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Expeditious synthesis of novel NK_1 antagonists based on a 1,2,4-trisubstituted cyclohexane

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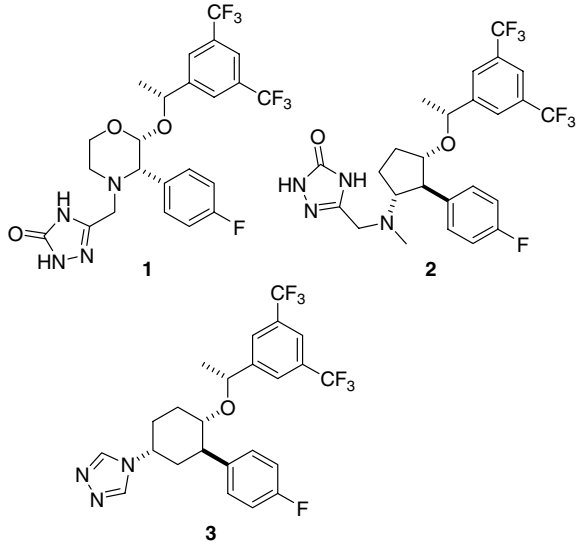
Abstract—A stereoselective asymmetric route to novel potent NK_1 antagonists based on a 1,2,4-trisubstituted cyclohexane core is discussed.

The utility of neurokinin-1 receptor (NK_1R) antagonists for the treatment of chemotherapy-induced emesis has now been established; Aprepitant (Emend®) **1** is currently the only commercially available drug in this class.[1] At one time, the 2,3-*cis* relationship seen in Aprepitant was believed to be essential for binding to the NK_1R, however, a number of compounds with *trans–trans* 1,2,3-trisubstituted five-[2] (exemplified by **2**) and six-[3] membered rings, with subnanomolar affinities, have been reported since. Herein, we report the discovery of potent NK_1R antagonists based on a 1,2,4-trisubstituted cyclohexane (exemplified by **3**), and two asymmetric routes to this core.



The need for an efficient and scalable synthesis of the key ketone **4** led us to investigate two routes. The first route started from the chiral pool and used a diastereoselective 1,4-addition onto **7**, followed by O-alkylation of **5** with **6** resulting in inversion of configuration. The second route started with α-arylation of **8** followed by an asymmetric reduction of the ketone to yield **5** (Scheme 1).

Our initial approach for the synthesis of **4** is shown in Scheme 2. The α,β-unsaturated ketone **9** was obtained in six steps from quinic acid in 15% yield and required only one column chromatography.[4] Numerous conditions were tested to perform a diastereoselective 1,4-addition onto **9** using various combinations of organometallic species (organolithium, Grignard), copper sources ($Li_2Cu(CN)$thienyl,[5] CuBr, CuI, CuCN), Lewis acid (none, $BF_3{\cdot}OEt_2$) and solvents (Et_2O, THF). Although most of these combinations did not give a satisfactory yield for the transformation (significant 1,2-addition was observed), gratifyingly a 92% yield of the trans-isomer **10** was obtained using 4-fluorophenyllithium and CuCN in THF. The deprotection of **10** was more problematic than expected, as TBAF in THF gave multiple degradation products. TBAF buffered with AcOH in THF avoided degradation but at the expense of a very long reaction time. A practical

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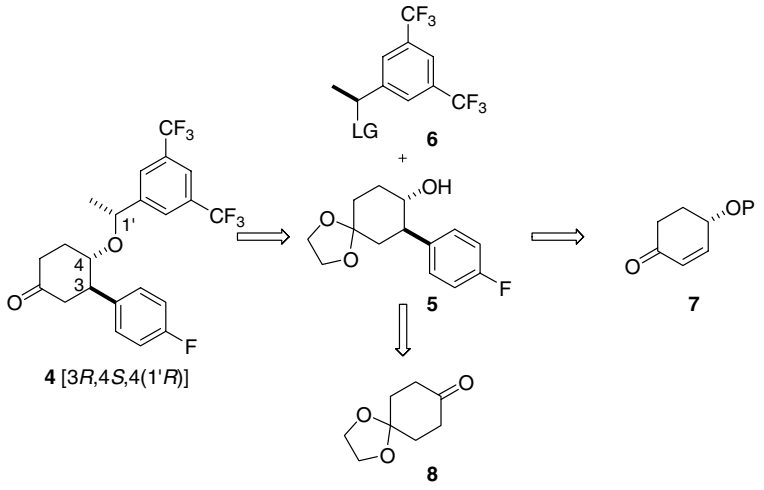
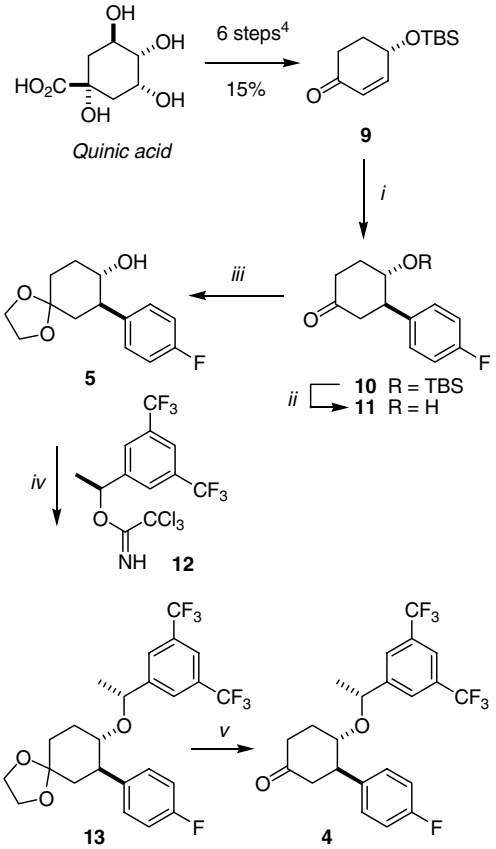


