-alkenylsilanes having the *N*-Boc α-amino acid ester as the acyloxy group that afforded vinylsilane-containing α-substituted α-amino acids with the complete transfer of the original

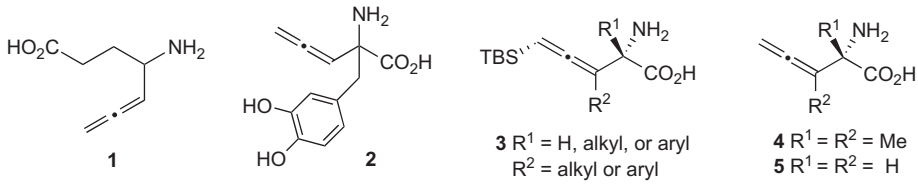

Figure 1.

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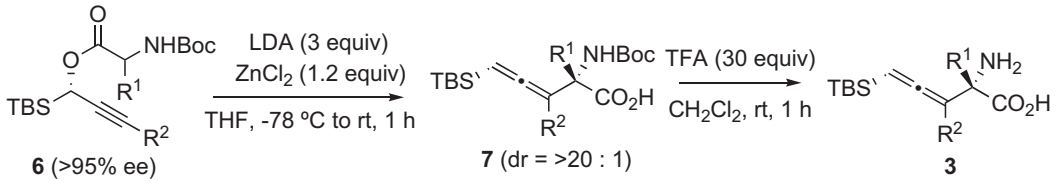
Table 1
Enolate Claisen rearrangement of **6** having various amino acid esters



Entry	R^1	R^2	Yield of **7**[a]	Yield of **3**[a]
1	H	Me (**6a**)	78% (**7a**)	70% (**3a**)[b]
2	Me	Me (**6b**)	52% (**7b**)	54% (**3b**)
3	Bn	Me (**6c**)	46% (**7c**)	70% (**3c**)
4	Ph	Me (**6d**)	61% (**7d**)	60% (**3d**)
5	Allyl	Me (**6e**)	58% (**7e**)	69% (**3e**)
6	Me	Ph (**6f**)	55% (**7f**)	70% (**3f**)
7	Me	Cy (**6g**)	62% (**7g**)	87% (**3g**)[b]

[a] Isolated yield after column chromatography.
[b] TMSOTf (3 equiv) and 2,6-lutidine (5 equiv) were used.

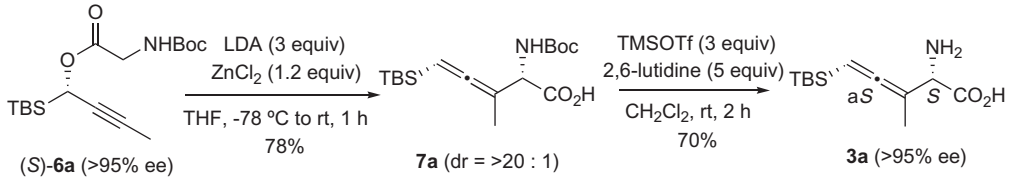
chirality to the γ-position (Eq. 1).[5] The TBS group in the α-alkenylsilane played an important role in the stereoselectivity and excellent yields due to its chemical stability as well as steric bulkiness. We considered that the enolate Claisen rearrangement of the optically active α-acyloxy-α-alkynylsilane **6** would afford allenylsilane-containing α-amino acids **7**, in which the original chirality is transferred not only to the allenic central carbon but also to the α-amino acid moiety. The silyl group-free α-(allenyl)glycines **4** and **5** would be obtained by the choice of the substituent on the silicon atom (Eq. 2).

