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Asymmetric synthesis of α,β-substituted γ-amino acids via conjugate addition

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ABSTRACT

The first conjugate addition reaction of organocuprates to *N*-enoyl oxazolidinone where a *N*-protected γ-nitrogen atom and an α-methyl group are present into α, β-unsaturated system is described. This reaction gave *anti*-products in moderate yields and high diastereomeric ratios. The *anti*-products have two contiguous stereogenic centers, one formed by the conjugate addition reaction and the other by a diastereoselective protonation reaction. The removal of chiral oxazolidinone moiety and *N*-deprotection of amino group furnished chiral α, β-disubstituted γ-amino acids.

(*S*)-Pregabalin is marketed as pharmaceutical for the treatment of diseases accompanied with GABA recepors [1]. (*S*)-Pregabalin has potent and robust activity in preclinical models predictive of clinical efficacy in anxiety [2], epilepsy [3] and neuropathic pain [4] since the molecule interacts with α_2-δ subunit of calcium channels [5] and is a substrate of the L transporter system [6]. The precise mechanism through which, pregabalin exhibits its pharmacological action has been the subject of many studies in recent years. It is noteworthy that (*R*)-pregabalin lacks antiepileptic, analgesic or anxiolytic activity *in vivo* animal models, since it has significantly weaker affinity for α_2-δ and system L transporter. The α-substituted γ-amino acid has reduced affinity for both the α_2-δ and the system L transporter [7]. This structure-activity relationship has led to put more emphasis on stereoselective synthesis of α-, β-substituted γ-amino acid derivatives. However, to date the methodologies to achieve α, β-disubstituted γ-amino acids are restricted [8]. Wustrow [7] described the synthesis of γ-amino acids analogs to pregabalin adding methyl group at position along the pregabalin backbone and determined the structure-activity relationship with their affinity for α_2-δ subunit and the system L transporter (biological activity) (Fig. 1). We report herein, the first diastereoselective conjugate addition reaction of organocuprates to chiral *N*-enoyl oxazolidinone, where the methyl group and protected nitrogen atom have been incorporated into the α, β-unsaturated system. The removal of chiral oxazolidinone from conjugate addition product and *N*-deprotection of nitrogen atom in amino group produced the α, β-disubstituted γ-amino acids.

The synthesis began with the development of the (*E*)-4-(dibenzylamino)-2-methylbut-2-enoic acid. The tiglic acid **1** was treated with concentrated H_2SO_4 and EtOH, which was used both as solvent as reagent, at reflux for 7 h to give the ethyl tiglate **2** in 91%, as shown in Scheme 1. Ester **2** was exposed to allylic bromination reaction conditions according to the Pronin's protocol, treating **2** with LDA solution (1 M, THF) and TMSCl in the presence of NBS at −78 °C to furnish the brominated compound **3** in 40% yield [9]. The brominated compound **3** was coupled with dibenzylamine in THF for 12 h at room temperature to yield (*E*)-ethyl-4-(dibenzylamino)-2-methylbut-2-enoate **4** as yellow liquid in 80% yield [10].

Ester **4** was hydrolyzed using an aqueous solution 5 N of NaOH in MeOH/H_2O at room temperature for 12 h affording (*E*)-4-(dibenzylamino)-2-methylbut-2-enoic acid **5** as a white solid in 95% yield, as shown in Scheme 2 [11]. This compound 5 was transformed to its respective anhydride using pyvaloyl chloride in the presence of Et_3N in anhydrous THF, for 15 min at −78 °C and subsequent stirring at 0 °C for 45 min to give compound **6** in a quantitative yield. This anhydride **6** was used in the next reaction without purification. The chiral oxazolidinone **7** was treated with a solution of *n*-butyllithium (2.5 M, hex.) in anhydrous THF at −78 °C for 15 min followed by the addition of anhydride **6** in anhydrous THF. The reaction mixture was stirred at room temperature

