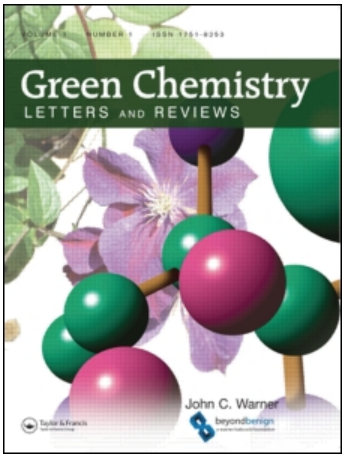

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Recycling of undesired isomers of key intermediate for aprepitant

Srinivas Gangula[a]; Chandrashekar R. Elati[a]; Anitha Nardela[a]; Apurba Bhattacharya[a]; Rakeshwar Bandichhor[a]; D. Ashok[b]
[a] Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd, Bachupalli, Qutubullapur, R.R. Dist, Andhra Pradesh, India [b] Department of Chemistry, Osmania University, Hyderabad, Andhra Pradesh, India

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RESEARCH ARTICLE

Recycling of undesired isomers of key intermediate for aprepitant

Srinivas Gangula[a], Chandrashekar R. Elati[a], Anitha Nardela[a], Apurba Bhattacharya[a], Rakeshwar Bandichhor[a]* and D. Ashok[b]

[a]*Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd, Bachupalli, Qutubullapur, R.R. Dist. 500072, Andhra Pradesh, India;* [b]*Department of Chemistry, Osmania University, Hyderabad 500007, Andhra Pradesh, India*

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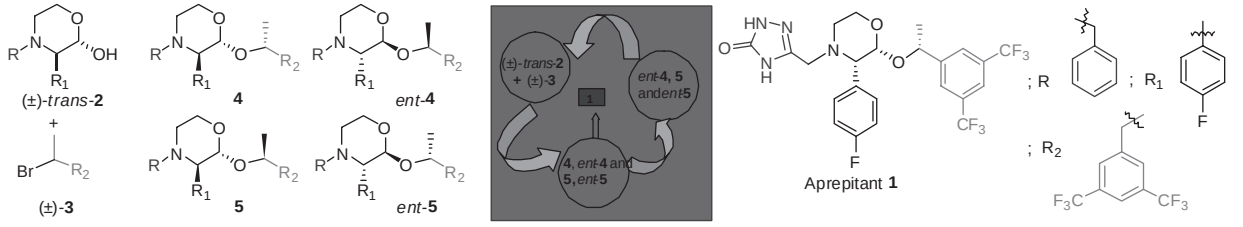
A protocol for regeneration of key intermediate of aprepitant from its undesired diastereomers is described. This work features the recycling of at least one-third of the undesired isomers (*ent*-**6**, **7** and *ent*-**7**) to desired isomer **4** as the key early intermediate for the synthesis of aprepitant **1**. The key step in our strategy involves diastereomeric salt preparation.



Keywords: diastereomers; dehydrohalogenation; elimination

Introduction

While designing the cost-effective and eco-friendly process for active pharmaceutical ingredients (APIs), attenuation of organic waste and enhancing the atom economy are the two top most intriguing current pursuits that are gaining importance in pharmaceutical industries (*1–3*). Herein, we wish to report a simple and practical approach for the recovering of key intermediate for aprepitant (API), by recycling its diastereomers. Aprepitant (**1**) (Figure 1) is an antagonist for NK1 receptors (*4–7*), marketed under the brand name of Emend (*8*). Structural features of **1** include three chiral centers (Figure 1): two of them present on morpholine core and the third one is on bis-trifluoro ethyl benzene. Recently we reported (*9,10*) a synthesis of aprepitant, by taking the advantage of the inherent tendency of (±)-*cis*-morpholinol-**2** to get converted into thermodynamically stable (±)-*trans*-morpholinol-**2** and utilizing diastereomeric salt resolution technique (Scheme 1).

The reported synthesis as shown in Scheme 1, involves nucleophilic substitution between (±)-*trans*-morpholinol-**2** and (±)-**3** that gives rise **4** & *ent*-**4** and **5** & *ent*-**5** pairs in 2:1 diastereomeric ratio. Subsequently, the debenzylation of pairs and diastereomeric salt crystallizations provided desired enantiomer **6** as a solid. Moreover, the resulting undesired *ent*-**6**, **7** and *ent*-**7** diastereomers were enriched in mother liquor. Dehydrohalogenation of **6** that afforded imine **8** and followed by stereo selective reduction of imine afforded compound *cis*-**9**. The resultant *cis*-**9** was used as a penultimate intermediate source of aprepitant.

