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A concise and practical catalytic asymmetric synthesis of (−)-CP-99,994 and (−)-L-733,061

Kouichi Takahashi, Hiroto Nakano* and Reiko Fujita

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan

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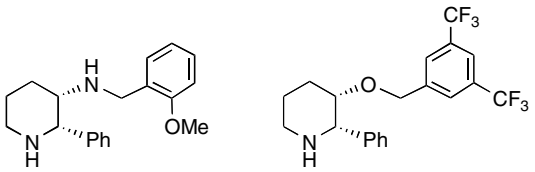
Abstract—A concise and practical catalytic asymmetric synthesis of (−)-CP-99,994 and (−)-L-733,061 was achieved. Key features involve the Pd-catalyzed asymmetric allylic amination and the ring-closing metathesis as key steps.

Substance P[1] (SP), an undecapeptide belonging to the tachykinin family of peptides, has extremely important biological activities involving binding to the neurokinin-1 (NK1) receptor. It has been established that the release of SP is closely related to the transmission of pain and the induction of neurogenic inflammatory responses.[2] Therefore, the SP antagonist[3] is expected to act as a remedy for a wide range of diseases, including arthritis, asthma, and migraines. It has recently been reported that the piperidine analogues CP-99,994 (**1**)[4] and L-733,060 (**2**)[5] have excellent affinity and selectivity with human NK1 receptor. Due to their important potential pharmacological applications, there have been several reports on the synthesis of **1** and **2** in both racemic[6,7] and optically active forms.[8,9]

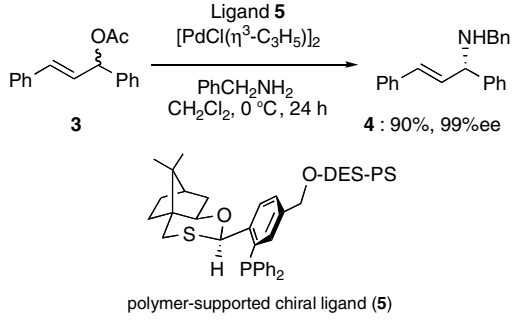


CP-99,994 (**1**) L-733,060 (**2**)

Figure 1.

As a synthetic methodology of optically active forms, previous most reported studies have included the methodologies that uses a chiral template or a diastereoselective reaction as a key step for the asymmetric induction. As an other methodology, catalytic enantioselective synthesis is strongly desirable for the synthesis of **1** and **2**. However, only one example for the catalytic asymmetric synthesis of **1** using the catalytic asymmetric nitro-Mannich reaction as a key step has been reported by Shibasaki and co-workers.[10] Their results, however, cannot necessarily be considered satisfactory due to the moderate enantioselectivity of the nitro-Mannich reaction and the low over all yield (6%).

Most recently, we have reported the highly enantioselective Pd-catalyzed asymmetric allylic amination of common allylacetate **3** using our polymer-supported phosphinooxathiane ligand **5** to afford the amino product **4** in excellent enantioselectivity.[11] Although the substrate **3** has been used as most general substrate of Pd-catalyzed allylic alkylation and amination,[12] only a few studies have utilized **4** as a chiral building block in



Scheme 1.

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* Corresponding author. Tel.: +81 22 234 4181; fax: +81 22 275 2013; e-mail: hnakano@tohoku-pharm.ac.jp

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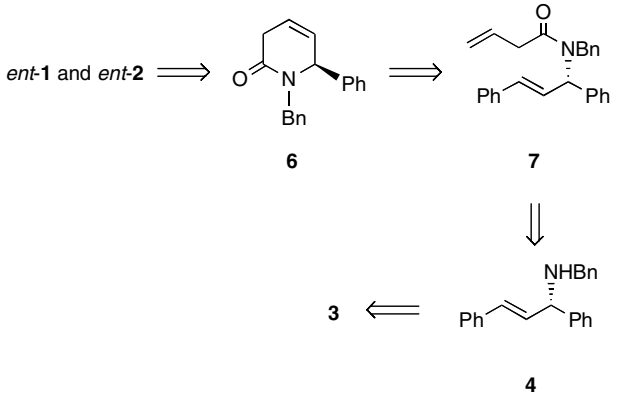
a stereocontrolled synthesis.[13] However, **4** includes a chiral α-phenyl amine unit, and it should be easily converted to chiral 2-phenylpiperidones. Our intent, therefore, was turned to synthesize **1** and **2** using **4** as a key starting material (Scheme 1).

