Organic Process Research & Development **2010,** *14,* 1464–1468

Novel Preparation of H_1 Receptor Antagonist Fexofenadine

Jun Huang,[†,‡] Wen Wang,[†] and Li-Xin Wang*[,†]

Key Laboratory of Asymmetric Synthesis and Chirotechnology of Sichuan Province, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, P.R. China, and Graduate School of Chinese Academy of Sciences, Beijing 100039, P.R. China

Abstract:

A novel synthetic route for the preparation of H_1 receptor antagonist fexofenadine is described. The synthetic route started from the para-substituted aromatic derivative of methyl 4-(cyanomethyl)benzoate, 2, and gave fexofenadine in 26.0% overall yield via six steps. The whole process featured a method wherein fexofenadine could be obtained in excellent quality without ortho- or meta-unpurified regioisomers.

Introduction

α,α-Dimethyl-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl] benzeneacetic acid (fexofenadine, Figure 1) is a nonsedating-type H_1 receptor antagonist and a useful antihistaminic drug,[1,2] which was launched by Hoechest Marion Roussel in 1996. Compared with its analogue terfenadine, fexofenadine has fewer systemic side effects because of its lower permeability into central nervous system tissues.[3,4]

The synthesis of fexofenadine was first disclosed in U.S. Patent 4,254,129,[5] starting from ethyl α,α-(dimethylphenyl)acetate and 4-chlorbutyroyl via Friedel−Crafts reaction, followed by condensation with α,α-diphenylpiperidine methanol to form a keto ester intermediate; subsequent reduction and hydrolysis afforded fexofenadine. After that, many methods have been developed to prepare this molecule.[6] Schroeder[7] reported a new method using Friedel−Crafts reaction of methyl α,α-(dimethyphenyl)acetate with succinic anhydride to introduce the para substituent. Natalini[8] developed a new route based on the conversion of α-halo-alkylarylketone into the corresponding substituted 2-arylalkanoic ester via a crucial Giordano's procedure catalyzed by $ZnBr_2$. Although improved Friedel−Crafts reactions were also reported by Krauss,[9] Wu,[10] and Richard,[11] Friedel−Crafts reactions unavoidably produced a mixture of ortho, meta, and para regioisomers, which made the separation and purification relatively difficult for stricter quality requirements. To circumvent the Friedel−Crafts reaction, another strategy is using 1,4-disubstituted or para-positioned phenyl derivatives. Kawai[12] reported an alternative route starting from commercially available 4-bromophenylacetic acid. In this process, a costly Pd(0) catalyst and environmental unfriendly mercury oxide were involved. Graziano[13] reported another analogous route starting from α,α-dimethyl-(4-bromophenyl)-acetic acid methyl ester, and HgO was replaced by costly $PtCl_2$ to avoid the byproduct. Milla[2b] reported an improved process for the same preparation while using 2-(4-bromophenyl)-2-methyl-propanenitrile as the starting material, which provided an easy separation of the final product since the nitrile intermediate is easily recrystallized. Ethyl 2-methyl-2-*p*-tolyl-propanoate,[14] 2-(4-bromophenyl)acetonitrile,[15] and methyl 2-(4-formylphenyl)-2-methylpropanoate[16] have also been used as starting material to avoid the Friedel−Crafts reaction. With the exception of the above two strategies, biooxidation of the methyl group of terfenadine is also an effective method to obtain fexofenadine.[3,17]

Summarily, Friedel−Crafts acetylation is a highly convenient and simple strategy for the preparation of fexofenadine or related intermediates; however, the process lacks selectivity and is of limited use in commercial production.[18] Therefore, it is still an industrial request to obtain more qualified fexofenadine, especially without (or with less) ortho and meta impurities in a commercially challenging, less costly, and more environmentally friendly manufacturing and easily scaled up process.