Our initial attempt was the enolate Claisen rearrangement of α-acyloxy-α-alkynyl-*tert*-butyldimethylsilane **6a** possessing Boc-Gly as the acyloxy group (Scheme 1). According to Kazmaier's protocol,[6] the preparation of the dianionic ester-enolate from **6a** was performed with LDA in the presence of $ZnCl_2$ at −78 °C. Upon warming to room temperature, the rearrangement smoothly proceeded to give **7a** in 78% yield as a single diastereomer. The enantiomeric excess of the rearrangement product was >95%, indicating that the original chirality was completely transferred to both the axial chiral center and α-amino acid moiety of the product. The absolute configuration of the α-carbon that was found to be *S* was determined by the modified Mosher's method of the (*R*)- and (*S*)-MTPA amide of **3a**.[7] The axial chiral center was assigned to a*S* in analogous with Kazmaier's assignment of a similar rearrangement product[6] together with our proposed stereochemical outcome of the present rearrangement (vide infra). Conversion into the protection-free allenylsilane-containing amino acid **3a** was performed using TMSOTf and 2,6-lutidine.[8]

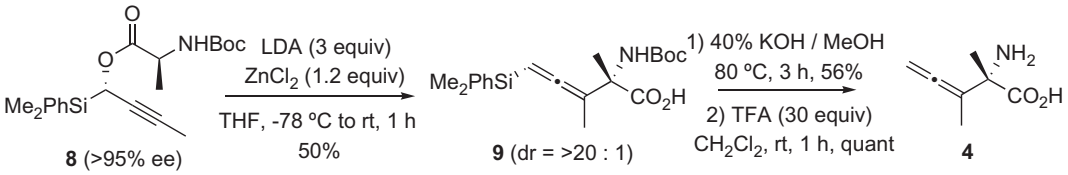
Next, we attempted the synthesis of the α-substituted-α-(allenyl)glycines **3b**–**3g** having various substituents (Table 1). The Claisen rearrangement of the alanyl, phenylalanyl, phenylglycyl, and allylglycyl esters proceeded in a manner similar to that of the glycyl ester **6a** to give the corresponding allenes **7b**–**7e** (entries 2–5), respectively. Other substituents at the alkyne terminus also gave the corresponding rearranged products **7f** and **7g** in good yields (entries 6 and 7). A high diastereoselectivity (dr = >20:1) was observed in all cases.[9] The rearranged products **7b**–**7g** were converted into amino acids **3b**–**3g** by treatment with TFA, respectively.

Our next approach was the synthesis of the silyl group-free α-allenyl-α-amino acids using the removable Me_2PhSi or TMS group under mild reaction conditions, since the TBS group attached to the allene terminus could not be removed under strongly acidic, basic, or fluoride ion conditions (Scheme 2). The α-acyloxy-α-alkynylsilane **8** (>95% ee) containing the Me_2PhSi group was treated under the standard conditions to give the corresponding allene **9** as a single diastereomer. Although several attempts to remove the Me_2PhSi group using protic acids (TFA, HCl, or HBF_4) were unsuccessful, the treatment with strongly basic conditions (40% KOH in MeOH, 80 °C) was found to be effective for the desilylation without troublesome isomerization of the allene moiety to an alkyne.[10] The removal of the Boc group by TFA gave the novel silyl group-free α-allenyl-α-amino acid **4** in the optically pure form.