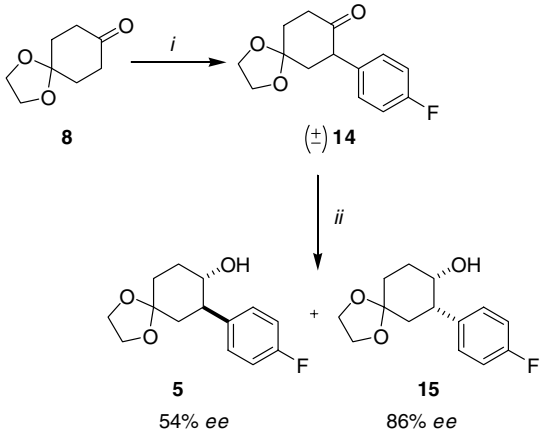
Scheme 1. Retrosynthetic analysis.



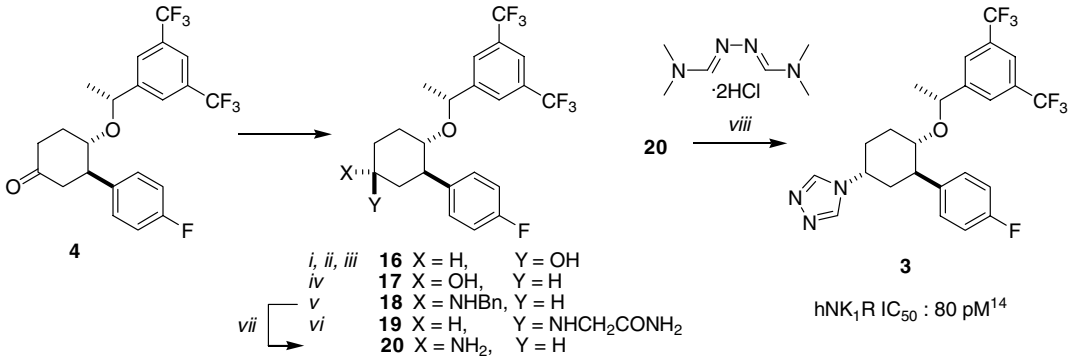
Scheme 2. Reagents and conditions: (i) 1-bromo-4-fluorobenzene, *n*-BuLi, CuCN, THF, −78 to −40 °C, 92%; (ii) TFA, DCM, rt, 76%; (iii) ethylene glycol, CSA, PhMe, Δ, 91%; (iv) **12**, HBF_4, DCE, DCM, hexanes, −18 °C, 50%; (v) TFA, H_2O, DCM, rt, 72%.

solution was the use of TFA in DCM, which gave 76% of the alcohol **11** in 1 h. Direct O-alkylation of **11** with trichloroimidate **12**[6] in the presence of a small amount of tetrafluoroboric acid gave only traces of **4** and mostly unreacted alcohol, but the same reaction conditions applied to the protected ketone **5** produced the desired stereoisomer **13** in 50% yield.[7] A simple deprotection using TFA in wet DCM gave the desired key ketone **4**[8] in 11 steps and 4% overall yield.

