Organic Process Research & Development **2007**, *11*, 455–457

An Alternative Approach to Achieve Enantiopure (3*S*)-4-Benzyl-3-(4-fluorophenyl)morpholin-2-one: A Key Intermediate of Aprepitant, an NK1 Receptor Antagonist†

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Abstract:

An efficient and alternative synthesis of enantiomerically pure (3*S*)-4-benzyl-3-(4-fluorophenyl)morpholin-2-one (*S*)-(+)-2), a key intermediate in the synthesis aprepitant (1), is described. The key resolution of *N*-benzylglycinamide, (±)-9, is achieved via diastereomeric salt crystallization using (+)-di-*p*-toluoyl-tartaric acid (DPTTA) as the resolving agent to furnish (*S*)-(+)-9. Alkylation of (*S*)-(+)-9 with 2-bromoethanol followed by stereocontrolled cyclization of obtained (*S*)-(+)-10 afforded the desired enantiomer (*S*)-(+)-2 with good yields and enantiopurity (>98%). The reaction conditions were optimized to make the process robust in order to implement at the commercial scale.

Introduction

Design of new resolving agents, through both rational concepts[1] and practical experience,[2] is an ongoing subject of research and development. Selective crystallization methods are still the most important techniques in preparing optically pure pharmaceutical products.[3] Solubility differences between diastereomers are often achieved by the selection of suitable resolving agents and/or a solvent systems during the resolution. In continuation of our interest in resolutions,[4] herein we are reporting a synthesis of (3*S*)-4-benzyl-3-(4-fluorophenyl)morpholin-2-one ((*S*)-(+)-**2**), a crucial and cost-contributing intermediate in the synthesis of aprepitant (**1**).

Aprepitant (**1**), a potent and orally active antiemetic drug well-known in the class of nonpeptide antagonists to the tachykinin neurokinin NK1 receptor, having some other widespread therapeutic activities,[5] has been approved by the U.S. FDA in the year 2003 and is currently being marketed under the brand name of Emend in the dosage of 40-, 80-, and 125-mg capsules.[6] Structurally, aprepitant (**1**) consists of three chiral centers, two of which are present on morpholine core, and the third one is on bis-trifluoro ethylbenzene (Figure 1). Efficient synthesis of enantiomerically pure (*S*)-morpholinone, (+)-**2**, is required to support different synthetic approaches designed for **1**.

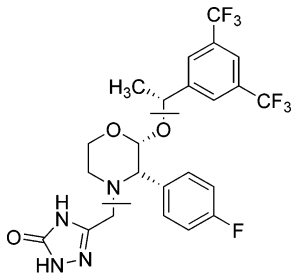

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Figure 1. **Structure of aprepitant (1).**

Dorn et al.[7] reported the first synthesis of (+)-**2** starting from (*S*)-(+)-4-fluorophenylglycine (**6**) in two steps which require a strict control of the process parameters such as reaction time and temperature to retain chirality during the conversion of **8** to (*S*)-(+)-**2,** thus making the process impractical at scale[8] (Scheme 1, Path A).

R. J. Alabaster et al.[9] reported the synthesis of (*S*)-morpholinone, (+)-**2**, through dynamic diastereomeric salt resolution of (±)-**2** using [(1*S*)-(*endo*,*anti*)]-(−)-3-bromocamphor-8-sulfonic acid (Scheme 1, Path B). A notable drawback of this synthesis is the use of expensive and commercially less viable resolving agent [(1*S*)-(*endo*,*anti*)]-(−)-3-bromocamphor-8-sulfonic acid.[10] With these limitations of reported approaches, development of new synthetic methods adequate to be carried out at large scale with low cost and cheaper raw materials is desirable. This paper reports a simple and economic process for large-scale synthesis of

† DRL-IPD Communication number: IPDO-IPM-00039.

