Non-racemic Diastereoselective Synthesis of gamma-lactams via Michael Addition of 1,3-dicarbonyl Compounds to Chiral Nitroalkenes.

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INTRODUCTION

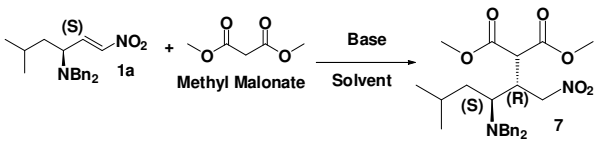
Nitroalkenes are one of the most versatile intermediates in organic synthesis[1]. Since they are electrondeficient alkenes participle of a huge number of reactions of carbon-carbon and carbon-heteroatom bond formation with varied nucleophiles in Michael addition, Baylis-Hillman and Friedel-Crafts reactions beyond cycloadditions ([3+2] and [4+2]). Stereoselective synthesis using natural aminoacids as chiral pool is very attractive since they are low cost and versatile starting materials.

Michael Addition of 1,3-dicarbonyl compounds to nitroalkenes is one very studied reaction. Nowadays, the enantioselective version to this reaction is widely accomplished via organocatalysis approach. A few examples via chiral pool were found in literature. The chiral nitroalkenes (**1a-c**) were synthesized by first time for us from natural L-aminoacids (**2a-c**) in 5 steps with an global average yield of 93-97%. Giving pursuit to our strategy of synthesizing new chirons and chiral bioactive substances via aliphatic nitroalkanes[2] we relate here the conjugate addition of methyl malonate to nitroalkene **1a** and the transformation in corresponding γ-lactam in high d.e. and yield.

RESULTS AND DISCUSSION

The addition of methyl malonate to **1a**, at room temperature, was investigated in several base-solvent systems (Table 1/Scheme 1). The best result was obtained using neat Amberlyst A-21 furnishing 72% of **7a** as a single diastereoisomer (entry 2).

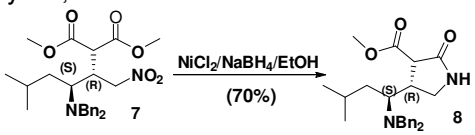
Table 1/Scheme 1: Reactivity of nitroalkene (**1a**) and methyl malonate in diverse reaction conditions.



Entry	Base	Solvent	Yield(%)[c]
1	Amberlyst-21	THF	53%
2	Amberlyst-21	---	72%
3	TBAF (40%)	THF	45%
4	TBAF (20%)	THF	40%
5	TEA	THF	---
6	TEA	MeCN	42%
7	TEA	DMSO	40%
8	TEA	DMF	32%
9	HMTA	THF	a
10	HMTA	DCM	a
11	HMTA	DMSO	b

a) Complex mixture of byproducts, yield not determined. *b)* Product degradation. *c)* Purified yield.

Next, the reduction of nitro group and cyclization was made in one pot to give the **8** as unique product in 70% yield, Scheme 2.



Scheme 2: Synthesis γ-lactam **8** from **7**.

CONCLUSION

We succeed to produce the γ-lactam **8** as one single diastereoisomer from chiral nitroalkene **1a.** NMR experiments are being accomplished to determine the relative configuration of the stereocenters formed. The synthesis of new γ-lactams from others nitroalkenes and their biological activity screening are in course.

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