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An efficient stereoselective synthesis of (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine

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Abstract—A concise enantioselective synthesis of *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **1** is described starting from L-phenyl-glycine and using a Grignard reaction as a key step.

Functionalised piperidines constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents. Consequently numerous methods have been developed for the synthesis of substituted piperidines in a stereo- and enantioselective manner.[1] *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **1** is an important intermediate from which nonpeptide neurokinin NK1 receptor antagonists **2**[2] and **3**[3] have been prepared (Fig. 1).

These nonpeptide ligands **2** and **3** are known to exhibit a variety of biological activities including neurogenic inflammation,[4] pain transmission and regulation of the immune response.[5] They have been implicated in a variety of disorders including migraine,[6] rheumatoid arthritis[7] and pain.[8] It has been established that the *cis*-relationship between the two substituents on the piperidine ring and 2*S*,3*S* configurations are essential for high-affinity binding to the human NK1 receptor.[2b,3,9] A few reports have appeared on the asymmetric synthesis of **1**. These involve the use of Sharpless asymmetric dihydroxylation of a silyl enol ether,[10a] L-glutamic acid[10b] or (*S*)-*N*-methoxy-*N*-methylpyroglutamide[10c] as chiral pool materials, the intramolecular ring opening of a chiral epoxide followed by ring expansion[10d] and the application of ring-closing metathesis[10e] for the preparation of enantiopure **1**. As part of our research program aimed at developing enantioselective syntheses of naturally occurring amino alcohols,[11] we became interested in developing a simple and feasible route to *N*-Boc-3-hydroxy-2-phenylpiperidine **1**. Here we report a new and highly enantio- and diastereoselective synthesis of **1** employing a Grignard reaction as a key step.

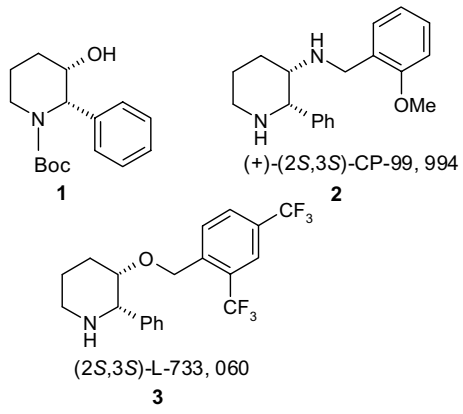

Figure 1.

The synthesis of the target compound **1** commenced from commercially available L-phenylglycine **4** as depicted in Scheme 1. Compound **4** was first converted into the *N*-Boc derivative and subsequently esterified with methyl iodide to give *N*-Boc methyl ester **5** in excellent yield. The ester **5** was reduced to alcohol **6** using $LiAlH_4$. The essential feature of our synthetic strategy was the presumption that the aldehyde derived from alcohol **6** would undergo chelation-controlled carbonyl addition[12] and provide preferentially the desired *threo* amino alcohol **7** in a stereoselective manner. Thus, Swern oxidation of **6** followed by in situ

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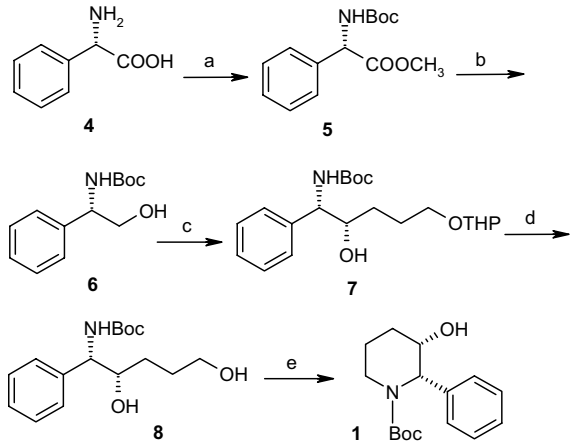

Scheme 1. Reagents and conditions: (a) (i) $(Boc)_2O$, 1 N NaOH, dioxane, 2 h, 0 °C–rt, 95%, (ii) K_2CO_3, DMF, CH_3I, 1 h, 0 °C–rt, 85%; (b) $LiAlH_4$, THF, 1 h, 0 °C–rt, 89%; (c) DMSO, $(COCl)_2$, DCM, *i*-Pr_2NEt then BrMg $(CH_2)_3OTHP$, THF, 2 h, rt, 58%; (d) TsOH, MeOH, 2 h, rt, 85%; (e) (i) MsCl, Et_3N, DCM, 3 h, 0 °C–rt, (ii) NaH, THF, rt, 78%.

reaction of the resulting aldehyde with 3-(tetrahydropyran-2-yloxy)propylmagnesium bromide afforded the amino alcohol **7** as a single diastereomer[13] in favour of the *syn* isomer, which is in accordance with the reported observation.[14] The THP group of **7** was removed using *p*-toluenesulfonic acid to give the amino diol **8** in 85% yield. The primary hydroxyl group was then mesylated followed by in situ cyclisation using NaH to furnish *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **1** in 78% yield, $[\alpha]_D^{20}$ +35.41° (*c* 1.2, $CHCl_3$) [Lit.[10e] $[\alpha]_D^{25}$ +38.30° (*c* 1.92, $CHCl_3$)]. The physical and spectroscopic data of **1** were in full agreement with the literature values.[10e] The intermediate **1** could easily be transformed into the nonpeptidic neurokinin NK1 receptor antagonists **2** and **3** as previously reported.[10b,e]

In summary, a highly enantio- and stereoselective synthesis of *N*-Boc-(2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **1** has been accomplished. The short reaction sequence and high overall yield of the target compound render our strategy a good alternative to the known methods.

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13. The diastereoselectivity was determined based on ^{13}C NMR spectral data. Spectral data of **7**: $[\alpha]_D^{20}$ +13.73° (*c* 0.82, $CHCl_3$) IR ($CHCl_3$, cm^{-1}) 3480, 3350, 2936, 2840, 1680, 1550, 1448; ^1H NMR (200 MHz, $CDCl_3$): δ 1.47 (s, 9H), 1.52–1.68 (m, 8H), 2.04–2.35 (m, 2H), 3.41–3.79 (m, 5H), 4.21–4.24 (m, 1H), 4.58 (m, 1H), 5.46 (br s, 1H), 7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.05, 25.08, 28.24, 30.22, 32.50, 34.93, 56.50, 63.82, 65.84, 79.65, 94.36, 98.60, 126.53, 127.26, 128.40, 140.02, 156.23; Mass (ESI): 397 ($M+NH_4^+$), 380 (M+1), 356, 279, 246.
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