Synthesis of (±)-1-Phenyl-2-azabicyclo[2.2.1]heptane Derivatives – Novel NK_1 Receptor Ligands

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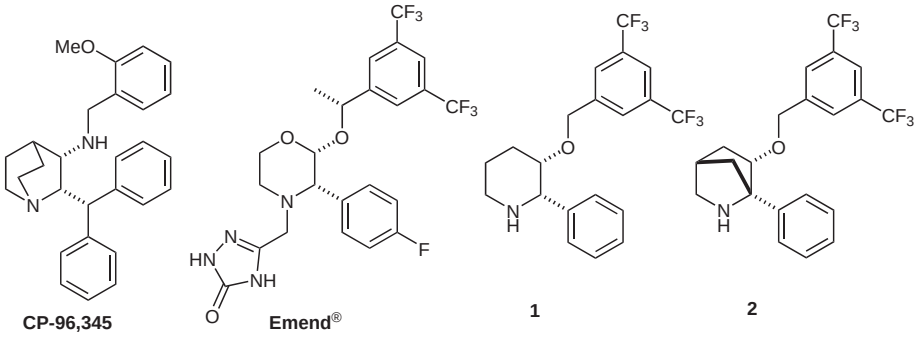
Abstract: The synthesis of the 1-phenyl-2-azabicyclo[2.2.1]heptane derivative **2**, a potential NK_1 receptor ligand, is reported. Ring-closing metathesis of diene **10** and regio- and stereoselective opening of the oxirane ring in **14** are key steps in the synthetic sequence.

Key words: bicyclic compounds, ring-closing olefin metathesis, McMurry coupling, opening of epoxides, NK_1 receptor

Neurokinin-1 (NK_1) receptor antagonists are of continuing interest since the natural ligand for the NK_1 receptor – Substance P – has been implicated in the pathophysiology of a wide range of disease conditions including neurogenic inflammation, transmission of pain, emesis and depression.[1] A demonstration of antidepressant activity by NK_1 receptor antagonists[2] significantly accelerated efforts in identification of new selective NK_1 receptor ligands. Furthermore, the Merck NK_1 antagonist, aprepitant (Emend®), has recently been approved for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Since 1991, when the first non-peptidic antagonist (CP-96,345) was reported,[3] numerous selective and structurally diverse NK_1 modulators have been identified and subsequently developed (Figure 1).[1,4] As part of an ongoing programme we were interested in examining the conformationally restricted piperidine derivative **2**.

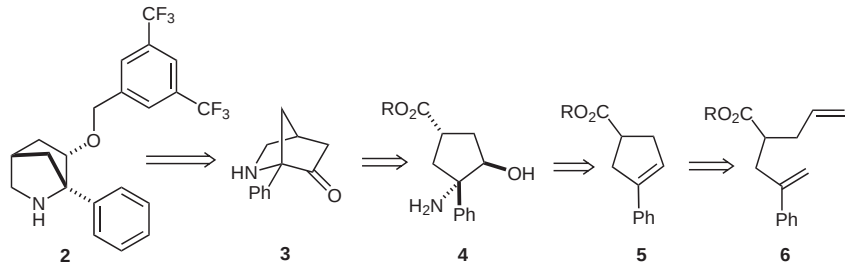
Substituted 3-hydroxy piperidines, such as **1**, were reported[5] from our laboratory as high affinity ligands at the human NK_1 receptor. The bicyclic analogue of **1**, 1-phenyl-2-azabicyclo[2.2.1]heptane (**2**), was selected for synthesis and biological evaluation. In this communication, we report a synthesis of the bicyclic ether **2** and disclose its NK_1 binding affinity data.

We envisaged that the bicyclic scaffold in **3** (Scheme 1) should be accessible from the cyclopentene derivative **5** through stereoselective manipulation of the double bond and subsequent lactamisation of the amino ester **4**. In turn, **5** could be obtained through ring-closing metathesis of diene **6**.



