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Enantioselective Synthesis of the (*syn,anti*)- 1-Amino -2,3- Diol Subunit of Renin Inhibitors by Reaction of β-Lactams with a Grignard Reagent

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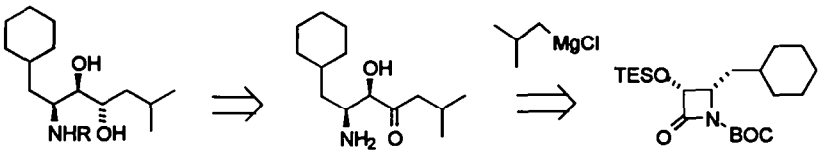
Summary: A new approach to the BOC-protected amino diol **1a** *via* the opening of 3,4-*cis*-disubstituted β-lactam **3** with isobutylmagnesium chloride is described. Nonracemic β-lactam **3** could be obtained by enzymatic resolution of the 3-acetoxy-β-lactam **4** or from a chiral precursor, methyl (R)-(-)-mandelate.

A number of research groups have been interested in the synthesis of the aminodiol **1a**.[1] This moiety is believed to mimic the transition state for the renin-catalyzed hydrolysis of the peptide angiotensinogen, and therefore its derivatives have been widely studied as potential antihypertensive agents.[2] We have developed a new synthesis of the BOC-protected aminodiol **1a** based on a Grignard opening of the 3,4-*cis*-disubstituted β-lactam **3** with isobutylmagnesium chloride. The *syn* relationship between the amino group and the adjacent hydroxyl group in compound **1a** is set in a [2+2] imine-ketene cycloaddition to form a 3,4-*cis*-disubstituted β-lactam, and the *anti* diol relationship is effected by a hydride reduction of the ketone **2** (Scheme 1).



1a R = BOC
1b R = H

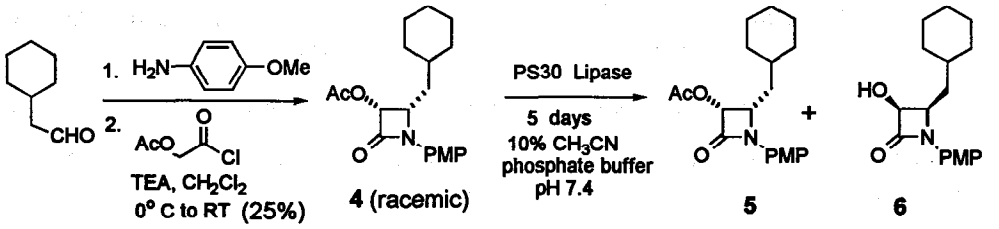
2 **3**

Scheme 1

We have developed two routes to the common intermediate **3**, both of which use a [2+2] imine-ketene cycloaddition to construct the azetidinone. The two routes differ in the way the chirality of the molecule is introduced; the first approach utilizes an enzymatic resolution to prepare nonracemic β-lactam **3** and the second constructs the β-lactam from the chiral precursor R-mandelic acid.

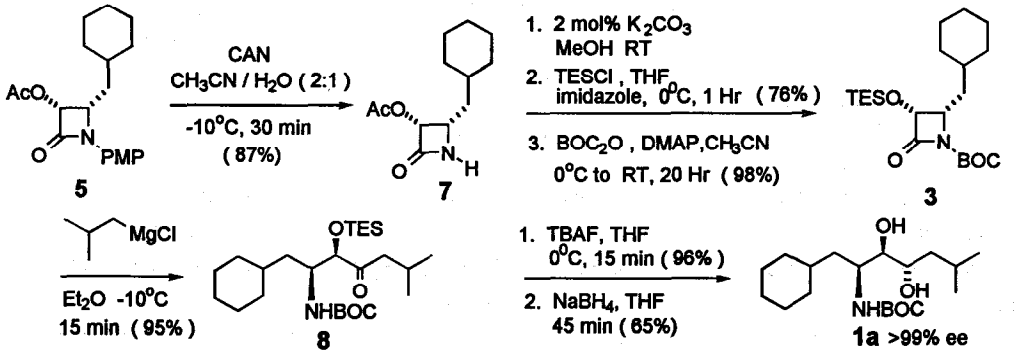
In the first approach the substrate chosen for enzymatic resolution was the 3-acetoxy-azetidinone **4**, which was constructed by a [2+2] cycloaddition between the imine derived from cyclohexylacetaldehyde[3] and *p*-methoxyaniline and the ketene generated from acetoxyacetyl chloride (Scheme 2). This cycloaddition occurs to give exclusively the *cis*-disubstituted β-lactam, but the yield for the transformation is low. Ojima has used an ester enolate-imine condensation to form 3,4-*cis*-disubstituted β-lactams.[4] However, we wanted to develop a method which would allow us to form a 3-acetoxy-substituted lactam directly without protecting group manipulations. To resolve the β-lactam **4**, we studied its reaction with a number of lipases: PPL and CCL gave less than 3% conversion to the chiral alcohol **6** after two weeks reaction time, AP and AK gave 25% and 30% conversion after three and five days, and PS-30[5] afforded the best results with 47% conversion after five days at

