ORGANIC LETTERS

2008
Vol. 10, No. 18
4105−4108

Enantioselective Synthesis of *anti*-β-Substituted γ,δ-Unsaturated Amino Acids: A Highly Selective Asymmetric Thio-Claisen Rearrangement

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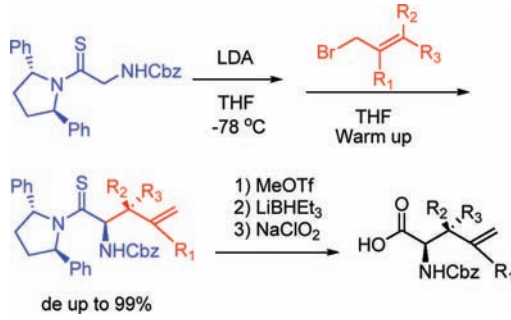
Received July 21, 2008

ABSTRACT



A novel synthesis of optically active *anti*-β-substituted γ,δ-unsaturated amino acids via a thio-Claisen rearrangement has been achieved. A 2,5-diphenylpyrrolidine was used as a C_2-symmetric chiral auxiliary to control the stereochemistry, giving good yields and excellent diastereoselectivities and enantioselectivities.

Synthesizing optically active nonproteinogenic amino acids has played a crucial role in the development of peptides and peptidomimetics as therapeutic agents.[1] β-Substituted γ,δ-unsaturated amino acids have turned out to be especially important building blocks for these studies due to the diversified reactivities of the terminal double bond and their ability to introduce biologically active functionalities.[2] Constructing this type of structural skeleton has been under investigation for many years, and one of the most powerful synthetic methods toward these goals is the Claisen rearrangement.[3] Kazmaier et al. have reported stereoselective syntheses of *syn*-β-substituted γ,δ-unsaturated amino acids via a chelate Claisen rearrangement.[4] However, progress on making *anti*-β-substituted γ,δ-unsaturated amino acids was

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(2) (a) Ruties, T. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, *24*, 4197. (b) Morimoto, Y.; Takaishi, M.; Kinoshita, T.; Sakaguchi, K.; Shibata, K. *Chem. Commun.* **2001**, *18*, 1820. (c) Gu, X.; Ying, J.; Min, B.; Cain, J.; Davis, P.; Willey, P.; Edita, N.; Yamamura, H.; Porreca, F.; Hruby, V. J. *Biopolymers* **2005**, *80*, 151. (d) Gu, X.; Cowell, S.; Ying, J.; Tang, X.; Hruby, V. J. *Tetrahedron Lett.* **2003**, *44*, 5863.

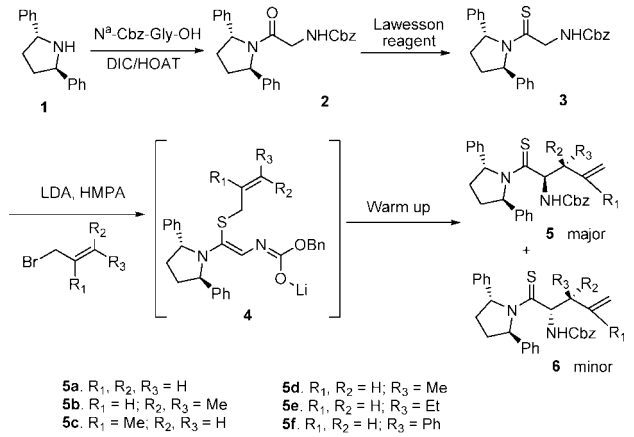
(3) (a) Kübel, B.; Höfle, G.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 58. (b) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.

10.1021/ol801657q CCC: $40.75
Published on Web 08/15/2008

not satisfying because of the relative unavailability of *Z*-allylic alcohol sources and the competing rearrangement boatlike transition state when a *Z*-allylic alcohol is applied.[5] The ester-enolate Claisen rearrangement has been reported for the synthesis of these molecules; however, limited chiral starting materials and epimerization during the synthesis are problems that remain to be solved.[6] Most recently, our group has achieved a synthesis of such amino acids via the Eschenmoser−Claisen rearrangement with excellent diastereoselectivity and good enantioselectivity.[7] Here we report on another novel, complementary synthesis via a thio-Claisen rearrangement. This method is straightforward and highly selective using a bulky C_2 symmetric chiral auxiliary, and the chiral auxiliary can be recycled after producing the final amino acids.