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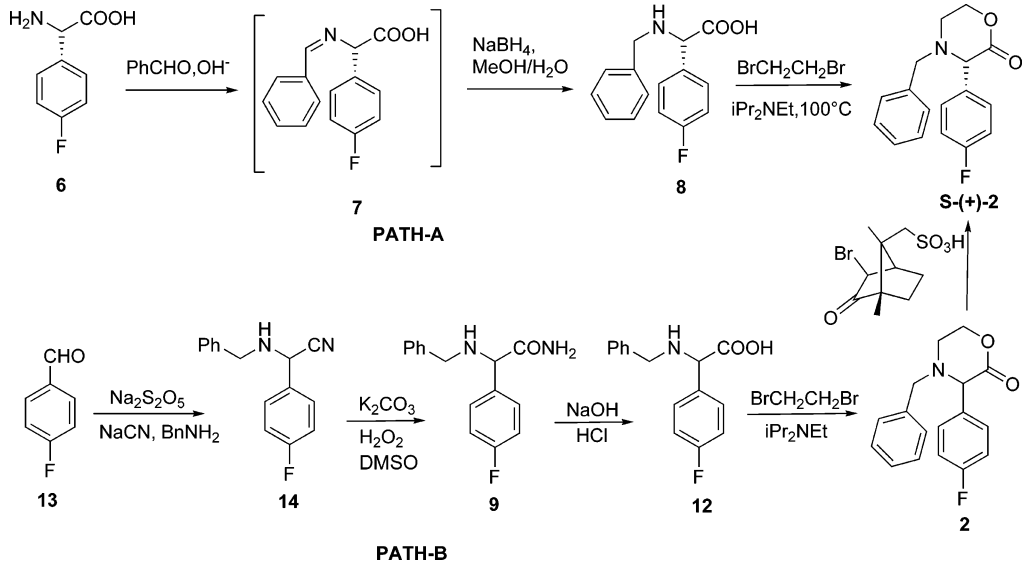
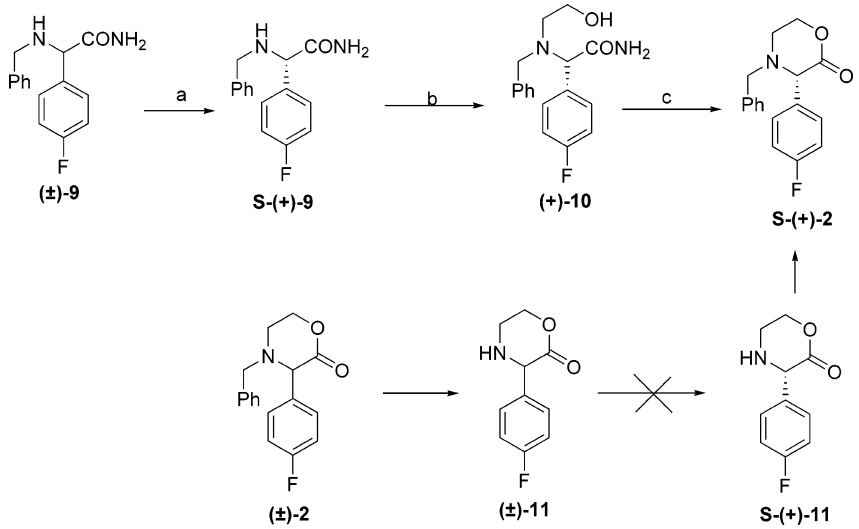
10.1021/op700030d CCC: $37.00
Published on Web 05/04/2007

Scheme 1. **Reported approaches for the synthesis of (*S*)-(+)-2**



Scheme 2. **New approach for (*S*)-(+)-morpholinone, (*S*)-(+)-2, synthesis[a]**



[a] Reagents and conditions: (a) D-(+)-DPTTA/methanol/60−65 °C/30−45 min; (b) 2-bromoethanol/EDIPA/DMF/80−85 °C/12−15 h; (c) acetic acid/55−60 °C/3−4 h.

(3*S*)-4-benzyl-3-(4-fluorophenyl)morpholin-2-one (**2**) through the resolution of (±)-**9** with a commercially available resolving agent. The resolved substrate (+)-**9** was subsequently converted to the desired chiral intermediate (+)-**2** in good yield and purity by simple chemical modifications.