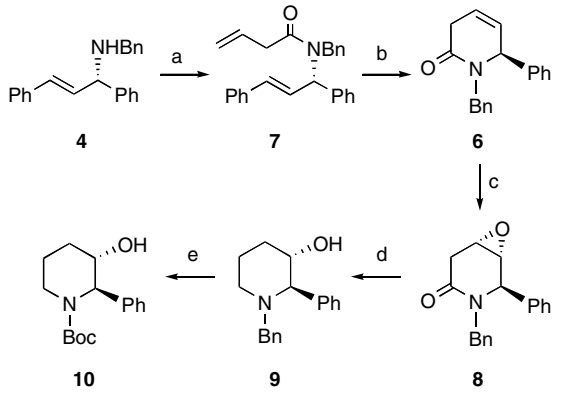
Herein, we report a concise and practical catalytic asymmetric synthesis of (−)-CP-99,994 (*ent*-**1**) and (−)-L-733,061 (*ent*-**2**) using Pd-catalyzed asymmetric allylic amination and ring-closing metathesis as key steps (Fig. 1).

Our retrosynthetic route for *ent*-**1** and *ent*-**2** is outlined in Scheme 2. These compounds were traced to 2-phenylpiperidinone (**6**), which is constructed by the ring-closing metathesis (RCM) of **7**. Furthermore, the starting building block **7** was obtained by Pd-catalyzed asymmetric allylic amination using our explored chiral polymer-supported phosphinooxathiane ligand **5**.

First, the synthesis of 2-phenylpiperidinol (**10**) was examined (Scheme 3). The Pd-catalyzed asymmetric allylic amination of allylacetate **3** using chiral ligand **5** afforded allylamine **4** in 90% yield and 99% ee. Product



Scheme 2.



Scheme 3. Reagents and conditions: (a) 3-butenoic acid, DCC, DMAP, CH_2Cl_2, room temperature, 24 h, 99%; (b) Grubbs' catalyst, CH_2Cl_2, reflux, 24 h, 94%; (c) *m*CPBA, CH_2Cl_2, room temperature, 24 h, 63%; (d) LAH, THF, room temperature, 24 h, 78%; (e) $(Boc)_2O$, $Pd(OH)_2$, H_2, AcOEt, 45 °C, 24 h, 98%.

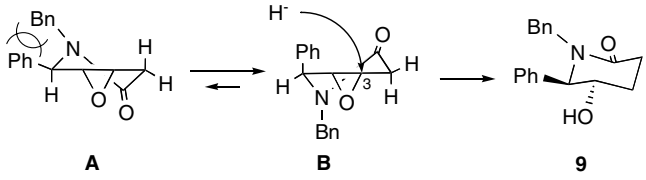
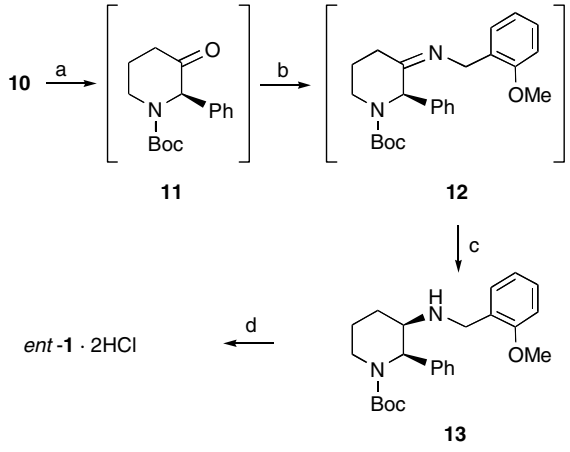


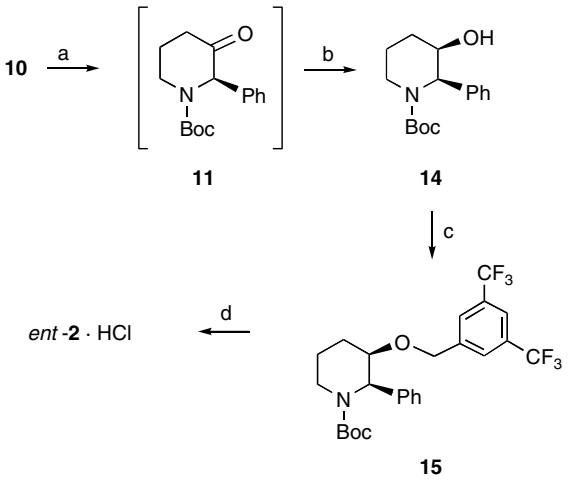
Figure 2.