RT. Examination of the chiral acetate **5** by NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ showed that less than 1% of the opposite enantiomer was present. To our knowledge, this is the first example of the enzymatic resolution of substrate **4**.[6]



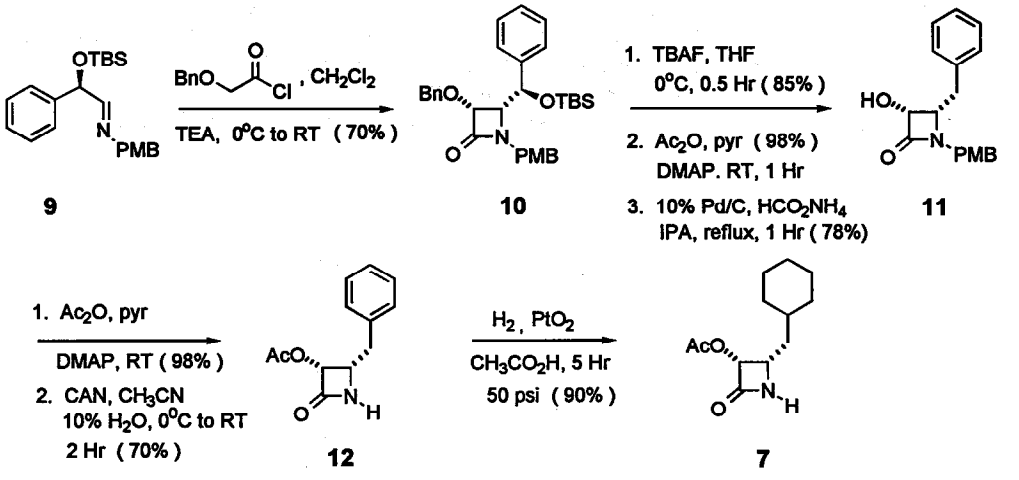
Scheme 2

With the chiral azetidinone **5** in hand, we needed to replace the *p*-methoxyphenyl group with a BOC group to facilitate the opening of the azetidinone with a Grignard reagent, and also replace the base-labile acetyl group with a silyl protecting group. First, the *p*-methoxyphenyl group was removed from lactam **5** by treatment with ceric ammonium nitrate to afford **7** in good yield. Next, hydrolysis of the acetyl group with K_2CO_3 in MeOH and silylation with TESCl gave a 76% overall yield of the 3-silyloxy β-lactam. Subsequent N-protection with BOC anhydride afforded our key intermediate **3**. The ring opening of azetidinones with Grignard reagents has not been widely exploited as a synthetic methodology[7] and the recent report by Palomo[7b] prompted us to publish our results in this area. Reaction of β-lactam **3** with three equivalents of isobutylmagnesium chloride proceeded smoothly in ether at -5 °C to give a 95% yield of the acyclic ketone **8**. We found that the yield of this reaction decreases if less than three equivalents of Grignard reagent are used, and also noted that the reaction is best carried out by fast addition of the Grignard to the lactam.[8] The synthesis was completed by desilylation with TBAF, and subsequent $NaBH_4$ reduction gave the target BOC-protected aminodiol **1a** in 65% yield (Scheme 3). HPLC analysis using a chiral column did not detect any (<0.5%) of the opposite enantiomer, using a racemic reference sample as a control.[9] All of the steps in this sequence proceeded well with the exception of the initial imine-ketene cycloaddition and we are attempting to improve the efficiency of this step.



