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Stereoselective synthesis of L-733,060☆

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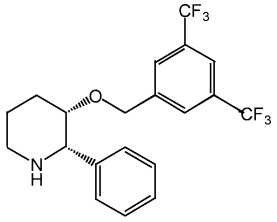
Abstract—Enantioselective synthesis of non-peptidic neurokinin NK1 receptor antagonist L-733,060 is described using ring-closing metathesis as a key step, starting from L-phenylglycine.

The non-peptidic neurokinin NK1 receptor antagonists **1** and **2** are known for having a variety of biological activities including neurogenic inflammation,[1] pain transmission and regulation of the immune response.[2] They have been implicated in a variety of disorders including migraine,[3] rheumatoid arthritis[4] and pain.[5]

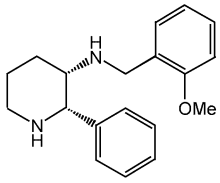
The *cis*-relationship between the two substituents on the piperidine ring is essential for high-affinity binding to the human NK1 (hNK1) receptor. Due to its potent biological activity, compound **1** is a good synthetic target. Only two total syntheses of **1** have been reported. The first synthesis[6a] by Harrison et al., describes a preparation of **1** in which the crucial chiral hydroxy piperidine intermediate was obtained by resolution, whereas the second synthesis[6b] by Tomooka et al., describes the preparation of **1** in racemic form. A few more formal syntheses of **1** have been reported where the intermediate (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine and its Boc derivative **3**[7] were prepared. Herein we report a stereoselective synthesis of L-733,060 using vinyl Grignard reagent and ring-closing metathesis as key steps, from L-phenylglycine. This is the first synthesis of **1** using metathesis and L-phenylglycine as a starting material.

The commercially available L-phenylglycine **4** was converted to *N*-Boc methyl ester **5** in the presence of acetyl chloride, methanol and $(Boc)_2O$, then the ester **5** was reduced to alcohol **6** using $LiBH_4$. Swern oxidation of **6** followed by in situ reaction of the resulting aldehyde with vinylmagnesium bromide yielded the corresponding allylic alcohol **7** with good diastereoselection (9:1 diastereomers from NMR, separated by column chromatography) in favour of the *syn* isomer, which is in accordance with an earlier reported observation.[8] The spectral data of **7** was in agreement with reported values.[9] The hydroxy group of **7** was protected with TBDMS-Cl in the presence of imidazole giving **8**, which was treated with allyl bromide in the presence of NaH to give *N*-allylic compound **9**. Desilylation of **9** gave **10**. Ring-closing metathesis[10,11] of **10** yielded **11**, then hydrogenation of the alkene produced intermediate *N*-Boc (2*S*,3*S*)-3-hydroxy-2-phenylpiperidine **3**. Protection of hydroxy group with 3,5-bis(trifluoromethyl)benzyl bromide in the presence of DMF and NaH yielded **12**. Finally, deprotection of the Boc group under standard conditions culminated in an efficient synthesis of the target L-733,060 **1** (Scheme 1), whose ^1H, ^{13}C NMR



1

L-733,060



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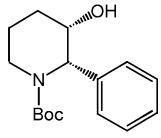

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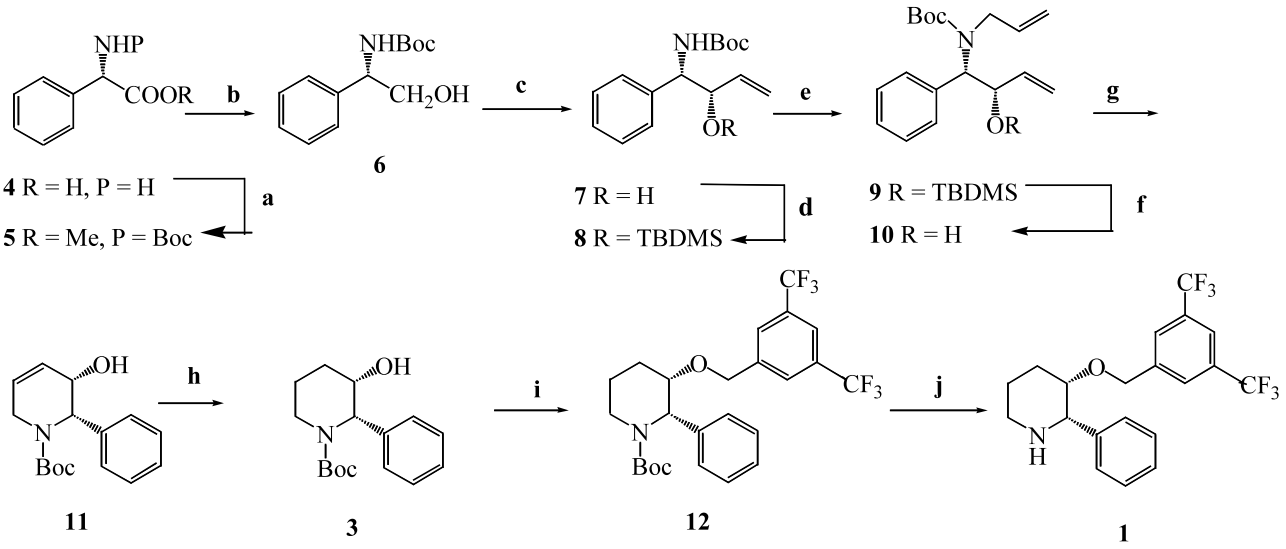

