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Synthesis of racemic and enantiopure 3,4-methanonipecotic acid

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ABSTRACT

The synthesis of both racemic and enantiomerically pure (1*R*,6*S*)-3,4-methanonipecotic acid, a cyclopropane-containing β-amino acid, which is a valuable building block for drug discovery, is described. The synthetic scheme commences from natural (*S*)-malic acid and allows for the preparation of the title compound in 12 steps in 28% overall yield. A novel approach to the racemic 3,4-methanonipecotic acid, which relies on a Simmons–Smith cyclopropanation as the key step, was also developed. In this case, the product was obtained in 8 steps and 38% total yield.

1. Introduction

Natural products provide us a boundless pool of ideas for design; many examples of the successful application of this concept can be found in the literature.[1] Non-proteinogenic amino acids exhibit a class of natural products that are rarely found in higher organisms but are widespread in bacteria and plants. The functions of these amino acids vary significantly, and in many cases are yet to be established. Cyclopropane amino acids represent a special subtype of non-proteinogenic natural amino acids that are embodied in coronamic acid **1** (*Pseudomonas corona-facience*), carnosadine **2** (*Grateloupia carmosa*), cleonine **3** (*Streptomyces verticillus*), *trans*-3,4-methanoglutamic acid **4** (*Blighia unuugata*) and 3,4-methanoproline **5** (*Aesculus parviflora*) (Fig. 1).[2] The latter compound is an example of bicyclic cyclopropane-containing amino acids which are also incorporated (as a part of polycyclic systems) into the molecules of lenticellarines **6**–**8** (*Dysoxylum lenticellare*).[3]

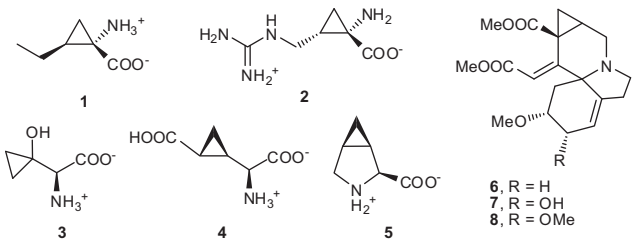

Figure 1. Naturally occurring cyclopropane amino acids and their derivatives.

The idea of bicyclic cyclopropane amino acids has previously been applied to the design of tailor-made α- and γ-amino acids, that is, proline analogues **9**[4] and **10**[5] and 3,4-methanoisonipecotic acid **11** (Fig. 2).[6] This concept was also used in the synthesis of β-proline analogues **12**,[7] **13**,[8] and **14**.[9] β-Amino acids have been shown to exhibit an intrinsic conformational behavior when incorporated into β-peptides; on the other hand, β-amino acid derivatives are often characterized by potent biological activity.[10] In particular, nipecotic acid **15** reveals GABA reuptake inhibitor activity;[11] the oligomers of **15** appear to adopt a regular secondary structure which is not stabilized by hydrogen bonds.[12]

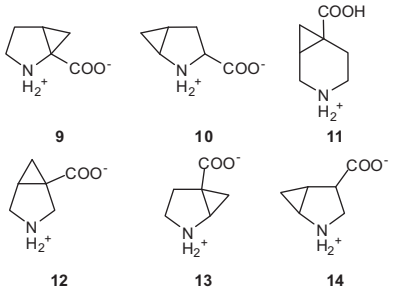

Figure 2. Synthetic bicyclic cyclopropane α- and γ-amino acids.

If the concept described above is applied to the molecule of amino acid **15**, structures **16**–**19** are generated (Fig. 3). Recently, the synthesis of the racemic compound **17** was described (Scheme 1).[13] The key step of this seven-step reaction sequence

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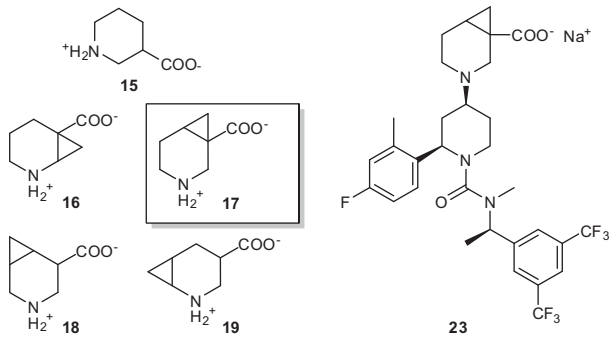
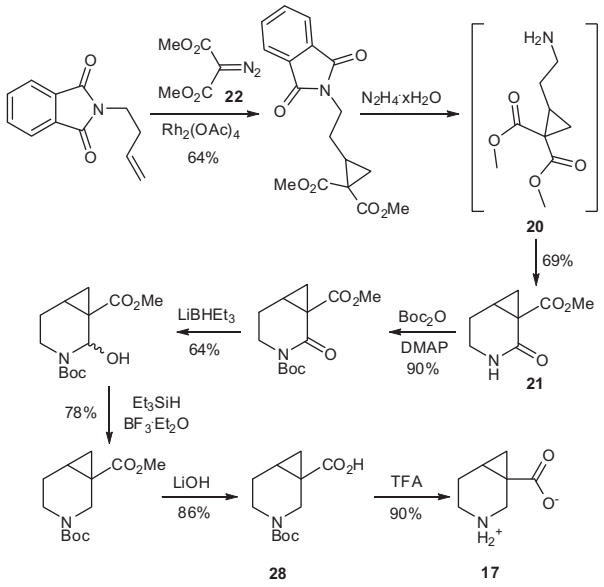


Figure 3. Nipecotic acid **15**, its cyclopropane-containing methanologues and biologically active derivative of **17**.