The C_2 symmetric chiral auxiliary (2*R*,5*R*)-2,5-diphenylpyrrolidine (**1**) was prepared in optically pure form[8] and coupled to N^{α}-Cbz glycine to generate amide **2** using DIC/HOAt as the coupling reagent. This coupling reaction gave excellent yields despite the steric hindrance of the phenyl rings (Scheme 1). A thionation reaction with Lawesson's

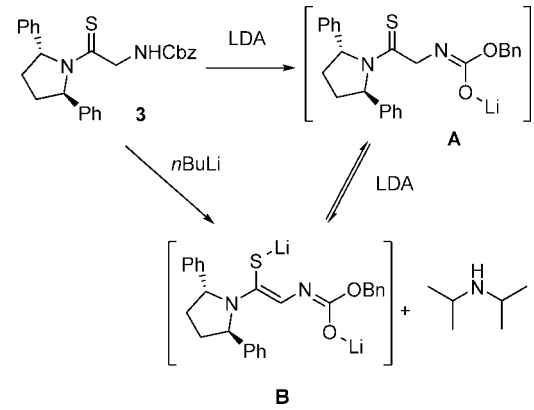
Scheme 1. Generation of Thio-Enolate Dianion and Asymmetric Thio-Claisen Rearrangement



reagent converted the amide to the thioamide **3** in quantitative yield.[9] The thio-enolate was made by treatment of **3** with freshly prepared LDA in THF at −78 °C, and then the allylic bromide was added to the reaction to alkylate the enolate at the sulfur position. Thio-Claisen rearrangement occurred when the reaction mixture was warmed up slowly to room temperature or higher (when necessary) to afford thioamides **5** and **6** (Scheme 1).

Our first attempts at this reaction with 2.2 equiv of LDA gave unsatisfactory results. The yields were extremely low with large amounts of starting materials recovered. After examining the structure more carefully, we realized that this might be caused by a two-step deprotonation. The proton on the α amino group is the most acidic one, which would be removed first to give **A**. However, this makes the deprotonation of the α proton much harder.[10] The resulting thioenolate dianion **B** is a new system that has never been examined before to our knowledge. We postulated that **B** might be capable of pulling the proton on the diisopropylamine back, making the dianion formation a reversible process (Scheme 2).[11] If so, an excess amount of LDA

Scheme 2. Equilibrium of Thio-Enolate Dianion Deprotonation



possibly can push the equilibrium toward the dianion, or using a stronger base to make it an irreversible process might solve the problem. To test this hypothesis, we increased the amount of LDA to 3.2 equiv, and a significant improvement in the reaction was observed: the yields were much better and no starting material was observed after work up. A 2.2-equiv portion of *n*BuLi also gave acceptable results, but extra *n*BuLi is not desired because of the nucleophilicity of the *n*-butyl anion. HMPA was also added before adding the allylic bromide, and this was found to increase the product yield and reduce the formation of C-alkylation side products. The results of the rearrangement studied on six commercially available allylic bromides are summarized in Table 1.

Despite higher temperatures being required in some cases, the diastereoselectivities generally were excellent, and only *anti* products were obtained as expected. In many cases, only optically pure compounds were obtained. The absolute configuration of the product **5d** was determined by X-ray

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(5) Kazmaier, U. *J. Org. Chem.* **1996**, *61*, 3694.

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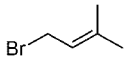
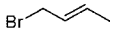
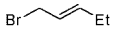
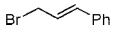
(11) (a) Laube, T.; Dunitz, T. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. (b) Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507.

