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A short enantioselective synthesis of (+)-L-733,060 via Shi epoxidation of a homoallylic carboxylate

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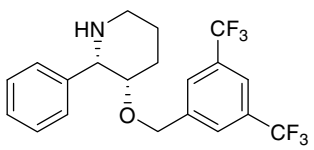
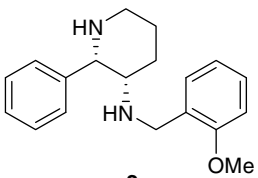
ABSTRACT

A short and efficient enantioselective synthesis of (+)-L-733,060 in 92% ee via Shi epoxidation of a homoallylic carboxylate is described. Johnson–Claisen rearrangement was employed to obtain the required carbon backbone, whilst intramolecular reductive O-to-N-ring expansion of a δ-azidolactone was used in the construction of the piperidine moiety.

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, (+)-L-733,060 (**1**)[1] and (+)-CP-99,994 (**2**)[2] possessing 2-alkyl-3-hydroxypiperidine and 2-alkyl-3-aminopiperidine structural units, respectively, have proven to be selective and potent non-peptide neurokinin substance P receptor antagonists. Also, they have been implicated in a variety of disorders including migraine, rheumatoid arthritis and pain.[3] Recent studies[4] have shown that (+)-L-733,060 (**1**) can act both as an antitumour agent and as a promising new target for the treatment of retinoblastoma. In view of these potential pharmacological applications, several reports on the synthesis of **1** and **2**, both in racemic and in optically active forms, have been published.[5] However, most of the reports deal with chiral pool strategies, classical resolution of racemates, use of expensive transition-metal complexes often involving lengthy steps. Herein, we report a practical, enantioselective synthesis of (+)-L-733,060 (**1**) via Shi epoxidation of homoallylic carboxylate **6** using ketone **12**, derived from D-fructose, as the chiral catalyst.



1



2

The retrosynthetic analysis of **1** reveals *syn* aminoalcohol **3** as a key intermediate (Scheme 1). We thus planned to employ intramolecular reductive cyclization of azidolactone **4** under Staudinger reduction conditions for the construction of the 6-membered heterocyclic ring in **3**. The azidolactone **4** can be readily made from the corresponding hydroxy lactone **5** by S_N2 displacement. We envisaged introduction of the chirality in **5** with trans stereochemistry via Shi epoxidation of potassium 5-phenylpent-4-enoate (**6**).

Our synthesis of L-733,060 (**1**) commenced with allylic alcohol **7**, which was subjected to Johnson–Claisen [3,3]-sigmatropic rearrangement[6] (trimethyl orthoacetate, catalytic amount of $CH_3CH_2CO_2H$, 135 °C) to give exclusively *E*-homoallylic ester **5** in 82% yield (Scheme 2). Alkaline hydrolysis of ester **8** using aq KOH furnished potassium alkenoate **6**, which was subjected to Shi epoxidation[7] using D-fructose-derived ketone **12** as the chiral catalyst (30 mol %) and Oxone as the stoichiometric oxidant to afford hydroxylactone **5** in 62% yield and 92% ee [%ee was determined from the ^1H NMR of the corresponding Mosher's ester and $[\alpha]_D^{25}$ −53.3 (*c* 0.22, $CHCl_3$)].[8] Mesylation (MsCl, Et_3N) of alcohol **5** gave the mesylate **9**, which was subjected to S_N2 displacement with NaN_3 (DMF, 60 °C) to afford azidolactone **4** {$[\alpha]_D^{25}$ +163.49 (*c* 0.7, $CHCl_3$)} with inversion of configuration. Reduction of azide **4** under either Staudinger conditions (PPh_3, THF, 25 °C, then H_2O, reflux) or catalytic hydrogenation [H_2 (1 atm.), 10% Pd/C] at ambient conditions produced lactam **10** in 91% yield, presumably via intramolecular O-to-N-ring expansion[9] of the amine generated in situ.

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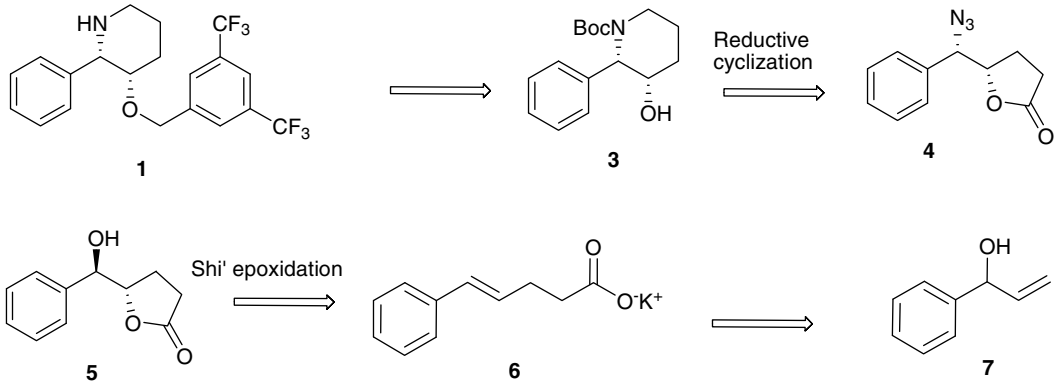
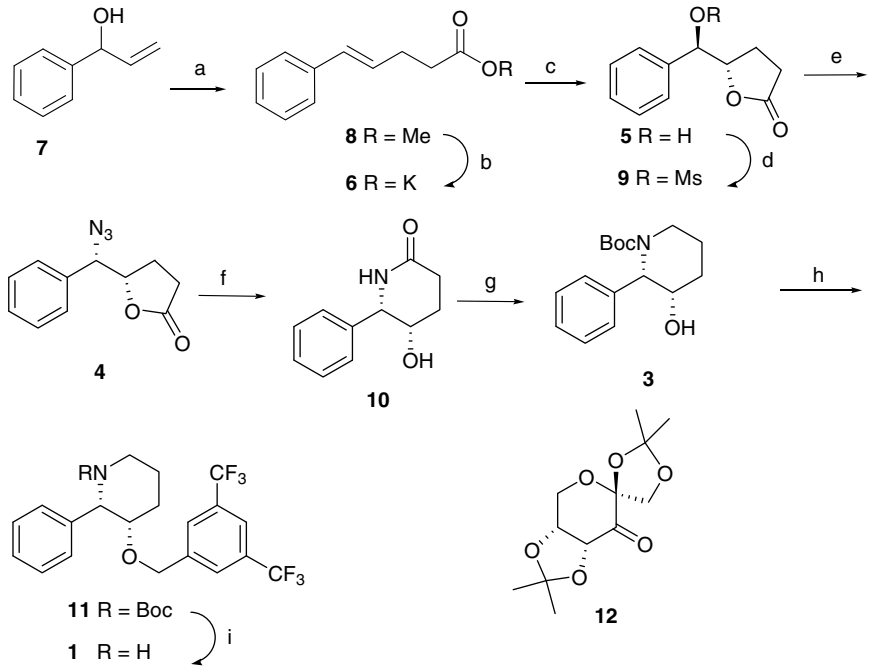


