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Asymmetric Total Synthesis of (+)-Desoxoprosophylline

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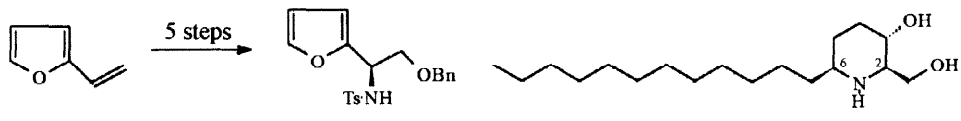
Abstract: Asymmetric total synthesis of (+)-desoxoprosophylline **2** from the α-furfuryl amine derivative **1** was accomplished via ten steps in an overall yield of 4%. The oxidation of **1** to dihydropyridone **3** was used as the key step.

Keywords: (+)-desoxoprosophylline; asymmetric total synthesis

During the past several years we have been interested in the preparation of chiral α-furfuryl amine derivatives and the application of these chiral building blocks to the total synthesis of natural products. We have developed two methods to prepare the optically active α-furfuryl amine derivative, one is the kinetic resolution of racemic α-furfuryl amine derivatives using the modified Sharpless asymmetric epoxidation reagent,[1] another is the diastereoselective addition of organometallic reagents to α-furfuryl imine derivatives.[2] Several natural products and their analogs, such as α-amino acids,[3] δ-hydroxy-α-aminolactones,[4] (+)-azimic acid,[5] dihydropinidine,[6] polyhydroxylated indolizidines,[7,8] and 1-deoxyazasugars,[9] have been successfully synthesized from the α-furfuryl amine derivatives we have prepared. Very recently, we developed a more convenient method to prepare the chiral α-furfuryl amine derivative **1** from α-furyl ethylene in five steps using a Sharpless dihydroxylation as the key step (Scheme 1).[10] This new method could provide a large quantity of **1**, which is a very useful building block for the stereocontrolled synthesis of the polysubstituted piperidines present in a wide variety of natural products. Here we report the application of this building block to the first synthesis of (+)-desoxoprosophylline **2**, a bioactive alkaloid isolated from *Prosopis africana* in a racemic form, which has attracted recent interest as a synthetic target.[11,12,13,14]



1 **2**

Scheme 1

Treatment of **1** with *m*-CPBA, as depicted in Scheme 2, afforded the dihydropyridone **3**, in which the hydroxyl group was protected to give **4**. Reduction of **4** with sodium borohydride in methanol gave the α-hydroxyl product **5**, in which the configuration of C_3 had been proved in our previous reports.[5,6,7] After protection of **5** with a benzyl group, we initially attempted to introduce the side chain at C_6 directly by reaction of **6** with a Grignard reagent ($C_{12}H_{25}MgBr$), but this reaction gave low stereoselectivity and yield. However

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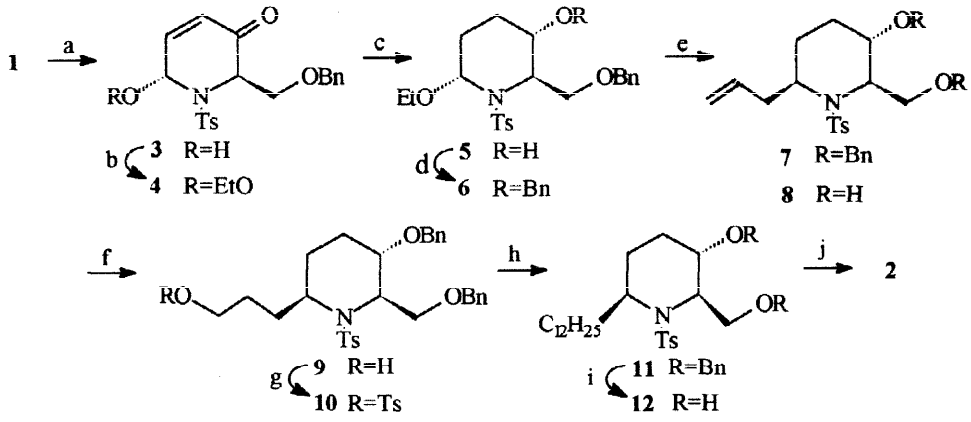
treatment of **6** with allyltrimethylsilane in the presence of 0.5 eq. of titanium tetrachloride at -75°C gave **7** exclusively, this reaction produced **8** as major product when 1.0 eq. of titanium tetrachloride was present. The stereochemistry of the allyl group was assigned by comparison with the results obtained in allylation of structurally related compounds.[5,6,15] Hydroboration of 7 with borane-methyl sulfide complex, followed by protection of hydroxy group with tosyl produced **10**, which was coupled with a Grignard reagent ($C_9H_{19}MgBr$) to afford **11**. Deprotection of hydroxy group of **11** resulted in **12**, the configuration of which was confirmed by 2D-NOESY analysis since there was no NOE correlation between H_2 and H_3, nor between H_3 and H_6. Finally deprotection of the amino group produced (+)-desoxoprosophylline **2**. mp 89-90°C; $[\alpha]^{20}_D$ +14.4° (c 0.32 in $CHCl_3$); [lit.[13] the enantiomer of **2** mp 90.5°C; $[\alpha]^{21}_D$ -14°.(c 0.24 in $CHCl_3$)]. The ^{1}H-NMR and the ^{13}C-NMR spectra as well as the mass spectra of **12** and **2** were identical with the literature data.[14]



Scheme 1. Reagents and conditions: a) *m*-CPBA, CH_2Cl_2, r.t. (82%); b) $HC(OEt)_3$, BF_3•OEt_2, 4A molecular sieves, THF, 0°C (97%); c) $NaBH_4$, MeOH, 0°C (88%); d) BnBr, NaH, THF, r.t. (85%); e) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78°C (67%); f) i. BH_3-SMe_2, THF; ii. NaOH, H_2O_2 (45%); g) Ts-Im, NaH, THF, 0°C (87%); h) $C_9H_{19}MgBr$, Li_2CuCl_4, THF, 0°C (68%); i) 10% Pd-C, H_2, EtOH (84%); j) Na/NH_3, -78°C (46%).

In summary, (+)-desoxoprosophylline has been synthesized using a new α-furfuryl amine derivative **1** as building block in ten steps (4% overall yield). The intermediate **7** is widely applicable to asymmetric synthesis of naturally polysubstituted piperidines. Work on prosophylline[13] is in progress.

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