As a part of our unceasing interest in active pharmaceutical ingredients (API) and related intermediates,[19,20] we report herein a novel synthetic route for the preparation of fexofenadine. The solely para-positioned raw material methyl 4-(cyanomethyl)-benzoate, **2**, is first devised as the starting material, and high-quality fexofenadine was efficiently obtained in 26.0% overall yield with convenient reactions and commercially available chemicals. The whole scheme, strategies, and synthetic route are depicted in Scheme 1.

Results and Discussion

Our design strategy lies in the following facts: unwanted isomers mainly come from the poorly selective Friedel−Crafts reaction, and separation cost comes mainly from the separation of the unwanted regioisomers. To overcome these disadvantages, we devised a novel synthetic route and chose the commercially available solely para-positioned phenyl derivative **2** as starting material, which is depicted in Scheme 1. Accordingly, methyl benzoate derivative **2** was converted to methyl 4-(2-cyanopropan-2-yl)benzoate, **3**, by methylation. The key step in our process is the condensation of **3** with γ-butyrolac-

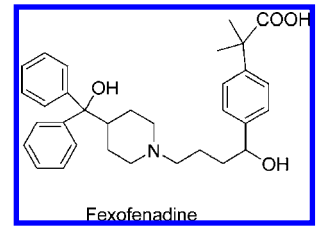


Figure 1. **Structure of fexofenadine.**

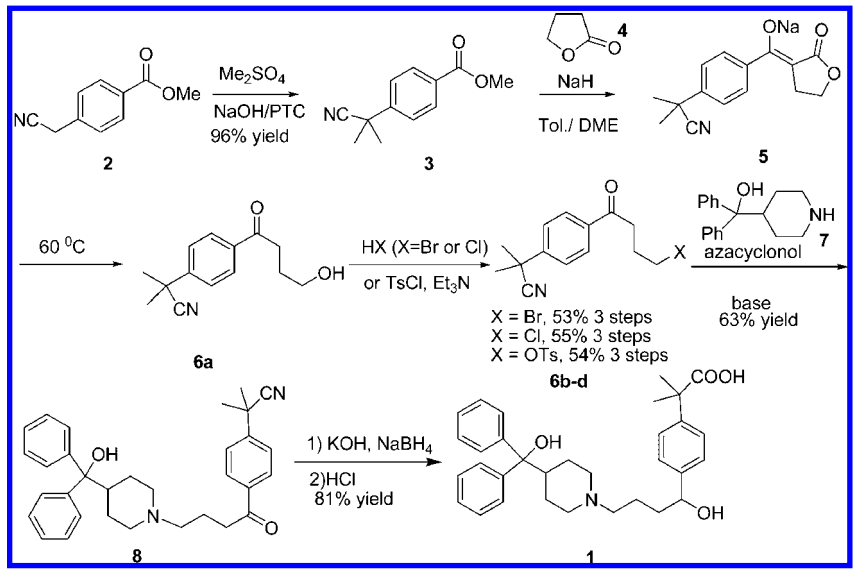
* Corresponding author. Telephone: (+86)-28-8525-5208. E-mail: wlxioc@cioc.ac.cn.

† Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences.

‡ Graduate School of Chinese Academy of Sciences.

10.1021/op100090j
Published on Web 10/04/2010

Scheme 1. **Novel preparation of fexofenadine**



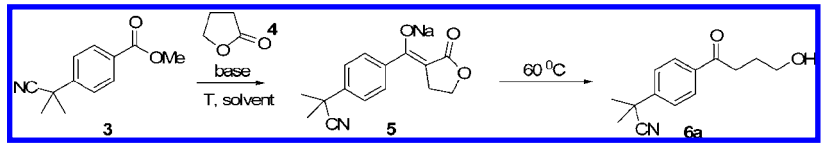
tone, **4**, in the presence of a strong base and afforded the primary alcohol **6a** via the desired key intermediate **5** which was easily purified by simple extraction and acid−base neutralization. Primary alcohol **6a** was easily converted to the key intermediate **6b** which was condensed with azacyclonol **7** to give nitrile **8**. Finally, fexofenadine was obtained after reduction with $NaBH_4$ and in situ hydrolysis in HCl.

