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Asymmetric synthesis of (+)-L-733,060

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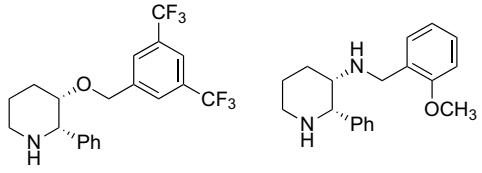
Abstract—A concise, stereocontrolled synthesis of (+)-L-733,060 was achieved. Key features involve diastereoselective oxazoline formation catalyzed by palladium(0) and intramolecular cyclization by catalytic hydrogenation of an oxazoline.

The neurokinin substance P, an 11 amino acid peptide, has been associated with a variety of biological effects including smooth muscle contraction, neurogenic inflammation and pain transmission. Recently, the development of nonpeptide neurokinin NK-1 receptor antagonists led to discovery of (+)-L-733,060 (**1**)[1] and (+)-CP-99,994 (**2**),[2] which have been shown to possess potent antiemetic activity (Fig. 1). Due to their important potential pharmacological applications,[1–3] there have been several reports on the total synthesis of (+)-L-733,060 (**1**)[4] and (+)-CP-99,994 (**2**)[5] in both racemic and optically active forms.



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

Figure 1.

Our retrosynthetic analysis of (+)-L-733,060 (**1**) was inspired by our longstanding interest in applying enantiopure oxazolines as chiral building blocks to the stereocontrolled synthesis of natural products (Scheme 1). We focused our initial efforts upon the enantioselective synthesis of hydroxyphenyl piperidinone **6**, envisioning that it would be accessible via a hydrogenolysis of the oxazoline compound **5**. It was also anticipated that the pendant vinyl group of oxazoline **3** could be easily converted to ester **5** in three steps. This study further demonstrates that utility through the asymmetric synthesis of **1** via the key intermediate **6**.

We have recently developed an efficient preparation of *trans*-oxazoline **3** in enantiopure form from L-*N*-benzoylphenylglycinol by employing the palladium(0)-catalyzed intramolecular cyclization reaction.[6]

The synthesis of **1** began with ozonolysis of **3** to give the corresponding aldehyde, which was reacted with trimethylphosphonoacetate to yield the α,β-unsaturated methyl ester in 87% yield. 1,4-Reduction[7] of **4** with copper bromide, Red-Al and 2-butanol gave the saturated methyl ester **5** in 83% yield (Scheme 2).[8] Hydrogenolysis of **5** with 20% $Pd(OH)_2$ in 1:10 AcOH/MeOH was performed under 70 psi of H_2 at ambient temperature. Under these conditions, we achieved not only hydrogenolysis of oxazoline moiety but also cyclization of the intermediate amino ester to piperidin-2-one.[9]

Reduction of **6** using borane–methyl sulfide complex and protection with $(Boc)_2O$ led to **7**[10] in 62% yield. Etherification of hydroxy group with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of NaH yielded **8**. Finally, *N*-Boc deprotection of **8** using TFA afforded (*2S*,*3S*)-L-733,060 (**1**). The spectroscopic (^1H and ^{13}C NMR) data for synthetic **1** were fully identical with those of synthetic one,[4e] and the properties of **1** showed

Keywords: Natural product; L-733,060; Asymmetric synthesis; Chiral oxazoline; Intramolecular cyclization.
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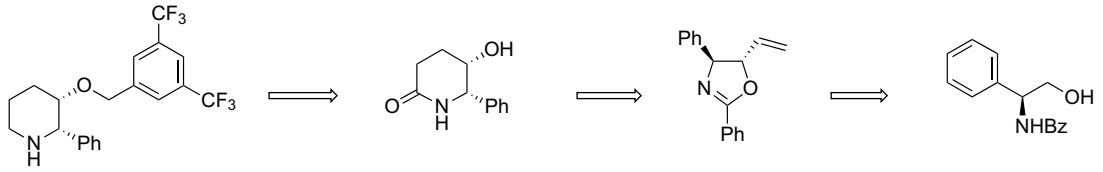
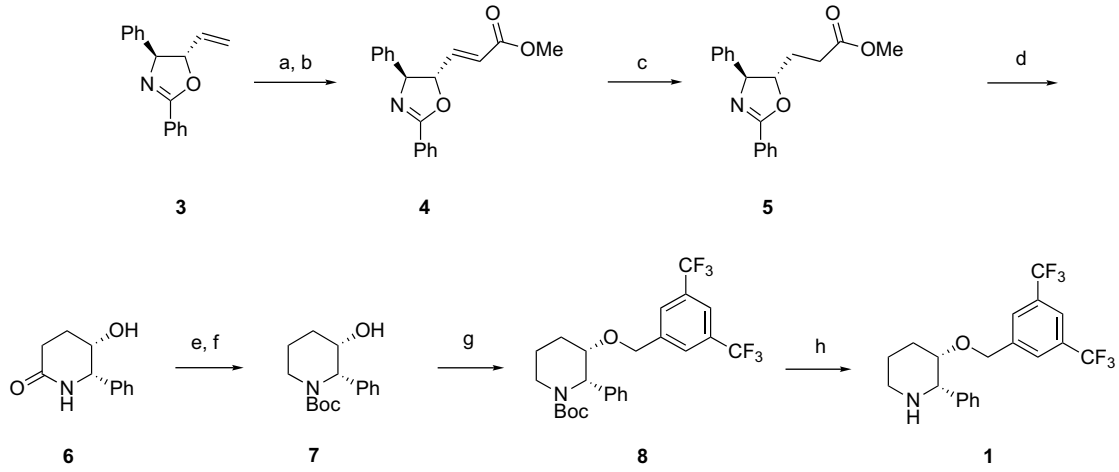