CP-96,345 Emend® 1 2

Figure 1



2 3 4 5 6

Scheme 1

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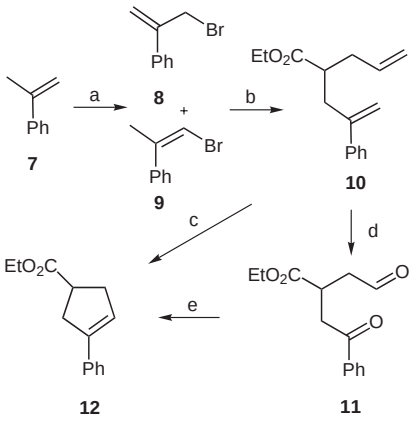
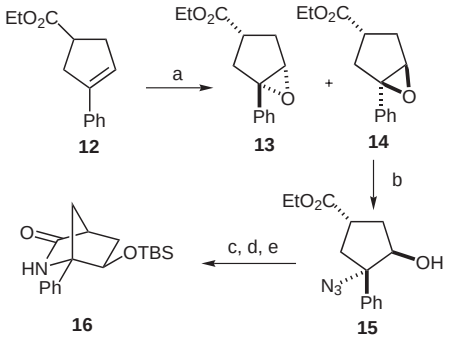
The synthesis began with bromination of α-methylstyrene (**7**) using *N*-bromosuccinimide (Scheme 2), giving a 4.5:1 mixture of the allyl bromide **8** and the vinyl bromide **9**. This mixture was allowed to react with the lithium enolate of ethyl pent-4-enoate providing the diene **10** in 61% overall yield. Ruthenium-catalysed ring-closing metathesis[6] (RCM) of the diene **10** smoothly gave the cyclopentene **12** in 80% yield. Alternatively to the RCM procedure, a two-step sequence was developed. This involved ozonolysis of the diene **10** followed by McMurry coupling[7] of the resulting keto aldehyde **11** using titanium tetrachloride and zinc powder in the presence of pyridine to afford **12** in 40% overall yield.[8,9]



Scheme 2 *Reagents and conditions*: a) NBS, PhCl, reflux, 15 min, 80%, **8**:**9** = 4.5:1; b) LiHMDS, ethyl pent-4-enoate, THF, –78 °C to –50 °C, 3.5 h, 77%; c) [Ru carbene] catalysed metathesis, PhMe, r.t., 20 h, 80%; d) O_3, CH_2Cl_2, MeOH, then Me_2S, –78 °C to r.t., 63%; e) $TiCl_4$, Zn, THF, pyridine, reflux, 18 h, 64%.

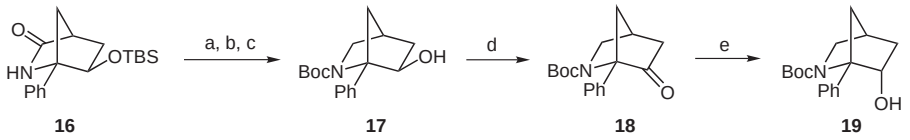
Formation of the desired 1-phenyl-2-azabicyclo[2.2.1]heptane ring was accomplished by a five-step sequence beginning with epoxidation of the double bond in **12** using *m*-chloroperbenzoic acid (MCPBA) in the presence of disodium hydrogen phosphate (Scheme 3). This reaction proceeded with only modest diastereocontrol, providing a readily separable 3:1 mixture of isomeric epoxides **14** and **13** in favour of the desired *anti* isomer **14**.[10]



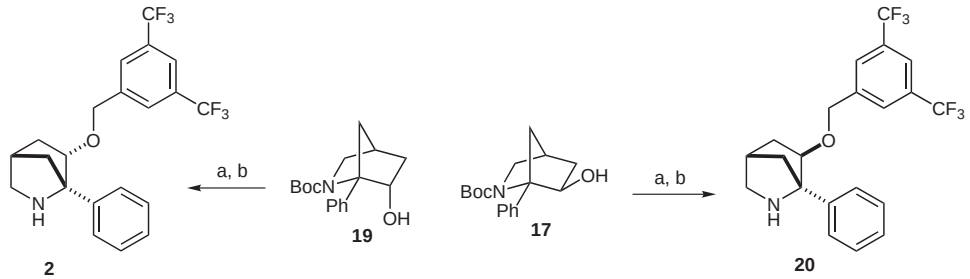
Scheme 3 *Reagents and conditions*: a) MCPBA, Na_2HPO_4, CH_2Cl_2, r.t., 30 min, 81%, **13**:**14** = 1:3; b) NaN_3, 18-crown-6, NH_4Cl, EtOH, reflux, 20 h, 96%; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 99%; d) Ph_3P, H_2O, 1,4-dioxane, reflux, 40 h; e) xylene, reflux, 6 h, 95%.