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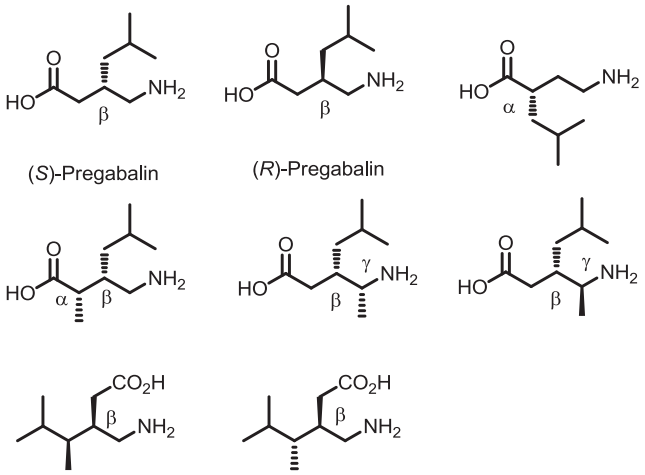
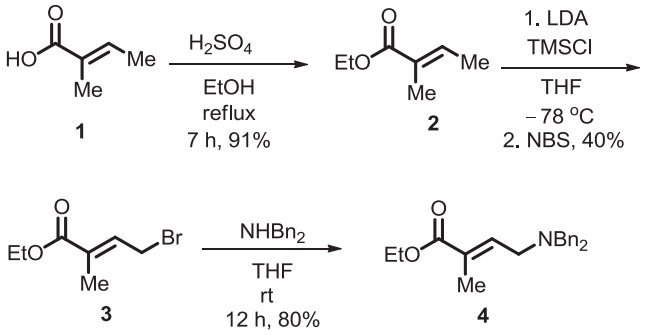
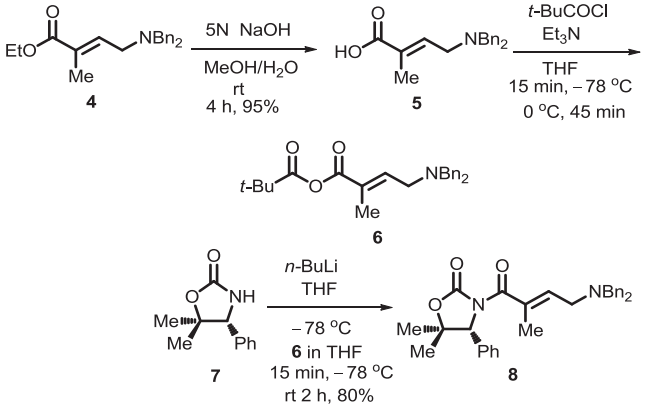


Fig. 1. Analog compounds to Pregabalin.



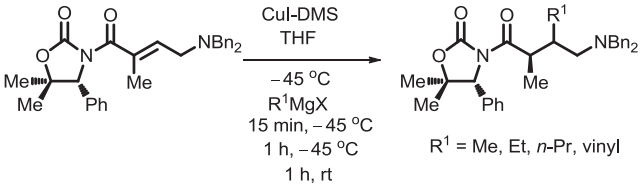
Scheme 1. Incorporation of *N*-protected amino group to α, β-unsaturated system.



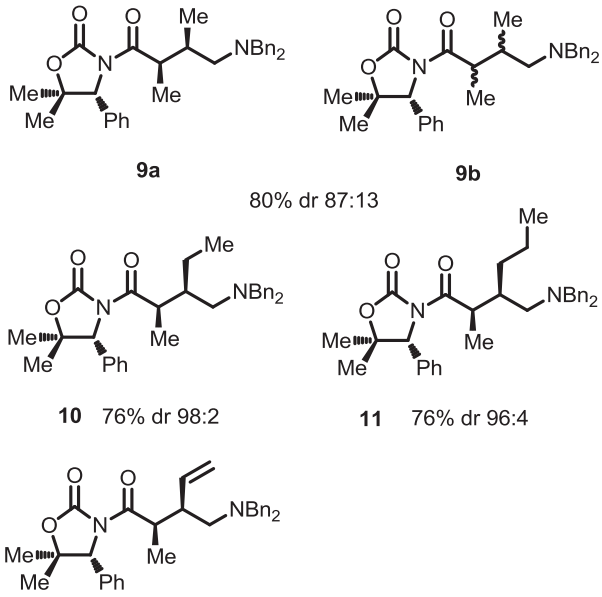
Scheme 2. Coupling reaction of γ-amino acid and chiral oxazolidinone.

for 2 h to give *N*-enoyl oxazolidinone **8** in 80% yield [12], as a white solid.

