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Straightforward entry to the pipecolic acid nucleus. Enantioselective synthesis of baikiain

Xavier Ginesta, Miquel A. Pericàs* and Antoni Riera*

Departament de Química Orgànica, Martí i Franquès, 1-11, Barcelona E-08028, Spain

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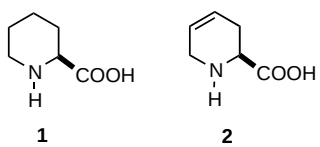
Abstract—New enantioselective syntheses of *N*-protected baikiain and pipecolic acid have been developed. The starting material is 2,3-epoxy-5-hexen-1-ol (**4**) readily available in high ee by Sharpless epoxidation. The regio- and stereoselective epoxide ring-opening by allylamine afforded a doubly unsaturated amine that was converted into a carbamate (Boc) and submitted to ring-closing metathesis. The resulting cyclic amino diol **6** is a key intermediate that was converted into *N*-Boc-baikiain and several pipecolic acid derivatives.

2-Piperidine carboxylic acid (pipecolic acid, **1**) is a nonproteinogenic amino acid present in several natural products, some of them with important pharmaceutical interest such as the immunosupresants FK506[1] and rapamicin[2] (Scheme 1). As a proline analogue (homoproline) it has been used in many modified peptides and synthetic drugs.[3] The importance of pipecolic acid as a starting material for those compounds[3,4] has fostered the development of many synthetic approaches involving enzymatic reactions,[5] alkylation of chiral glycine enolates,[6] derivatization of natural amino acids,[7] enantioselective reactions[8] and resolution.[9] On the other hand, 4,5-dehydropipecolic acid (baikiain, **2**) is a natural product isolated from *Baikiaea plurijuga* and other plants.[10] Few syntheses of baikiain have been described up to now, featuring glycine synthons or ring-closing metathesis of allyl glycine derivatives.[11] Nevertheless, the use of baikiain as a synthetic precursor has been very limited,[12] hampered by lack of simple synthetic methods for its preparation in high enantiomeric purity.



1 **2**

Scheme 1.

In the last decade we have been involved[13] in a project devoted to the synthesis of several structural types of amino acids using the catalytic Sharpless epoxidation[14] as a source of chirality. The amazing potential of the ring-closing metathesis (RCM) reactions[15] drove our attention to the possible use of unsaturated epoxy alcohols in the preparation of heterocyclic amino acids. In this context we envisaged a new entry to 2-piperidine carboxylic acids by RCM of a bis-olefinic compound, potentially accessible by nucleophilic ring-opening of an unsaturated epoxy alcohol by an unsaturated amine (Fig. 1). We report here a new enantioselective synthesis of baikiain and of several pipecolic acid derivatives based on this strategy.

Our synthesis started with the preparation of the known allyl alcohol **3** from propargyl alcohol.[16] The catalytic Sharpless epoxidation of **3** was initially performed as described,[17] using D-DIPT in the preparation of the catalyst, to afford epoxy alcohol **4** in 82% yield and 87–92% ee.[18] As we have found in similar cases,[13g] this enantioselectivity could be slightly improved (up to 93% ee) by using DET instead of DIPT. Then, enan-

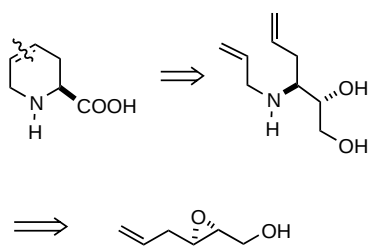


Figure 1. Retrosynthetic analysis for baikiain.

* Corresponding authors. Tel.: 34 934021245; fax: 34 933397878; e-mail: a.riera@qo.ub.es; mapericas@qo.ub.es

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tiomerically enriched **4** was subjected to nucleophilic epoxide ring-opening using allylamine (Scheme 2). Under Sharpless conditions[19] [$Ti(O^iPr)_4$, CH_2Cl_2, reflux], the reaction took place uneventfully affording a crude aminodiol that, since free amino groups have a deleterious effect in RCM, was treated without purification with Boc_2O in order to block the secondary amine. In this way *N*-Boc-protected doubly-unsaturated aminodiol **5** was obtained in 60% overall yield (two steps).[20] Although the reaction was completely regioselective, the product had to be carefully purified by chromatography. Application of Crotti's conditions[21] ($LiClO_4$, CH_3CN) also followed by Boc-protection afforded aminodiol **5** in the same yield. In this case the reaction was not completely regioselective (10:1) but the crude was cleaner and the regioisomer (6%) was easily removed by chromatography.

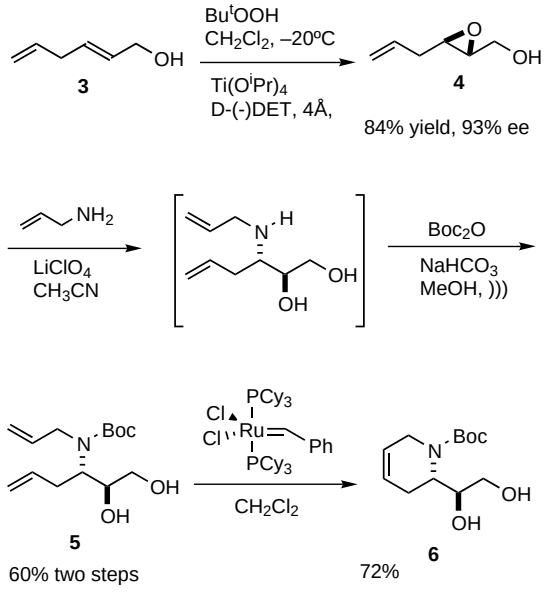
Using 2×4% mol of Grubbs's catalyst in CH_2Cl_2 at room temperature, the RCM of the doubly unsaturated amine **5** took place in 72% yield affording *N*-Boc-tetrahydropyridinyletandiol **6**. This is the key intermediate in our approach, since hydrogenation of the double bond would lead to pipecolic acid derivatives, whereas oxidation of the diol fragment would give *N*-protected baikiain. Gratifyingly enough, compound **6** was a crystalline compound [mp 92–3°C; $[\alpha]_D = +39.5$ (1.0, $CHCl_3$)], providing a possibility for enantiomeric enrichment.

