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A convergent approach to the synthesis of aprepitant: a potent human NK-1 receptor antagonist☆

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Abstract—A simple and convergent approach to enantiomerically pure 5-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)morpholin-4-yl]methyl]-1,2-dihydro-1,2,4-triazol-3-one **1**, a potent orally active antagonist of the human neurokinin-1 (NK-1) receptor, is described. The synthetic procedure starts from *p*-fluorobenzaldehyde to access the racemic morpholinone **2** via a modified Strecker synthesis and utilizes a diastereomeric salt resolution technique to accomplish the synthesis of **1** in enantiomerically pure form and good yield.

Resolution by diastereomeric salt crystallization is an important and cost effective tool to obtain chiral molecules.[1] It is often the case that, when a molecule possesses several stereogenic centres, one can envisage that transformations leading to the synthesis of the desired isomer, would have occurred through one of the following general processes: (a) resolution, (b) chiral pool based transformation using amino acids, carbohydrates, etc. (c) involve temporary installation of a readily removable chiral auxiliary, which would dictate facial selectivity in a key stereo defining transformation or (d) involve an enantioselective catalytic process to introduce chirality during reactions.

In this Letter, we report an efficient synthesis of aprepitant (**1**), which possesses three stereogenic centres by exploiting resolution techniques. Aprepitant (see Fig. 1) is a drug known to elicit activity against the human neurokinin-1 (NK-1) receptor.[2]

Aprepitant **1** has been synthesized previously[3a–c] and the reported routes have certain disadvantages: (a) carrying out a moisture sensitive and reversible imidate reaction on a large scale, (b) control of the amount of ruthenium metal, which was used in the form of *cis*-aminoindano-Ru (*p*-cymene) for the preparation of chiral-alcohol used in the final active pharmaceutical to acceptable limits, and (c) involving expensive reagents and harsh conditions.

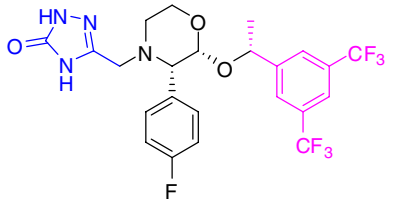

Figure 1. Aprepitant (**1**).

Herein, we report a cost-effective and practical approach for the large scale preparation of aprepitant (**1**), from (±)-morpholinone (**2**), 1-(1-bromoethyl)-3,5-bis-trifluoromethylbenzene (**11**) and chloroacetamidrazone (Schemes 2–5). This process does not require any chiral pool starting material, chiral auxiliary, enantioselective catalyst, pyrophoric or expensive or toxic reagent, and has the advantage of relative simplicity over the previously reported approaches.

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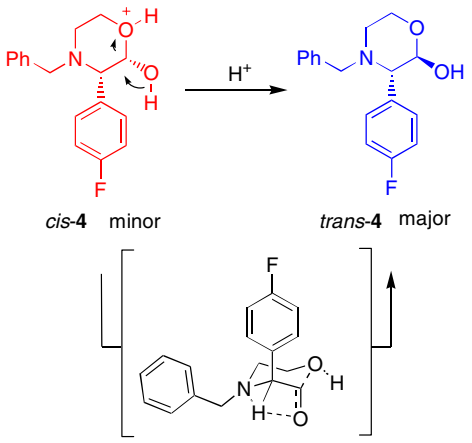
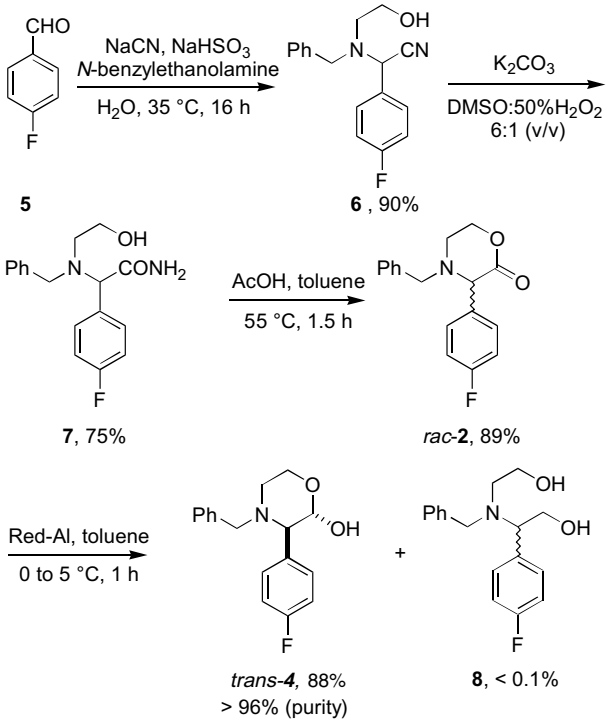


Scheme 1. Acid catalyzed stereoinversion.

In our preliminary approach to **1** the isolation of *cis*-morpholinol (*cis*-**4**) was unsuccessful because of the preferred formation of the thermodynamically stable *trans*-morpholinol (*trans*-**4**) at room temperature (Scheme 1).