N-enoyloxazolidinone **8** was treated under conjugate addition reaction conditions [12]. The Gilman's reagent was achieved from the reaction of CuI-DMS complex and methyl magnesium bromide at −45 °C to provide the respective diorganocuprate, which was added to *N*-enoyloxazolidinone **8** in anhydrous THF, as shown in Scheme 3. The reaction mixture was stirred for 1 h at −45 °C and for 1 h at room temperature to provide a mixture of diastereoisomers **9a**/**9b** in 80% yield and with 87/13 diastereomeric ratio (Scheme 4), which was determined by NMR of crude reaction



Scheme 3. Reaction conditions to conjugate addition.



Scheme 4. *Anti*-products from conjugate addition.

mixture. The products were isolated by silica gel column chromatography with hexane:ethyl acetate 97:3 as eluent. The stereochemistry of the major product **9a** was possible to establish from the structure achieved by X-ray diffraction and the configuration at newly formed chiral centers is (*R*, *R*). The major product **9a** corresponds to the *anti*-product, as shown in Fig. 2. High diastereoselectivity was observed, when the *N*-enoyloxazolidinone **8** was treated under the same conjugate addition reaction conditions using other organocuprates (Et, *n*-Pr, vinyl) to give the *anti*-products **10**, **11** and **12** with 75–76% yields and diastereomeric ratios (98:2) which were determined by NMR of crude reaction mixtures, as shown in Scheme 4.

The stereoselectivity of the major *anti*-products **9a**-**12** can be rationalized when *N*-enoyloxazolidinone **8** adopts *syn*-s-*cis* conformation, where the organocuprate reagent attacks at C β of α, β-unsaturated system by the less hindered side, on the opposite side to the phenyl group, and a diastereoselective protonation reaction is carried out for the same side of the phenyl group, as shown in Scheme 5.

The removal of chiral oxazolidinone moiety of compounds **9a**-**12** was carried out with Evans' protocol using LiOH, H_2O_2 in THF-H_2O at room temperature to give *N*-protected γ-amino acids **13**–**16** in good yields (85–90%) and recovering chiral oxazolidinone in 80% yield [13], as shown in Scheme 6.

For the *N*-deprotection of amino group, the compounds **13**–**16** were exposed to hydrogenation reaction conditions using a catalytic amount of Pd/C in EtOH at room temperature for 16 h to

