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Synthesis of Anti-*β*-Substituted *γ*,*δ*-Unsaturated Amino Acids via Eschenmoser–Claisen Rearrangement

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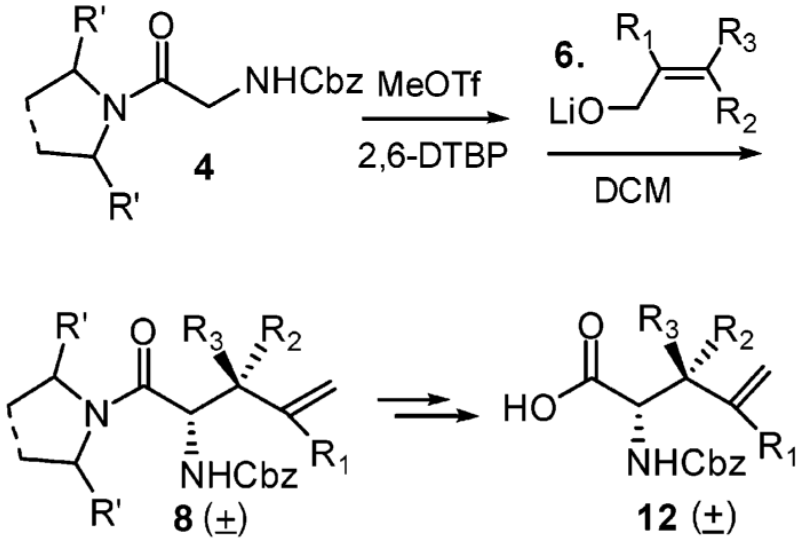
Abstract



Anti-*β*-substituted *γ*,*δ*-unsaturated amino acids have been synthesized via a novel design of the Eschenmoser–Claisen rearrangement. The rearrangement gives good isolated yields and excellent diastereoselectivity due to (*Z*)-*N*,*O*-ketene acetal formation and the pseudochairlike conformations of the reaction intermediates. Upon reductive hydrolysis, important novel amino acids and amino alcohols were synthesized for the first time via this methodology.

In the course of synthesis and conformational studies of biological active peptide ligands, a universal methodology is needed for the synthesis of nonproteinogenic amino acids with terminal unsaturation.[1] The double bond has been a useful building block in organic synthesis due to its potential conversion to aldehydes, alcohols, halides, epoxides, amines, or carboxylic acids.[2] It also can be used in peptide macro-cyclization via ring-closing metathesis.[3] In addition, various *β*-side chain groups can be introduced in the synthesis so that the amino acid will provide biologically active functionalities in conformational constrained peptides.[4] The Kazmaier–Claisen rearrangement has turned out to be very useful in the synthesis of this kind of amino acids and their applications in peptidomimetics.[5] However, the Kazmaier strategy does not work well for racemic anti-*β*-substituted *γ*,*δ*-unsaturated amino acids. It is difficult to introduce an anti-*β*-substituent using the *Z*-allyl alcohol as a starting material, which is not always commercially available. Furthermore, the cis-oriented side chain can destabilize the

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Supporting Information **Available:** Experimental procedures and spectroscopic characterization (^{1}H NMR, ^{13}C NMR, HRMS, IR) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

chairlike transition state resulting in poor diastereoselectivities.[6] The rearrangement product is a diastereomeric mixture that is usually hard to purify. Previous studies also have generated other *ω*-unsaturation by Ni(II) complex alkylation.[7] However, attempts to prepare the anti product have failed due to epimerization. On the other hand, the Eschenmoser–Claisen rearrangement has been developed as a useful methodology for synthesis of *γ*,*δ*-unsaturated carboxylic amide derivatives.[8] We envisioned that if an *N*,*O*-ketene acetal intermediate could be generated in its cis configuration, a chairlike transition state conformation would provide an anti-*β*-substituted product after rearrangement (Figure 1). During this study, we found that the Eschenmoser–Claisen rearrangement was a straightforward methodology for the synthesis of the desired amino acids. This methodology also can be used for the synthesis of amino alcohols which are common structural components in bioactive nature products and important synthetic building blocks in organic synthesis.[9]

