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Tetrahedron Letters 46 (2005) 7221–7223
Tetrahedron Letters

A stereoselective route to *cis*-2-phenyl-3-piperidinol

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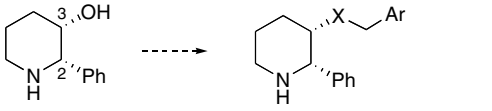
Received 2 August 2005; accepted 15 August 2005
Available online 2 September 2005

Abstract—Enantiopure *cis*-2-phenyl-3-piperidinol is a commonly used synthon for the obtention of a potent class of neurokinin substance P receptor antagonists. Starting from (*R*)-phenylglycine, the present report describes an efficient route for the stereoselective synthesis of the above piperidinol structural core.

Chiral polysubstituted piperidine structural framework is a common feature present in a large number of natural and nonnatural compounds of biological significance.[1] Consequently, development of new and efficient methods for the stereoselective synthesis of functionalized piperidines continues to be an active area of research.[2,3] In the search for nonpeptidic neurokinin NK-1 receptor antagonists, the 2,3-disubstituted piperidine derivatives **2** and **3** (Scheme 1) were found to display potent and selective antagonist activity at the human NK-1 receptor site.[4,5]

In recent years, several methods have been developed towards the synthesis and structural modification studies of the above compounds.[6] Structure–activity relationship studies have shown that the cis-relationship between C2 and C3 substituents on the piperidine ring of **2** and **3** is required for optimum binding activity.[7] In the majority of the synthetic studies reported so far, appropriately protected piperidinol **1** has been a commonly utilized precursor for the synthesis of the corresponding aryl ether derivative **2**.[6] Interestingly, the piperidinol **1** could also be stereoselectively transformed to the corresponding 3-amino derivative toward synthesizing the 3-aminoaryl analog **3**.[6e,g] In continuation of our studies on amino acid chiral template assisted stereoselective synthesis of bioactive compounds,[8] we report herein an efficient route to the enantiopure 2-phenyl-3-piperidinol structural core.



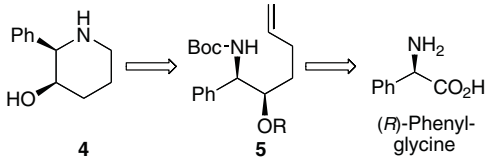
1

2, X = O; Ar = 3,5-$(CF_3)_2C_6H_3$: [(+)-L-733,060]
3a, X = NH; Ar = 2-$(MeO)C_6H_4$: [(+)-CP-99,994]
3b, X = NH; Ar = 2-(MeO)-5-$(OCF_3)C_6H_3$: [(+)-CP-122,721]

Scheme 1.

Our plan for the construction of the piperidine framework is shown below (Fig. 1). The key bond forming reactions in the delineated strategy are envisioned to be (i) a chelation controlled, stereoselective addition of an appropriate Grignard reagent to enantiopure *N*-Boc-phenylglycinal and (ii) an oxidative cyclization of the resulting δ-alkenylcarbamate **5** toward formation of the target piperidine core **4**.

Following a known procedure, readily available (*R*)-phenylglycine was converted to *N*-Boc-phenylglycinol (**6**, Scheme 2) in good yield.[9] The next step in the sequence required stereoselective construction of the



4 **5**

Figure 1. Retrosynthetic strategy and approach.

Keywords: Piperidine; Bioactive; Phenylglycine; Stereoselective; Chelation controlled.
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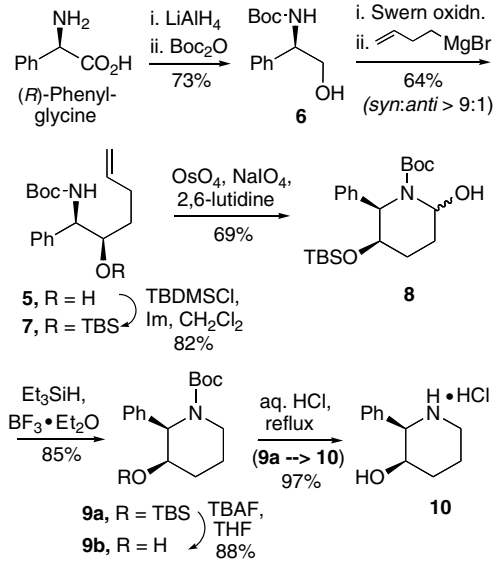
doi:10.1016/j.tetlet.2005.08.060



