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Enantioselective synthesis of NK-1 receptor antagonists (+)-CP-99,994 and (+)-CP-122,721

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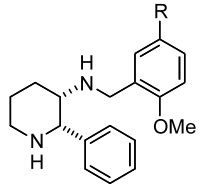
Abstract—An enantioselective total synthesis of NK-1 receptor antagonists, (+)-CP-99,994 and (+)-CP-122,721, is described. The key steps are diastereoselective addition of vinyllithium to a chiral benzaldehyde oxime ether and diastereoselective borane reduction of a cyclic oxime ether.

The neuropeptide substance P (SP) is involved in a variety of biological actions, including pain transmission, vasodilatation, smooth muscle contraction, and neurogenic inflammation.[1] It binds preferentially to the neurokinin-1 (NK-1) receptor. Although the physiological role of the NK-1 receptor remains to be more clearly defined, selective SP receptor antagonists might be of potential therapeutic value. Recently, the search for nonpeptide antagonists of the NK-1 receptor led to the discovery of CP-99,994 (**1**), which has been shown to bind with high affinity to the human and rodent NK-1 receptors and to possess potent anti-emetic activity.[2] Since the discovery of **1**, numerous 3-amino or 3-alkoxy-2-phenylpiperidines have been tested, and it has been established that a *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 NK-1 receptor.[3] More recently, the trifluoromethoxy analog, CP-122,721 (**2**), was developed as a second-generation NK-1 receptor antagonist, which shows a significant increase in efficacy for in vivo blockade of NK-1 receptor-mediated responses, together with its potent anti-emetic activity.[4] These nonpeptide ligands **1** and **2** were indicated to be much more potent NK-1 receptor antagonists than the enantiomerical antipodes designated as CP-100,263 (*ent*-**1**) and CP-132,687 (*ent*-**2**), respectively.[2,4]



(+)-CP-99,994 (**1**) R = H
(+)-CP-122,721 (**2**) R = OCF_3

We have recently reported that chiral arylaldehyde oxime ethers on treatment with methyllithium undergo efficient nucleophilic addition leading to an enantioselective preparation of 1-(aryl)ethylamines.[5] This methodology has been applied to an enantioselective synthesis of the calcium receptor agonist NPS R-568 and its thio analog.[5] Here we report further extension of this methodology to an enantioselective total synthesis of the NK-1 antagonists CP-99,994 (**1**)[6,7] and CP-122,721 (**2**).[8]

Our first objective toward the synthesis of (+)-CP-99,994 was the enantioselective formation of (1*R*)-1-phenyl-2-propen-1-amine (**7**). To this end, the benzaldehyde oxime ether **4**, prepared using (*R*)-1-phenyl-1,2-ethanediol [(*R*)-**3**] as a chiral auxiliary according to the procedure previously reported from our laboratory,[5] was subjected to treatment with vinyllithium (5 equiv.) in toluene at 0°C, resulting in a 5:1 diastereomeric mixture (79% combined yield) of the 1-vinyl adducts favoring the 1*R* epimer **5** (Scheme 1), which was isolated in a pure form by silica gel chromatography using hexane–AcOEt (70:20).

The *re* face selectivity observed in this reaction can be accounted for in terms of a six-membered lithium-coordinated transition state consistent with our previous

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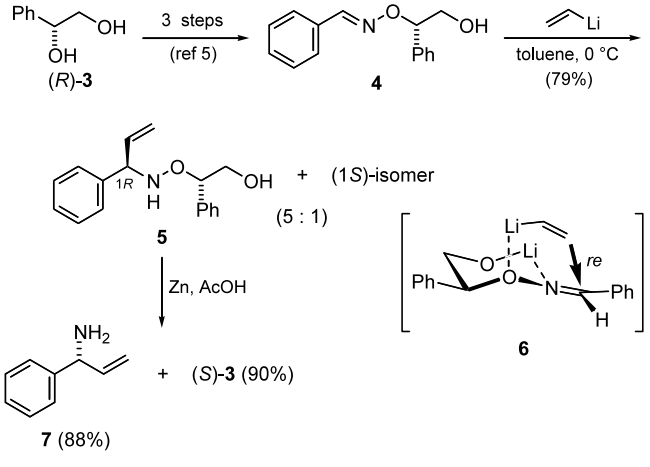
results in nucleophilic addition of methyllithium to chiral oxime ethers.[5] Accordingly, a chair-like chelated transition state **6** can be invoked, which activates the imino group with respect to nucleophilic addition of vinyllithium. Thus, the second molecule of vinyllithium coordinates to the oxygen atom at an axial position to avoid the 1,3-allylic strain,[9] and a subsequent internal delivery of the vinyl group could occur to the *re* face of the imino group, leading predominantly to the 1*R* adduct **5**.[10]