The objective of this work is to recycle at least one-third of the undesired isomers (*ent*-**6,** **7** and *ent*-**7**) to desired isomer **4**, which serves as the key early intermediate for the synthesis of aprepitant **1** (Figure 2).

Referring to our previous work (*9,10*), mother liquors containing the diastereomeric salts of *ent*-**6**, **7** and *ent*-**7** that were subjected to hydrolysis under aqueous basic conditions that afforded free amines (*ent*-**6**, **7** and *ent*-**7**) and subsequently used for *N*-benzylation to furnish *ent*-**4**, **5** and *ent*-**5** (*11*).

It is imperative that the key intermediate (**4** and **5**), as shown in Figure 2, can be regenerated through the selective cleavage followed by re-etherification (*11,12*).

*Corresponding author. Email: rakeshwarb@drreddys.com; ashokdou@gmail.com

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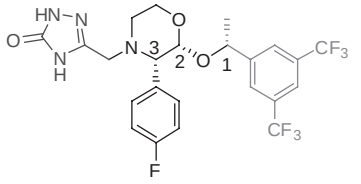
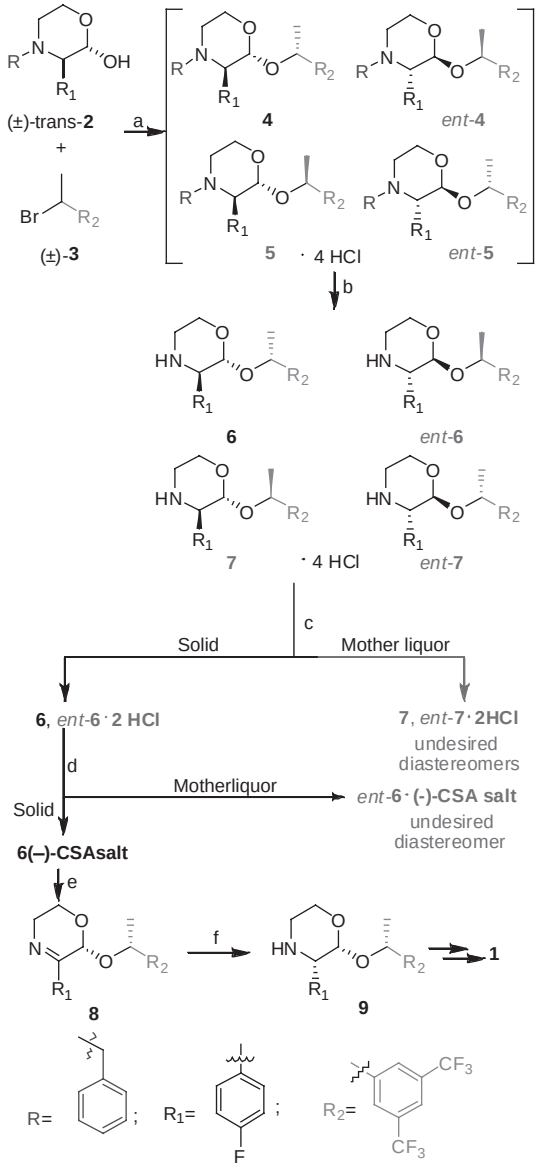


Figure 1. Aprepitant 1.



Scheme 1. Reported synthetic route for aprepitant. Reaction conditions: (a) KOH, acetone, 60°C, 6 h, aq. HCl, toluene, *n*-hexane; (b) 5% Pd-C, MeOH, 4.0 kg/cm^2, 35°C, 2 h; (c) IPA, 55°C; (d) 1. Toluene/water, NaOH, 2. MeOH, L-(–)-CSA; (e) 1. CH_2Cl_2/water, NaOH, 2. NCS, DBU, DMF, 25–30°C; (f) 1. $NaBH_4$, MeOH, 0–5°C, 2. Oxalic acid, MeOH, 3. Toluene/water, NaOH.