Results and Discussion

As part of wider study on the original resolution of (±)-**2**,[9] other commercially available chiral acids (mandelic acid, camphor sulfonic acid, tartaric acid, dibenzoyl tartaric acid and di-*p*-toluoyl tartaric acid) were selected and tested for the resolution of (±)-**2** at our end. Among these, resolution with di-*p*-toluoyl tartaric acid though successful, yielded diastereomeric salt in only 10−15% yield with 92−94% enantiomeric purity. These results on direct resolution of (±)-**2** were highly discouraging. We then explored an alternative approach for the efficient synthesis of (*S*)-(+)-**2**. Careful evaluation of the original synthesis[8] of (±)-**2** led us to identify two precursors **9** and **11** (Scheme 2) for the present resolution study. Among the commercially viable chiral acids (mandelic acid, camphorsulphonic acid, tartaric acid, dibenzoyl tartaric acid, and di-*p*-toluoyl tartaric acid) screened for the resolution of either (±)-**9** and (±)-**11**, (+)-DPTTA was found to be the best choice for the resolution of (±)-**9** using methanol as a solvent. Interestingly, the diastereomeric salt having the same podes, (+)-**9**·(+)-DPTTA, is precipitated in methanol in contrast to the preceding reports.[11−12] The final procedure for resolution (after optimizing solvent, solvent volume, time, temperature, and molar ratio of DPTTA) is as follows: A mixture of (+)-DPTTA and methanol was stirred at room temperature until a clear solution was obtained. A solution of compound (±)-**9** in methanol was added to the above solution, and the resulting mixture was heated to reflux for about 45−60 min.

(11) Kozma, D. *CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation*; CRC Press: Boca Raton, FL, 2002.
(12) On the other hand, the diastereomeric salt (−)-**9**·(−)-DPTTA is precipitated in methanol to optionally access (−)-**9**.

The reaction mixture was then cooled to 0−5 °C and stirred for 1−2 h at this temperature. The resulting diastereomeric salt (+)-**9**·(+)-DPTTA was collected by filtration and washed with chilled methanol. Recrystallization of the wet solid in methanol furnished the desired isomer (*S*)-(+)-**9** with good enantiomeric purity[13] (>98%) and yield (60%).

Alkylation of the resolved substrate, (*S*)-amide ((*S*)-(+)-**9)**, with 2-bromoethanol at 80−85 °C in DMF offered the corresponding alkylated product (+)-**10**. Cyclization of (*S*)-(+)-amide (**10)** in acidic medium furnished the desired lactone (*S*)-(+)-**2** as a thick syrup. Subsequent conversion of the resulting lactone (*S*)-(+)-**2** to hydrochloride salt afforded pure (*S*)-(+)-**2** with >98.0% purity by HPLC.[14] The temperature in the alkylation step is a critical parameter in the process as alkylation of (*S*)-(+)-**9** with 2-bromoethanol at >95 °C resulted in **2** as a racemic compound, which could be due to the deprotonation of benzylic proton under the reaction conditions. The other process parameters involved in all the stages were also optimized, and the final process was successfully implemented in our scale-up facilities.

This newly developed process is around 1.5-fold cost advantageous over the literature-reported procedures to the best of our knowledge. We are in the process of recovering the undesired (*R*)-(−)-**9** and converting it to the desired (*S*)-(+)-**9** via racemisation and resolution process. This will further improve the economy of our process.

Conclusion

In conclusion, we have developed an efficient, alternative, and industrially scaleable process for the preparation of (*S*)-(+)-4-benzyl-3-(4-fluorophenyl)morpholin-2-one ((*S*)-(+)-**2**), a key and cost-contributing intermediate of aprepitant (NK_1 receptor antagonist).

Experimental Section

The ^{1}H NMR spectra were measured in $CDCl_3$ and DMSO-d_6 on a Varian Gemini 2000 (200 MHz) FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. The FT-IR spectra were recorded in the solid state as a KBr dispersion using Perkin-Elmer 1650 FT-IR spectrophotometer. The mass spectrum (70 eV) was recorded on an HP-5989A LC/MS spectrometer. The melting points were determined by using the capillary method on a POLMON (model MP-96) melting point apparatus. The solvents and reagents were used without further purification.