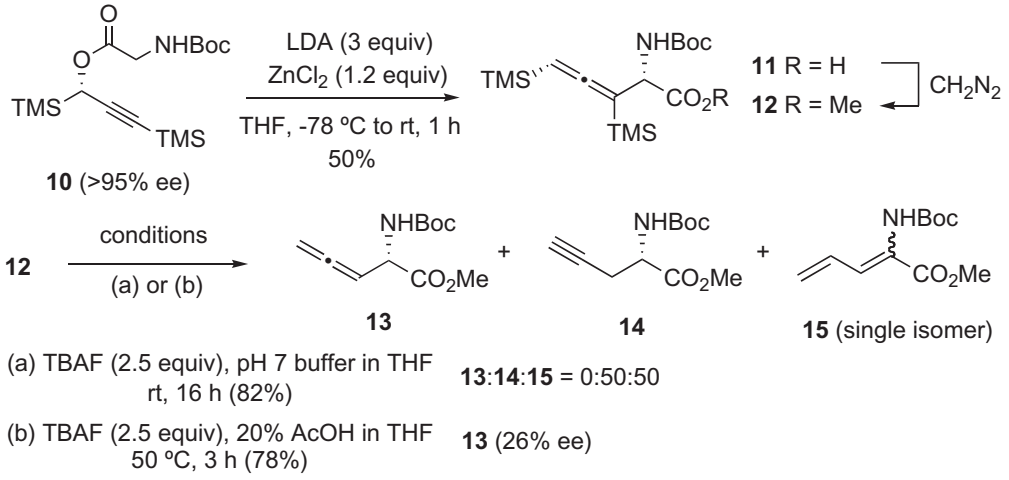
α-(Allenyl)glycine (**5**) has not been found in nature to date, but is presumed to be a congener of α-(propargyl)glycine, a potent anti-metabolite of L-Met and L-Leu isolated from the fermentation broth of an unidentified streptomycete.[11] Due to its instability against the allene isomerization to the alkyne or diene, only one report for the synthesis of **5** in the racemic form has appeared.[12] We envisioned that the use of the TMS group at the α-position and alkyne terminus would produce **11**,[13] from which both the silyl groups attached to the allene moiety could be removed without the above-mentioned problems (Scheme 3). The rearrangement of **10** (>95% ee)[7] proceeded in a highly stereoselective manner to give **11** in 50% yield. Several attempts revealed that (1) tetrabutylammonium fluoride (TBAF) is an efficient reagent to remove the silyl groups, (2) the use of its methyl ester **12** afforded a mixture of the undesired alkyne **14** and diene **15** (**13a**:**14** = 1:1) even under neutral conditions, and (3) the undesired CC double bond migration was prevented by the addition of acetic acid, but the product's ee decreased to 26%. The racemization, which occurred during the

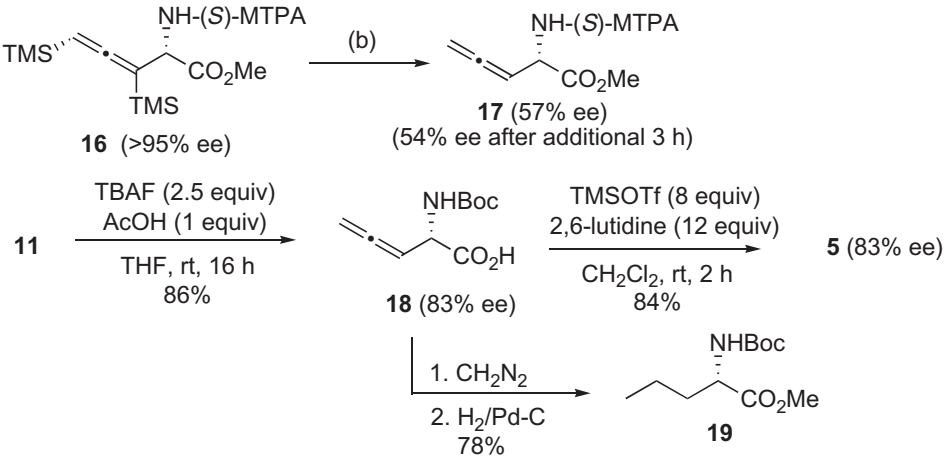


Scheme 1.

