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Asymmetric synthesis of (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine via ring expansion

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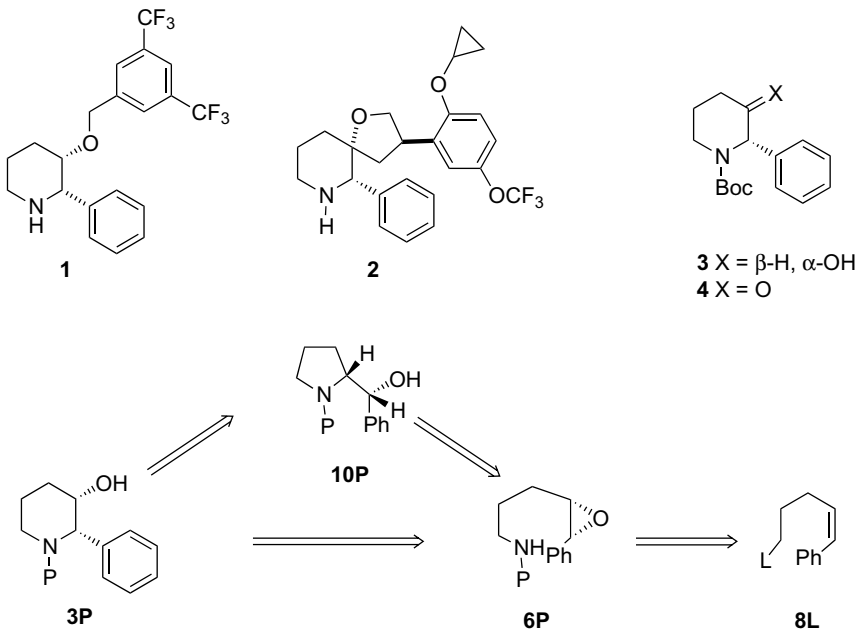
Abstract—A catalytic highly enantioselective (99% ee) preparation of *N*-*tert*-butyloxycarbonyl-(2*S*,3*S*)-3-hydroxy-2-phenyl-piperidine and *N*-*tert*-butyloxycarbonyl-(2*S*)-2-phenyl-piperidin-3-one was developed using an intramolecular epoxide opening followed by ring expansion. The *cis*-epoxide starting material was available in high ee via Jacobsen epoxidation.

Functionalized piperidines have attracted increasing interest as synthetic targets because of important activity as pharmacophores in medicinally active compounds. Various methods have been developed for the synthesis of substituted piperidines in a diastero- and enantioselective manner.[1] Neuropeptide substance-P (Neurokinin-1) receptor antagonists **1**[2] and **2**[3] have been prepared via the piperidine intermediates (2*S*,3*S*)-3-hydroxy-2-phenyl-piperidine **3** and the derived piperidinone **4**, respectively. Although a number of methods have been developed to access compound **3** using the chiral pool method or racemic synthesis followed by resolution, the challenge of a catalytic asymmetric synthesis of **3** and **4** remained.[2b,4] In this report, we describe a catalytic, highly enantioselective preparation of these important intermediates.

We envisioned a retrosynthetic strategy (Scheme 1) whereby **3P** might arise from the formal 6-*endo* mode[5]



Scheme 1.

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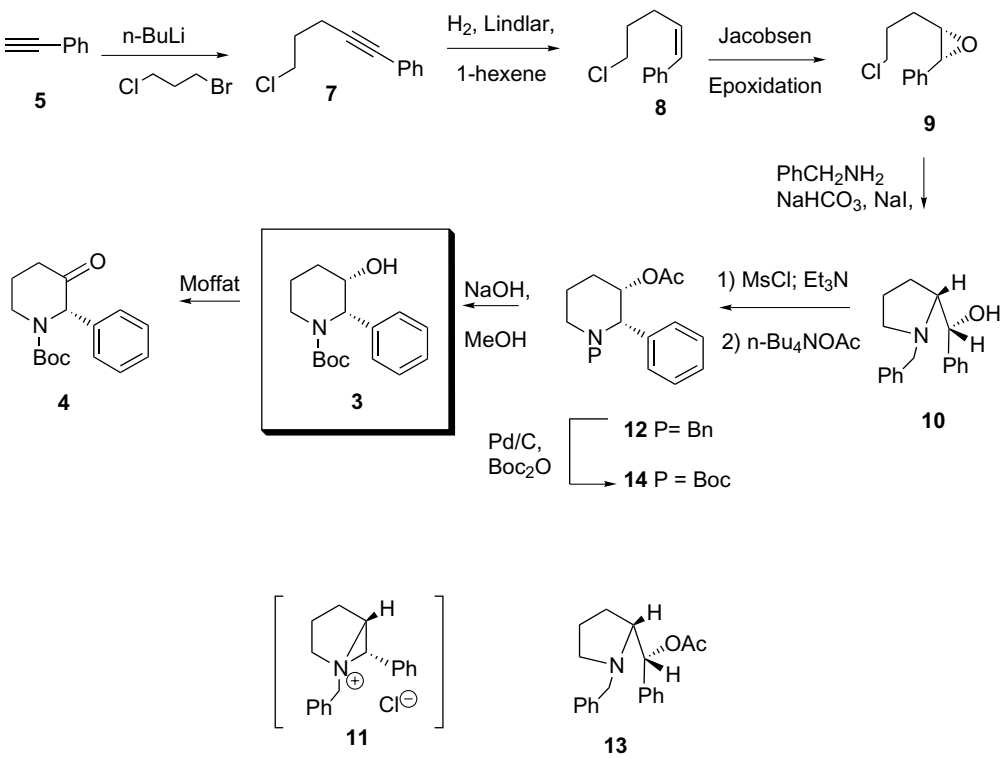
cyclization of *cis*-epoxide **6P** to give the desired piperidine.[6,7] Alternatively, the selective cyclization of **6P** via 5-*exo* mode[5] to pyrrolidinol **10P** followed by ring expansion[8] would provide the desired piperidine ring system **3P**.[4a] Epoxide **6P** would be available in asymmetric form via enantioselective Jacobsen epoxidation of *cis*-olefin **8L**.

