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Synthesis of enantiopure cyclic amino acid derivatives via a sequential diastereoselective Petasis reaction/ring closing olefin metathesis process

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ABSTRACT

A novel approach to the synthesis of enantiopure cyclic amino esters is reported. The utilization of allylboronic acid together with (*S*)-α-methylbenzylamine as a chiral auxiliary in the Petasis/Mannich reaction led to the formation of allylglycine derivatives in good yield and with high diastereoselectivity. Subsequent esterification, N-allylation followed by ring-closing metathesis (RCM) reaction enabled the preparation of enantiomerically pure cyclic α-amino acid derivatives.

1. Introduction

Peptides modified by nonproteinogenic amino acids are useful building blocks for drug discovery. In particular, cyclic amino acids have been the subject of growing interest because their incorporation into is one of the most prominent pathways leading to conformationally constrained peptides and can lead to specific biological activities.[1] For example, (*R*)- and (*S*)-pipecolic acid are frequently used fragments in a variety of physiologically active peptides and drugs.[2]

The Petasis boronic acid Mannich reaction is a versatile multicomponent reaction of boronic acids, amines, and aldehydes, which generates highly functionalized α-amino acids and α-amino alcohols.[3] The Petasis reaction is a powerful and atom-economical method for the construction of structurally diverse secondary or tertiary amine derivatives, and has been widely utilized as a key step in the synthesis of many bioactive molecules and complex natural products.[4] In general, the Petasis reaction involves the addition of a borono nucleophile to an iminium ion, resulting in an assortment of compounds depending on the nature of the starting compounds.

The ring-closing metathesis (RCM) of dienes is one of the most important methodologies used for the assembly of cyclic organic compounds. Olefin metathesis has risen to prominence in organic synthesis over the past decades, largely due to the development of easy to handle catalysts that enable controlled reactions.[5] RCM represents a key step in many synthetic sequences: recent articles describe its use in the construction of synthetically valuable building blocks, such as heterocyclic rings containing phosphorus,[6] oxygen or nitrogen,[7] and have found wide application in natural product synthesis,[8] pharmaceutical research and drug development.[9] In certain cases cyclic amino acids were obtained by olefin metathesis in high yields.[10] However those methods are limited by serious problems concerning the synthesis of metathesis precursors, especially when enantiomerically pure compounds are required, and are often accompanied by complicated techniques and non-trivial synthetic approaches.

Herein we report a novel pathway to the synthesis of enantiopure cyclic amino acid derivatives which consists of: (i) Petasis/Mannich reaction utilizing glyoxylic acid and allylboronic acid together with (*S*)-α-methylbenzylamine as the chiral auxiliary to afford, in one-step, an allylglycine derivative; (ii) subsequent etherification and N-allylation followed by Ru-mediated intramolecular carbocyclization via ring-closing metathesis. Herein we propose a simple inexpensive pathway to enantiopure cyclic amino esters. Typical applications of this methodology are demonstrated by the preparation of (*R*)- or (*S*)-pipecolic acid derivatives.

2. Results and discussion

The Petasis/Mannich reaction was used to synthesize optically active allylglycine derivatives. In order to stimulate the stereoselective constraction of the newly formed stereogenic center, the following available enantiomerically pure amines and sulfinamides were applied to the Petasis/Mannich reaction: (*S*)-1-phenylethylamine **5**, (*S*)-*N*-allyl-1-phenylethylamine, (*S*)-*N*-Boc-1-

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phenylethylamine, (*S*)-*p*-toluenesulfinamide and (*R*)-*t*-butanesulfinamide. The choice of these substrates has been made so that the nitrogen atom could further be readily deprotected and the chiral auxiliary removed via hydrogenation or acid hydrolysis. It was found that only (*S*)-1-phenylethylamine **5** afforded the desired amino acid in high yield and with good diastereoselectivity. The three-component reaction of this amine with glyoxylic acid and allylboronic acid was performed in dichloromethane at room temperature to give allylglycine derivative **3** in 81% yield and with 93:7 dr (Scheme 1).

(*S*)-*N*-Allyl-1-phenylethylamine and (*S*)-*N*-Boc-1-phenylethylamine appeared to be ineffective under same reaction conditions. This is probably due to the steric hindrance and/or insufficient nucleophilicity of the nitrogen atom, which prevents formation of the iminium intermediate. Chiral sulfinamides were examined as alternative auxiliaries, but reacted too slowly and the reaction mixture required heating up to 50 °C. It was observed that (*S*)-*p*-toluenesulfinamide provided the desired amino acid in low yield (8%). (*R*)-*t*-Butanesulfinamide did not react at all.

Allylboronic acid pinacolate **4** was utilized as a starting allylborono compound, which is stable and easy to handle in chemical transformations (Scheme 1).

Unfortunately, pinacolate **4** provided worse results; 30% yield and 37% de. The pinacol ester moiety is too bulky and thus makes it more difficult for the allyl group to couple to the imine in comparison to unsubstituted allylboronic acid **2**.

The application of (*S*)-1-phenylethylamine in the Petasis/Mannich reaction furnished product **3** with high diastereoselectivity (de 86%). A similar asymmetric reaction of 2-phenylvinylboronic acid with glyoxylic acid and (*S*)-1-phenylethylamine described by Petasis and Zavialov[11] gave a diastereoselectivity of only 66%.