Regioselective opening of the oxirane ring in **14** with sodium azide in the presence of 18-crown-6 and ammonium chloride occurred, at the benzylic position, furnishing the required azido alcohol **15** in 96% yield. For operational expediency, the hydroxyl group in **15** was protected as its *tert*-butyldimethylsilyl ether and the azide was reduced to the primary amine using the Staudinger reaction.[11] Thermal cyclisation of the amino ester afforded the desired bicyclic lactam **16** in excellent overall yield.

Reduction of the lactam **16** (Scheme 4) with lithium aluminium hydride, followed by protection of the amine as a *tert*-butyl carbamate and subsequent removal of the *tert*-butyldimethylsilyl protecting group, yielded the *endo*-alcohol **17**[12] in 74% yield. Swern oxidation of the alcohol **17** followed by stereoselective reduction of the resulting ketone **18** with sodium borohydride gave the *exo*-alcohol **19** as a single diastereoisomer in excellent overall yield.



Scheme 4 *Reagents and conditions*: a) $LiAlH_4$, THF, reflux, 2 h, 97%; b) Boc_2O, CH_2Cl_2, r.t., 5 h, 99%; c) TBAF, NH_4OAc, THF, reflux, 2.5 h, 76%; d) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N, 2 h, 96%; e) $NaBH_4$, MeOH, 15 min, 99%.

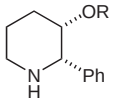
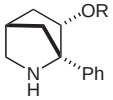
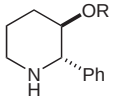
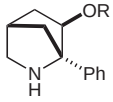


Scheme 5 *Reagents and conditions*: a) NaH, 3,5-bis(trifluoromethyl)benzyl bromide, DMF, 60 °C, 20 min, 94–99%; b) TFA, CH_2Cl_2, r.t., 30 min, 53%.

Both epimeric alcohols **17** and **19** were then converted into their 3,5-bis(trifluoromethyl)benzyl ethers and the Boc protecting group removed by treatment with trifluoroacetic acid to give bicyclic amines **20** and **2**, respectively (Scheme 5).

The NK_1 receptor binding affinity for both bicyclic ethers **2** and **20** was determined (Table 1).[13] Similar IC_{50} values were found for the bicyclic ether **2** and piperidine analogue **1**. The *exo* ether **2** (hNK_1 IC_{50} 2.7 nM) was about 100-fold more potent then the *endo* epimer **20** in this assay. These results suggest that the 1-phenyl-2-azabicyclo[2.2.1]heptane ring could be considered as a 2-phenylpiperidine mimic in NK_1 receptor modulators.

Table 1 The NK_1 Receptor Binding Affinity

Compound	Structure[a]	hNK_1 IC_{50} (nM)[b]
1		1.4[5]
2		2.7
21		300[5]
20		370

[a] Racemate; R = 3,5-bis(trifluoromethyl)benzyl.
[b] Displacement of labelled [^{125}I] Substance P from the cloned receptor expressed in CHO cells. Data are mean of three independent determinations.[13]

In conclusion, the stereoselective synthesis of novel NK_1 antagonists based upon the 1-phenyl-2-azabicyclo[2.2.1]heptane framework was developed and binding affinity of selected compounds at the human NK_1 receptor determined. The bicyclic ether **2** exhibited similar binding affinity at the NK_1 receptor to the known piperidine derivative **1**, providing a novel class of NK_1 receptor modulators confirming the relative topology of the binding site.

