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An efficient and scalable synthesis of *N*-(benzyloxycarbonyl)- and *N*-(methyloxycarbonyl)-(*S*)-vinylglycinol

Alexandre Lumbroso, Vincent Coeffard, Erwan Le Grognec *, Isabelle Beaudet, Jean-Paul Quintard *

Université de Nantes, CNRS, Chimie Et Interdisciplinarité: Synthèse, Analyse et Modélisation (CEISAM), UMR CNRS 6230, Faculté des Sciences et des Techniques, 2, rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France

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ABSTRACT

An efficient and scalable synthesis of *N*-(benzyloxycarbonyl)- and *N*-(methyloxycarbonyl)-(*S*)-vinylglycinol has been reported starting from the commercially available L-methionine. The scale-up preparation consisted of 5 steps and delivered up to 50 g of the desired *N*-protected β-amino alcohols in 32% and 36% overall yields.

1. Introduction

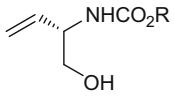
The synthesis of enantioenriched β-amino alcohols continues to be an intense area of research due to the importance of these compounds as stereochemical control elements in asymmetric synthesis[1] or as building blocks for the preparation of biologically active molecules.[2] In particular, enantiomerically pure *N*-protected vinylglycinol has found a widespread use for the construction of natural products and functionalized chiral molecules.[3]

To date, most of the syntheses related to chiral vinylglycinol or vinylglycine deal with *N*-Cbz-(*S*)-vinylglycinate and *N*-Boc-(*S*)-vinylglycinate and start from the commercially available and inexpensive L-methionine,[4,3c] L-serine,[5] (*S*)-glutamic acid,[6] (*S*)-homoserine[7] or (*S*)-homocysteine.[8] In addition, several stereocontrolled approaches involving a transition-metal catalyzed reaction as the key step with palladium,[3f,9] nickel[10] and iridium[11] complexes have also been described. However, these routes have been scarcely used probably due to the cost of the metal catalyst when large quantities of the β-amino alcohols are required. The *N*-Cbz and *N*-Boc vinylglycinols have also been synthesized in racemic form starting from 2-butene-1,4-diol. A subsequent kinetic resolution achieved with a lipase afforded the enantioenriched β-amino alcohols.[12]

Our recent studies on the preparation of chiral tributylstannyl β-amino alcohols have prompted us to consider a large variety of *N*-protected β-amino alcohols as chiral auxiliaries.[13] In this context, we required gram quantities of *N*-protected (*S*)-vinylglycinol in enantiomerically pure form to prepare novel tributylstannyl β-amino alcohols able to undergo olefin metathesis reactions.[14] We report herein an improved, scalable and efficient preparation of enantiopure *N*-(benzyloxycarbonyl)-(*S*)-vinylglycinol **1a** and the first synthesis of *N*-(methyloxycarbonyl)-(*S*)-vinylglycinol **1b** (Scheme 1).

2. Results and discussion

Although an efficient synthesis of *N*-Boc-(*S*)-vinylglycinol starting from L-serine has already been described,[5] we decided to take advantage of the lower cost of the reagents required for the transformation of L-methionine to consider the use of this starting material in our synthetic approach since we needed a scalable preparation of **1a** and **1b**. Therefore L-methionine **2** was first allowed to react with 2,2-dimethoxypropane according to the procedure reported by Rachele.[4a] Under these conditions, the hydrochloride salt **3** was isolated in 82% yield (Scheme 2).



1a, R = Bn
1b, R = Me

Scheme 1. *N*-Alkoxycarbonyl-(*S*)-vinylglycinol.

* Corresponding authors. Tel.: +33 2 51 12 54 09; fax: +33 2 51 12 54 02 (E.L.G.).
E-mail addresses: erwan.legrognec@univ-nantes.fr (E. Le Grognec), jean-paul.quintard@univ-nantes.fr (J.-P. Quintard).

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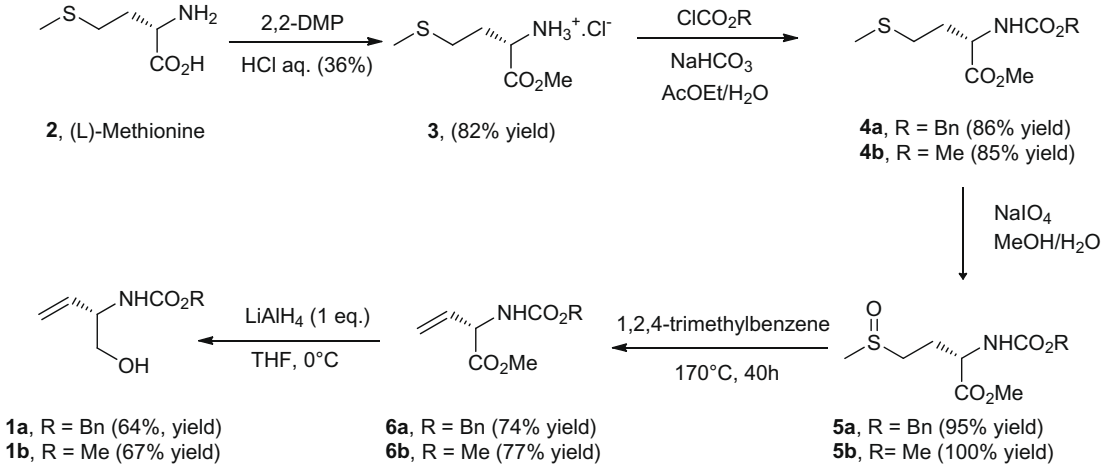
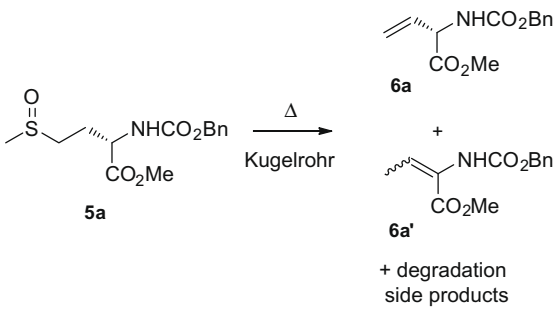