This original approach has the advantage of being stereoselective and reliable, but the length and the yield of the sequence made it impractical for speedy delivery of **4** in large quantities (>50 g). Accordingly, a shorter synthesis of **5** was developed starting from the cheap commercially available ketone **8** (Scheme 3). Using Buchwald's α-arylation conditions,[9] **14** was synthesized in 70% yield on a 100 g scale. This racemic ketone was reduced asymmetrically using Corey's CBS oxazaborolidine giving a 1/1 ratio of cis/trans diastereoisomers by NMR (isolated yields: **5**, 45%; **15**, 38%) in modest ee for the desired trans isomer **5** (54%) and good ee for the cis isomer (86%).[10,11] The next step of the sequence (i.e., the preparation of **4**) installed in a new chiral centre with excellent stereoselectivity. Using enantioimpure (54% ee) **5** in this reaction created a mixture of diastereoisomers, which could be easily separated by column chromatography to yield a single stereoiso-



Scheme 3. Reagents and conditions: (i) 1-bromo-4-fluorobenzene, $Pd_2(dba)_3$ (1 mol %), Xantphos (2 mol %), NaO*t*-Bu, THF, Δ, 70%; (ii) (*R*)-2-methyl-CBS-oxazaborolidine, BH_3·DMS, PhMe, −40 to −6 °C, **5** 45%, **15** 38%.



Scheme 4. Reagents and conditions: (i) $NaBH_4$, MeOH, 0 °C, 99%, **16**/**17**: 6/1; (ii) (*R*)-2-methyl-CBS-oxaborolidine, BH_3·DMS, PhMe, −40 to −20 °C, 75%, **16**/**17**: 20/1; (iii) (*S*)-2-methyl-CBS-oxaborolidine, BH_3·DMS, PhMe, −40 to −20 °C, 75%, **16**/**17**: 20/1; (iv) L-Selectride, THF, −78 °C, 80%, **16**/**17**: 1/8; (v) $BnNH_2$, $NaBH(OAc)_3$, DCE, rt, 80%, **18**/*epi*-**18**: 20/1; (vi) $H_2NCH_2CONH_2$, $NaBH_3CN$, MeOH, rt, 90%, **19**/*epi*-**19**: 3/1; (vii) H_2 (1 atm), Pd/C, AcOEt, rt, 94%; (viii) **20**, TMSCl, pyridine, 110 °C, 42%.

mer. As a result, the isolated yield from the transformation was reduced from 50% when the reaction was performed with enantiopure **5**, to 36%. This new sequence for the synthesis of **4** is now only four steps and gave an 8% overall yield. Although this yield is only double that of the first sequence, the shortness of the route allowed us to process over 100 g of **4**.

Hydride addition to ketone **4** or its imine derivatives gave rise to some interesting observations (Scheme 4). While, as expected, a 'small' hydride gave preferentially axial attack with a 6/1 ratio (i), to our surprise, both enantiomers of Corey's bulky 2-methyl-CBS-oxazaborolidine also gave axial attack with an improved ratio of 20/1 ((ii) and (iii)). Finally, a 'large' hydride (L-Selectride) gave, as expected, equatorial attack with an 8/1 ratio (iv). These unexpected substrate controlled reactions ((ii) and (iii)) could be explained by the coordination of the boron reducing agent to the ether oxygen, allowing an intramolecular axial delivery of the hydride. Hydride additions to imine derivatives of **4** also gave rise to useful selectivities. Reductive amination with benzylamine using sodium triacetoxyborohydride gave excellent selectivity for the axial product **18**, whereas reductive amination with glycinamide using sodium cyanoborohydride gave a 3/1 ratio in favour of the equatorial amine **19**. Compound **3**[12] was then easily obtained from **18** by hydrogenolysis and triazole formation using *N*,*N*-dimethylformamidazine.[13]

In conclusion, we have developed a concise asymmetric synthesis of the key ketone intermediate **4** using a palladium-catalyzed α-arylation of **8**, followed by an asymmetric reduction of the ketone. The shorter second route delivered large amounts of **4** (>100 g), which enabled us to assess the in vitro and in vivo properties of NK_1R antagonists based around this structure. The reductions of **4** and its derivatives under a variety of conditions gave rise to some interesting and useful selectivities. Compounds derived from **4** generally display very potent hNK_1R affinities, as exemplified by **3**, which is an 80 pM hNK_1R[14] antagonist. A full account of the medicinal chemistry of these compounds will be given elsewhere.