Glycine amide derivatives **4** were synthesized using the secondary amine pyrrolidine **3a** and *N*,*N*-diisopropylamine **3b** (Scheme 1), as we expected that a 2,5-diphenylpyrrolidine C_2-symmetric auxiliary and other enantiopure secondary amines would provide an excellent enantioselective rearrangement later on.[10] Various commercially available allyl alcohols were used successfully for the rearrangement as shown in Table 1. After Meerwein salt formation and lithium allyl oxide **6** addition, rearrangement provided products with different *β*-substituents upon warmup. It should be indicated that the *β*,*β*-dimethyl-*γ*,*δ*-unsaturated amino acid derivative **8a-2** could not be synthesized by direct alkylation using 3-bromo-3-methyl-1-butene because an S_N2' addition would happen instead.

The Eschenmoser–Claisen rearrangement results are summarized in Table 1. Various amounts of MeOTf were investigated and 2.2 equiv was found to be the best. Mechanistically, two equivs of methyl triflate was consumed in intermediate **5** (Scheme 1). In practice, a minimum of 2.2 equiv of the alcohol was needed to get good yields. Larger amounts of alcohol usually gave higher yields. Stoichiometric amounts of 2,6-di-*tert*-butyl-pyridine were used to scavenge triflic acid formed during the Meerwein salt formation.[11]

The diastereomeric ratios were determined via proton NMR spectra of the crude samples. We were delighted to see that the reaction generated good to excellent diastereoselectivities. *N*,*N*-Diisopropylamine (Scheme 1, **4b**) provided a little better result in entry 5 (Table 1). These good diastereoselectivities can be explained via unique (*Z*)-*N*,*O*-ketene acetal formation and an excellent chairlike transition state in the rearrangement.[12] Unlike the Kazmaier–Claisen intermediate where the enolate oxygen stays preferentially cis to the glycyl nitrogen due to chelation control, the Eschenmoser–Claisen intermediate could adopt two possible configurations (Figure 2) due to the lack of the enolate oxygen. Presumably, the thermodynamically more stable intermediate **9** is the predominant configuration.[13] It should be noted that we tried to quench intermediate **9** using several saturated alcohols. However, this *N*,*O*-ketene acetal intermediate was unstable and hydrolyzed easily even in neutral aqueous solution.

The hydrolysis of these rearranged amides was tricky because of the presence of a terminal double bond and the *N*-Cbz protecting group. There are many amide bond hydrolysis methods reported.[14] However, basic conditions cleaved the Cbz group and caused epimerization. Strong acidic conditions also removed the Cbz group and led to partial hydrolysis of the terminal double bond. A reduction–hydrolysis approach was convenient in this case, and among many reducing agents, lithium trimethoxyaluminum hydride[15] and sodium aluminum hydride[16] worked well.

Epimerization was observed during workup because amino aldehydes are notorious for racemerization under either basic or acidic conditions.[17] The presence of a *β*-substituent and

a γ-double bond makes the α-proton even more labile. The side reaction was initiated upon aldehyde generation during the hydrolysis of the reduced complex. To minimize epimerization, we developed in situ modified Lindgren oxidation[18] at low temperature (Scheme 2). In this way, the aldehyde was oxidized simultaneously to the carboxylic acid. Several amino alcohols were obtained from further reduction of the amino aldehydes that were isolated at low temperature by extraction (Scheme 2). Little epimerization was observed during the workup process. The diastereomerically pure amino alcohols were obtained after flash column chromatography purification.

The lack of epimerization using the modified reductive hydrolysis and aldehyde oxidation was demonstrated using an ^{1}H NMR spectra comparison between the epimerized and the diastereomerically pure product **12-5** (Figure 3). The downfield minor diastereomeric peaks from in situ oxidation are almost undetectable, indicating minimum epimerization. The broad peak at 4.63 ppm was likely from a rotamer of the product. This was proven by NOE experiments (Figure 4).[19] Irradiation of the peak at 4.63 ppm resulted in the inversion of its exchange peak at 4.78 ppm. The size of the exchange peak increased as the NOE mixing time was increased.

The relative stereochemistry of **12-3** was confirmed by comparing its ^{13}C NMR chemical shift to the minor product synthesized from an ester enolate Claisen rearrangement.[1] A single-crystal X-ray structure of compound **8b-5** also was obtained (Figure 5). An anti relationship of the α-amino group and the β-phenyl group was unambiguously shown in this structure.