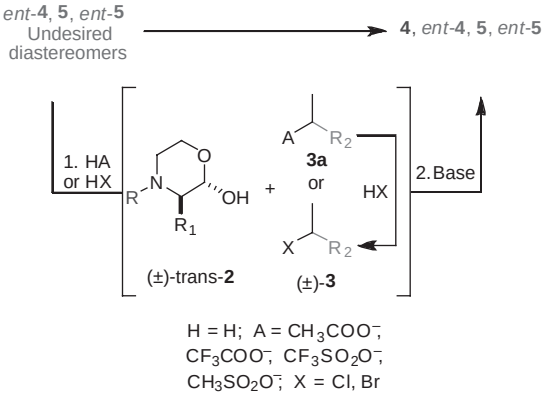
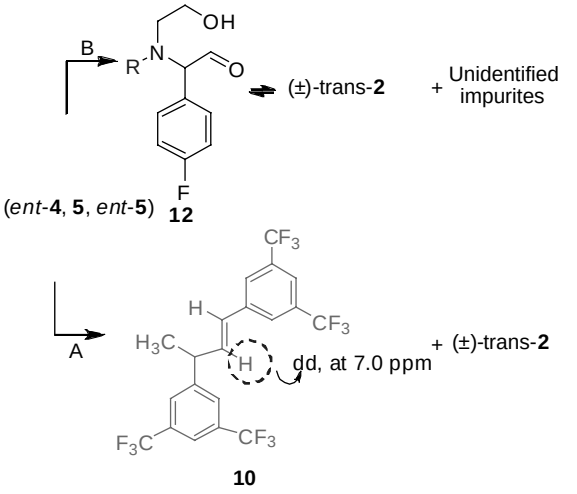


Figure 2. Synthetic strategy for recycling the undesired diastereomers (*ent*-**4**, **5** and *ent*-**5**).

Results and discussion

In our early attempts to cleave the C1–O–C2 bond in *ent*-**4**, **5** and *ent*-**5** diastereomers through *o*-debenzylation with Pd-C/H_2 was not realized (results are not included). Hence, we diverted our attention toward utilizing aqueous mineral acids such as HBr or HCl to get the (±)-*trans*-**2** and (±)-**3** intermediates as shown in Figure 2. However, the poor nucleophilicity of Br^- or Cl^- anion failed to initiate the reaction. Additionally, the combination of acids (aq. HBr or HCl) with AcOH or sulfuric acid did not promote the reaction. We found that the methane sulfonic acid when used as a reaction media at 25–35°C facilitated the complete cleavage of C1–O–C2 bond to yield desired product (±)-*trans*-**2** along with substantial amount of **10** (Scheme 2, path A).



Scheme 2. Selective C1–O–C2 bond cleavage in *ent*-4, 5 and *ent*-5.Reaction conditions: (A) MsOH/25–35°C/5–6 h; (B) TfOH or TFA/70–80°C/5–6 h.

In another instance where trifluoro methane sulfonic acid (TfOH) or trifluoro acetic acid (TFA) was used alone, aldehyde **12** (in equilibrium with hemiacetal (±)-*trans*-**2**; since the ^{1}H NMR was not conclusive therefore this mixture was only characterized by mass spectroscopy) was obtained as a major by-product along with several other unidentified impurities (Scheme 2, path B).

The structural elucidation of unexpected and unprecedented by-product **10** was achieved by spectroscopic techniques. In the ^{1}H NMR a multiplet around δ 4.08 for tertiary carbon proton was observed. A doublet of a doublet signal around δ 7.06 for secondary carbon proton, similarly another doublet at δ 6.77 was observed for the two olefenic protons. Moreover, ^{13}C NMR and mass spectral studies supported the proposed 1-ethyl-3, 5-bis-trifluoromethylbenzene structure **10** (Figure 3).

After confirmation of structure **10**, our efforts were aimed to minimize the formation of impurity **10**. We reasoned that the addition of neat methane sulfonic acid to *ent*-**4**, **5** and *ent*-**5** mixture facilitated the C1–O–C2 bond cleavage and plausibly afforded the mesylate derivative **3a** and (±)-*trans*-**2**.

Furthermore, elimination of methane sulfonic acid from **3a** leads to the formation of plausibly styrene derivative **11** that again reacted with a molecule of **3a** to afford impurity **10** (Figure 2). It appears that the formation of styrene derivative **11** can be avoided by using appropriate nucleophile.