Acknowledgements

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6. Prepared from enantiomerically pure (*S*)-1-[3,5-bis(trifluoromethyl)phenyl]ethanol (see Ref. 2) using trichloroacetonitrile and DBU in dichloromethane in a quantitative yield.
7. Procedure: To a solution of **5** (1.7 g, 7.2 mmol) in a mixture of dichloroethane (20 mL) and hexanes (40 mL) at −20 °C, was added **12** (5.81 g, 14.5 mmol), followed by tetrafluoroboric acid (0.13 mL, 0.72 mmol) and the mixture was stirred at −16 °C overnight. The solvent was then removed in vacuo and **13** (1.73 g, 3.6 mmol) was isolated after column chromatography on silica gel with a gradient of ethyl acetate in hexanes 1–3% in 50% yield as a single stereoisomer. ^1H NMR (500 MHz, $CDCl_3$): δ 7.66 (s, 1H); 7.21 (s, 2H); 7.00 (m, 2H); 6.85 (m, 2H); 4.42 (q, $J = 6.4$ Hz, 1H); 3.96 (m, 4H); 3.23 (dt, $J = 4.1$, 10.3 Hz, 1H); 2.95 (m, 1H); 2.19 (m, 1H); 1.90–1.60 (m, 5H); 1.28 (d, $J = 6.4$ Hz, 3H). HRMS (ESI). Calcd for $C_{24}H_{23}F_7O_3$: 492.1535. Found: 492.1524.
8. ^1H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H); 7.40 (s, 2H); 7.00 (m, 2H); 6.89 (m, 2H); 4.58 (q, $J = 6.4$ Hz, 1H); 3.61 (m, 1H); 3.17 (m, 1H); 2.68–2.52 (m, 3H); 2.42 (m, 1H); 2.27 (m, 1H); 1.89 (m, 1H); 1.26 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 209.5, 163.5, 160.8, 146.5,

137.3 (d), 131.8 (q), 129.2 (d), 126.6, 125.1, 122.0 (q), 115.8 (d), 77.9, 75.2, 48.9, 45.2, 38.2, 28.8, 24.8. HRMS (ESI). Calcd for $C_{22}H_{19}F_7O_2$: 448.1273. Found: 448.1262.

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10. Determined by chiral HPLC (chiralpak AD-H 250* 4.6 mm i.d. ethanol/isohexane gradient. Baseline separation rt 5.1 and 8.4 min for **5**, and 4.2 and 6.9 min for **15**).
11. Procedure: Compound **8** (100 g, 0.64 mol), tris(dibenzylideneacetone)dipalladium(0) (3.4 g, 3.7 mmol), xantphos (4.7 g, 8.05 mmol), sodium *t*-butoxide (81 g, 0.84 mol) and tetrahydrofuran (450 mL) were mixed and degassed by bubbling nitrogen through the mixture for 20 min. The mixture was heated to 80 °C under a nitrogen atmosphere, and 1-bromo-4-fluorobenzene (64 g, 0.36 mol) was added. After 10 h at this temperature, the mixture was cooled to room temperature, and ethyl acetate and water were added, the layers separated, the organic layer washed with a saturated solution of sodium bicarbonate and brine, dried over sodium sulfate, filtered and evaporated in vacuo. Compound **14** (64 g, 0.26 mol) (slightly less polar than **8**) was isolated after column chromatography on silica gel with a gradient of ethyl acetate in hexanes 10–20% in 70% yield.
    To a solution of (*R*)-2-methyl-CBS-oxazaborolidine (1 M in toluene) (22 mL, 22 mmol) in toluene (1 L) was added borane dimethyl sulfide (12.4 mL, 130 mmol), and the mixture was cooled to −40 °C. A solution of **14** (54 g, 216 mmol) in toluene (270 mL) was added dropwise over 1.5 h and the mixture was stirred for 2 h at −20 °C then warmed to −6 °C and stirred for one additional hour. Methanol was then added and the mixture warmed to room temperature. Ethyl acetate and water were added and the layers separated. The organic layer was washed with a saturated solution of sodium bicarbonate and brine, dried over sodium sulfate, filtered and evaporated in vacuo. Compound **5** (24.5 g, 97 mmol) (the more polar diastereoisomer) was isolated after column chromatography on silica gel with a gradient of ethyl acetate in hexanes 10–20% in 45% yield as a white solid.
12. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (s, 2H); 7.71 (s, 1H); 7.29 (s, 2H); 6.99 (dd, $J = 5.4$, 8.6 Hz, 2H); 6.92 (t, $J = 8.5$ Hz, 2H); 4.50 (q, $J = 6.4$ Hz, 1H); 4.44 (t, $J = 3.9$ Hz, 1H); 3.41–3.35 (m, 1H); 2.82–2.76 (m, 1H); 2.46–2.40 (m, 1H); 2.21–2.13 (m, 2H); 2.08–2.01 (m, 1H); 1.66–1.59 (m, 2H); 1.32 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR (91 MHz, $CDCl_3$): δ 163.6, 160.8, 146.3, 141.9, 136.9 (d), 131.8 (q), 129.2 (d), 126.5, 125.1, 121.9 (q), 115.8 (d), 78.1, 74.7, 51.2, 44.1, 36.3, 28.7, 26.3, 24.9. HRMS (ESI). Calcd for $C_{24}H_{22}F_7N_3ONa$: 524.1549. Found: 524.1538.
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