Methyl 4-(2-cyanopropan-2-yl)benzoate **3** was easily prepared from methyl benzoate derivative **2** with Me_2SO_4 in the presence of a phase transfer catalyst, e.g. tetrabutylammonium bromide, at low temperature (0−3 °C) in almost quantitative yield (96%). The temperature of this conversion is crucial; higher temperatures led to the hydrolysis of the ester in alkaline conditions.

The key step of the whole process is the preparation of ketone **6a**. Ketone **6a** and its structural analogues are the key intermediates for the preparation of fexofenadine in the reported methods which mainly focused on the construction of these interesting structures. Among them, Friedel−Crafts reaction[5,7,18] was one of the straightforward methods to manufacture these key intermediates in spite of the unavoidable formation of ortho and meta isomers. Except Friedel−Crafts reaction, coupling of methyl 2-(4-bromophenyl)-2-methylpropanoate and 3-butyne-1-ol in the presence of Pd(0)/Cu_2Br_2 and addition of 2-(1,3-dioxolan-2-yl)ethyl magnesium bromide to 4-subsituted benzaldehyde[14,16] were also used. In our strategy, a decarboxylative condensation between methyl benzoate derivative **3** and γ-butyrolactone **4** was first employed to introduce the key intermediate **6a** via salt **5** which is water-soluble and easily to be separated and purified by simple extraction and acid−base neutralization. Methyl benzoate derivative **3** was transformed