In summary, we have developed a convenient methodology for the synthesis of anti-β-substituted γ,δ-unsaturated amino acids for the first time using a Meerwein Eschenmoser–Claisen rearrangement. This [3,3]-sigmatropic rearrangement gives excellent diastereoselectivities. Both the amino acid and the amino alcohol can be easily purified and are ready for scale-up. The enantiomerically pure synthesis of these novel compounds using enantiopure C_2-symmetric 2,5-diphenylpyrrolidine is currently under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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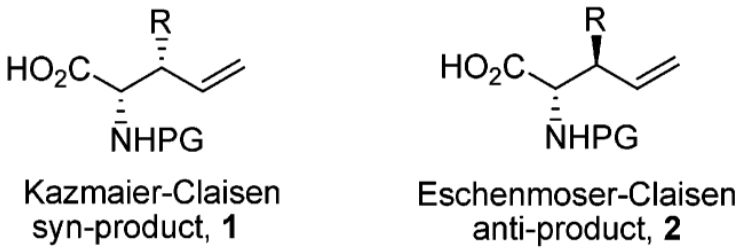
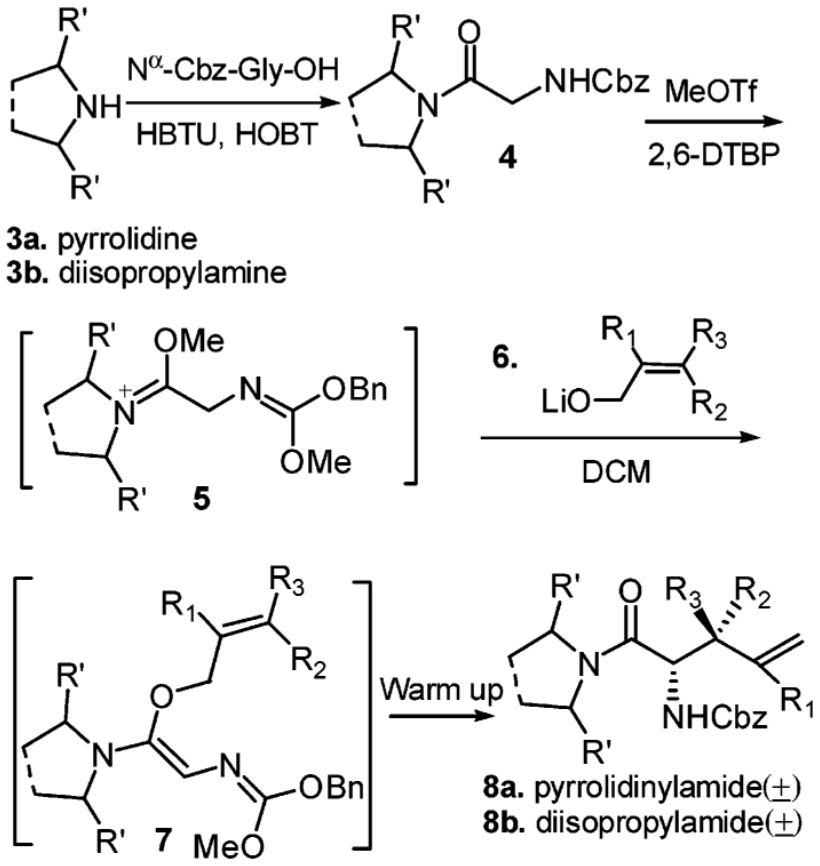


Figure 1.
Syn- and anti-β-substituted γ,δ-unsaturated amino acids.



