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High-Enantioselective Synthesis of Pyrrolidine Derivatives as Chiral Building Blocks

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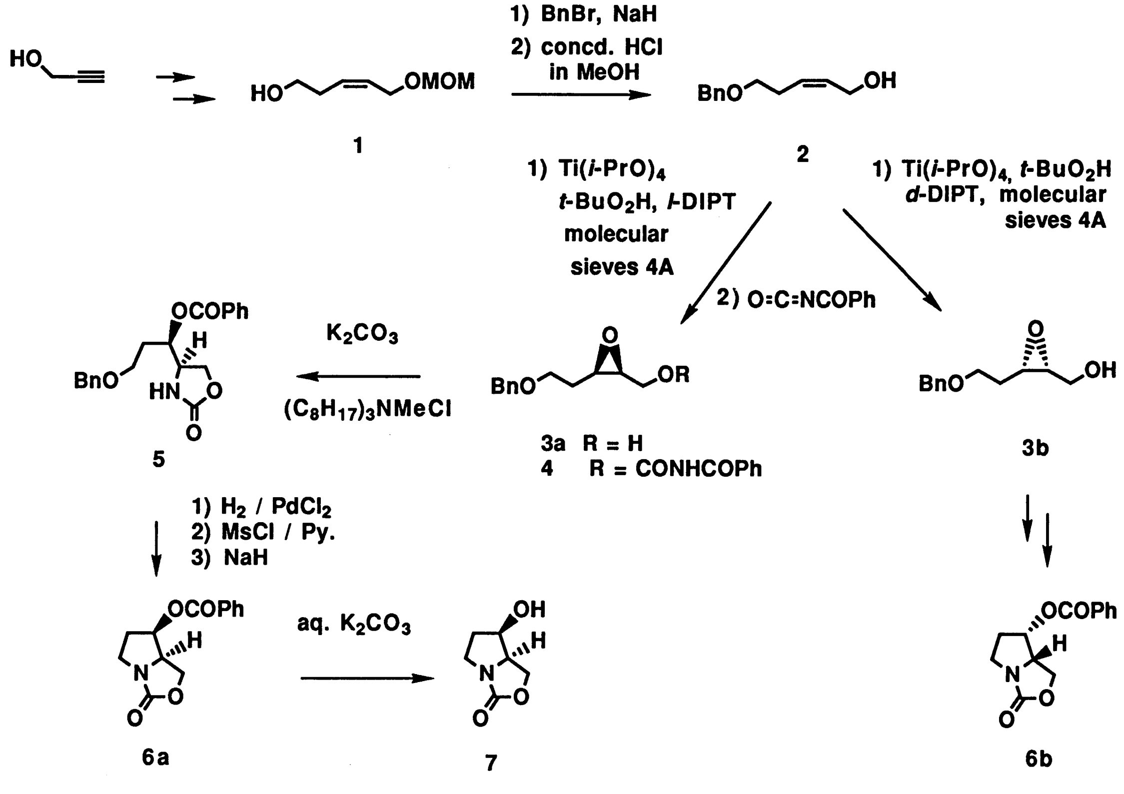
All four stereoisomers of a pyrrolidine derivative, which is useful as a versatile chiral building block for synthesis of several pyrrolizidine alkaloids, were prepared in high enantioselectivity by utilizing the Sharpless epoxidation of the intermediate allyl alcohol starting from propargyl alcohol.

Pyrrolizidine alkaloids have received considerable attention because of their unique structure and a variety of pharmacological activities.$^{1)}$ Although a number of methods for the synthesis of a necine base of pyrrolizidine alkaloids have been reported,$^{2)}$ there are few documented examples of their asymmetric syntheses.$^{3)}$ In connection with our approach toward the synthesis of pyrrolizidine alkaloids, we began with asymmetric synthesis of the chiral building block for necine bases by employing the Sharpless asymmetric epoxidation. Here we describe the enantioselective synthesis of all four stereoisomers of a pyrrolidine derivative having a 3-hydroxy-2-hydroxymethyl group as a chiral building block for the synthesis of necine bases starting from the same material.

As shown in scheme 1, benzylation of the cis-olefin (**1**),$^{4)}$ readily obtained from propargyl alcohol, and subsequent removal of the methoxymethyl group (concd. HCl, MeOH), gave the cis-allylic alcohol (**2**)$^{5)}$ in 70% yield. The Sharpless asymmetric epoxidation [Ti(iso-PrO)$_4$, diisopropyl l-tartrate(l-DIPT), tert-butyl hydroperoxide (TBHP), molecular sieves 4A]$^{6)}$ of **2** afforded the 2,3-epoxy alcohol (**3a**)[[α]$^{23}_{D}$ +8.5°(c 1.88, $CHCl_3$)] in 75% yield (92% ee).$^{7)}$ Its enantiomer (**3b**) [[α]$^{22}_{D}$ -6.7°(c 2.63, $CHCl_3$)] was obtained in 88% yield (92% ee)$^{7)}$ by using d-DIPT on epoxidation of **2**. Treatment of **3a** with N-benzoyl isocyanate$^{8)}$ gave the Nbenzoylcarbamate (**4**)[$[\alpha]^{23}_D$ -17.8°(c 1.75, $CHCl_3$)] in quantitative yield. Cyclization of **4** was effected efficiently by treatment with K_2CO_3 in the presence of methyltrioctylammonium chloride to give 2-oxazolidinone (**5**)[$[\alpha]^{23}_D$ -17.4°(c 2.33, $CHCl_3$)] in 88% yield with migration of the N-benzoyl group. Debenzylation (H_2, $PdCl_2$) of **5**, followed by subsequent O-sulfonylation and cyclization (NaH, THF), furnished the target pyrrolidine derivative (**6a**)[$[\alpha]^{23}_D$ +10.0°(c 1.81, $CHCl_3$)] in 73% yield. Hydrolytic removal of the benzoyl group of (**6a**) afforded the alcohol (**7**)[$[\alpha]^{23}_D$ -36.9°(c 1.34, $CHCl_3$)] in 91% yield, whose spectral data were consistent with those of the racemic authentic sample.[9] The enantiomer **6b** [$[\alpha]^{23}_D$ -10.3°(c 0.59, $CHCl_3$)] was also derived from the 2,3-epoxy alcohol (**3b**) in 44% yield (5 steps) by the similar procedure described above.