Scheme 1. *Reagents and conditions*: (a) AcCl, MeOH then $(Boc)_2O$, Et_3N, THF, 0°C–rt, 8 h, 97%; (b) LiCl, $NaBH_4$, EtOH, THF, 0°C–rt, 12 h, 87%; (c) DMSO, $(COCl)_2$, DCM, *i*-Pr_2NEt then CH_2=CHMgBr, THF, 2 h, rt, 61%; (d) TBDMS–Cl, imidazole, DCM, 0°C–rt, 24 h, 90%; (e) CH_2=$CHCH_2Br$, NaH, DMF, 0°C–rt, 24 h, 90%; (f) TBAF–AcOH, THF, 0°C–rt, 24 h, 85%; (g) Grubbs' catalyst, DCM, rt, 6 h, 82%; (h) Pd/C, H_2, EtOH, 4 h, rt, 65%; (i) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF, 80°C, 13 h, 80%; (j) trifluoroacetic acid, rt, 1 h, 79%.

spectral data were in agreement with the reported values.[12,13]

In summary, we have accomplished the synthesis of L-733,060 **1** using ring-closing metathesis starting from L-phenylglycine. This strategy may also be helpful for the synthesis of analogues.

Acknowledgements

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13. Spectral data for some key compounds:
Compound **10**: $[\alpha]_D^{25}$ = +11.31 (*c* 1.1, $CHCl_3$); IR (neat, cm^{-1}): 3400, 2970, 1670, 1445, 1400, 1350, 1245, 1160, 915, 680; ^1H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.52–3.86 (m, 3H), 4.72 (br s, 2H), 4.96–5.19 (m, 3H), 5.36 (d, 1H, J = 17.7 Hz), 5.52–5.96 (m, 2H), 7.20–7.42 (m, 5H); FAB-MS m/z: 304 (M+1), 246, 230, 204, 190.
Compound **11**: $[\alpha]_D^{25}$ = +64.10 (*c* 1.05, $CHCl_3$); IR (neat, cm^{-1}): 3415, 2984, 1676, 1400, 1350, 1150; ^1H NMR (200 MHz, $CDCl_3$): δ 1.44 (s, 9 H), 3.54 (ddd, 1H, J = 1.4, 3.9, 19.0 Hz), 4.16 (ddd, 1H, J = 3.2, 5.6, 19.0 Hz), 4.66 (br s,

1H), 5.53 (d, 1H, $J=6.7$ Hz), 5.70–5.98 (m, 2H), 7.14–7.48 (m, 5H).

Compound **3**: $[\alpha]_D^{25}=+38.30$ (c 1.92, $CHCl_3$); IR (neat, cm^{-1}): 3430, 2910, 1692, 1400, 1350,1230, 1160; ^1H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 9H), 1.58–1.88 (m, 5H), 3.01 (ddd, $J=4.5$,11.5,13.5 Hz, 1H), 3.88–4.16 (m, 2H), 5.27 (d, $J=5.6$ Hz, 1H), 7.18–7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.12, 27.65, 28.29, 39.43, 59.17, 70.05, 79.87, 127.09, 128.29, 128.37, 138.45, 155.39; FAB-MS m/z: 278 (M+1), 222, 204, 176. Compound **12**: $[\alpha]_D^{25}=+30.38$ (c 1.55, $CHCl_3$); IR (neat, cm^{-1}): 2920, 1677, 1384, 1350, 1250, 1170, 1125, 875, 665; ^1H NMR (200 MHz, $CDCl_3$): δ 1.42 (s, 9H), 1.44–1.78 (m, 2H), 1.88–2.08 (m, 2H), 2.74 (ddd, 1H, $J=4.3$, 12.0, 13.4 Hz), 3.80–3.98 (m, 2H), 4.68 (d, 1H, $J=12.6$ Hz), 4.75 (d, 1H, $J=12.6$ Hz), 5.67 (d, 1H, $J=4.8$ Hz), 7.18–7.38 (m, 3H), 7.44–7.58 (m, 2H), 7.69 (s, 2H), 7.76 (s, 1H); FAB-MS m/z: 504 (M+1), 448, 402, 387.

Compound **1**: $[\alpha]_D^{25}=+34.29$ (c 1.32, $CHCl_3$); IR (neat, cm^{-1}): 2950, 1370, 1277, 1170, 1123, 877, 660; ^1H NMR (200 MHz, $CDCl_3$): δ 1.44–2.04 (m, 3H), 2.22 (br d, 1H, $J=13.4$ Hz), 2.62 (br s, 1H), 2.83 (dt, 1H, $J=3.0$,11.9,11.9 Hz), 3.22–3.38 (m, 1H), 3.66 (br s, 1H), 3.84 (br s, 1H), 4.12 (d, 1H, $J=12.6$ Hz), 4.52 (d, 1H, $J=12.6$ Hz), 7.18–7.48 (m, 7H), 7.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.25, 28.27, 46.86, 64.06, 69.96, 77.40, 121.12 (m), 123.22 (q, $J=272.6$ Hz), 126.72, 127.16, 127.37, 128.11, 131.26 (q, $J=33.3$), 141.11, 141.41; FAB-MS m/z: 404 (M+1), 227, 176, 160.