Synthesis of phenylpiperidinol **3** (Scheme 2) commenced with 3-carbon homologation of phenylacetylene with 1-bromo-3-chloropropane (THF, reflux, 16 h) to afford acetylene **7** (89%). The acetylene was hydrogenated with Lindlar's catalyst (45 psi H_2, EtOAc) to afford β-alkylated *cis*-styrene **8** (95%). Jacobsen's asymmetric epoxidation of **8** gave the corresponding *cis*-epoxide **9** with a high degree of enantioselectivity at 5°C (94% ee, 75% yield).[9] Treatment of the chloro *cis*-epoxide **9** with benzylamine in refluxing acetonitrile afforded the presumed 5-*exo*-*tet* mode cyclization product pyrrolidinol **10** in 65% yield.

With **10** in hand, we next pursued the ring expansion study.[8] The ring expansion of 2-((phenyl)-hydroxymethyl)-pyrrolidine to the piperidine isomer has been reported in which *trans*-3-chloro-2-phenylpiperidine was obtained exclusively by treatment of the pyrrolidine with methanesulfonyl chloride at room temperature.[4a,10] We speculated that the bicyclic aziridinium intermediate **11**, formed from methanesulfonyl chloride and **10**, might be trapped by acetate ion by employing a lower reaction temperature and acetate as an external nucleophile to form the desired 3-acetoxy-piperidine. In practice, pyrrolidinol **10** was treated with methanesulfonyl chloride and triethylamine in THF at −20°C to form the aziridinium intermediate **11** with no chloropiperidine detected.[10] Subsequent treatment with 4.5 equiv. of tetra-*n*-butylammonium acetate (−20°C to room temperature) afforded the desired acetoxy-piperidine **12** in 85% yield and 99% ee as a white crystalline solid. In this way, the bicyclic aziridinium intermediate **11** was trapped efficiently with acetate ion at low temperature (−20°C) and resulted in a high degree of chirality transfer.[11] The enantiomeric purity of **12** was efficiently upgraded during the crystallization step (ethyl acetate–hexanes, mp 105∼106°C). Interestingly, only a small amount of the isomeric pyrrolidinyl acetate **13** (≤5%) was detected in the crude reaction mixture.

The next step involved a selective *N*-debenzylation/Boc protection using Pd/C, H_2 (45 psi) in the presence of Boc_2O to afford **14** (95%).[4a] The acetate **14** was hydrolyzed to the piperidinol **3** using NaOH in MeOH[12] (95%). Oxidation of piperidinol **3** was accomplished using Moffatt conditions[13] (EDC, DMSO, pyridine, TFA) to afford 2-phenyl-*N*-*tert*-butyloxylcarbonyl-piperidine-3-one **4** without epimerization (86%).

The synthesis described herein provides *N*-Boc-piperidinol **3** in seven steps and 32% overall yield from phenylacetylene, and demonstrates the Jacobsen epoxidation/ring enlargement strategy as an efficient asymmetric method for the synthesis of *cis*-α-aryl-β-hydroxy-piperidines.



Scheme 2.

Acknowledgements

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   For the reaction condition; *N*-phenylpyridine-*N*-oxide (PPO), (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride, methylene chloride, NaCl, NaOCl (13%), 5°C for 48 h (assay conditions: (*S*,*S*) Whelko column, 0.5% *i*-PrOH/hexanes; 1.0 ml/min, 20°C; 250 nm).
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11. Aziridium intermediate **11** could be isolated by trituation of hexanes at −20°C. For the experimental details of ring expansion; *N*-benzyl-hydroxy-pyrrolidine **10** (6.65 g, 22.4 mmol) was placed in dry THF (110 ml) and cooled to −20°C. Methanesulfonyl chloride (2.08 mL, 26.9 mmol) was introduced into the solution followed by triethylamine (12.5 mL, 89.6 mmol). The resulting solution was aged for 1 h at this temperature. Tetra-*n*-butylammonium acetate (39 g, 129 mmol) was added and the resulting mixture was warmed to room temperature over a period of 1 h. After aging for 16 h at room temperature, the reaction mixture was extracted with EtOAc (2×200 mL) and washed sequentially with 100 mL of sat. $NaHCO_3$, and 50 mL of saturated aq NaCl. After concentration of the organic layer, the crude mixture was purified by flash chromatography on silica gel (hexanes–EtOAc, 9:1 (v/v) gradient to 7:3 (v/v)) followed by recrystallization from EtOAc–hexanes to afford the desired 3-acetoxypiperidine **12** in 85% yield with 99% ee (assay conditions: SFC method, Chiralcel OJ column, 4% MeOH in CO_2, 300 bar, 35°C, 1.5 mL/min at 215 nm); mp 105–106°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.55 (m, 1H), 1.56 (m, 1H), 1.93 (s, 3H), 2.06 (m, 3H), 2.95 (d, 1H), 3.05 (d, 1H), 3.41 (d, 1H), 3.84 (d, 1H), 5.03 (d, 1H), 7.28 (m, 8H), 7.47 (d, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 21.1, 29.4, 52.8, 59.7, 70.3, 71.7, 126.8, 127.4, 128.1, 128.1, 128.7, 128.9, 170.2.
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