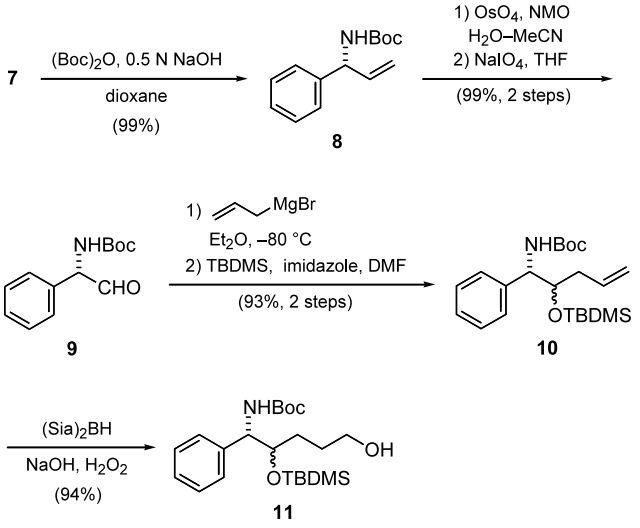
The 1*R*-vinyl adduct **5** underwent N–O bond cleavage using Zn–AcOH to give the amine **7** with recovery of the antipodal chiral auxiliary (*S*)-**3**, allowing us to confirm the absolute configuration of the newly formed stereocenter of **7** to be desired *R* based on comparison of the optical rotation of synthetic **7**, $[\alpha]_D^{25}$ +10.2 (*c* 1, $CHCl_3$), with the published value,[11] $[\alpha]_D^{25}$ +10.23 (*c* 4, $CHCl_3$).

After protection of **7** as its *N*-Boc derivative **8**, the olefinic double bond was cleaved by a two-step sequence via OsO_4-catalyzed dihydroxylation followed by oxidation with $NaIO_4$ to afford the aldehyde **9** in an almost quantitative yield (Scheme 2). Allylation of **9** with allylmagnesium bromide (Et_2O, –80°C) provided a diastereomeric mixture of the secondary alcohols (α-OH:β-OH = 1.2:1), which was protected as the TBDMS ether to give **10** as a diastereomeric mixture. Hydroboration of **10** using siamylborane followed by a hydrogen peroxide basic working-up yielded the primary alcohol **11** (94%).

Mesylation of the primary alcohol of **11** afforded the corresponding mesylate, which underwent *t*-BuOK-mediated cyclization at room temperature to provide the piperidine derivative **12** in 96% overall yield (Scheme 3). After deprotection of the TBDMS group with TBAF, the hydroxypiperidine derivative **13** was subjected to Dess–Martin oxidation[12] to form the ketone **14** (88%). Treatment of **14** with *O*-methylhydroxylamine hydrochloride and pyridine at room temperature yielded (*E*)-oxime ether **15** (95%) as a single geometrical isomer. Upon treatment of **15** with borane–



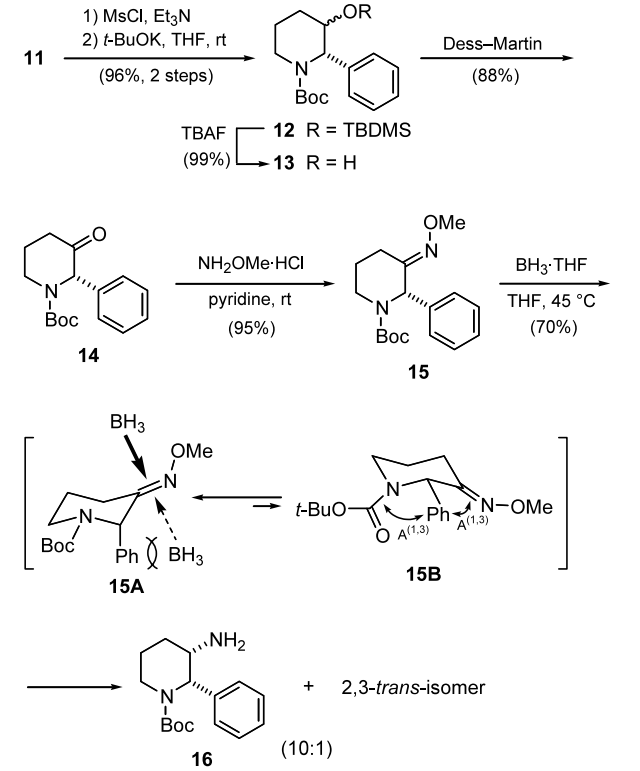
Scheme 1.