4 was converted to diene **7** in quantitative yield by the reaction with 3-butenoic acid in the presence of DCC. The RCM of **7** using the second-generation Grubbs catalyst proceeded smoothly to afford the desired 2-phenylpiperidinone **6** in 94% yield.[14] Furthermore, the epoxidation of **6** with *m*-chloroperbenzoic acid (*m*CPBA) gave the corresponding epoxide (**8**)[15] in 63% yield as a single stereoisomer. Reduction of amide moiety followed by regioselective ring opening of the epoxide in **8** with lithium aluminum hydride (LAH) afforded *trans*-*N*-Bn-hydroxyphenyl piperidine **9**[15] in 78% yield. The reaction might be through the conformer **A** that has a less steric interaction between a benzyl group on nitrogen and a phenyl group at 2-position rather than conformer **B**. Then the hydride anion might attack from the β-axial site at 3-position to afford the desired trans-product **9** (Fig. 2).[16] Then, product **9** was easily converted to the desired *N*-Boc-2-phenyl-hydroxyphenyl piperidine (**10**) in 98% yield.

Next, the synthesis of *ent*-**1** was examined. We planned to access compound *ent*-**1** by the oxidation of **10**, followed by imine formation using **11** and reduction of imine **12**, as shown in Scheme 4. Although this is a convenient pathway and some research groups carried out this synthetic route to **1**, it has been known that 2-phenyl-piperidinone **11** is prone to racemization.[17] Therefore, we examined the derivation to *N*-Boc-**13** without isolation of either ketone **11** or imine **12**. Thus, the Swern oxidation of **10** and imine formation with 2-methoxybenzylamine at −20 °C, followed by the



Scheme 4. Reagents and conditions: (a) Swern oxidation; (b) 2-methoxybenzylamine, $TiCl_4$, −20 °C, 24 h; (c) $NaCNBH_3$, MeOH, −20 °C, 12 h, 49% (three steps); (d) HCl, CH_2Cl_2, room temperature, 24 h, 99%.



Scheme 5. Reagents and conditions: (a) Swern oxidation; (b) L-Selectride, THF, −20 °C, 83% (two steps); (c) NaH, 3,5-bistrifluoromethylbenzyl bromide, DMF, room temperature, 24 h, 77%; (d) HCl, CH_2Cl_2, room temperature, 24 h, 98%.

stereoselective reduction of imine (**12**) using sodium cyanoborohydride, gave the desired *N*-Boc-*ent*-**1** in 49% yield from **10**. Using this method, the racemization of **11** was not observed. Finally, the removal of the Boc group with HCl afforded *ent*-**1** in 99% yield.[18]

Furthermore, this methodology was applied to the synthesis of *ent*-**2**. Thus, the Swern oxidation of **10**, followed by the stereoselective reduction of **11**, using L-Selectride at −20 °C gave the desired *N*-Boc-2,3-*cis*-hydroxy piperidine **14** in 83% yield from **10**. Furthermore, the reaction of **14** with bistrifluoromethyl bromide using NaH as a base afforded *N*-Boc-*ent*-**2** in 77% yield, which was then easily converted to *ent*-**2** in 98% yield (Scheme 5).[19]

In conclusion, we demonstrated both the catalytic asymmetric synthesis of *ent*-**1** and the first catalytic asymmetric synthesis of *ent*-**2** using the Pd-catalyzed asymmetric allylic amination and the ring closing metathesis as key steps. All of reactions proceeded stereo- and regioselectively in the synthetic route. The synthesis of *ent*-**1** completed in 10 steps and the overall yield was 26%, which is better than the result (6%) of Shibasaki's group. In addition, the synthesis of *ent*-**2** also completed the overall yield of *ent*-**2** was 20%. Further applications of this methodology using chiral building block **4** will be reported in due course.