In view of the above observation, addition of aq. HBr and MsOH to *ent*-**4**, **5** and *ent*-**5** mixture afforded (±)-*trans*-**2** and (±)-**3** intermediates along with a negligible amount of **10** and in turn recovery of these two species was increased by 20 and 100%, respectively. Recovery of morpholine core can be increased

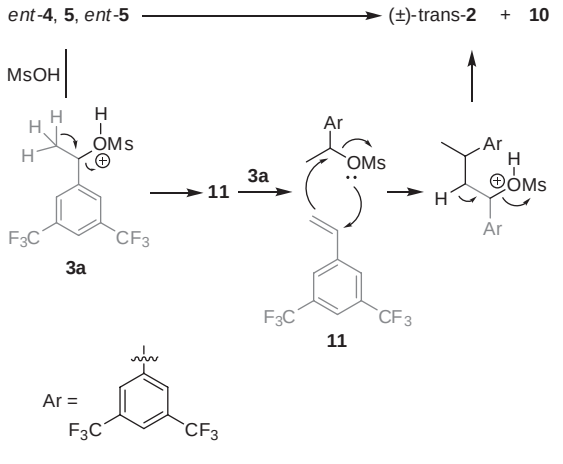
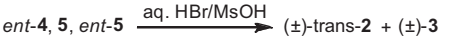


Figure 3. Plausible mechanism for the synthesis of **10**.

to 100% by accessing (±)-*trans*-**2** starting from *ent*-**4** and *ent*-**5** via analogous *N*-debenzylation and imine formation as shown in Scheme 1. Mechanistically, in the presence of aq. HBr the formation of styrene **11** was suppressed and in turn the dimer impurity **10** was avoided as shown in Scheme 3. Plausibly, bromide-nucleophile might have substituted the methane sulfonate anion that did not allow the resultant product **3** to undergo elimination reaction to afford intermediate **11** because bromide is not a better leaving group than the methane sulfonate.

In this transformation we were able to recover the readily reusable (±)-*trans*-**2** (precursor of **4**) in 65% yield, 95% HPLC purity and (±)-**3** in 86% yield with 97% G.C. purity. The developed processes allowed to recycle one of the undesired diastereomers.



Scheme 3. Selective C1–O–C2 bond cleavage in *ent*-4, 5 and *ent*-5 to get (±)-*trans*-2 and (±)-3.

Experimental

General

The ^{1}H, ^{13}C NMR, and Distortionless Enhancement by Polanization Transfer (DEPT) spectra were measured in $CDCl_3$ and DMSO-d_6, by using 200, 50, and 200 MHz, respectively, on a Varian Gemini FT NMR spectrometer, the chemical shifts are reported in Δ ppm relative to Tetramethysilane (TMS). The mass spectrum (70 ev) was recorded on HP-5989A LC-MS spectrometer.

Hydrochloride salt of 4-benzyl-2[1-(3, 5-bis-trifluoromethyl-phenyl)-ethoxy]-3-(4-fluoro-phenyl)-morpholine (ent-4, 5 and ent-5)

During the diastereomeric salt crystallization of **6** and **7**, mother liquor was collected and concentrated to get undesired isomers (*ent*-**6**, **7** and *ent*-**7**) as crude (100 g). This crude material was suspended in a mixture of water (300 mL), toluene (200 mL), and the pH of the mixture was adjusted to 9.5–10 by using NaOH solution. Thereafter, toluene layer separated and the aqueous layer was washed with toluene (600 mL). The toluene layers were combined and washed with water (3 × 300 mL). Distillation of excess toluene under vacuum furnished *ent*-**6**, **7** and *ent*-**7** isomers as free amines as a viscous material (82 g). To a solution of *ent*-**6**, **7** and *ent*-**7** isomers (80 g, 0.18 mol) and triethylamine (22.2 g, 0.21 mol) was added benzyl bromide (37.8 g, 0.21 mol) in about 15–20 min at 40–45°C and stirred for 4–5 h at 50–55°C. After the

completion of reaction, the reaction mixture was concentrated under vacuum to get thick crude and subsequently it was dissolved in toluene (600 mL) and washed with water (2 × 200 mL) and subjected to distillation to obtain *N*-benzylated *ent*-**4**, **5** and *ent*-**5** compound in 90% yield (87 g). To a solution of *ent*-**4**, **5** and *ent*-**5** (87 g, 0.16 mol) in toluene (180 mL) was added 37% aq. HCl (18.3 mL, 0.18 mol) at 25–30°C about 5–10 min and stirred for 30–40 min. To this suspension, *n*-heptane (540 mL) was added and stirred for 1–2 h. Filtration of precipitated solid afforded *ent*-**4**, **5** and *ent*-**5** as off-white hydrochloride salts in 85% yield (79.2 g). ^{1}H NMR (400 MHz, $CDCl_3$) (major: **5** & *ent*-**5**): δ 7.87 (s, 1H), 7.42–7.37 (m, 4H), 7.28–7.05 (m, 7H), 5.05 (q, $J = 6.8$ Hz, 1H), 4.26 (d, $J = 7.6$ Hz, 1H), 3.90 (dd, $J = 2.0$, 2.0 Hz, 1H), 3.66–3.59 (m, 1H), 3.51–3.40 (m, 1H), 3.19 (d, $J = 7.6$ Hz, 1H), 2.93 (d, $J = 13.2$ Hz, 1H), 2.58 (d, $J = 11.2$ Hz, 1H), 2.22 (t, $J = 3.2$, 3.6 Hz, 1H), 1.31 (d, $J = 6.4$ Hz, 3H).; MS., calculated for $C_{27}H_{24}F_7NO_2$ (M^+) 527.47 found (MH^+) 528.