The diastereomeric excess of **3** was determined by ^{1}H NMR spectroscopy and confirmed by chromatographic separation. The spectrum of the diastereomeric mixture consisted of two sets of signals corresponding to the major and minor isomers. Mostly the identical signals of both isomers are overlapped but the peaks assigned to CH_3-group are distinctively different. The doublets at 1.66 and 1.60 ppm correspond to the major and minor isomer, respectively, and their intensity can be easily integrated (Fig. 1).

2.1. Synthesis of enantiopure cyclic amino esters via ring-closing metathesis

After esterification of enantiomerically enriched derivative **3** (de 86%) with methanol or ethanol, the major and minor diastereomers of the resulting amino esters **6** and **7** were isolated separately by conventional silica chromatography (Scheme 2). The pure major (*R*,*S*)-isomers were obtained in 84% yield in both reactions.

The assignment of the absolute configuration for the stereogenic α-carbon of the main isomer was achieved via an additional experiment. Subsequent hydrogenation of the major diastereomer of **6** furnished enantiomerically pure norvaline methyl ester **8** (Scheme 3). Comparing the value of the specific rotation of **8** with the literature data confirmed its (*R*)-configuration. Consequently, we deduced that the (*R*,*S*)-configured amino acid **3** was predominantly obtained under Petasis/Mannich conditions.

The RCM precursors **9** and **10** were prepared via allylation of the corresponding amino esters (*R*,*S*)-**6** and (*R*,*S*)-**7** by interaction with allyl bromide (Scheme 4). This reaction failed under a variety of conditions, which may be due to the steric hindrance caused by the α-methylbenzyl group. It was relatively difficult to determine the optimal solvent, base and temperature conditions to overcome the main drawbacks: the low product yield and undesired by-products formation, which impeded the isolation of the amino esters. We found that (*R*,*S*)-**6** and (*R*,*S*)-**7** were allylated (allyl bromide, DMF, K_2CO_3, 80 °C, 12 h) to furnish compounds **9** and **10** in good yield (60%). Unfortunately, amino esters underwent partial epimerization during the course of reaction due to the slightly acidic character of the hydrogen atom at the α-carbon. Epimerization was detected by means of NMR spectroscopy. Chromatographic separation of the diastereomers for **9** and **10** was unsuccessful.

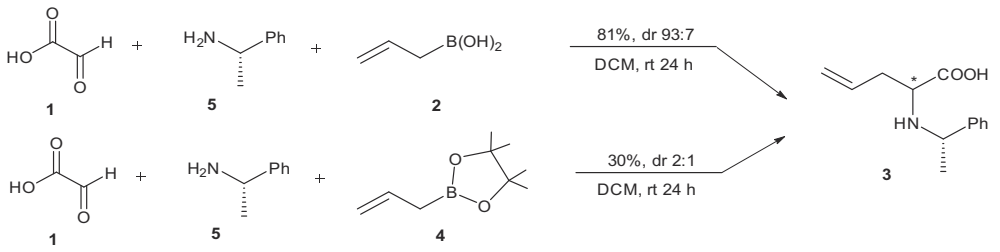
It is well known that olefin metathesis of compounds containing a basic and nucleophilic nitrogen atom is difficult to achieve because the Grubbs' catalyst can be 'poisoned' which stops the reaction. Our first attempt to carry out carbocyclization of amino ester **9** using 5 mol % 1st generation Grubbs' catalyst confirmed this problem; the presence of an amino group resulted in a low yield of **9** (Table 1, entry 1). Two approaches were applied to increase the product yield: (i) the application of the more active 2nd generation Grubbs' catalyst; (ii) the addition of the Lewis acid $Ti(OEt)_4$ to suppress nitrogen nucleophilicity.[14]

The catalyst system screening indicated that the RCM reaction of **9** gave satisfactory result (63% isolated yield of **11**) when 2nd generation Grubbs' catalyst was used (Table 1, entry 2). When the reaction of **10** was catalyzed by the 1st generation Grubbs' catalyst in the presence of 0.5 equiv of $Ti(OEt)_4$ the expected RCM product **12** was obtained in 57% isolated yield (Table 1, entry 3). The combination of 2nd generation Grubbs' catalyst with 0.5 equiv of $Ti(OEt)_4$ gave 91% yield of **12** (Table 1, entry 4).

The major and minor diastereomers of cyclic amino esters **11** and **12** were successfully separated by conventional silica chromatography and each diastereomer was fully characterized by ^{1}H and ^{13}C spectroscopy as well as elemental analysis.

It should be noted that deprotection of the amino function accompanied by reduction of the double bond is possible via hydrogenation/hydrogenolysis. The optically active ethyl esters of (*R*)- and (*S*)-pipecolic acid can be easily obtained starting from (*R*,*S*)-**12** and (*S*,*S*)-**12** (Scheme 5).[15]

Subsequent treatment with HCl furnished (*R*)- and (*S*)-pipecolic acid ethyl ester hydrochlorides (*R*)-**13** and (*S*)-**13** in 80% overall yield. Optical rotation $[\alpha]_D^{22}$ of (*R*)-**13** was +1.8 (*c* 0.2, H_2O), whereas the specific rotation of (*S*)-**13** is −2.1 (*c* 0.15, H_2O). Estimation of the enantiomeric purity of the enantiomers was carried out by converting them into free pipecolic acid by acidic hydrolysis (6 M HCl).



Scheme 1. Comparison of Petasis reactions using **2** and **4**.