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14. For the experimental details of (6*S*)-*N*-benzyl-6-phenyl-3,6-dihydropyridin-2-one (**6**): a mixture of **7** (1380 mg, 3.76 mmol) and second-Grubbs catalyst (39 mg, 0.046 mmol) in dry dichloromethane (500 mL) was stirred at 60 °C under argon. After 24 h, the solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel (1:1 AcOEt–hexane) to give **6** (1138 mg, 94%) as a white solid. HPLC analysis indicated that the enantiomeric excess of **6** was 98% [Chiralcel OD-H; hexane–2-propanol = 9:1; flow rate = 0.5 mL/min; t_R = 14.5 (major), 17.1 (minor) min]. Mp 103 °C; $[\alpha]_D^{20}$ −97.76 (*c* 5.23, $CHCl_3$, 98% ee); IR (KBr) 701, 1451, 1640, 3023 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.12–3.33 (m, 2H), 3.41 (d, J = 15.0 Hz, 1H), 4.79–4.83 (m, 1H), 5.61 (d, J = 15.0 Hz, 1H), 5.65–5.79 (m, 2H), 7.15–7.21 (m, 4H), 7.25–7.38 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 32.11, 46.29, 61.65, 120.50, 126.36, 127.04 (2C), 127.41, 128.19, 128.24 (2C), 128.61 (2C), 129.10 (2C), 136.76, 140.06, 167.56; MS *m*/*z* 263 (M^+); HRMS calcd for $C_{18}H_{17}NO$ (M^+) 263.1310, found: 263.1312.
15. Spectral data for some key compounds: compound **8**: HPLC analysis indicated that the enantiomeric excess of **8** was 98% [Chiralcel OD-H; hexane–2-propanol = 9:1; flow rate = 0.5 mL/min; t_R = 31.9 (major), 45.3 (minor) min]. Mp 120 °C; $[\alpha]_D^{20}$ −21.80 (*c* 2.73, $CHCl_3$, 98% ee); IR (KBr) 698, 746, 1226, 1434, 1598 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.02 (d, J = 18.5 Hz, 1H), 3.24 (d, J = 18.5 Hz, 1H), 3.32 (s, 1H), 3.42 (s, 1H), 3.48 (d, J = 15.5 Hz, 1H), 4.79 (s, 1H), 5.54 (d, J = 15.3 Hz, 1H), 7.19–7.35 (m, 7H), 7.37–7.46 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 33.14, 47.33, 50.91, 53.74, 59.46, 126.75 (2C), 127.28, 127.60 (2C), 128.57 (2C), 128.65, 129.33 (2C), 135.85, 136.74, 166.02; MS *m*/*z* 279 (M^+); HRMS calcd for

$C_{18}H_{17}NO_2$ (M^+) 279.1259, found: 279.1257. Compound **9**: HPLC analysis indicated that the enantiomeric excess of **9** was 98 % [Chiralcel OD-H; hexane–2-propanol = 9:1; flow rate = 0.5 mL/min; t_R = 9.5 (major), 10.3 (minor) min]. Mp 105 °C; $[\alpha]_D^{20}$ −26.95 (*c* 1.30, $CHCl_3$, 98% ee); IR (KBr) 704, 761, 2937, 3437 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38–1.48 (m, 2H), 1.55–1.70 (m, 2H), 1.90–2.00 (m, 1H), 2.09–2.15 (m, 1H), 2.83–2.95 (m, 3H), 3.58–3.63 (m, 1H), 3.67 (d, J = 13.4 Hz, 1H), 7.19–7.33 (m, 6H), 7.36–7.41 (m, 2H), 7.52 (d, J = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 23.29, 32.42, 52.39, 59.24, 73.92, 75.96, 126.64 (2C), 127.96, 128.04 (2C), 128.51 (2C), 128.81, 128.85 (2C), 139.53, 140.95; MS *m*/*z* 267 (M^+); HRMS calcd for $C_{18}H_{21}NO$ (M^+) 267.1623, found: 267.1607.

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18. Mp 236 °C (lit.[4] 255 °C); $[\alpha]_D^{20}$ −73.0 (*c* 1.00, MeOH) {lit.[4] $[\alpha]_D^{20}$ +77 (*c* 1.0, MeOH) for (2*S*,3*S*)-CP-99,994}. The spectra data of (2*R*,3*R*)-CP-99,994 are identical with those of (2*S*,3*S*)-CP-99,994.[8b,9b]
19. Mp 210 °C (lit.[9d] 215–216 °C); $[\alpha]_D^{20}$ −86.0 (*c* 1.00, MeOH) {lit.[9d] $[\alpha]_D^{23}$ −86.9 (*c* 1.0, MeOH)}. The spectra data of (2*R*,3*R*)-L-733,061 are identical with those of (2*S*,3*S*)-L-733,060.[9b]