4-benzyl-3-(4-fluoro-phenyl)-morpholin-2-ol [(±)-trans-2] and 1-(1-bromo-ethyl)-3, 5-bis-trifluoromethyl-benzene ((±)-3)

To a suspension of *ent*-**4**, **5** and *ent*-**5** hydrochloride salts (20 g, 0.03 mol) in 47% aq. HBr solution (14 mL, 0.08 mol), was added methanesulfonic acid (160 mL) at 25–30°C in about 15–20 min and stirred for about 5–6 h. After completion of reaction, the reaction mixture was quenched with water (250 mL) at 0–5°C and extracted the compound (±)-**3** with toluene (3 × 200 mL). Subsequent distillation of toluene provided (±)-**3** in 86% yields (9 g) with 97% purity by G.C. Furthermore, the pH of (±)-*trans*-**2** containing aqueous layer was adjusted to 7.0–7.5 by using lye solution and extracted with toluene (3 × 300 mL). After distillation under vacuum, thick syrup (8.0 g) was obtained. Subsequently, the syrup was diluted with *n*-heptane (20 mol) at 25–35°C and stirred for 2.0–2.5 h followed by the filtration to afford (±) *trans*-**2** as off-white solid in 65% (6.12 g) yields and 95% HPLC purity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.50 (m, 2H), 7.49–7.44 (m, 5H), 7.29–7.05 (m, 2H), 4.69 (t, $J = 6.4$, 6.4 Hz, 1H), 3.95 (dd, $J = 1.2$, 1.0 Hz, 1H), 3.84–3.81 (m, 1H), 3.77–3.61 (m, 1H), 3.11 (d, $J = 6.8$ Hz, 1H), 2.95–2.80 (m, 1H), 2.73–2.68 (m, 1H), 2.33–2.3 (m, 1H).; ^{13}C NMR (50 MHz, $CDCl_3$) Δ 159.9, 138.1, 134.4, 130.2, 128.7, 128.1, 127.1, 115.5, 97.6, 71.9, 64.3, 58.7, and 50.4.; MS., calculated for $C_{17}H_{18}FNO_2$ (M^+) 287.13 and found (MH^+) 288. (±)-**3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.88–7.80 (br, 3H), 5.24 (q, $J = 7.0$ Hz, 1H), 2.09 (d, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.4, 131.6, 129.6, 121.6, 119.8, 47.0, and 25.6; MS., calculated for $C_{10}H_7BrF_6$ (M^+) 319.96 found (MH^+) 320.06.

Synthesis of 10

To a mixture of *ent*-**4, 5** and *ent*-**5** (20 g, 0.03 mol), methanesulfonic acid (MsOH, 120 mL) was added in about 15–20 min at 25–30°C and stirred for 4–5 h. After completion of reaction, water was added (250 mL) at 0–5°C and extracted the compound **10** into toluene (3 × 200 mL). Subsequently, the distillation of toluene layer under vacuum afforded **10** as a thick syrup and it was purified by column chromatography (silica gel, cyclohexane) to give colorless liquid with 86% yield and 99.5% G.C purity. ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.15–7.88 (br, 6H), 7.06 (dd, $J = 7.4$, 7.4 Hz, 1H), 6.77 (d, $J = 16.0$ Hz, 1H), 3.95–4.08 (m, 1H), 1.52 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 M Hz, $CDCl_3$) δ 147.1, 138.9, 13.8, 133.8, 132.9, 132.0, 131.9, 128.0, 126.5, 121.8, 115.3, 42.6, and 20.5; MS., calculated for $C_{20}H_{12}F_{12}$ (M^+) 480.29 found (MH^+) 481.

Conclusion

In conclusion, we have developed an expeditious process for regeneration of the key intermediate of aprepitant from its undesired diastereomers. The work on recovering the other undesired diaseteromers is under progress.

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