(1) (a) Slater, J. W.; Zechnich, A. D.; Haxby, D. G. *Drugs* **1999**, *57*, 31–47. (b) Markham, A.; Wagstaff, A. J. *Drugs* **1998**, *55*, 269–274.
(2) (a) Honig, P. K.; Woosley, R. L.; Zamani, K.; Conner, D. P.; Cantilena, L. R. *Clin. Pharmacol. Ther.* **1992**, *52*, 231–238. (b) Zaragoza, F. J. M. U.S. Patent 2003/0166682A1, 2003.
(3) Ouarradi, A. E.; Arnaud, I. S.; Buisson, D. *Tetrahedron* **2008**, *64*, 11738–11744.
(4) Monahan, B. P.; Ferguson, C. L.; Killeavy, E. S.; Lloyd, B. K.; Troy, J.; Cantilena, L. R. *J. Am. Med. Assoc.* **1990**, *264*, 2788–2790.
(5) Carr, A. A.; Dolfini, J. E.; Ohio, C.; Wright, G. J. U.S. Patent 4,254,129, 1981.
(6) Reviews see: (a) Liu, B.; Rong, R.-B.; Yuan, H.; Yu, Z.-Y. *Huaxue Yu ShengwuGongcheng* **2005**, *2*, 54–56. (b) Hu, C.-D.; Zhang, J. *Guangzhou Huagong.* **2009**, *37*, 30–31.
(7) Collin, S.; Ryan, H.; Richard, C. WO Patent 02/102776A1, 2002.
(8) Giacomo, B. D.; Coletta, D.; Natalini, B.; Ni, M.-H.; Pellicciari, R. *Farmaco* **1999**, *54*, 600–610.
(9) Krauss, R. C.; Strom, R. M.; Scortichini, C. L.; Kruper, W. J.; Wolf, R. A.; Wu, W. W.; Carr, A. A.; Hay, D. A.; Rudisill, D. E.; Panzone, G. U.S. Patent 6,348,597, 2001.
(10) Lv, B. H.; Yang, X. Y.; Wu, F. H. *Chin. J. Med. Chem.* **2004**, *14*, 96.
(11) Richard, K. C. H.; Michelea, K. WO Patent 93/21156 A1, 1993.
(12) (a) Kawai, S. H.; Hambalek, R. J.; Just, G. *J. Org. Chem.* **1994**, *59*, 2620–2622. (b) Ambra, T. E. D.; Pilling, G. M. WO Patent 97/23213A1, 1997.
(13) Graziano, C.; Giuseppe, B.; Domenico, M. EP Patent 1260505A1, 2002.
(14) Fang, Q. K.; Senanayake, C. H.; Wilkinson, H. S.; Wald, S. A.; Li, H. *Tetrahedron Lett.* **1998**, *39*, 2701–2704. Sun, Y.; Tang, L. H.; Tao, L.; Qin, X. H. *Chin. J. Pharm.* **2006**, *37*, 439.
(15) Patel, S.; Waykole, L.; Repic, O.; Chen, K.-M. *Synth. Commun.* **1996**, *26*, 4699–4710.
(16) (a) Senanayake, C. H.; Fang, Q. K.; Wilkinson, S. H. U.S. Patent 6,147,217, 2000. (b) Miroslav, V.; Andrej, B.; Miroslav, K.; Ivan, V. WO Patent 2004/043922 A1, 2004.;(c) Venkateswaran, S. C.; Singh, J. P.; Lalit, W. WO Patent 2007/135693A2, 2007.
(17) Mazier, C.; Jaouen, M.; Sari, M.-A.; Buisson, D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5423.
(18) Selected examples: (a) Ambra, T. E. D. U.S. Patent 5,589,487, 1996. (b) Ambra, T. E. D. U.S. Patent 5,663,412, 1997. (c) Ambra, T. E. D. U.S. Patent 5,750,703, 1998. (d) Krauss, R. C.; Strom, R. M.; Scortichini, C. L.; Kruper, W. J.; Wolf, R. A.; Wu, W. W.; Carr, A. A.; Hay, D. A.; Rudisill, D. E.; Panzone, G. U.S. Patent 6,242,606B1, 2001. (e) Krauss, R. C.; Strom, R. M.; Scortichini, C. L.; Kruper, W. J.; Wolf, R. A.; Wu, W. W.; Carr, A. A.; Hay, D. A.; Rudisill, D. E.; Panzone, G. U.S. Patent 6,147,216, 2000. (f) Ambra, T. E. D. U.S. Patent 2002/0007068A1, 2002. (g) Ma, L.; Gan, M.-Y.; Chen, F.-Q.; Chen, C.; Lu, W. CN Patent 101182306A, 2008. (h) Ramachandra, R. D.; Narayanrao, K. R.; Gopaldas, G. M.; Ramdas, B. D. WO Patent 2005/019175A1, 2005. (i) Ayers, T. A.; Brown, P. W. U.S. Patent 2003/0022919 A1, 2003.
(19) (a) Wang, L.-X.; Shen, J.-F.; Tang, Y.; Chen, Y.; Wang, W.; Cai, Z.-G.; Du, Z.-J. *Org Process Res. Dev.* **2007**, *11*, 487–489. (b) Li, Y.; Xu, X.-Y.; Pan, S.-Y.; Wang, L.-X.; Xia, C.-Q. *Chin. J. Chem.* **2009**, *27*, 433–436.
(20) (a) Wang, L.-X.; Tang, Y.; Chen, Y.; Tian, F. EP Patent 1942110A1, 2008. (b) Wang, L.-X.; Tang, Y.; Chen, Y.; Tian, F. WO Patent 2007028337 A1, 2007. (c) Wang, L.-X.; Tang, Y.; Chen, Y.; Tian, F. U.S. Patent 2008249311 A1, 2008. (d) Wang, L.-X.; Tang, Y.; Chen, Y.; Tian, F. CN Patent ZL200510060721.2, 2007; (e) Wang, L.-X.; Tang, Y.; Chen, Y.; Tian, F. CN Patent ZL200510061230.X, 2007; (f) Wang, L.-X.; Tang, Y.; Chen, Y.; Tian, F. CN Patent ZL200510061231.4, 2007; (g) Wang, L.-X.; Peng, H. Q.; Du, Z. J.; Lan, H. F. Chinese Patent CN 200610027596.X, 2006.

