VERSATILE SYNTHESIS OF ENANTIOMERICALLY PURE *trans*-2,5-DISUBSTITUTED PYRROLIDINES[#]

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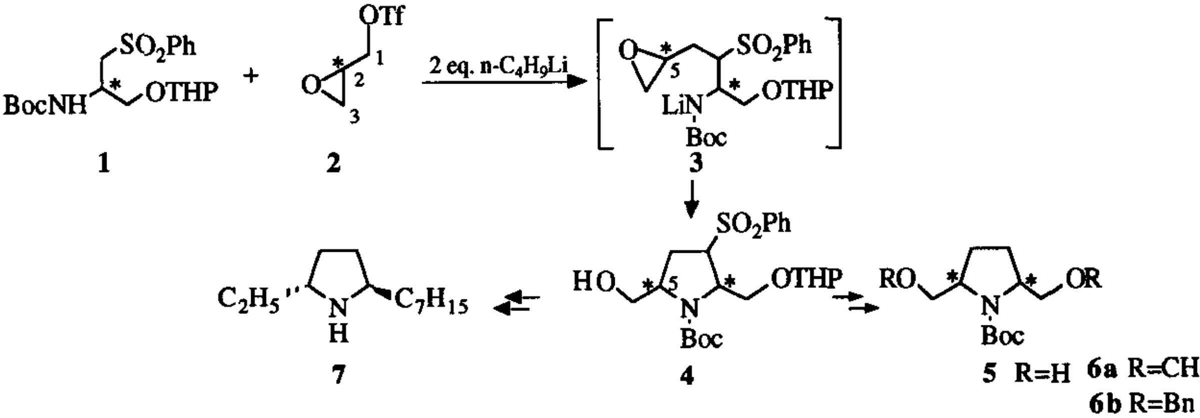
Abstract - Enantiomerically pure *trans*-(2*S*,5*S*)-2,5-disubstituted pyrrolidine was synthesized starting from the versatile chiral synthon (*R*)-(**8**) and chiral 2,3-O-isopropylideneglycerol triflate (*S*)-(**9**).

Considerable effort has been extended in recent years on the synthesis of *trans* 2,5-disubstituted pyrrolidines. The importance of this class of compounds is due to the fact that *trans* 2,5-bisalkyl- and bisalkoxymethyl-pyrrolidines are very useful as C_2 symmetry chiral auxiliaries and many naturally occurring *trans* 2,5-disubstituted pyrrolidines display significant biological activities.[1,2]

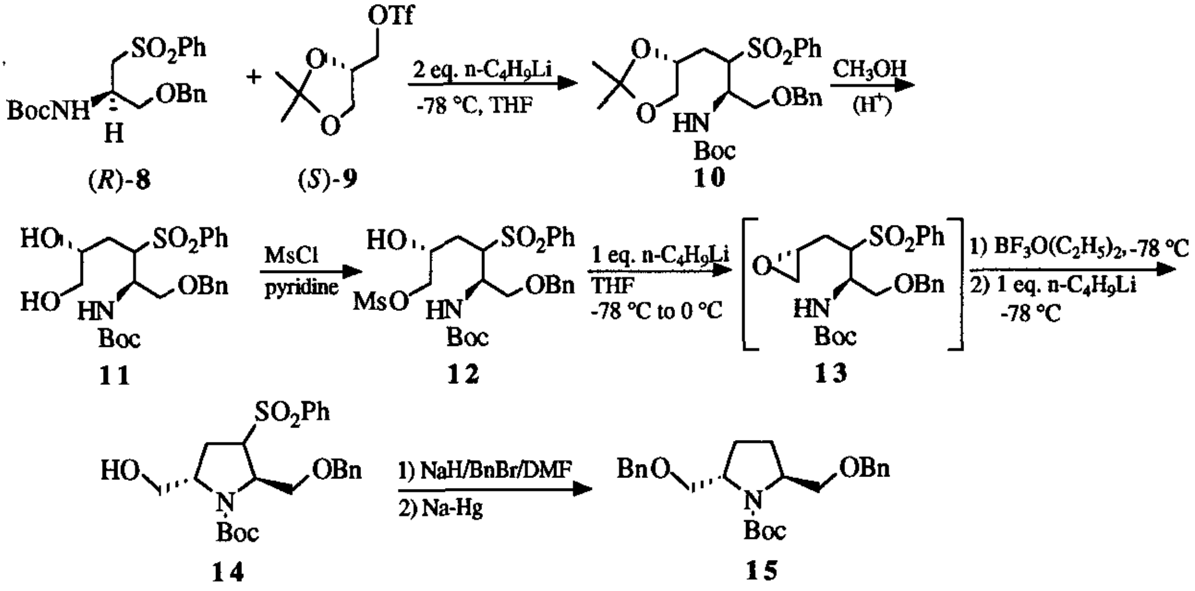
We have recently reported a novel method for the diastereoselective synthesis of 2,5-disubstituted pyrrolidines starting from the versatile chiral synthon (**1**) and chiral glycidyl triflate (**2**), as depicted in Scheme 1.[3]



Scheme 1

[#] Dedicated to the memory of the late Professor Yoshio Ban.