Firstly, we studied the access to the saturated pipecolic acid nucleus. To this end, dehydropiperidine **6** was hydrogenated to give aminodiol **7** in 89% yield. This compound was also nicely crystalline [mp 108–9°C; $[\alpha]_D = -59.5$ (0.9, $CHCl_3$)]. Subsequent oxidation of the diol fragment of **7** afforded *N*-Boc-pipecolic acid **8** in 98% yield. The possibility of increasing the enantiomeric purity by crystallization was checked by HPLC (Chiralcel OD) analysis of the *N*-Boc pipecolic acid methyl ester. Starting from an epoxy alcohol **4** of 90% ee, a simple crystallization of **7**, followed by the previously described sequence, afforded the protected pipecolic acid **8** in 94% ee. As expected, starting from an epoxy alcohol of 93% ee and crystallizing intermediate **7**, it was easy to achieve enantiomerically pure pipecolic acid (>99% by HPLC).

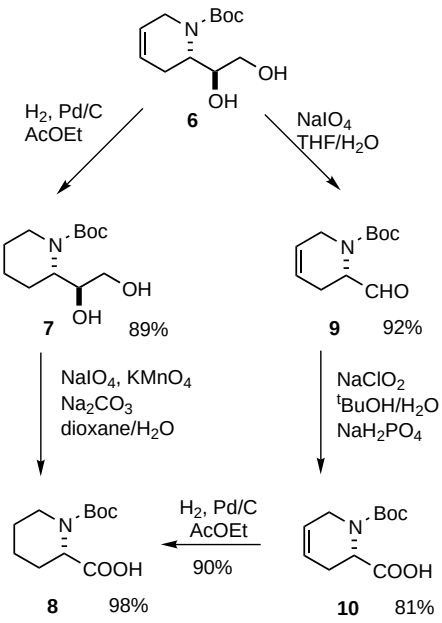
Oxidation of dehydropiperidine **6** was anticipated to be a more difficult task due to the presence of the double bond. According to our experience in the synthesis of unsaturated amino acids,[17] the diol fragment in **6** was first oxidatively cleaved by $NaIO_4$ to give aldehyde **9** in excellent yield. This aldehyde was immediately oxidized to *N*-Boc-baikiain **10** by sodium chlorite[22] also in excellent yield. At this point it was crucial to measure the enantiomeric excess of the final product in order to check both the possible racemization of the aldehyde and the possibility of enantiomeric enrichment by crystallization of aminodiol **6**.

Thus, (*S*)-Boc-baikiain (**10**) was hydrogenated to pipecolic acid **8** and the corresponding methyl ester was analyzed by HPLC (Chiralcel OD). Starting from an epoxy alcohol **4** of 93% ee, without any crystallization along the sequence, the observed enantiomeric purity of the product (91% ee) showed that none or very little racemization had taken place and proved the viability of the present approach. The same reaction sequence was subsequently performed starting from recrystallized aminodiol **6**. To our satisfaction, it provided (*S*)-Boc-baikiain (**10**) in 99% ee (by HPLC) (Scheme 3).

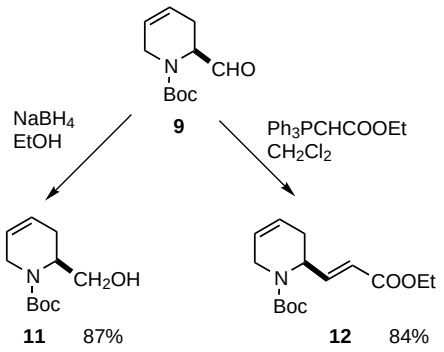
The high enantiomeric purity of amino acids **8** and **10** and the configurational stability of aldehyde **9**, convert them in valuable synthetic intermediates. To start exploring this possibility, **9** was reduced with sodium borohydride to afford tetrahydropiridylmethanol **11** in



Scheme 2.



Scheme 3.



Scheme 4.

excellent yield (Scheme 4). The enantiomeric excess (94% ee) was measured by chiral HPLC and confirmed the absence of racemization of aldehyde **9**. This compound was also submitted to Wittig olefination providing unsaturated ester **12** in good yield, and, starting from enantiomerically pure piperidine diol **6**, high enantiomeric purity (99% ee by HPLC). It is worth mentioning that hydrogenated analogous of **11** and **12** have been extensively used in the synthesis of natural products.[23]

In summary, we have developed a new enantioselective entry to the synthesis of *N*-protected baikiain and pipecolic acid. The present approach is based in the regio- and stereoselective epoxide ring-opening of unsaturated epoxy alcohol **4**, followed by ring-closing metathesis and oxidation. In this way, (*S*)-Boc-baikiain has been prepared in only five steps (two of them without purification of the product) in 32% overall yield. The final products can be obtained in any configuration in very high enantiomeric purity (99% ee). This approach can be used in the synthesis of other heterocyclic rings, possibility that is currently being explored in our group.

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