Scheme 1. Retrosynthesis of (+)-L-733,060.



Scheme 2. Reagents and conditions: (a) O_3, MeOH, −78 °C then DMS; (b) $(MeO)_2POCH_2CO_2Me$, LiCl, *i*-Pr_2NEt, CH_3CN, 87% for two steps; (c) CuBr, Red-Al, 2-butanol, THF, 83%; (d) 20% $Pd(OH)_2/C$, 70 psi H_2, MeOH/AcOH (10:1), 76%; (e) BH_3SMe_2, MeOH, THF; (f) $(Boc)_2O$, CH_2C1_2, 62% for two steps; (g) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 76%; (h) trifluoroacetic acid, 93%.

good agreements with those reported. ($[\alpha]_D^{25}$ + 32.65 (*c* 1.0, $CHCl_3$) [lit.[4e] $[\alpha]_D^{25}$ + 34.29 (*c* 1.32, $CHCl_3$)]).

Acknowledgements

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8. *Spectral data for some key compounds*: compound **4**: $[\alpha]_D^{25}$ + 28.64 (*c* 1.0, CH_2Cl_2); IR (neat) ν_{max}: 3030, 2949, 2360, 1725, 1650, 1319, 1273, 1171, 1062, 760, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09–7.28 (m, 10H), 7.11 (dd, *J* = 5.4 Hz, 15.6 Hz, 1H), 6.12 (dd, *J* = 1.5 Hz, 15.6 Hz, 1H), 5.11 (d, *J* = 7.8 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.47, 164.09, 144.52, 141.25, 132.20, 129.26, 128.85, 128.80, 128.36, 127.30, 126.92, 121.94, 86.07, 76.35, 52.17; HRMS *m/e* calcd for $C_{19}H_{17}NO_3$: 308.1287; found: 308.1301. Compound **5**: $[\alpha]_D^{25}$ − 34.66 (*c* 1.0, CH_2Cl_2); IR (neat) ν_{max}: 3061, 3029, 2949, 1737, 1646, 1494, 1448, 1168, 1063, 1024, 758, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 8.05–7.26 (m, 10H), 4.92 (d, *J* = 6.9 Hz, 1H), 4.53 (m, 1H), 3.66 (s, 3H), 2.62–2.53 (m, 2H), 2.22–2.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.46, 164.12, 142.19, 131.89,

129.10, 128.74, 128.67, 128.04, 127.86, 126.94, 86.91, 75.86, 52.04, 30.77, 30.37; HRMS *m/e* calcd for $C_{19}H_{19}NO_3$: 310.1443; found: 310.1440.

9. *For the experimental details of piperidin-2-one* **6**: a solution of **5** (983 mg, 3.18 mmol) in AcOH/MeOH (1:9, 40 mL), to which was added of 20% $Pd(OH)_2$, was vigorously shaken under 70 psi H_2 for three days at ambient temperature. The reaction mixture was then filtered through a pad of silica and concentrated in vacuo. The resulting slurry was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine, dried with $MgSO_4$ and evaporated in vacuo. Purification by silica gel chromatography (ethyl acetate) gave **6** (459 mg, 76%); yellowish solid; mp: 87–88 °C; $[\alpha]_D^{25}$ + 32.48 (*c* 1.0, CH_2Cl_2); IR (neat) ν_{max}: 3282, 2933, 1648, 1455, 1403, 1352, 1321, 1196, 748, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.44–7.30 (m, 5H), 6.17 (s, 1H), 4.65 (d, J = 3 Hz, 1H), 4.066 (m, 1H), 2.75–2.63 (m, 1H), 2.40–2.31 (m, 1H), 2.17–2.07 (m, 1H), 2.04–1.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.95, 138.13, 129.33, 128.86, 127.37, 66.42, 62.03, 26.87, 26.32; HRMS *m/e* calcd for $C_{11}H_{13}NO_2$: 192.1025; found: 192.1023.
10. The conversion of **7** to **2** has been earlier reported by Kibayashi and Huang group.[4f,5c]