Scheme 1.
Meerwein Salt Formation and Eschenmoser–Claisen Rearrangement

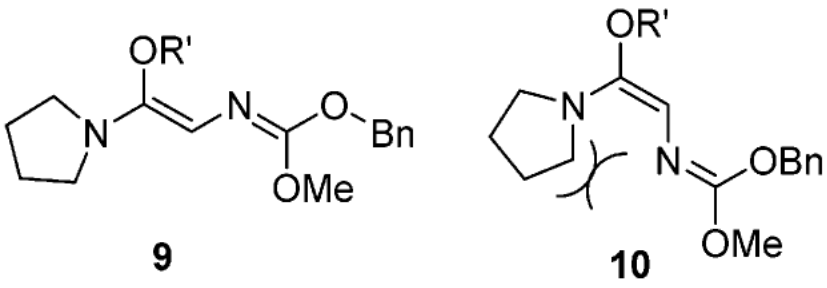
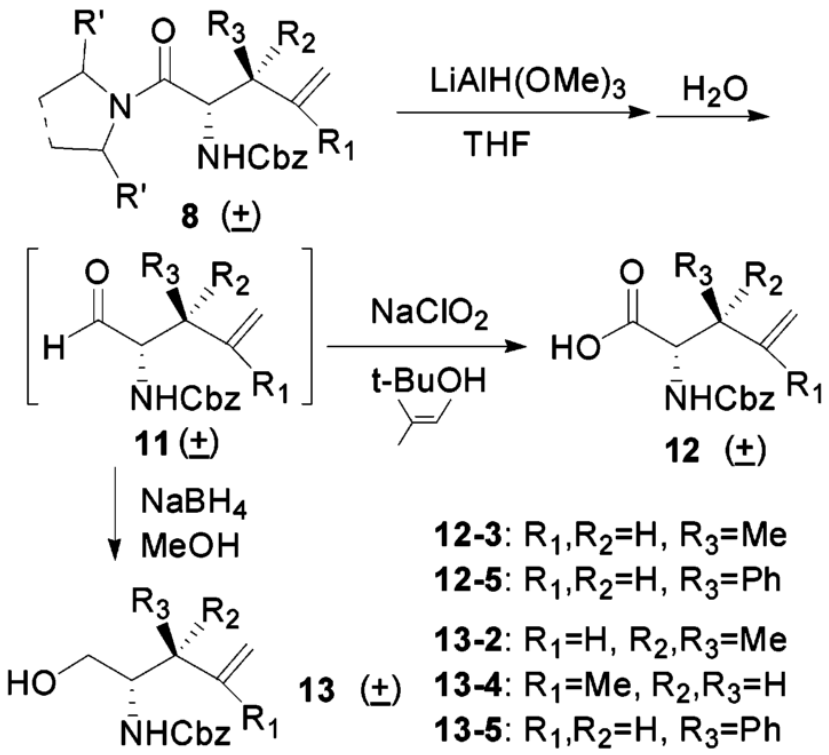


Figure 2.
(*Z*)- and (*E*)-*N*,*O*-ketene acetal reaction intermediates.



Scheme 2.
Reductive Hydrolysis, Amino Acid, and Amino Alcohol Generation

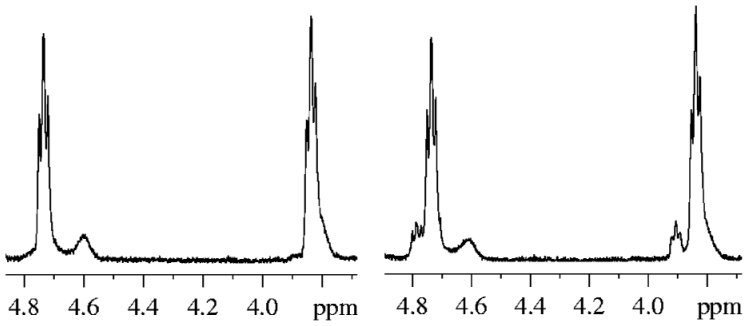


Figure 3.
^{1}H NMR spectra of **12-5** from different oxidation approaches. Left: in situ oxidation. Right: oxidation after workup.