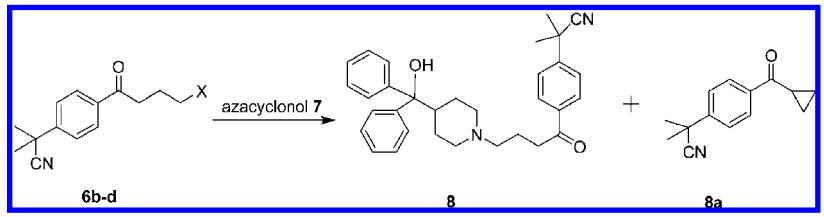
Table 1. **Condensation of 3 with 4 in various bases**[a]



entry	base	solvent	T^b [°C]	yield[c] [%]
1	NaH	benzene	80	45
2	Na	benzene	80	32
3	$NaNH_2$	benzene	80	35
4	NaH	toulene	110	55
5	NaH	toluene/DMF = 10:1	110	63
6	NaH	toluene/DME[d] = 10:1	80	61

[a] Experimental conditions: mixture of **3** (0.1 mol), 0.125 mol base, and 0.12 mol γ-butyrolactone **4** in solvent was mechanically stirred at the designed temperature. [b] Reaction temperature of **3** with **4**. [c] Isolated yield of **6a**. [d] DME = 1,2-dimethoxyethane.

Table 2. **Coupling of 6b−d with azacyclonol 7 in the presence of various bases and solvents**



entry	X	solvent	base	T [°C]	yield[a] **8** [%]	yield[a] **8a** [%]
1	Br (**6b**)	THF	Na_2CO_3	60	0	83
2	Br (**6b**)	THF	$NaHCO_3$	60	5	74
3	Br (**6b**)	DMF	Et_3N	25	32	31
4	Br (**6b**)	THF	Et_3N	25	63	5
5	Br (**6b**)	THF	DIPA	25	55	5
6	Cl (**6c**)	acetone	$NaHCO_3$	60	48	12
7	OTs (**6d**)	acetone	Et_3N	60	55	6

[a] Isolated yield.

to the salt **5** in the presence of base followed by decarboxylation to give the desired intermediate **6a**. Initially, sodium, sodium amide, and NaH were investigated, and NaH was recommended in terms of the yield of **6a** (Table 1). The reaction performed in toluene[21] may give a better yield. In this process, we found that the solubility of the formed target sodium **5** in toluene was not ideal, and 1,2-dimethoxyethane (DME) was added as cosolvent; the solubility and stirring state of the reactants were improved, and 61% yield was obtained.[22] Therefore, in larger-scale processing, the cosolvent of toluene and DME was used. After the condensation was completed, some water was added to dissolve the product **5**, and the organic phase which contained the unreacted **3** and byproduct (mainly 4-(2-cyanopropan-2-yl)benzoic acid) may be easily separated and reused by simple extraction with toluene. The aqueous phase was adjusted to weak basicity with 1 N HCl, heated to 60 °C, and hydrolyzed to the desired intermediate **6a** which could be used directly in the next step. During the process of hydrolysis, the pH value should be controlled below 10 to avoid hydrolysis of nitrile. The crude **6a** could easily transform to bromide **6b**, chloride **6c**, or sulfonic ester **6d**.

Bromide **6b** was coupled with azacyclonol **7** in the presence of base and suitable solvent. The base is crucial for the coupling reaction to avoid the undesired cyclization byproduct **8a**, and the ratio of **8** to **8a** greatly changes with different bases. Several bases have been studied and the results are shown in Table 2. Coupling product **8** was mainly formed (entries 4−5), when organic bases such as Et_3N or diisopropylamine (DIPA) used. By contrast, inorganic bases such as Na_2CO_3 and $NaHCO_3$ mainly afforded unwanted cyclization **8a** (entries 1, 2), and during a larger scale-up processing, large volume of CO_2 foamed fiercely. Solvent also greatly affects the formation of **8** and **8a** when Et_3N used as base. Product **8** was dominated in THF (entry 4), whereas **8** was almost equal to **8a** in DMF (entry 3). Chloride **6c** and sulfonic esters **6d** could also react with azacyclonol **7** while giving relatively lower yields (entries 6−7). The recommended scale-up reaction conditions were found to be Et_3N as base, THF as solvent, and **6b** as substrate at room temperature.

