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A CONCISE ENANTIOSELECTIVE SYNTHESIS OF (+)-α-CONHYDRINE

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Abstract – A short step synthesis of (+)-α-conhydrine was achieved employing a kinetic resolution of 2-(1-hydroxypropyl)pyridine with lipase PS and a chelation-controlled diastereoselective reduction of pyridine ring as key reactions.

There are many biologically active piperidine alkaloids containing 1-hydroxyalkyl substituent at an α-position of nitrogen.[1] (+)-α-Conhydrine is one of the class of alkaloids which was isolated from the poisonous plant *Conium maculatum*.[2] Although various methods for the synthesis of conhydrine were reported[3] since the elucidation of the structure,[4] enantioselective synthesis of naturally occurring (+)-α-conhydrine has been less developed. Moreover, total synthesis of (+)-α-conhydrine reported thus far required rather long steps despite its simple structure. We have found a new method for the synthesis of (+)-α-conhydrine in short steps using a kinetic resolution and a diastereoselective resolution as key steps. In this communication we report these results.

Synthesis of (+)-α-conhydrine was commenced using commercially available 2-pyridinecarbaldehyde (**1**) as a starting material (Scheme 1). 2-(1-Hydroxypropyl)pyridine (**2**), which was obtained from the reaction of **1** with ethylmagnesium bromide, was subjected to an enzymatic resolution[5] with lipase PS (Amano) to provide a chiral acetate (**3**) (yield 45%, 98% ee) along with an unreacted enantiomer (recovery 45%, 96% ee).[6] After hydrolysis of **3**, pyridine ring was reduced with $LiBEt_3H$,[7] and subsequent trapping with benzyloxycarbonyl chloride gave **5** in 93% yield in three steps. Although $LiBEt_3H$ reduction produced α-conhydrine, it was difficult to isolate the product from the reaction mixture. Thus the benzyloxycarbonylation step was necessary to isolate and purify the product. Finally, benzyloxycarbonyl group was removed by catalytic hydrogenation to give (+)-α-conhydrine in

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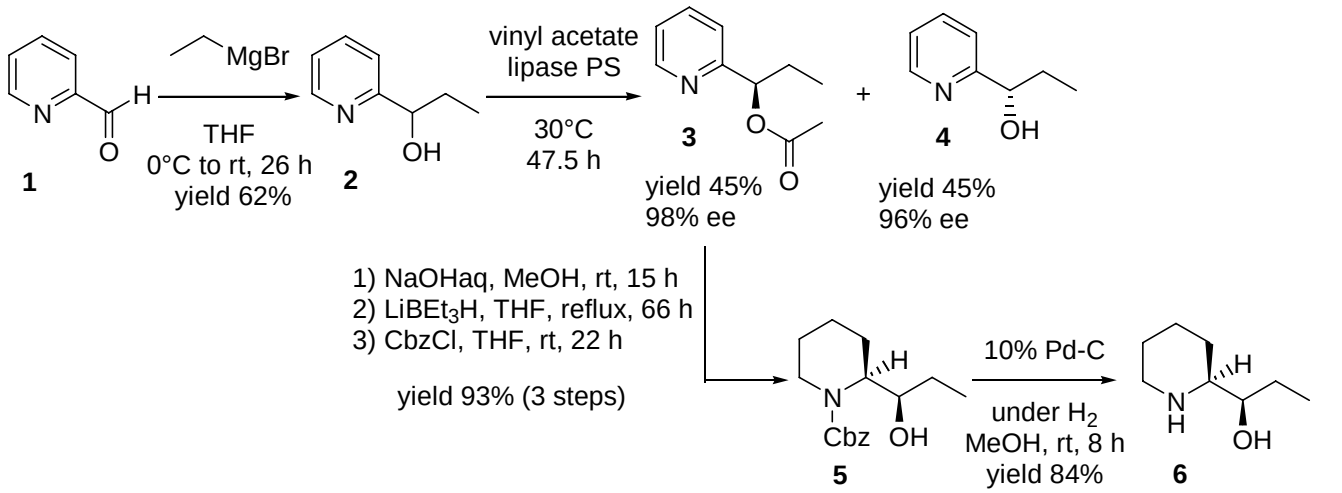
This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of the University of Tokyo.



Scheme 1

84% yield as a single diastereomer. The diastereoselective reduction by $LiBEt_3H$ can be rationalized by the chelation-controlled reaction as shown in Figure 1. It was considered that nitrogen of pyridine ring and hydroxyl group coordinated to lithium cation to form a chelate, and hydride attack occurred from the opposite side of the ethyl group. The synthetic (+)-α-conhydrine thus obtained was spectroscopically identical with reported one,[3f, 8] and its optical rotation corresponded closely with that reported for natural (+)-α-conhydrine ($[\alpha]^{27}_D$ +8.6° (c 0.37, EtOH); lit.,[3b] $[\alpha]^{20}_D$ +8.9°(EtOH)).

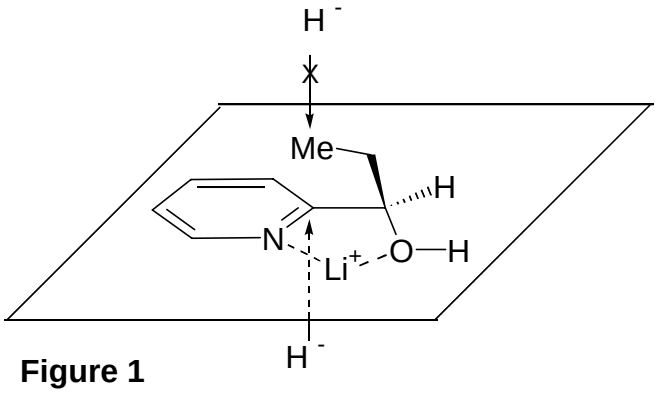


Figure 1

In conclution, a concise and practical synthesis of (+)-α-conhydrine was accomplished in six steps from commercially available 2-pyridinecarbaldehyde. By use of (*S*)-(1-hydroxypropyl)pyridine (**4**), which was recovered in the kinetic resolution step, (-)-α-conhydrine can also be synthesized. Thus the method shown above is thought to provide a new approach for the synthesis of both enantiomers of piperidine alkaloids which have 1-hydroxyalkyl-side-chain at α-position of nitrogen. Application of the present method to the synthesis of other bioactive piperidine alkaloids is currently under investigation.

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6. Enantiomeric excess of **4** was determined, after converting to the corresponding *t*-butyldimethylsilyl ether, by HPLC analysis using a chiral column (DAICEL Chiralcel OD) with hexane/2-propanol=200 as the solvent system. Compound **3** was hydrolyzed to afford **4**, then enantiomeric excess was determined.
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8. (+)-α-conhydrine (**6**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J*= 7.3 Hz), 1.26-1.52 (m, 5H), 1.62 (m, 2H), 1.84 (m, 1H), 2.35 (br s, 2H), 2.59 (m, 1H), 2.69 (td, 1H, J= 10.8, 2.6 Hz), 3.13 (m, 1H), 3.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 24.3, 25.0, 25.4, 26.3, 47.0, 60.2, 75.7.