This prompted us to investigate the synthesis of **1** starting from *trans*-**4**. Taking the advantage of the inherent tendency of morpholinol (*cis*-**4**) to form the stable *trans*-isomer (*trans*-**4**) we succeeded in developing a simple, cost effective and scalable process for aprepitant (**1**).

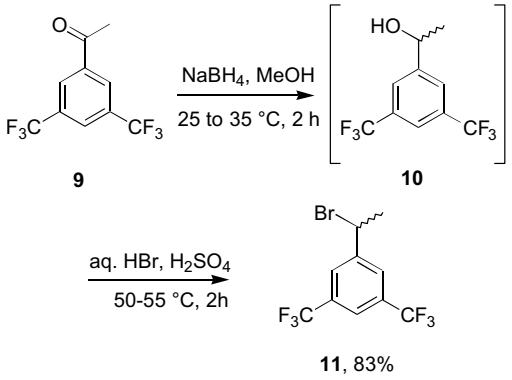
First, (±)-morpholinone **2** was prepared from commercially available *p*-fluorobenzaldehyde **5** by modifying the literature procedure[4] as presented in Scheme 2. *p*-Fluorobenzaldehyde **5** was converted to α-aminonitrile **6** in excellent yield (90%) under standard reaction conditions. The α-aminonitrile thus obtained was hydrolyzed with alkaline hydrogen peroxide to furnish amide **7** as a white crystalline solid in 75% yield. Cyclization of amide **7** in the presence of acetic acid afforded (±)-morpholinone **2** in 89% yield. Conversion of **2** to (±)-*trans*-morpholinol was attempted with reducing agents such as sodium borohydride and Red-Al. Reduction of **2** using 0.7 equiv of Red-Al was found to be efficient and gave *trans*-**4** in 88% yield, >96% purity and with <0.1% of over reduction product **8**. The small quantity of over reduction product is in contrast with Nelson's study on morpholinone reduction.[5] In our hands, the conditions for the preparation of this key intermediate *trans*-**4** are ideal with respect to cost, convenience and scalability and have been demonstrated successfully on multi kilogram scale.



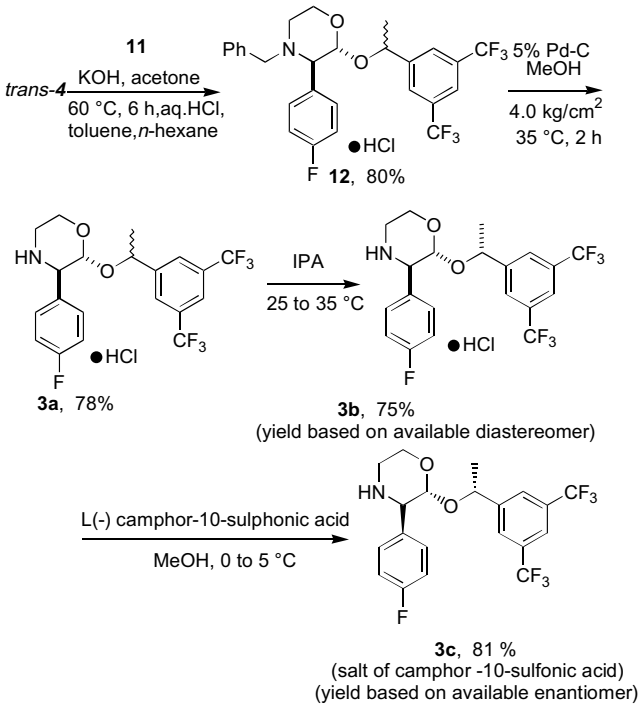
Scheme 2. Synthesis of morpholinol *trans*-**4**.

The preparation of **11** was achieved by the procedure shown in Scheme 3. Reduction of the acetophenone derivative **9** using sodium borohydride in methanol gave the corresponding hydroxy compound as a crystalline solid in 98% yield. Subsequent treatment with HBr/H_2SO_4 gave the desired bromo compound **11** in 83% yield.