References and Notes

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(8) **Experimental Procedure for the Preparation of 11.** Ozone was passed through a stirred mixture of **10** (30.5 g, 124 mmol), MeOH (1.4 mL) and CH_2Cl_2 (350 mL) at –70 °C to –65 °C until the reaction mixture turned blue. Then, DMS (90 mL, 1.24 mol) was added keeping the temperature of the reaction mixture below –60 °C. The mixture was slowly warmed up to r.t. and stirred for an additional 48 h. Then the mixture was filtered through a pad of Celite® and concentrated. The residue was purified on silica gel (*i*-hexane–EtOAc, 0–30%) to give the keto aldehyde **11** as an oil (19.5 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (3 H, t, *J* = 7.1 Hz), 2.81 (1 H, ddd, *J* = 1.0, 5.4, 18.2 Hz), 2.99 (1 H, ddd, *J* = 1.0, 6.2, 18.1 Hz), 3.25 (1 H, dd, *J* = 8.1, 19.4 Hz), 3.48–3.54 (2 H, m), 4.16 (2 H, q, *J* = 7.2 Hz), 7.46 (2 H, m), 7.58 (1 H, m), 7.96 (2 H, m), 9.80 (1 H, s).
(9) **Experimental Procedure for the Preparation of 12.** $TiCl_4$ (15.5 mL, 140 mmol) was added dropwise to THF (800 mL) to form a yellow slurry. Zinc dust (21 g, 325 mmol) was added in one portion to this slurry. The resulting mixture was stirred for 1 h and pyridine (13 mL, 160 mmol) was added. The mixture was stirred for 30 min and a solution of **11** (19.3 g, 78 mmol) in THF (30 mL) was added. The resulting black mixture was stirred at reflux overnight. After cooling to r.t., Et_3N (75 mL) and EtOH (75 mL) were added and the mixture stirred for 30 min. Then, H_2O (15 mL) and EtOAc (800 mL) were added and the mixture was stirred until a white solid was formed. This mixture was filtered through a pad of Celite® and concentrated. The residue was purified on silica gel (*i*-hexane–Et_2O, 0–30%) to give the cyclopentene **12** as an oil (10.8 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (3 H, t, *J* = 7.2 Hz), 2.83 (2 H, m), 2.97–3.11 (2 H, m), 3.28 (1 H, m), 4.18 (2 H, q, *J* = 7.2 Hz), 6.08 (1 H, m), 7.23 (1 H, m), 7.31 (2 H, m), 7.42 (2 H, m).
(10) **Experimental Procedure for the Preparation of 14.** MCPBA (60%, 5 g) was added to a stirred mixture of **12** (1.62 g, 7.5 mmol), Na_2HPO_4 (5 g, 35 mmol) and CH_2Cl_2 (50 mL). The mixture was stirred for 30 min and a solution of Na_2SO_3 (10 g) in H_2O (50 mL) was added. The mixture was

extracted into *i*-hexane (150 mL) and an organic layer was washed with 2 M aq NaOH solution and brine, then dried (Na_2SO_4) and concentrated. The residue was purified on silica gel (*i*-hexane–Et_2O, 0–20%) to give the epoxide **14** (1.1 g, 63%) and the epoxide **13** (0.33 g, 18%). ^{1}H NMR of **14** (400 MHz, $CDCl_3$): δ = 1.28 (3 H, t, *J* = 7.2 Hz), 2.08 (1 H, dd, *J* = 10.2, 14.0 Hz), 2.45 (1 H, dd, *J* = 8.0, 14.0 Hz), 2.53 (2 H, d, *J* = 9.2 Hz), 2.86 (1 H, pent., *J* = 9.2 Hz), 3.61 (1 H, s), 4.17 (2 H, q, *J* = 7.1 Hz), 7.26–7.39 (5 H, m). Relative stereochemistry of **14** was assigned by ^{1}H NMR/NOE experiments. ^{1}H NMR of **13** (400 MHz, $CDCl_3$): δ = 1.27 (3 H, t, *J* = 7.1 Hz), 2.06 (1 H, dd, *J* = 8.5, 14.5 Hz), 2.44 (1 H, dd, *J* = 8.8, 14.0 Hz), 2.81 (1 H, d, *J* = 14.4 Hz), 2.84 (1 H, m), 2.91 (1 H, d, *J* = 14.1 Hz), 3.56 (1 H, s), 4.16 (2 H, q, *J* = 7.1 Hz), 7.27–7.37 (5 H, m).

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(12) Relative stereochemistry of **17** was assigned by ^{1}H NMR/NOE experiments. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (9 H, s), 1.67 (1 H, m), 1.88 (1 H, br), 2.08–2.13 (3 H, m), 2.52 (1 H, m), 3.19 (1 H, dd, *J* = 1.6, 9.3 Hz), 3.50 (1 H, dt, *J* = 2.5, 9.4 Hz), 4.56 (1 H, d, *J* = 6.2 Hz), 7.25 (1 H, m), 7.32 (2 H, m), 7.58 (2 H, m).

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