Versatility of this method was demonstrated in the synthesis of *N*-Boc-(2*S*,5*S*)-bis(methoxymethyl)- and bis(benzyloxymethyl)pyrrolidine, (**6a**) and (**6b**), respectively, and their (2*R*,5*R*) analogues as well as (2*R*,5*R*)-2-hepty-5-ethylpyrrolidine (**7**), an important component of the venom of the fire ants (*Solenopsis punctaticeps*). According to this approach, the pyrrolidine (**4**) was formed in "one-pot" in 85% yield. Although the intermediate (**3**) undergoes cyclization exclusively *via* 5-*exo* manner, the initial nucleophilic attack of the sulfonyl carbanion of **1** at C-1 of gycidyl triflate (**2**) was found to proceed with 92% regioselectivity. The nucleophilic ring-opening of epoxide by the sulfone carbanion at C-3 of glycidyl triflate (**2**) also forms the epoxide (**3**) but with opposite stereochemistry at C-5. Consequently, the diastereomeric excess of the newly formed pyrrolidine derivatives remains to be 84%. The *trans* and *cis* diols (**5**) can be easily separated by preparative hplc.[3] In the case of the total synthesis of the dialkylated pyrrolidine (**7**), the minor *cis* diastereomer of a key intermediate could be eliminated by simple recrystallization procedure. Our initial approach for the "one-pot" cyclization was efficient. However, we wished to establish a more practical and stereospecific methodology for the synthesis of 2,5-disubstituted pyrrolidines. To this end, use of homochiral 2,3-O-isopropylideneglycerol triflate (**9**) in place of the glycidyl triflate (**2**) seemed to be an appropriate alternative since it would eliminate the possibility of the nucleophilic attack at C-3 of the epoxide (**2**) as seen in Scheme 1. Our new route to the enantiomerically and diasteremerically pure *trans* 2,5-disubstituted pyrrolidines is illustrated in Scheme 2.



Scheme 2

Treatment of the slight excess of the dilithiated species of (*R*)- **8** with 1 eq. of glycerol triflate (*S*)-(**9**) at -78 °C gave the addition product (**10**) which was directly hydrolyzed in the presence of a catalytic amount of HCl in MeOH to provide diol (**11**) in 90% yield (in two steps). After separation of unreacted (*R*)-(**8**) by chromatography over silica gel (EtOAc/heptane: 1/1), diol (**11**) was converted to mono mesylate (**12**) in 77% yield. Mesylate (**12**) in THF was first added with 1 eq. of n-BuLi at -78 °C. The reaction mixture was warmed gradually to room temperature to form epoxide (**13**), then cooled back to -78 °C and treated *in situ* with 1 eq. of BF_3 etherate followed by addition of 1 eq. n-BuLi at -78 °C. The reaction mixture was warmed to 0 °C and quenched with saturated ammonium chloride solution. The usual work-up provided desired (2*S*,5*S*)-pyrrolidine (**14**).[3,4] Two step sequence conversion (benzylation and desulfonylation) of **14** to chiral auxiriary (**15**) was effected in 75% overall yield in order to demonstrate the effectiveness of our approach. Optical purity of **15** was determined to be more than 99% by converting this compound to (2*S*,5*S*)-2,5-dihydroxymethylpyrrolidine (treatment with trifluoroacetic acid and catalytic hydrogenation) and comparing with the authentic *trans* diol (**5**) by hplc.[3]

Since both antipodes of **8** *and* **9** *are also readily available in enantiomerically pure form,*[5] it is now possible to synthesize any one of the four stereoisomers of 2,5-disubstituted pyrrolidines in enantiomerically and diastereomerically pure form according to our method. In this context, naturally occurring *trans* 2,5-dialkylsubstituted pyrrolidines can be prepared from **14** (or from its (2*R*,5*R*) stereomer) without any problem of the isomer separation. Furthermore, it is to be noted that mesylate (**12**) can serve as a suitable intermediate in the enantiospecific synthesis of 2,5-disubstituted piperidine. We are currently pursuing investigation on these points.

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