

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

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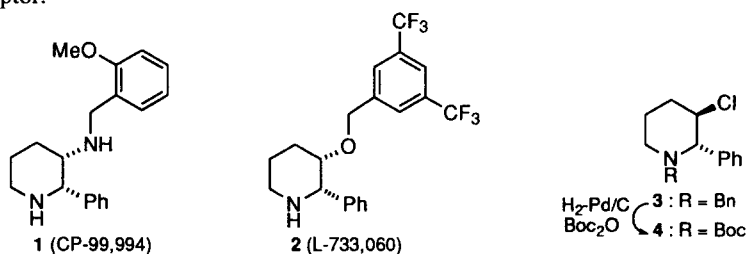
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**Abstract** : (2*S*)-*N*-Boc-3-oxo-2-phenylpiperidine **5** and (2*S*,3*S*)-*N*-Boc-3-hydroxy-2-phenylpiperidine **6**, known chiral building blocks for the synthesis of non-peptidic substance P antagonists, were prepared from *erythro* (2*S*)-*N*-benzyl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

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The family of neuropeptides tachykinins is implicated in a variety of physiological processes related to diverse diseases such as arthritis and asthma.<sup>1</sup> 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.<sup>2</sup> Since the discovery of CP-99,994 **1**,<sup>3</sup> numerous 3-amino or 3-alkoxy-2-phenylpiperidines such as **2** have been tested<sup>4</sup> 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.<sup>2,3,5</sup>

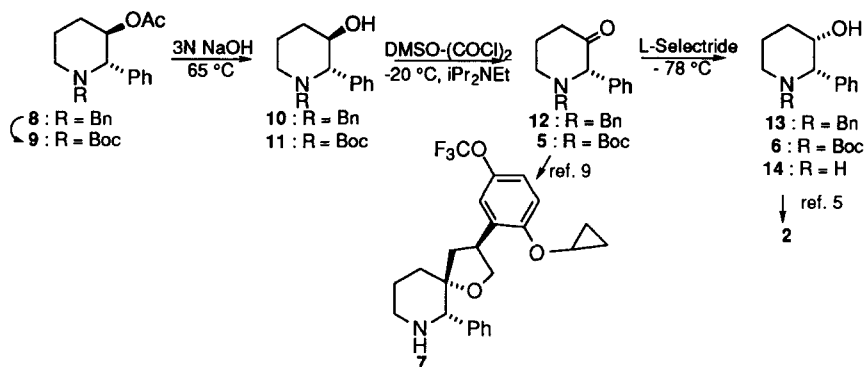


In the aim to synthesize the active enantiomers of piperidines related to **1**, (2*S*,3*R*)-1-benzyl-3-chloro-2-phenylpiperidine **3**, easily accessible in high yield through a ring enlargement of *erythro* (2*S*)-1-benzyl-2-hydroxybenzylpyrrolidine,<sup>6</sup> seemed to be a suitable starting material. However, as in the case of C-2 unsubstituted 3-chloropiperidines,<sup>7</sup> 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,<sup>8</sup> the reaction led only to substitution at the benzylic carbon with ring contraction, albeit in poor yield. So, the compound **3** was hydrogenolyzed (H<sub>2</sub>-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<sub>N</sub>2 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 **25** and of the orally active NK1 receptor antagonist oxazaspirodecane **7**.<sup>9</sup> 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.<sup>10</sup> So, our previous results were extended to these targets. Accordingly, the *trans* (2*S*,3*R*)-*N*-benzyl-3-acetoxy-2-phenylpiperidine **8**<sup>6</sup> 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** (3*N* 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-stereoselective reduction sequence rather than under Mitsunobu conditions.<sup>11-13</sup> Both alcohols **10** and **11** were efficiently oxidized by DMSO and SO<sub>3</sub>-pyridine complex at 20 °C,<sup>14</sup> but racemization was observed in both cases. Swern's protocol using iPr<sub>2</sub>NEt as base and carefully buffered aqueous workup was preferred. The oxidation of **11** under these conditions gave better result than **10**,<sup>15</sup> 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<sub>2</sub>Cl<sub>2</sub>, 99%) gave rise to the known (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **14**,<sup>9,10</sup> allowing to check the enantiomeric purity of its precursors.

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## References and Notes

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- This reaction was anticipated to be complicated by the formation of side-products such as pyrrolidine or tetrahydro pyridine.<sup>12,13</sup>
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- The crude ketone **12** was directly reduced to **13** in 65% yield (2 steps).