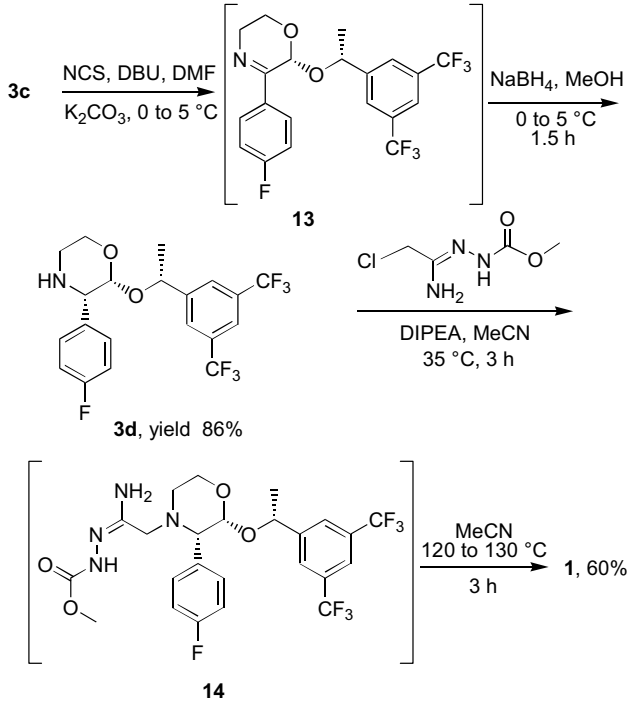
Treatment of racemic *trans*-**4** with 1-(1-bromoethyl)-3,5-bis-trifluoromethylbenzene **11** in the presence of potassium carbonate furnished the ether derivative **12** as a mixture of racemic diastereomers in a 2:1 ratio. The diastereomeric and enantiomeric relationship of the isomers formed in the reaction was apparent by means of HPLC[6] and LCMS (Scheme 4). Upon hydrogenolysis of the hydrochloride salt of ether **12** in the presence of Pd–C/H_2amine **3a**[7] was obtained in the same diastereomeric ratio. The major pair of amine enantiomers **3b** was isolated by crystallization from isopropyl alcohol. Resolution of **3b** was accomplished using L-(−)-camphorsulfonic acid in methanol, which gave **3c** in 81% yield and 95% purity. The structure of the L-(−)-CSA salt of **3c** was confirmed by X-ray analysis. The X-ray structure clearly showed that **3c** had the configuration as indicated in Figure 2, in which the morpholine core has a trans arrangement, both the fluorophenyl and alkoxy groups are in equatorial orientations, and the methyl group is α disposed.



Scheme 3. Synthesis of intermediate **11**.



Scheme 4. Synthesis of intermediate **3c**.



Scheme 5. Completion of the synthesis of **1**.

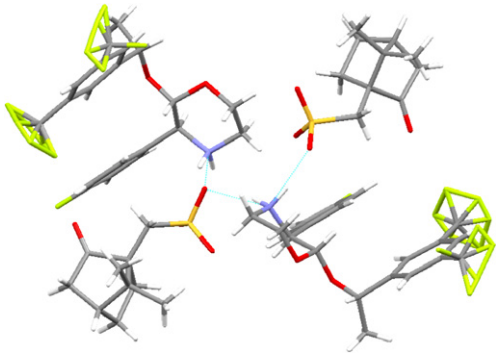


Figure 2. ORTEP representation of the L-(−)-CSA salt of **3c**.

At this stage conversion of **3c** into **3d** was carried out according to Zhao and co-workers[3b] (Scheme 5). The crystalline imine **13** was reduced with sodium borohydride with complete cis-stereoselectivity[8] to afford **3d**. The stereochemical outcome of this reduction process is due to the presence of a bulky 2-alkoxy group in **13**, which directed the addition of hydride from the opposite face of the plane of the molecule. Subsequent condensation with chloroacetamidrazone following a known process[9] and in situ cyclization of the resulting intermediate **14** at 120 °C in a closed autoclave system gave 5-[[2-[1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)morpholin-4-yl]methyl]-1,2-dihydro-1,2,4-triazol-3-one **1** in 60% yield.

DSC (differential scanning calorimetry), ^{1}H NMR, IR, SOR (specific optical rotation) and chiral HPLC[10] of the synthesized material **1** were in complete agreement with reported values.

In summary, we have demonstrated an efficient synthesis of aprepitant without using any chiral starting materials, except L-(−)-CSA (used for resolution), or expensive reagents, which has the considerable advantage of relative simplicity over the reported syntheses.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.051.

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6. The diastereopurity of **12** was estimated by HPLC analysis with symmetry shield RP/18, 100×4.6 mm $\times$ 3.5 μL; mobile phase—A: mixture of buffer (1.36 g of potassium dihydrogen phosphate in 1000 mL of water, adjust pH to 6 with triethylamine) and acetonitrile in the ratio of 70:30; mobile phase—B: mixture of Buffer and acetonitrile in the ratio of 20:80; 1.0 mL/min; 210 nm.
Gradient profile:

Time (min)	00	25	35	50	52	60
A (%)	75	75	10	10	75	75
B (%)	25	25	90	90	25	25

7. This compound is a mixture of diastereomers as HPLC data indicated.
8. The enantiopurity of **3d** was determined by using chiral HPLC analysis with chiral cell/ODH, 150×4.6 mm, 20 μL; mobile phase: *n*-hexane, 2-propanol, trifluoroacetic acid and diethylamine in the ratio of 980:20:1:0.2 (v/v); 0.8 mL/min; 210 nm.
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10. (a) The enantiopurity of **1** was determined by using chiral HPLC analysis with chiral cell/ADH, 250×4.6 mm, 20 μL; mobile phase: *n*-hexane and ethanol 90:10 (v/v); 0.5 mL/min; 210 nm; (b) The title compound could be obtained in 100% ee by single crystallization from MeCN.