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Enantioselective Synthesis of (-)-Desoxoprosopinine by Radical Cyclization

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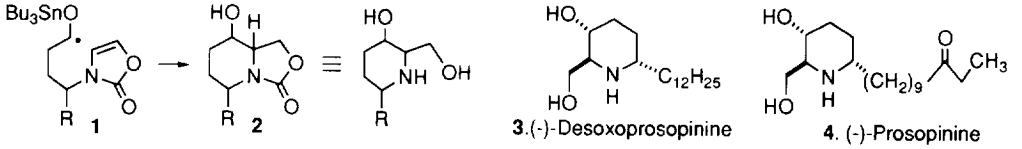
Abstract: Reaction of the aldehyde **12** with tributyltin hydride in the presence of AIBN gave a mixture of **13** as a 2:1 mixture of 8β-ol and 8α-ol. Conversion of **14**, derived from **13**, to (-)-desoxoprosopinine **3** was successfully achieved.

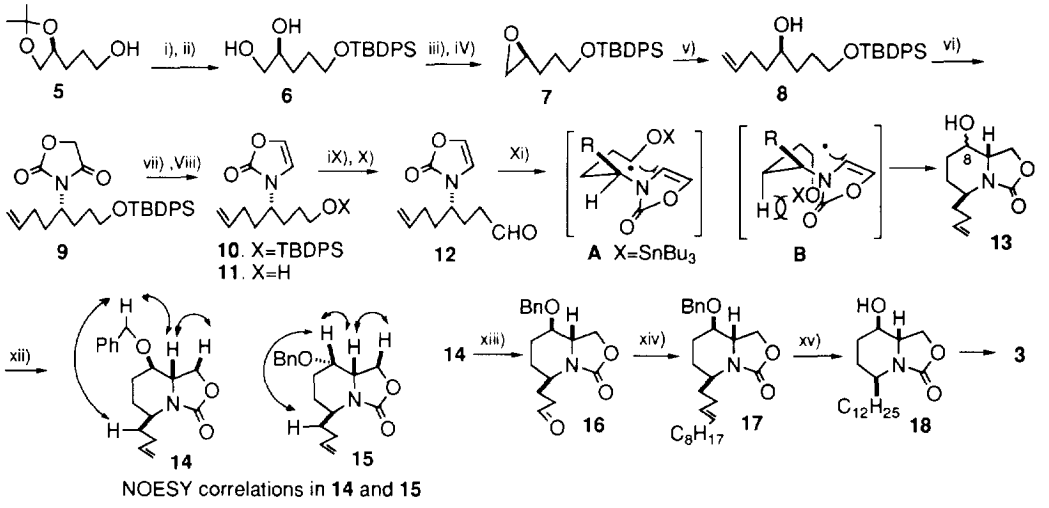
Cyclization of *O*-stannyl ketyls, generated by treatment of aldehydes or ketones with tributyltin hydride, with alkenes has opend up new synthetic methodology for the synthesis of cycloalkanols.[1] We have examined the cyclization of the *O*-stannyl ketyl intermediate **1** by using $\Delta^{4,5}$-oxazolidinone[2] as the radical acceptor to get oxazolopiperidines **2**, which would be the equivalent of 6-substituted 3-hydroxy-2-hydroxymethylpiperidines, a key structural feature of some piperidine alkaloids. In this paper we wish to disclose a highly diastereoselective synthesis of (-)-desoxoprosopinine **3**,[3] the reduction product of naturally occurring prosopinine **4**[4] which possesses a variety of antibiotic and anesthetic properties.



The aldehyde **12**, used as the precursor for the *O*-stanylketyl, was synthesised from the 1,2,5-triol acetonide **5**[5] through the procedure given below. *O*-Silylation of **5** with TBDPSCl and imidazole, followed by ring cleavage of the acetonide with *p*-TsOH in methanol afforded the diol **6**, which was converted to epoxide **7** by the selective mesitylenesulfonylation of **6** at the primary hydroxy group and subsequent treatment wtih NaH in the presence of 18-crown-6. The reaction of **7** with allylmagnesium bromide gave alcohol **8**, which was condensed with oxazolidine-2,4-dione by the Mitsunobu reaction affording **9**. Reduction of **9** with $NaBH_4$ followed by treatment with methanesulfonyl chloride in the presence of triethylamine and subsequent treatment wtih triethylamine at room temperature gave **10**. Desilylation of **10** with tetraethylammonium fluoride, followed by Swern oxidation of the reulting alcohol **11**, $[\alpha]_D$ +9.73(c 1.32 $CHCl_3$), safely afforded aldehyde **12**, $[\alpha]_D$ +9.62 (c 1.26 $CHCl_3$). The reaction of **12** with tributyltin hydride in the presence of AIBN (benzene reflux) afforded the desired 8-hydroxyoxazolopiperidine **13** as a diastereomeric mixture (8β-OH:8α-OH=2:1), the key intermediate for a synthesis of prosopinine and deoxoprosopinine, in 83% yield. A paticularly noteworthy feature was that the radical cyclization proceeded via **A** and **B** with complete facial selectivity because of $A^{1,3}$-strain between the butenyl substituent and the carbonyl. Thus high *trans*-selectivity was observed for 5-H/8a-H. Although separation of diastereomers failed, *O*-benzyl derivatives **14** and **15**, obtained by benzylation of **13**, were obtained in a pure state. Both relative configurations of C_{8a}-H/C_8-H and C_{8a}-H/C_5-H as trans for **14**, obtained in 50% yield, $[\alpha]_D$ -49.9(c 1.13 $CHCl_3$) were assigned, by the study of their

NOESY experiments (as shown in scheme 1). On the other hand, by this method the relative configurations of C_{8a}-H/C_8-H were assigned as cis and C_{8a}-H/C_5-H as trans for **15**, obtained in 25% yield, $[\alpha]_D$ +21.4(c 1.17 $CHCl_3$). The olefination of aldehyde **16**, obtained by ozonolysis of **14**, was achieved with nonyl-phosphonium bromide and BuLi to afford **17**, $[\alpha]_D$ -53.5(c 0.89 $CHCl_3$), in 88 % yield. Hydrogenation of **17** (H_2/Pd-C) in methanol-conc.HCl (30:0.6) afforded **18**, mp 107-109°C (lit.[3b], 103-104°C), $[\alpha]_D$ -19.4(c 0.78, $CHCl_3$), (lit.[3b], $[\alpha]_D^{24}$ -18.6(c 0.44, $CHCl_3$). The spectral data of **18** were identical with those in the literature[3b] and those donated from Prof. K. Tadano, Keio University in all respects. Since a conversion of **18** to (-)-desoxoprosopinine has already accomplished, this work constitutes a formal synthesis (-)-desoxo-prosopinine.

Schme 1



Reagent and Condition
i) TBDPSCl, imidazole, DMF. ii) *p*-TsOH, MeOH. iii) MESCl, Pyridine. iv) NaH, 18-crown-6, THF. v) allyl-magnesium bromide, CuI, THF. vi) Ph_3P, diisopropylazodicarboxylate, oxazolidine-2,4-dione.vii) $NaBH_4$, MeOH. viii) MesCl, Et_3N, ix) Bu_4NF, THF. x) $(COCl)_2$, DMSO, Et_3N. xi)Bu_3SnH,AIBN, benzene.xii) NaH, BnBr,Bu_4NBr, THF. Xiii) O_3, MeOH-CH_2Cl_2 then Me_2S. xiv) n-$C_9H_{19}Ph_3PBr$, *n*-BuLi. xv) H_2, 10% Pd-C, MeOH-c.HCl.

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