Table 1. Results of Asymmetric Thio-Claisen Rearrangement

entry	allylation agent	t(°C)	anti:syn[a]	de(%, **5**/**6**)[a]	yield (%)[b]
a		-78-rt	NA	>99	82
b		-78-reflux	NA	>99	66
c		-78-rt	NA	>99	74
d		-78-40	>99:1	>99	78
e		-78-40	>99:1	78	76
f		-78-rt	>73:1	75	65

[a] Determined by chiral HPLC. [b] Isolated yield of total isomers.

crystal structural analysis (Figure 1). It shows an *R*-configuration at all of the four chiral centers. This result is consistent with the model (Figure 2) suggested by He et al.[12] when they studied the thio-Claisen reaction on tertiarythioamide. Deprotonation of the thioamide **3** gives the *Z*-

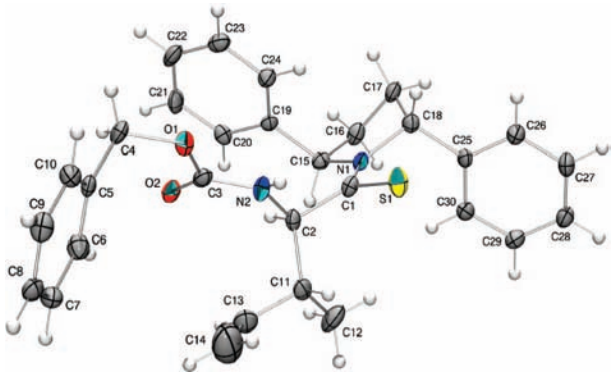


Figure 1. X-ray crystal structure of **5d**.

thioenolate as the primary product.[13] The two possible chairlike transition states are shown as **C** and **D** in Figure 2, and **C** is favored for the obvious steric reasons. A decrease of the diastereoselectivity was observed during the study as the size of R_3 was increased (entries e and f). Presumably, this was caused by the increasing steric repulsion between the Cbz group and R_3.

The diastereoselectivity was determined by chiral HPLC after converting the thioamide to an amide.[14] It should be pointed out that although most products contain only one diastereomer, the ^{1}H NMR shows two sets of peaks, which was confirmed to be caused by Cbz rotamers after we performed an NOE study (Figure 3).[15] Irradiation of the peak

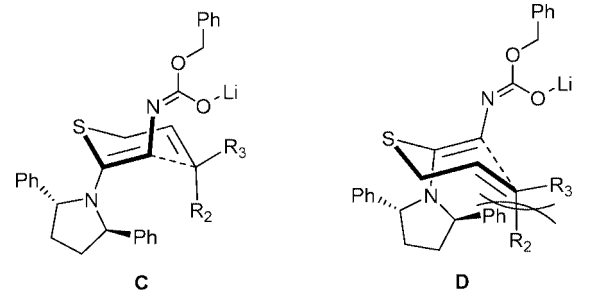


Figure 2. Proposed transition state model of thio-Claisen rearrangement.

at 5.61 ppm resulted in the inversion of its exchange peak at 5.51 ppm, which indicates these two peaks arise from the same proton. The relative intensity of the exchange peak increased as the NOE mixing time was increased, which demonstrated that the irradiation selectivity was good.

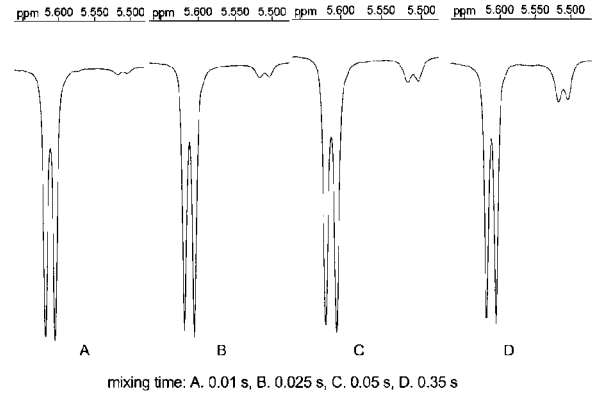


Figure 3. Rotational interexchange study of **5c** by NOE.

The step of removing the chiral auxiliary was tricky. Regular acidic or basic hydrolysis is obviously not good because such harsh conditions will cause epimerization at the α carbon and may cleave the N^{α}-Cbz protecting group. Besides, it is impossible to reduce a thioamide like an amide to an alcohol or aldehyde because thioamides are inert to regular metal hydride reducing reagents.[16] In our case, α-amino thioamides are especially unreactive due to a possible hydrogen bonding between the NH and the sulfur.[17] It shows no reactivity when using the common BF_4OEt_2 method[12,18] even when the reaction was performed in dichloroethane at 80 °C. Fortunately, we were finally able

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(14) (a) Kochhar, K. S.; Cottrell, D. A.; Pinnick, H. W. *Tetrahedron Lett.* **1983**, *24*, 1323. (b) See Supporting Information for details.