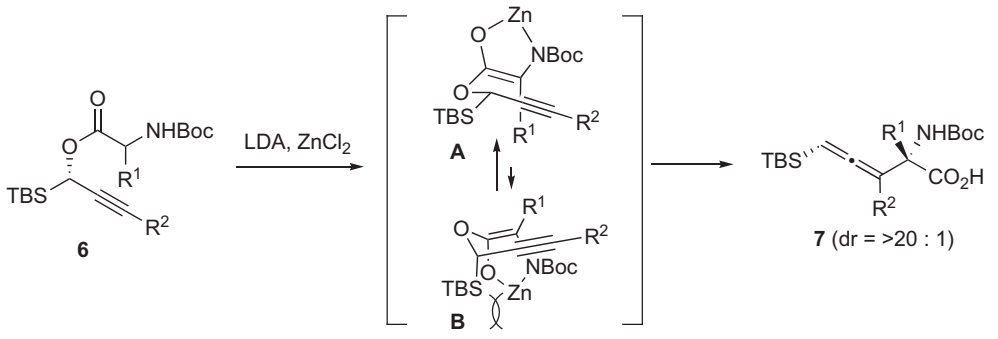


Scheme 2.





Scheme 3.



Scheme 4.

desilylation, was ascertained by the use of the diastereomerically homogeneous (*S*)-MTPA amide **16**. Upon treatment of **16** under the same conditions as stated above (3), the de of the product **17** decreased to 57%, and its further treatment showed a slight

decrease in its de (54%). Fortunately, the use of the carboxylic acid-free **11** in the presence of 1 equiv acetic acid minimized the racemization to give **18** in 86% yield (83% ee) in which a small amount of the alkyne product (~5%) was contaminated. The absolute configuration at C2 was ascertained by converting it to the known *N*-Boc-L-norvaline-OMe **19**.[14] Finally, removal of the Boc group of **18** with TMSOTf afforded **5** (84% yield, 83% ee).[15]

The observed high diastereoselectivity (dr = >20:1) in all cases can be explained by the preferential formation of the *Z*-enolate and subsequent rearrangement via transition state **A**, in which the sterically bulky silyl group is oriented in an equatorial position in a manner similar to an alkyl group reported by Kazmaier[6] (Scheme 4). The sterically bulky silyl group would play a key role in the high diastereoselectivity.[5]

In summary, various types of optically active α-(allenylsilane-containing)glycines, **3a**–**3g**, were synthesized using the dianionic enolate Claisen rearrangement of α-acyloxy-α-alkynylsilanes as the key steps. The Me_2PhSi- or TMS group was removable from the allene terminus to give the silicon-free α-(allenyl)glycines **4** and **5**. Biological evaluation of the synthetic α-(allenyl)glycines as well as an application of the present method for the synthesis of biologically active compounds is currently in progress in our laboratory.

Acknowledgment

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Supplementary data

Supplementary data (full experimental details and characterization data of all synthetic compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.042.

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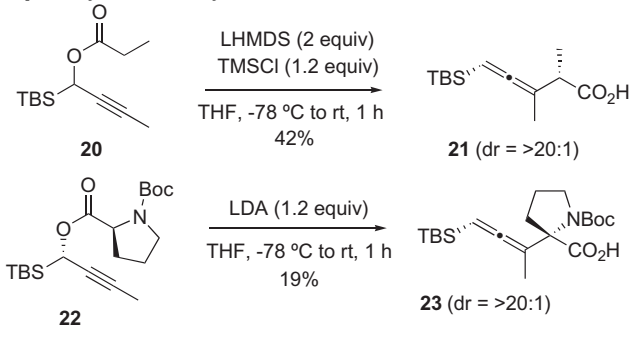
8. Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870–876. In this case, treatment of **7a** with TFA was accompanied by the partial epimerization of the α-position (dr = 4:1).
9. The mono-anionic enolate Claisen rearrangement of the propionate **20** and Boc-Pro ester **22** gave the corresponding allenylsilane **21** and **23** (dr = >20:1), respectively, in moderate yields.



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15. Contaminated α-(propargyl)glycine (~5%) could not be removed by the repeated recrystallization (H_2O, MeOH, EtOH). The ee of **5** was determined by converting it into **17**. Compound **5**: mp 173–175 °C (decomp); $[\alpha]_D^{26}$ −20.2 (*c* 2.00, H_2O, 83% ee).