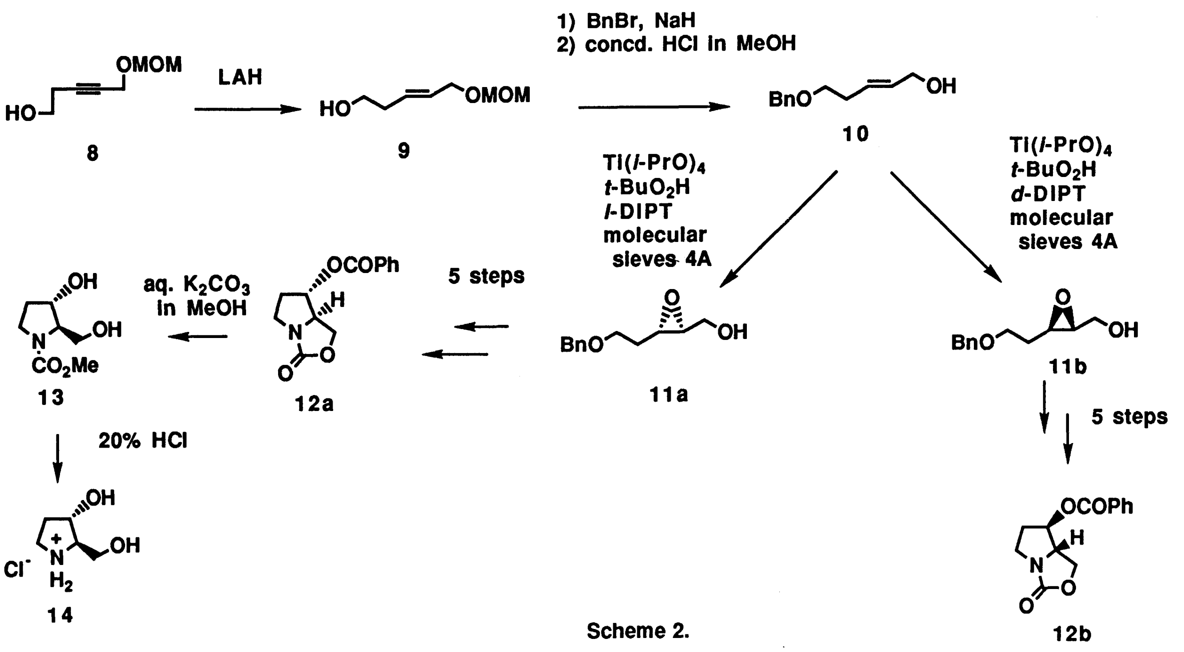
Scheme 1.

The synthesis of compounds **12a** and **12b**, the diastereoisomers of **6a** and **6b**, was examined as shown in Scheme 2. Reduction of the alkyne compound (**8**), readily obtained from propargyl alcohol, with lithium aluminum hydride in tetrahydrofuran-ether (1:3) gave the trans-olefin (**9**) in 67% yield. Benzylation of **9** was followed by removal of the methoxymethyl group to afford the trans-allylic alcohol

(**10**) in 84% yield. The Sharpless epoxidation of **10** [l-DIPT, TBHP, Ti(iso-PrO)$_4$, molecular sieves 4A] gave the 2,3-epoxy alcohol (**11a**)[[α] $^{23}{}_D$ +33.3°(c 2.20, $CHCl_3$)] in 80% yield (>90% ee).[10] The enantiomer (**11b**)[11][[α]$^{23}{}_D$ +32.3°(c 2.01, $CHCl_3$)] was obtained in 72% yield (>90% ee) by use of d-DIPT on the epoxidation of **10.** These 2,3-epoxy alcohols (**11a** and **11b**) were converted to the pyrrolidine derivatives (**12a**)[[α]$^{23}{}_D$ +18.5°(c 0.61, $CHCl_3$)] and (**12b**)[[α]$^{23}{}_D$ -16.6°(c 0.79, $CHCl_3$)] in 40% and 45% yields (5 steps), respectively, by using the procedure described above. The absolute configuration of **12a** was determined by its conversion to a compound whose absolute configuration is already known. Thus, the basic hydrolysis of **12a** (96% yield) and subsequent acidic hydrolysis gave 3-hydroxy-2-hydroxymethylpyrrolidine hydrochloride [**14**, [α]$^{23}{}_D$ +43.8°(c 1.00, H_2O)] in 93% yield, which was identified by comparison with an authentic sample [[α]$^{21}{}_D$ +46.5°(H_2O)].[12]

Thus, all four stereoisomers of the pyrrolidine derivative, which is useful as a versatile chiral building block, were very conveniently prepared from propargyl alcohol in high enantioselectivity. The use of these pyrrolidine derivatives in the synthesis of pyrrolizidine alkaloids is now being examined.

We are grateful to Professor Y. Tamaru, Nagasaki University, for his kindly providing us with the ^{1}H and ^{13}C NMR charts of the racemate of **7**.



Scheme 2.

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