Scheme 3

The second approach to nonracemic BOC-protected aminodiol **1a** starts with a [2+2] cycloaddition between the chiral imine **9** and a ketene derived from benzyloxyacetyl chloride (Scheme 4). The chiral imine **9** is synthesized from methyl (*R*)-(-)-mandelate according to the method of Terashima.[3] This cycloaddition affords the β-lactam **10** in good yield (70%) with one of the possible two *trans* compounds observed in small amounts (<10%) by NMR spectroscopy. We have converted this material to the 4' deoxygenated lactam **7** by first desilylating the 4' hydroxyl group with TBAF, followed by acetylation with acetic anhydride . Hydrogenolysis of the C-4 acetoxy group and simultaneous cleavage of the benzyl ether was achieved using ammonium formate and 10% Pd/C, to afford **11** in 78% yield. Typically for this reaction we use 20% by weight of the Pd catalyst; if greater than 20% is used, reductive cleavage of the N/C-4 bond is observed. At this point we desired to directly convert lactam **11** to the common intermediate **3** by silylation of the C-3 oxygen, replacement of the *p*-methoxybenzyl group with a BOC group, and finally saturation of the phenyl ring. Silylation of the C-3 hydroxyl group of compound **11** was accomplished with TESCl; however, the subsequent N-debenzylation with ceric ammonium nitrate also removed the silyl protecting group. Attempted silylation of **11** with more sterically hindered protecting groups such as TIPS and TBDMS gave only recovered starting material. To circumvent this problem, compound **11** was converted to the C-3 acetoxy protected **7**, for we already had the methodology in place to convert lactam **7** to the N-BOC protected substrate **3**. To effect this conversion, the C-3 hydroxyl group of **11** was acetylated with Ac_2O and then the *p*-methoxybenzyl protecting group was smoothly removed in 70% yield to afford lactam **12**. Finally, saturation of the phenyl ring with H_2 over PtO_2 at 50 psi afforded a 90% yield of the common intermediate **7**, thus completing a formal synthesis of the BOC protected amino diol **1a**.[10]



Scheme 4

Acknowledgement. The authors thank Dr. Kenneth Cohen for HPLC analysis of the target compound **1a**.

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4. For an example of an efficient and patented chiral ester enolate-imine condensation to form 1-(4-methoxyphenyl)-3-triisopropylsilyloxy-4-(2-cyclohexylmethyl)-2-azetidinone see Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y.H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.
5. PS-30 was purchased from Amano. PPL (*porcine pancreas lipase*) and CCL (*Candida cylindracea*) were purchased from Aldrich. AP (*Aspergillus niger*) was purchased from Fluka and AK (*Pseudomonas sp.*) from Amano. Percent conversions were measured by C-18 reverse phase HPLC eluting with CH_3CN/ H_2O (80 : 20).
6. For the enzymatic resolution of other azetidinones see: Brieva, R.; Crich, J. Z.; Sih, C. J. *J. Org. Chem.* **1993**, *58*, 1068.
7. (a) Gallucci, J. C.; Ha, D. C.; Hart, D. J. *Tetrahedron* **1989**, *45*, 1283. (b) Palomo, C.; Aizpurua, J. M.; Iturburu, M.; Odriozola, J. M. *J. Org. Chem.* **1994**, *59*, 5184.
8. To a stirred solution of **3** (0.125 g, 0.31 mmol) in dry ether (5 mL) at -10°C was added isobutylmagnesium chloride (0.88 mmol) in one portion. The reaction mixture was stirred for 15 min then quenched with aqueous saturated ammonium chloride (5 mL), diluted with Et_2O (20 mL) and washed with water (2 x 10 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification was achieved by passing the residue through a plug of silica (10% ether/hex) to afford **8** in 95% yield.
9. Chiracel OD; Hexane/ IPA (98:2), column temperature = 35°C
10. All new compounds were characterized by 270Mz NMR and MS which are consistent with the assigned structures.

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