(15) Hatano, T.; Hemingwei, R. W. *J. Chem. Soc., Perkin Trans. 2* **1997**, *5*, 1035.

(16) To the best of our knowledge, direct metal hydride reduction of thioamides has not been reported to date.

(17) (a) Hollósi, M.; Majer, Zs.; Zewdu, M.; Ruff, F.; Kajtár, M.; Kövér, K. E. *Tetrahedron* **1988**, *44*, 195. (b) Hansen, P. E.; Duus, F.; Bolvig, S.; Jagodzinski, T. S. *J. Mol. Struct.* **1996**, *378*, 45.

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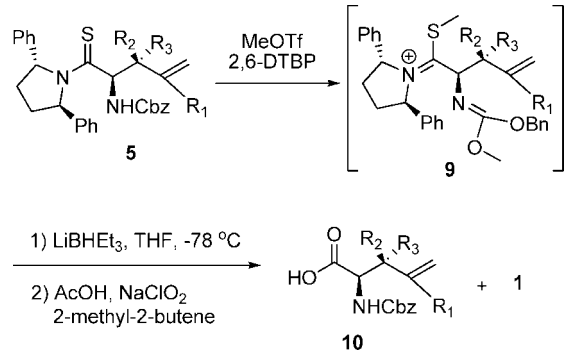
to develop a one-pot alkylation−reduction−oxidation reaction that could readily recycle the chiral auxiliary and turn the amino thioamide into amino acids with a minimal loss of optical activity. To our knowledge, this is the first example of successfully reducing an α-amino tertiarythioamide to an aldehyde. After screening several alkylation reagents and conditions, we found that methyl triflate provided a high-yield *S*-alkylation at ambient temperatures, and this allowed the resulting thioiminium salt **9** to be reduced to an *N*,*S*-acetal by Superhydride. This was followed by amino aldehyde generation by quenching and an in situ modified Lindgren oxidation at low temperature[19] to provide the desired products **10** with little or no epimerization (Scheme 3). The results of this reaction are summarized in Table 2.

Scheme 3. Alkylation−reduction−oxidation for Amino Acids Generation and Chiral Auxiliary Recycle



The *anti*/*syn* ratio and enantioselectivity were determined by ^{1}H NMR and chiral HPLC by comparing them with authentic samples, respectively. An increase of ee value with a decrease of *anti*/*syn* ratio at the same time was observed in the last three entries. This should be caused by losing chirality at the α-carbon but not at the β-carbon during the synthesis. The results are consistent with the results of compounds **5**. When the aldehyde was separated and purified, we observed a complete loss of optical activity as this type of compound was known not to be stable at room temperature.[20]

(19) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825.

Table 2. Results of Amino Acid Generation

compound **10**	*anti*:*syn*[a]	ee[b] (%)	yield (%)[c] (three steps)
a	NA	94	42
b	NA	95	37
c	NA	96	32
d	100:9	98	40
e	100:22	87	44
f	100:12	81	34

[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC by comparison with the racemic compounds prepared from previously reported Eschenmoser−Claisen rearrangement.[7a] [c] Isolated yield of total isomers after three-step reaction.

In summary, we have developed a novel method to synthesize *anti*-β-substituted γ,δ-unsaturated amino acids. The thio-Claisen rearrangement gives excellent diastereoselectivities, and optically active amino acids were obtained after a low-racemization one-pot alkylation−reduction−oxidation reaction to cleave the chiral auxiliary. This reaction is ready to be scaled up, and the application of these amino acids for preparing cyclic peptideomimetics will be reported in the future.

Acknowledgment. This work was supported by U.S. Public Health Service grants DK 17420 and the National Institute of Drug Abuse DA 06284, DA 13449. We also thank Prof. Richard Glass (the University of Arizona) for useful discussions.

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.

OL801657Q

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