Finally, excellent quality of target molecule fexofenadine **1** without unwanted regioisomers may be easily obtained after

(21) The original process used benzene as solvent.
(22) DMF was also added as auxiliary solvent, the solubility and stirring state of the reactants were adequately improved, and the yield was increased up to 63%. The amount of DMF used may be adjusted as needed, and this process was scaled up to a 20-kg scale without observation of safety hazards. Before further industrial testing, we were advised by the OPRD reviewers to recheck related cases to find that DMF/NaH is a known process safety hazard (http://www.crhf.org.uk/incident101.html). We immediately informed our partner to re-evaluate this step and cease the scale-up attempt.

one-pot-wise hydrolysis and reduction in 81% yield as is well documented.[2b]

Conclusions

In conclusion, we have devised and reported a novel synthetic route for the preparation of fexofenadine of excellent quality. The solely para-positioned fexofenadine and its salt were obtained in excellent quality and at acceptable raw material cost without ortho or meta unpurified regioisomers. The whole process and all of the procedures are now under processing evaluation in a 20-kg scale reaction in China Huahai Pharmaceuticals Co., Ltd.

Experimental Section

Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker-300 (300/75 MHz) spectrometer using $CDCl_3$, DMSO-d_6 as solvent, and TMS as internal standard. The IR spectra were performed on a NICOLET MX-1E FT-IR instrument. ESI mass spectra were performed on a Finnigan LCQDECA, and high-resolution MS spectral data were recorded on a Bruker Daltonics Bio TOF.

Methyl 4-(2-cyanopropan-2-yl)benzoate (3).[19] NaOH (3 kg, 75 mol) was dissolved in 10 L of water; after it cooled to room temperature, 20 g of PTC (tetrabutylammonium bromide) and methyl 4-(cyanomethyl)benzoate **2** (1.05 kg, 6 mol) were then added in a suitable reactor. After further cooling to 0−3 °C, dimethyl sulfate (2.65 kg, 21 mol) was added dropwise at 0−3 °C. The mixture was adequately stirred for 4 h, water (5 L) and CH_2Cl_2 (3 × 2 L) were then added. The organic phase was separated and washed with saturated aq solution of NH_4Cl and concentrated under reduced pressure. Colorless solid **3** (1.17 kg, 5.76 mol) was obtained. Yield: 96%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.70 (s, 6H, CH_3), 3.88 (s, 3H, CH_3), 7.52 (d, 2H, J = 6 Hz, Ar), 8.01 (d, 2H, J = 6 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.8, 37.2, 52.0, 123.7, 125.1, 129.6, 130.0, 146.1, 166.1.

2-(4-(4-Hydroxybutanoyl)phenyl)-2-methylpropanenitrile (6a). To a stirred solution of methyl 4-(2-cyanopropan-2-yl) benzoate **3** (200 g, 1 mol) and sodium hydride (30 g, 1.25 mol, 60% mineral oil dispersion) in 1 L solvent ($V_{toluene/DME}$ = 10:1), was added dropwise to the solution of dihydrofuran-2(3H)-one **4** (104 g, 1.2 mol) in 500 mL of toluene for 1 h at 80 °C. The mixture was refluxed for a further 4 h. Then 2 × 500 mL water was added to extract salt **5**. After phase separation, the aqueous solution was extracted with toluene, and the organic phase was combined and recycled. The aqueous solution was adjusted to pH = 9−10 with 1 N HCl, and then hydrolyzed at 60 °C for 4 h and extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layer was washed with saturated aq solution of NH_4Cl (500 mL) and concentrated under reduced pressure. After removal of the solvent, the crude oil liquid product **6a** (165 g, HPLC: 79.8%) was obtained and used for the next step without further purification.