Scheme 2.

THF complex in THF at 45°C, stereoselective reduction of the imine moiety proceeded along with reductive cleavage of the N–O bond, affording the 2,3-*cis*-disubstituted piperidine derivative **16**, as a major diastereomer, and its *trans*-isomer in 10:1 ratio and 70% combined yield. The configuration and conformation of **16** were determined by the coupling constants and NOE difference data (Fig. 1).

The stereoselectivity observed in the reduction of **15** can be rationalized by invoking a chair-like conformation **15A** with an axially disposed phenyl group, which



Scheme 3.

minimizes the unfavorable 1,3-allylic interactions[9] existing in the alternative conformation **15B**. The bottom face of the C=N bond of the conformation **15A** is sterically hindered by the axial phenyl group, so that the approach of borane can take place preferentially from the less hindered top face.

The 3-aminopiperidine derivative **16** thus obtained was converted to **18** via reductive amination with 2-methoxybenzaldehyde (**17**) under conditions using sodiumcyanoborohydride in HCl–MeOH at room temperature. Deprotection of the *N*-Boc group with HCl–MeOH provided CP-99,994 hydrochloride (**1**·2HCl), mp 254.5°C (EtOH) [lit.[6a] mp 255°C (EtOH)]; $[\alpha]_D^{25}$ +75.5 (*c* 1.1, MeOH) [lit.[6a] $[\alpha]_D^{25}$ +77 (*c* 1.0, MeOH)], in 83% yield. The ^{1}H NMR data for the free base **1** was identical with those reported[6a] for racemic **1** in the literature.

The same protocol was applied to the preparation of CP-122,721 (**2**). Thus, 3-aminopiperidine **16** was subjected to reductive amination using 5-trifluoromehyl-2-methoxybenzaldehyde (**19**) and sodiumcyanoborohydride (HCl–MeOH, rt) to give an unsatisfactory yield of **20** (38%). The low yield of this reaction most likely results from the presence of the electron-withdrawing 5-trifluoromethyl group in **19**, which decreases the electrophilicity of the intermediary imine. The electrophilicity of the imine can be enhanced by complexation with a Lewis acid to form a reactive iminium salt.[13] Therefore after treatment of **16** with **19** in the presence of

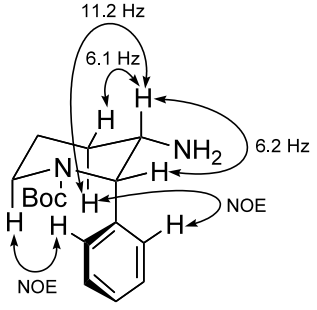
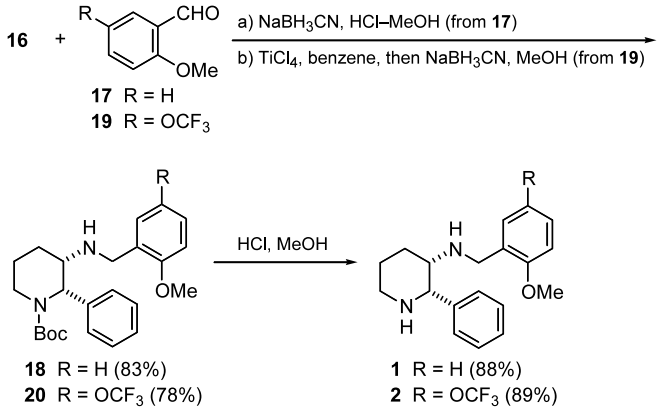


Figure 1. Selected NOE and coupling constants for compound **16**.



Scheme 4.

$TiCl_4$ (3 equiv.) in benzene at 0°C, the resulting iminium ion was treated with a methanol solution of sodiumcyanoborohydride at room temperature. In this manner, the yield of the reductive amination product **20** was significantly improved up to 78%. Deprotection of the *N*-Boc group in HCl–MeOH furnished in 89% yield CP-122,721 (**2**) as the hydrochloride salt (**2**·2HCl), mp 275–276°C (EtOH–Et_2O) (lit.[8] mp 277–278°C); $[\alpha]_D^{26}$ +75.6 (*c* 1.0, MeOH) [lit.[8] $[\alpha]_D^{20}$ +71.2 (*c* 1.0, MeOH)] (Scheme 4).

In conclusion, we have developed a new and efficient route for the enantioselective synthesis of the NK-1 receptor antagonists, (+)-CP-99,994 and (+)-CP-122,721, based on diastereoselective addition of vinyllithium to the chiral benzaldehyde oxime ether and diastereoselective borane reduction of the cyclic oxime ether.

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