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Stereoselective Synthesis of (2*S*,3*S*)-3-Hydroxy-2-phenylpiperidines, Precursors of Non-peptidic Substance P Antagonists

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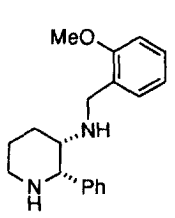
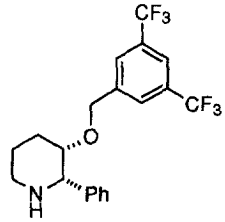
Abstract : (2*S*)-*N*-Boc-3-oxo-2-phenylpiperidine **5** and (2*S*,3*S*)-*N*-Boc-3-hydroxy-2-phenylpiperidine **6**, known chiral building blocks for the synthesis of non-peptidic substance P antagonists, were prepared from *erythro* (2*S*)-*N*-benzyl 2-hydroxybenzylpyrrolidine derived from (*S*)-*N*-methoxy-*N*-methylpyroglutamide.

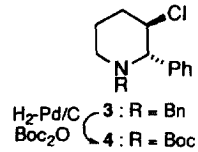
The family of neuropeptides tachykinins is implicated in a variety of physiological processes related to diverse diseases such as arthritis and asthma.[1] So, a great interest is devoted to this research area. Particularly, the development of non-peptidic neurokinin NK1 receptor antagonists have received considerable attention in recent years.[2] Since the discovery of CP-99,994 **1**,[3] numerous 3-amino or 3-alkoxy-2-phenylpiperidines such as **2** have been tested[4] and it has been established that *cis* relationship between the two substituents on the piperidine ring and 2*S*, 3*S* configurations are required for high affinity binding to the human NK1 receptor.[2,3,5]



1 (CP-99,994)



2 (L-733,060)



In the aim to synthesize the active enantiomers of piperidines related to **1**, (2*S*,3*R*)-1-benzyl-3-chloro-2-phenylpiperidine **3**, easily accessible in high yield through a ring enlargment of *erythro* (2*S*)-1-benzyl-2-hydroxybenzylpyrrolidine,[6] seemed to be a suitable starting material. However, as in the case of C-2 unsubstituted 3-chloropiperidines,[7] anchimeric assistance of the nitrogen electron pair with the formation of an aziridinium ion intermediate could not be avoided ; even using trimethylsilylazide-stannic chloride as reagents,[8] the reaction led only to substitution at the benzylic carbon with ring contraction, albeit in poor yield. So, the compound **3** was hydrogenolyzed (H_2-Pd/C) in the presence of di-*tert*-butyldicarbonate to give the carbamate **4** (87%), but attempts to introduce azanucleophiles at C-3 by S_N2 direct displacement of the chlorine were unsuccessful.

We turned then towards the preparation of *N*-protected *cis* (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **6**, which constitutes, as well as the corresponding ketone **5**, the pivotal intermediates in the synthesis of **2**[5] and of the orally active NK1 receptor antagonist oxaazaspirodecane **7**.[9] To our knowledge, these intermediates are

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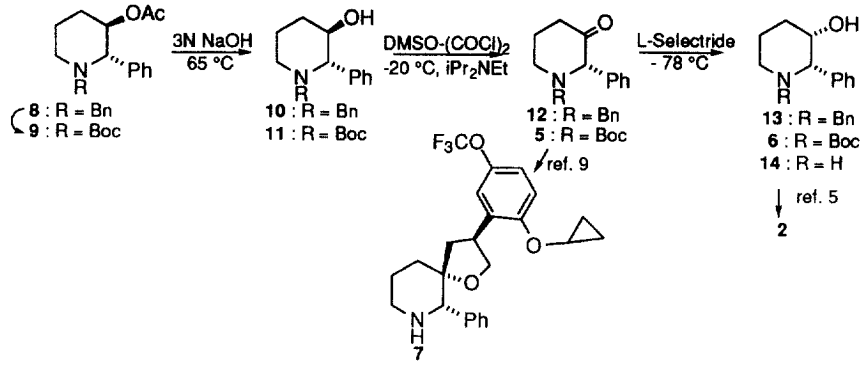
obtained by resolution and only one enantioselective synthesis of the piperidine **14** has been described.[10] So, our previous results were extended to these targets. Accordingly, the *trans* (2*S*,3*R*)-*N*-benzyl-3-acetoxy-2-phenylpiperidine **8**[6] was converted to the carbamate **9** in 98% yield, as described above for **3**. The acetates **8** and **9** were hydrolyzed to **10** and **11** (3N NaOH, THF-MeOH, 65 °C, 99% and 94% respectively).



The inversion of the configuration at C-3 of **10** and **11** was planned to occur through an oxidation-stereo selective reduction sequence rather than under Mitsunobu conditions.[11-13] Both alcohols **10** and **11** were efficiently oxidized by DMSO and SO_3-pyridine complex at 20 °C,[14] but racemization was observed in both cases. Swern's protocol using iPr_2NEt as base and carefully buffered aqueous workup was preferred. The oxidation of **11** under these conditions gave better result than **10**,[15] affording quantitatively the ketone **5**. This ketone was directly reduced to **6** by L-Selectride with high diastereoselectivity (only one diastereomer was observed, 76% for 2 steps). *N*-deprotection of **6** under classical acidic conditions (TFA-CH_2Cl_2, 99%) gave rise to the known (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **14**,[9,10] allowing to check the enantiomeric purity of its precursors.

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15. The crude ketone **12** was directly reduced to **13** in 65% yield(2 steps).