2-Methyl-2-(4-(2-oxo-tetrahydrofuran-3-carbonyl)phenyl)propanenitrile (Free Ketone 5). Colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.75 (s, 6H, CH_3), 2.54−2.93 (m, 2H, CH_2), 4.45−4.59 (m, 3H, COCHCO, OCH_2), 7.62 (d, 2H, J = 12 Hz, Ar), 8.11 (d, 2H, J = 12 Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6, 28.6, 37.2, 47.9, 67.64, 125.2, 125.5, 130.0, 130.6, 147.2, 172.7, 192.2. IR (cm^{-1}): 3062, 2990, 2237, 1749, 1679, 1604, 1570, 1481, 1452, 1409, 1370, 1016,950, 857, 812, 683. HR-MS (ESI) Calcd for $C_{15}H_{15}NNaO_3$: 280.0944. Found: 280.0941.

2-(4-(4-Hydroxybutanoyl)phenyl)-2-methylpropanenitrile (6a).[2b] Isolated yield: 63% (two steps). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.73 (s, 6H, CH_3), 1.96−2.06 (m, 2H, CH_2), 3.13 (t, 2H, J = 6 Hz, $COCH_2$), 3.75 (t, 2H, J = 6 Hz, OCH_2), 7.58 (d, 2H, J = 6 Hz, Ar), 8.01 (d, 2H, J = 6 Hz, Ar).

Procedure for 6b,c. The solution of the crude **6a** (160 g) in 1.5 L of CH_2Cl_2 and 40% HBr or 36% HCl (500 mL) was mechanically stirred at 25 °C for 8 h. The mixture was diluted with 2.5 L of CH_2Cl_2 and 2.5 L of water. The organic phase was separated and washed with brine (2 × 1 L). After removal of the solvent, the residue was recrystallized in ethanol to provide white solid **6b**,**c**.

2-(4-(4-Bromobutanoyl)phenyl)-2-methylpropanenitrile (6b)[2b] (X = Br). Yield: (160 g), 53% for three steps from **3**. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.75 (s, 6H, CH_3), 2.27−2.35 (m, 2H, CH_2), 3.18 (t, 2H, J = 6 Hz, $COCH_2$), 3.45 (t, 2H, J = 6 Hz, $BrCH_2$), 7.59 (d, 2H, J = 12 Hz, Ar), 8.00 (d, 2H, J = 12 Hz, Ar).

2-(4-(4-Chlorobutanoyl)phenyl)-2-methylpropanenitrile (6c)[8] (X = Cl). Yield: (130 g), 55% for three steps from **3**. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.75 (s, 6H, CH_3), 2.21−2.27 (m, 2H, CH_2), 3.18 (t, 2H, J = 6 Hz, $COCH_2$), 3.68 (t, 2H, J = 9 Hz, $ClCH_2$), 7.59 (d, 2H, J = 6 Hz, Ar), 8.01 (d, 2H, J = 6 Hz, Ar).

4-(4-(2-Cyanopropan-2-yl)phenyl)-4-oxobutyl-4-methylbenzenesulfonate (6d) (X = OTs). 4-Methylbenzene-1-sulfonyl chloride (260 g, 1.37 mol) in 1.5 L of CH_2Cl_2 was added dropwise to the solution of the crude **6a** (160 g) and Et_3N (350 g, 3.46 mol) in 1.5 L of CH_2Cl_2. The mixture was mechanically stirred at 25 °C for 8 h, diluted with 2.5 L of CH_2Cl_2 and 2.5 L of water. The organic phase was separated and washed with brine (2 × 1 L). After removal of the solvent, the residue was recrystallized in ethanol to provide white solid **6d** (205 g). Yield: 54% for three steps from **3**. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.75 (s, 6H, CH_3), 2.08−2.14 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 3.05 (t, 2H, J = 6 Hz, $COCH_2$), 4.15 (t, 2H, J = 6 Hz, $ClCH_2$), 7.30 (d, 2H, J = 6 Hz, Ar), 7.57 (d, 2H, J = 6 Hz, Ar), 7.76 (d, 2H, J = 6 Hz, Ar), 7.92 (d, 2H, J = 6 Hz, Ar).