(2*S*)-2-(Benzylamino)-2-(4-fluorophenyl)acetamide ((*S*)-(+)-9). To a stirred and clear solution of intermediate (±)-**9** (150 g, 0.58 mol) in methanol (1500 mL) was slowly added a solution of (+)-DPTTA (224 g, 0.58 mol) in methanol (1140 mL) over a period of 15−30 min at 60−65 °C. The mixture was stirred at the same temperature for an additional 30−45 min. The reaction mixture was cooled to 25−35 °C, and then the resulting solid was isolated by filtration. The filtered cake was washed with cold methanol (300 mL) and vacuum dried to get 144 g of the enriched diastereomeric salt (*S*)-(+)-**9**·(+) DPTTA (enantiomeric purity, 88%). This wet salt was recrystallized from methanol (2250 mL) to get enantiopure (*S*)-(+)-**9** as a DPTTA diastereomeric salt. Yield: 112 g (30%; 60% of theory). The diastereomeric salt was hydrolyzed in water by adjusting the pH of the solution to11−12 using a solution of sodium hydroxide and was extracted with dichloromethane. Concentration of the organic layer furnished (*S*)-(+)-**9** free base as a thick syrup. $[\alpha]_D$ = +93.8 (*c* 1, methanol); chiral purity: 99.1%; MS; *m*/*z* 259 ($M^+ + H$). ^{1}H NMR (C_2D_6SO): δ 7.5 (s, 2H), 7.1−7.45 (m, 9H), 4.1 (s, 1H), 3.6 (t, J = 7.1, 2H), 2.9 (s, 1H).

(2S)-2-[Benzyl(2-hydroxyethyl)amino]-2-(4-fluorophenyl)acetamide (10). A mixture of (*S*)-(+)-**9** (100 g, 0.38 mol), *N*,*N*-diisopropylethylamine (220 g, 1.7 mol), and 2-bromoethanol (384 g, 3.0 mol) in DMF (1000 mL) were heated at 80−85 °C for 12−15 h. After completion of the reaction, the contents were cooled to room temperature, and water (1000 mL) was added and then extracted with ethyl acetate (2 × 750 mL). The combined organic layers were washed with water (2 × 1000 mL) and concentrated under vacuum to obtain **10** as thick syrup. Yield: 88 g (75.2%); MS; *m*/*z* 303 ($M^+ + H$). ^{1}H NMR ($CDCl_3$): δ 7.0−7.4 (m, 9H), 5.6 (s, 2H), 4.4 (s, 1H), 3.8 (s, 2H), 3.5−3.9 (m, 2H), 2.6 (t, 2H), 1.7 (s, 1H).

(3*S*)-4-Benzyl-3-(4-fluorophenyl)morpholin-2-one ((*S*)-(+)-2). A mixture of **10** (200 g, 0. 66 mol) and acetic acid (200 mL) was heated at 50−60 °C for 3−4 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 25−35 °C, water (1000 mL) was added and then extracted with toluene (2 × 1000 mL). The combined organic layers were washed with aqueous 5% Na_2CO_3 (2 × 1000 mL) solution followed by water (2 × 1000 mL). The organic layer was concentrated under vacuum to obtain a thick residue of (*S*)-(+)-**2** as a free base which was subsequently converted to the corresponding pure-white, crystalline hydrochloride salt using concentrated HCl(65 mL) in toluene(200 mL)/hexane(1800 mL) medium. Yield: 182 g (94.5%); purity by HPLC: 98.56%; enantiomeric purity by HPLC: 98.7%; $[\alpha]_D$ = +63.8 (*c* 1, methanol); MS; *m*/*z* 286 ($M^+ + H$). ^{1}H NMR (C_2D_6SO): δ 7.0−7.6 (m, 9H), 4.7 (s, 2H), 4.4 (s, 1H), 3.8 (s, 2H), 3.5−3.9 (m, 2H), 2.6 (t, 2H), 1.7 (s, 1H).

Acknowledgment

We thank the management of R&D-IPDO, Dr. Reddy's Laboratories Ltd., for supporting this work. Support from the colleagues from analytical research and development is highly appreciated.

Received for review February 8, 2007.

OP700030D

(13) Enantiopurity of (*S*)-(+)-9 was determined by chiral HPLC analysis with Chiralpak ODH, 5.0 μm, 250 mm × 4.6 mm; mobile phase: *n*-hexane, ethanol, and diethylamine in the ratio of 95:5:0.01 (v/v); 1.0 mL/min; 210 nm. The retention times of (*S*)-(+)-**9** and (*R*)-(−)-**9** were around 33.23 and 28.14 min, respectively.

(14) Enantiopurity of (*S*)-(+)-2 was determined by chiral HPLC analysis with Chiralpak ODH, 5.0 μm, 250 mm × 4.6 mm; mobile phase: *n*-hexane, ethanol, and diethylamine in the ratio of 95:5:0.01 (v/v); 0.8 mL/min; 210 nm. The retention times of (*S*)-(+)-**2** and (*R*)-(−)-**2** were around 23 and 19 min, respectively.