Scheme 2.

syn-1,2-aminoalcohol functionality as depicted in the desired intermediate **5**. In a previous research from our group, it has been demonstrated that under appropriate reaction conditions, reaction of in situ generated *N*-protected chiral α-aminoaldehydes with Grignard reagents results in a chelation-controlled addition of the organometallic nucleophile to the aldehyde carbonyl, leading to the formation of the corresponding enantiopure 1,2-aminoalcohol adduct with high *syn*-selectivity.[3b,10] Following this protocol, oxidation of **6** to the corresponding aldehyde and its in situ reaction with an excess of homoallylmagnesium bromide afforded the required *syn*-aminoalcohol derivative **5** with good diastereoselection (>9:1).

The hydroxy group of **5** was subsequently protected as its silylether derivative **7**. As per our synthetic strategy, the Boc-amino group and the terminal olefinic moiety of the δ-alkenylcarbamate **7** represent ideal functionalities to carry out the required heterocyclic ring forming reaction. Accordingly, in an efficient one-pot three step reaction cascade, treatment of **7** with catalytic osmium tetroxide in the presence of sodium periodate and 2,6-lutidine[11] resulted in the formation of the cyclic carbinolamine **8** in good overall yield. Reductive conversion[12] of **8** to the corresponding amine uneventfully afforded the fully protected 2-phenyl-3-piperidinol derivative **9a**. At this stage, partial deprotection via selective removal of the silyl-protecting group yielded the known *N*-Boc-2-phenyl-3-piperidinol (**9b**),[6c] spectral and analytical data $\{[\alpha]_D^{25} -50.4$ (*c* 1, $CHCl_3$): Lit.[6c] $[\alpha]_D^{20} -51.1$ (*c* 1, $CHCl_3$)} of which were found to be in good agreement with the reported values, thereby confirming the assigned structure and absolute configuration of **9b** and its precursors. In a separate experiment, simultaneous removal of both the *O*- and *N*-protecting groups by treatment of **9a** with refluxing aq HCl culminated in an efficient route to the hydrochloride salt of *cis*-2-phenyl-3-hydroxypiperidine (**10**/***ent*-1**).[13]

In conclusion, starting from easily available (*R*)-phenylglycine and utilizing an elegant oxidative heterocyclization of an appropriately functionalized δ-alkenylcarbamate intermediate, an efficient route to enantiopure *cis*-2-phenyl-3-piperidinol has been developed. In terms of brevity and efficiency, the present synthesis compares well with the earlier reported methods[6] and is expected to offer an attractive alternative route to the title compound. Furthermore, as chiral nonracemic piperidines are common structural subunits found in a variety of compounds of pharmaceutical significance, the strategy and the approach described herein can be easily extended towards synthesizing various functionalized piperidines of potential biomedical application.

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13. Spectral and analytical data of compound **10**: light yellow flaky solid; mp 264–268 °C; $[\alpha]_D^{25}$ −62.54 (*c* 1.03, H_2O); ^1H NMR (400 MHz, D_2O): δ 1.69–1.99 (m, 4H), 3.07–3.13 (m, 1H), 3.40–3.43 (m, 1H), 4.12 (br s, 1H), 4.32 (br s, 1H), 7.24–7.57 (m, 5H); ^{13}C NMR (100.6 MHz, D_2O): δ 16.0, 28.8, 45.1, 62.6, 66.7, 126.3, 128.2, 128.9, 129.0, 129.5, 134.8; HRMS Calcd for $C_{11}O_{16}NO$ (free amine) *m*/*z* (M+H) 178.1232, found 178.1224.