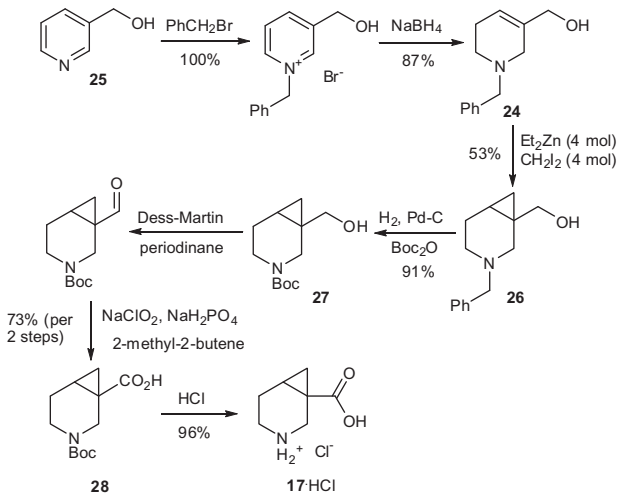
Scheme 1. Literature synthesis of racemic compound **17**.

included intramolecular cyclization of the in situ generated amino ester **20** to give bicyclic lactone **21**. This method involved the use of explosive and shock sensitive diazomalonate **22** in refluxing chlorobenzene in the first step, which might limit scaling up of the synthesis.

It was found that a derivative of amino acid **17**, compound **23**, was found to be a subnanomolar neurokinin NK1 receptor antagonist ($pK_i = 9.8$) (Fig. 3).[14] This result demonstrates the utility of compound **17** as a building block for medicinal chemistry. Herein we report a novel approach to racemic amino acid **17**, as well as synthesis of its enantiomerically pure (1*R*,6*S*)-isomer.

2. Results and discussion

Our approach to the synthesis of racemic **17** relied on a Simmons–Smith cyclopropanation of the known amino alcohol **24**, prepared in two steps from the readily available 3-pyridinylmethanol **25** (Scheme 2).[15] It should be noted that previous work stated that the cyclopropanation of analogues of **24** under various conditions was unsuccessful.[13] We have found that reaction of **24** with a 4-fold excess of diethylzinc–diiodomethane system gave the expected product **26** in 53% yield. This reaction was performed successfully on a 100 g scale. After changing the



Scheme 2. Our synthesis of racemic amino acid **17**.

protecting group, alcohol **27** was subjected to a two-step oxidation sequence (first with Dess–Martin periodinane, then using Pinnick reaction) to give the Boc derivative **28**. Removal of the protecting group in the molecule of **28** using a modified known procedure[13] allowed amino acid **17** to be obtained as the hydrochloride.

For the preparation of enantiomerically pure amino acid **17**, we used a strategy similar to that described for the preparation of racemic **17**.[13] However, for the preparation of enantiomerically pure amino ester **20**, the known enantiopure chloride **29** was taken, which was previously used in the syntheses of cyclopropane-containing amino acids, such as 2,3-methanoproline **9**.[16] Compound **29** can be prepared from natural (*S*)-malic acid **30** in three steps (Scheme 3). The reaction of **29** with diethyl malonate and NaH gave the cyclopropane derivative **31**. In turn, the reaction of **29** with NaN_3 in CH_3CN led to the formation of azide **31**. Catalytic hydrogenation of **31** was accompanied by partial cyclization, to give a mixture of (*S*)-**20** and (1*R*,6*S*)-**21**. To complete the cyclization of (*R*)-**20**, this mixture was refluxed in methanol. Finally, the bicyclic lactone (1*R*,6*S*)-**21** was transformed into enantiomerically pure (1*R*,6*S*)-**17** (as the hydrochloride) in five steps analogous to those shown in Scheme 1 for the racemate. It should be noted that in our hands, the reduction of lactam **33** with $LiBHEt_3$ under the reaction conditions described for the racemate[13] did not give reproducible results. An alternative procedure involving the use of DIBAL as the reducing agent[17] was employed instead, which gave excellent results.

To prove the enantiomeric purity of the product, ester **34** was reduced with $LiBH_4$ to give alcohol (1*R*,6*S*)-**27** (Scheme 4). Both racemic and enantiopure samples of **27** were analyzed by chiral stationary phase HPLC; the enantiomeric excess of (1*R*,6*S*)-**27** was found to be 91.5%.

3. Conclusion

A novel approach to racemic 3,4-methanonipecotic acid was developed. An eight-step reaction sequence involving a Simmons–Smith cyclopropanation as the key step allowed the title compound to be obtained in 38% overall yield. An approach to enantiomerically pure (1*R*,6*S*)-3,4-methanonipecotic acid has also been described. In this case, the target product was obtained in 12 steps and 28% overall yield from natural (*S*)-malic acid.