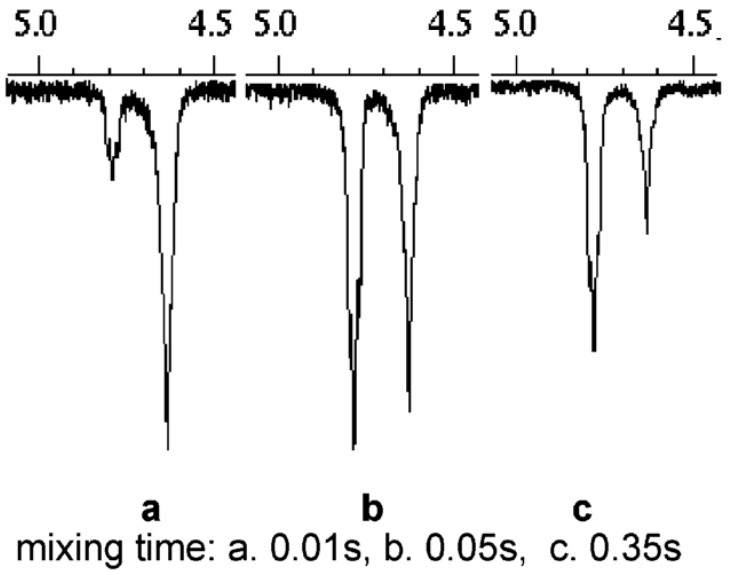


Figure 4.
Rotational interexchange study of **12-5** by NOE.

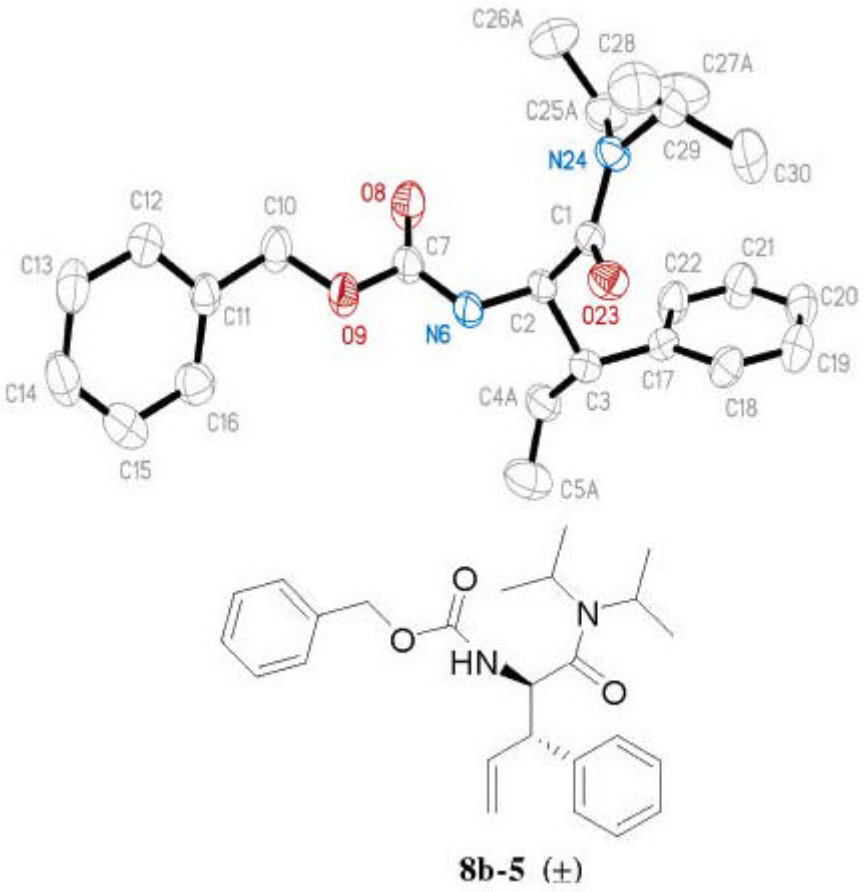
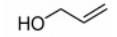
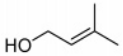
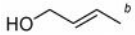
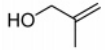
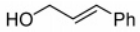


Figure 5.
X-ray structure of product **8b-5** with an anti-*β*-substituent.

Table 1

Results of Eschenmoser–Claisen Rearrangement

entry	allylation agent	alcohol equiv.	reaction temp °C	reaction time h	anti/syn	yield (%)[a]
1		4	−35–rt	3.5	N/A	**8a-1, 75**
2		2.2	−35–35	4	N/A	**8a-2, 44**
3		2.2 2.2	−35–rt	2 4	9.6:1 8.0:1	**8a-3, 61** **8b-3, 56**
4		4	−35–rt	6	N/A	**8a-4, 72**
5		4 2.2	−35–rt	4 17	16.8:1 20:1	**8a-5, 74** **8b-5, 77**

[a] Isolated yields. Compounds **a** are from pyrrolidinylamide, and compounds **b** are from diisopropylamide.

[b] Crotyl alcohol is a trans/cis mixture (19:1) from Sigma-Aldrich.