Scheme 1. Retrosynthesis of (+)-L-733,060 (**1**).



Scheme 2. Reagents and conditions: (a) $CH_3C(OMe)_3$, propanoic acid, 135 °C, 6 h, 82%; (b) aq KOH, reflux; (c) pH 10–11, Oxone, **12**, KOH, CH_3CN, −5 °C, 1 h, then 15 °C, 5 h, 62%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 96%; (e) NaN_3, DMF, 60 °C, 12 h, 94%; (f) PPh_3, THF, 25 °C , 2 h, then H_2O reflux 3 h, 91%; (g) (i) $Me_2S{\cdot}BH_3$, THF, reflux, 6 h; (ii) $(Boc)_2O$, Et_3N, cat. DMAP, CH_2Cl_2, 0–25 °C, 73% over two steps; (h) 3,5-bis(trifluoromethyl)benzyl bromide, NaH, DMF/THF (3:1), 0 °C, 6 h; (i) TFA, CH_2Cl_2, 18 h, 81% over two steps.

Reduction of lactam **10** with $BH_3{\cdot}SMe_2$ in THF followed by the protection of the secondary amine with $(Boc)_2O$ gave the *syn* aminoalcohol **3** in 73% yield over two steps.

Having constructed the piperidine ring with the desired *syn* stereochemistry, O-alkylation of **3** with 3,5-bis(trifluoromethyl)-benzyl bromide in the presence of NaH was performed to yield **11** {$[\alpha]_D^{25}$ +27.9 (*c* 0.8, $CHCl_3$); lit.[5h] $[\alpha]_D^{25}$ +30.38 (*c* 1.55, $CHCl_3$)}. Finally, deprotection of the Boc group under acidic conditions afforded L-733,060 (**1**) in 81% yield {$[\alpha]_D^{25}$ +31.7 (*c* 0.5, $CHCl_3$); lit.[5h] $[\alpha]_D^{25}$ +34.29 (*c* 1.32, $CHCl_3$)}. ^1H, ^{13}C NMR and other spectral data were in complete agreement with the reported values.

In conclusion, the enantioselective synthesis of (+)-L-733,060 (**1**) has been achieved using Shi epoxidation of homoallylic carboxylate **6** as the chiral inducing step. Intramolecular reductive cyclization of azidolactone **9** was used to construct the piperidine ring, whilst a Johnson–Claisen rearrangement was employed to generate the required carbon backbone. The synthetic strategy described herein has significant potential for further extension to piperidine-based bioactive molecules as well as other NK1 receptor antagonists.

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8. *Experimental data for selected compounds: (S)-Dihydro-5-((R)-hydroxy(phenyl)-methyl)furan-2(3H)-one* (**5**): Colourless solid; mp: 102 °C; $[\alpha]_D^{25}$ −53.3 (*c* 0.22, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.37 (m, 5H), 5.12 (d, *J* = 2.9 Hz, 1H), 4.7 (m, 1H), 2.50 (m, 2H), 2.30 (m, 1H), 1.94 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 177.92, 138.52, 128.71, 128.50, 125.98, 83.37, 73.23, 28.54, 20.54; IR ($CHCl_3$, cm^{-1}): 3448, 2939, 2864, 1768, 1612, 1512, 1462, 1363, 1247, 1180, 1097, 1033, 918, 820, 733. Elemental Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.46; H, 6.62.
(2S,3S)-Tert-butyl 3-hydroxy-2-phenylpiperidine-1-carboxylate (**3**): Gum; $[\alpha]_D^{25}$ +33.0 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.13–7.35 (m, 5H), 5.32 (m, 1H), 4.45–4.49 (m, 1H), 4.0–4.09 (m, 1H), 2.74–2.89 (ddd, *J* = 3.15, 9.73, 12.88 Hz, 1H), 1.55–2.01 (m, 5H), 1.40 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.98, 25.92, 28.36, 39.90, 60.24, 67.48, 80.11, 126.86, 126.89, 138.15, 156.70; IR ($CHCl_3$, cm^{-1}): 3447, 3018, 2979, 2955, 1676, 1602, 1495, 1418, 1367, 1327, 1168, 1137, 984, 876, 851, 756. Elemental Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.33; H, 8.13; N, 4.92.
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