2-(4-(4-(4-(Hydroxydiphenylmethyl)piperidin-1-yl)butanoyl)phenyl)-2-methylpropanenitrile (8).[7] Diphenyl(piperidin-4-yl)methanol **7** (340 g, 1.2 mol) and triethylamine (120 g, 1.2 mol) were added to a solution of **6b** (290 g, 1 mol) in 1 L of THF. The mixture was mechanically stirred at 25 °C for 8 h. After filtration of excessive diphenyl(piperidin-4-yl)methanol and evaporation of the solvent, the crude solid was recrystallized in ethyl acetate/petroleum ether (v/v, 1:2) to provide white solid **8** (300 g, 0.63 mol). Yield: 63%. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 1.49−1.52 (4H, m, CH_2), 1.75 (6H, s, CH_3), 1.99−2.04 (4H, m, CH_2, CH), 2.45−2.50 (4H, m, NCH_2), 2.99−3.07 (4H, m, NCH_2, CH_2CO), 7.15−7.60 and 7.96−8.00 (14H, m, Ar).

2-(4-(Cyclopropanecarbonyl)phenyl)-2-methylpropanenitrile (8a).[2b] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): $\delta = 1.04-1.10$ (m, 2H, CH_2), 1.23−1.28 (m, 2H, CH_2), 2.64 (s, 6H, CH_3), 2.64−2.69 (m, 1H, COCH), 7.59 (d, 2H, $J = 6$ Hz, ArH), 8.04 (d, 2H, $J = 6$ Hz, ArH).

α,α,-Dimethyl-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]benzeneacetic Acid (1), Fexofenadine.[8] $NaBH_4$ (140 g, 3.7 mol) and KOH (2.8 kg, 50 mol) were added to a solution of **8** (480 g, 1 mol) in solvent (5 L of ethanol: 500 mL of water). The resulting mixture was mechanically stirred at 20 °C for 1 h and refluxed for 12 h. After the mixture was adjusted to pH = 5−6 by 2 N hydrochloric acid, the solvent was removed in vacuum. The residue was then diluted with water (5 L) and extracted with ethyl acetate (3 × 3 L). The combined organic phase was washed with brine (5 L) and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded crude **1**. The crude solid was recrystallized from the mixture of water and ethanol (v/v, 2:1) to give white solid **1** (410 g, HPLC: 99.7%, single impurity <0.1% and total impurities <0.3%). Yield: 81%. ^{1}H NMR (300 MHz, DMSO): $\delta =$ 1.35−1.39 (m, 2H), 1.45 (s, 6H, 2 × CH_3), 1.65−1.77 (m, 6H, CH_2), 2.80−2.88 (m, 5H, CH_2N, CH), 3.28−3.32 (m, 2H, CH_2N), 4.52 (1H, m, C*H*OH), 5.62 (s, 1H, OH), 7.12−7.17 (m, 2H, Ar), 7.25−7.31 (m, 8H, Ar), 7.52 (d, 4H, $J = 7.64$ Hz, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.36$, 23.73, 26.44, 35.85, 41.16, 45.48, 45.48, 51.59, 55.77, 71.35, 78.22, 125.20, 125.64, 125.68, 126.05, 127.89, 143.50, 144.04, 146.66, 177.56.

Acknowledgment

This project was financially supported by Huahai Pharmaceuticals Co., Ltd., Zhejiang, China.

Received for review March 31, 2010.

OP100090J