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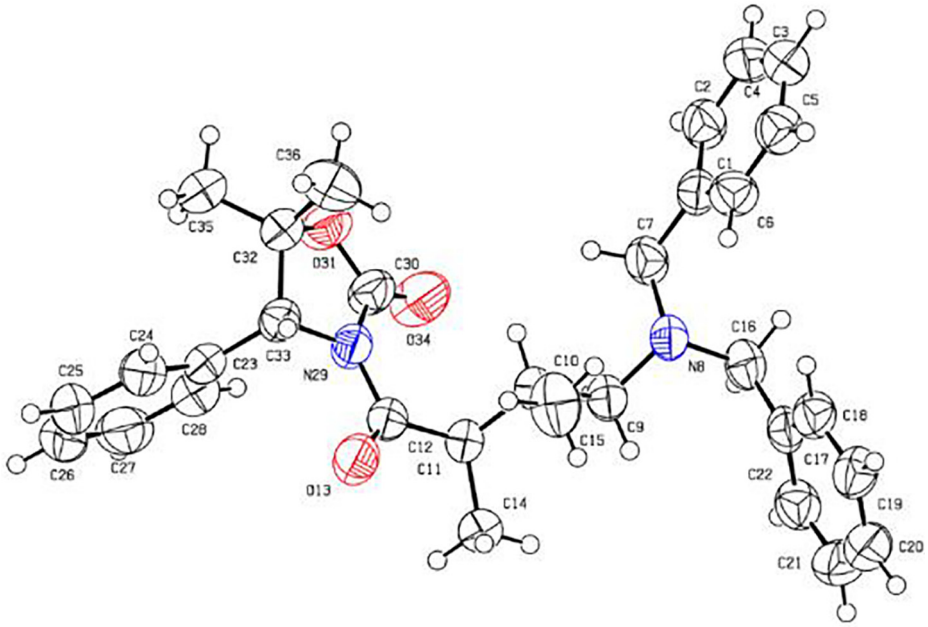
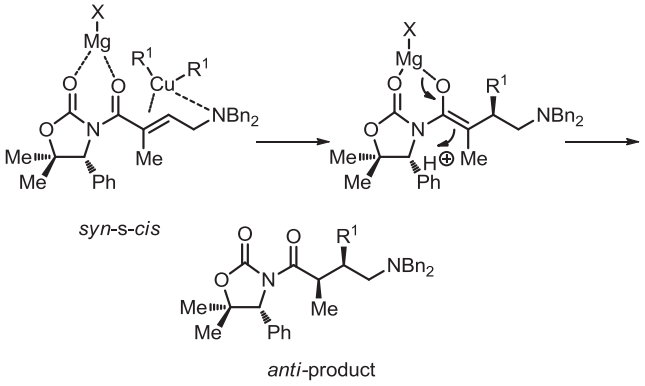
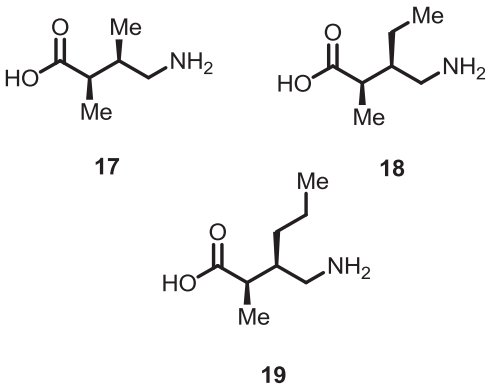


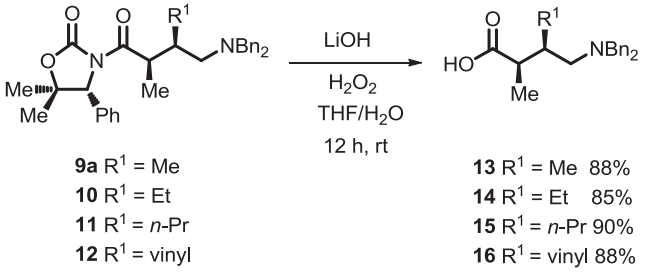
Fig. 2. Molecular structure of the compound **9a.** Summary of Data CCDC 1916099.



Scheme 5. The stereoselectivity can be rationalized by this possible transition state.



Scheme 7. Chiral α, β-disubstituted γ-amino acids.



9a R^1 = Me
10 R^1 = Et
11 R^1 = *n*-Pr
12 R^1 = vinyl

13 R^1 = Me 88%
14 R^1 = Et 85%
15 R^1 = *n*-Pr 90%
16 R^1 = vinyl 88%

Scheme 6. Chiral oxazolidinone moiety removal.

deliver α, β-disubstituted γ-amino acids **17**–**19** in quantitative yields (93–94%). The compound **16** was exposed to hydrogenation conditions, and both *N*-deprotection of the amino group and vinyl group double bond hydrogenation were carried out giving the α, β-disubstituted γ-amino acid **18** in 90% yield, as shown in Scheme 7.

In conclusion, we have described the first conjugate addition reaction of organocuprates to *N*-enoyloxazolidinone, where γ-nitrogen atom and α-methyl group are presents into α,β-unsaturated system. The reaction furnished the *anti*-products in moderated yields and with high diastereomeric ratios (98:2). The addition products have two contiguous stereogenic centers, one formed by the conjugate addition reaction and the other by a diastereoselective protonation reaction. The removal of the chiral oxazolidinone moiety and *N*-deprotection produced α, β-substituted γ-amino acids. Our research is ongoing to study the role that nitrogen atom and methyl group are playing in transition state of the conjugate addition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.05.060.

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