Scheme 2. Preparation of *N*-alkoxycarbonyl-(*S*)-vinylglycinol.

According to the literature,[4b] treatment of **3** in classical Schotten–Bauman conditions with benzylchloroformate afforded **4a** in 86% yield. A similar procedure using methylchloroformate gave rise to **4b** in 85% yield. Sulfur oxidation with sodium periodate provided the corresponding sulfoxides **5a** and **5b** in 95 and 100% yields, respectively.

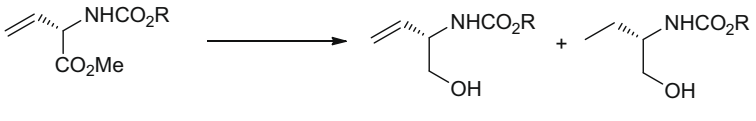
For the subsequent elimination, we first considered solvent-free conditions by using a Kugelrohr distillation as described by Rapoport.[4b] However, starting from **5a**, this procedure led to a mixture of the desired olefin **6a** along with **6a**′ resulting from a shift of the double bond, and some side products which were not characterized (Scheme 3). It is worthwhile noting that the isomerization of **6a** in **6a'** has already been observed by Rapoport and confirmed later on by Göbel.[4f,g] To prevent the formation of **6a**′, various strategies have been reported. In particular, the β-elimination step can be performed in mesitylene (Eb_{760} = 162–164 °C) rather than neat, to afford the desired product in 62% yield.



Scheme 3. Synthesis of the *N*-benzyloxycarbonyl-vinylglycinate **6a**.

Based on this work, various high-boiling point solvents were screened and 1,2,4-trimethylbenzene turned out to be the best solvent by affording **6a** in 74% yield after 40 h of reaction without any formation of **6a**′. Starting from **5b**, this procedure furnished also selectively **6b** in 77% yield. In addition, this procedure was found to be amenable to scale-up to 50 g of **6a** and **6b**. The last step was the selective reduction of the ester function which was reported to proceed with $LiBH_4$/MeOH in diethyl ether.[15] This procedure failed to be clean in our hands and the desired vinylglycinols **1a** and **1b** were obtained as mixtures containing up to 20% of ethylglycinol derivatives **7a** and **7b** (Table 1). The amount of **7a** and **7b** produced was depending on the $LiBH_4$ batch or commercial sources and all our efforts to avoid its formation were unsuccessful. In addition, all attempts to separate **7a** from **7b** by flash chromatography were unsuccessful. The formation of **7a** and **7b** can be explained by an hydroboration of the double bond by the in situ-formed BH_3 which led to the ethylglycinol derivatives after hydrolysis. By using $LiAlH_4$ at 0 °C in THF, no by-products were observed and **1a** and **1b** were isolated as pure compounds in 64% and 67% yields, respectively. The reduction was performed at 0 °C in order to avoid the reduction of the carbamate into its *N*-methyl

Table 1
Reduction of *N*-protected vinylglycinate into *N*-protected vinylglycinol



Entry	R	Conditions	Yield (%)	**1a/7a** or **1b/7b** ratio (%)
1	Bn	$LiBH_4$/MeOH (2 equiv), Et_2O, rt	64	80/20
2	Me	$LiBH_4$/MeOH (2 equiv), Et_2O, rt	75	84/16
3	Bn	$LiAlH_4$ (1 equiv), THF, 0 °C	64	100/0
4	Me	$LiAlH_4$ (1 equiv), THF, 0 °C	67	100/0

derivative.[16] It has also to be noted that attempts to replace $LiBH_4$/MeOH by Red-Al® failed affording only by-products. The observed optical rotation of **1a** $[\alpha]_D^{19}$ −32.0, (c = 1.0, $CHCl_3$) was in excellent agreement with the literature value of $[\alpha]_D^{25}$ −32.2, (c = 1.47, $CHCl_3$) or $[\alpha]_D^{25}$ −32.1, (c = 3.1, $CHCl_3$) for the compound having the *S* absolute configuration,[9a] while the observed optical rotation of **1b** was found to be $[\alpha]_D^{19}$ −23.6 (c = 1.0, $CHCl_3$).

3. Conclusion

This improved synthesis enables an easier and lower cost access to *N*-(benzyloxycarbonyl)-(*S*)-vinylglycinol (five steps, overall yield of 32% from L-methionine) without formation of ethylglycinol derivative. Furthermore, this improved route has been successfully extended to the preparation of *N*-(methyloxycarbonyl)-(*S*)-vinylglycinol (36% overall yield). In addition, the procedure can be scaled up to 50 g and does not involve tedious purification of over-reduced products. The simplicity, scalability and the low cost of this route to *N*-protected vinylglycinol should find many applications in asymmetric synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.059.

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