Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(4):1473-1478

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Practical synthesis of Mirabegron

Ravindra Vedantham[a,c*], Bhaskar Kandagatla[b] , Sunitha Vyala[a] , Prasada Raju V. V. N. K. V.[a], Praveen Cherukupalli[a], Javed Iqbal[b], Vilas H. Dahanukar[a], Mukkanti Kagga[c], Rakeshwar Bandichhor[a*] and Srinivas Oruganti[b*]

[a]*API R&D, IPDO-Innovation Plaza, Dr. Reddy's Laboratories Ltd, Bachupally, Qutubullapur, Hyderabad, India*
[b]*Center for Process Research & Innovation, Dr. Reddy's Institute of Life Sciences, Gachibowli, Hyderabad, India*
[c]*Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, India*

ABSTRACT

A short and practical synthesis of Mirabegron, a novel β_3-adrenoceptor (AR) agonist for the symptomatic treatment of overactive bladder (OAB), starting from (R)-styrene epoxide in 4 steps is reported.

Keywords: Mirabegron, Overactive bladder, (R)-Styrene epoxide, Regioselectivity, Reductive amination, Amidation, Oxazolidinone.

INTRODUCTION

Mirabegron (YM-178, Astellas Pharma), is an orally active, first-in-class selective β_3-adrenoceptor agonist for the symptomatic treatment of overactive bladder (OAB), and has been approved for urinary frequency and urinary incontinence associated with OAB.[1] Mirabegron **1** is chemically distinct to other drugs in OAB treatment like solifenacin, tolterodine etc. (Figure 1).

The first synthesis of Mirabegron reported by Yamanouchi Pharmaceutical utilized R-Styrene epoxide as the chiral precursor for the generation of the chiral benzylic alcohol, using an epoxide ring opening with 2-(4-nitrophenyl)ethanamine hydrochloride.[2] Another reported approach utilized (R)-mandelic acid as a chiral starting material, and involves a controlled borane-reduction step.[3]

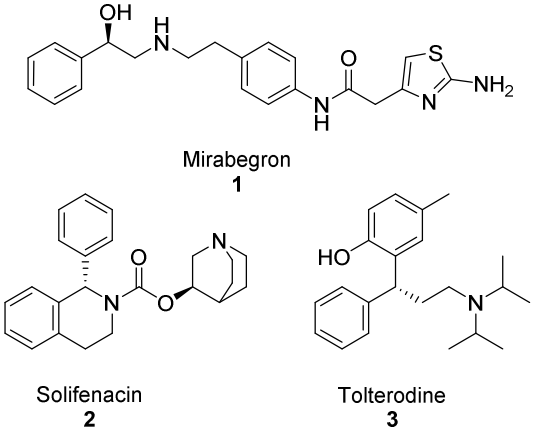


Figure 1. Known APIs for treatment of OAB

As a part of our ongoing program on the identification of scalable and cost-effective processes for active

pharmaceutical ingredients, we were interested in identifying inexpensive and readily available chemicals which would serve as the starting point for the synthesis. The major limitations in the reported syntheses [2] of Mirabegron **1** include tedious chromatographic purifications, possible formation of significant amount of undesired reaction products etc. The need for a scalable and efficient synthetic process for Mirabegron is necessary.

EXPERIMENTAL SECTION

Preparation of tert-butyl 4-nitrophenethylcarbamate (5). To a stirred solution of 2-(4-nitrophenyl)ethanamine **4** (50 g, 0.30 mol) in THF (1 L), slowly added 2N NaOH solution at 0-5 °C followed by the addition of Boc anhydride (87.5 mL, 0.36 mol). The resulting reaction mixture was stirred for 3h at RT. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ice cold water (400 mL). The organic layer was separated and aqueous layer was extracted with Ethyl acetate (2 x 250 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The obtained crude compound was triturated with n-hexane. The separated solid was filtered and dried to furnish desired compound **5** (57 g, 70.8%). **^{1}H NMR** (400 MHz, DMSO-d6): δ 8.15 (d, 2H, J = 8.8 Hz), 7.48 (d, 2H, J = 8.4 Hz), 6.91 (br s, 1H), 3.20 (q, 2H), 2.83 (t, 2H), 1.34 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.76, 146.96, 146.64, 129.65, 123.69, 79.46, 41.28, 36.17, 28.30. **MS**: (m/z) 166.5 [M-Boc]+.

Preparation of tert-butyl 4-aminophenethylcarbamate (6). The mixture of **5** (56 g, 0.21 mol), Pd/C (11.2 g) and methanol (560 mL) was hydrogenated using hydrogenator under Hydrogen gas pressure (60 psi) at RT for 16h. The progress of the reaction was monitored by TLC. After completion of starting material, the reaction mixture was filtered through celite bed and washed with methanol (2 x 100 mL). The filtrate was concentrated under reduced pressure to give compound **6** (42 g, 84.5%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d6): δ 6.81 (d, 2H, J = 8 Hz), 6.79 (br s, 1H), 6.47 (d, 2H, J = 8.4 Hz), 4.82 (br s, 2H), 3.01 (q, 2H), 2.48 (t, 2H), 1.36 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 155.91, 144.78, 129.57, 128.77, 115.32, 79.05, 41.98, 35.20, 28.40. **MS**: (m/z) 137.1 [M-Boc]$^+$.

Preparation of tert-butyl 4-(2-(2-aminothiazol-4-yl)acetamido) phenethylcarbamate (8). The mixture of **6** (20 g, 0.08 mol), 2-(2-amino thiazole-4-yl) acetic acid, **7** (14.7 g, 0.09 mol), EDC (40 g, 0.21 mol), HOBt (5.7 g, 0.04 mol) and DIPEA (21 mL, 0.17 mol) in DMF (400 mL) was stirred at RT for 2h.The progress of reaction was monitored by TLC and after completion of starting material, the reaction mixture was diluted with ice cold water and stirred at 0-5 °C for 1h. The obtained solid was filtered and washed with water. Compound was dried under vacuum to give the desired compound **8** (25 g, 78%) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d6): δ 10.02 (brs, 1H), 7.49 (d, 2H, J = 8 Hz), 7.10 (d, 2H, J = 8.8 Hz), 7.00(brs, 1H), 6.83 (brs, 1H), 6.33 (s, 1H), 3.47 (s, 2H), 3.09 (q, 2H), 2.62 (t, 2H), 1.36 (s, 9H). **^{13}C NMR** (100 MHz, DMSO-d6): δ 168.67, 168.25, 155.93, 146.23, 137.73, 134.53, 129.18, 119.39, 102.98, 77.91, 42.00, 40.15, 35.33, 28.67; MS (m/z) 276.7 [M-Boc]+.

Preparation of N-(4-(2-aminoethyl)phenyl)-2-(2-aminothiazol-4-yl)acetamide (9). To a stirred solution of **8** (1 g, 0.003 mol) in DCM (10 mL) added Trifluoro acetic acid (5 mL) at 0-5 °C and stirred for 3h. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The obtained solid material was neutralized with aq. ammonia. Then the product was extracted with DCM (2 x 30 mL) and combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give compound **9** (600 mg, 81%) as a pale yellow solid. **^{1}H NMR** (400 MHz, DMSO-d6): δ 10.20 (brs, 1H), 7.54 (d, 2H, J = 7.2 Hz), 7.40 (brs, 2H), 7.22 (d, 2H, J = 7.6 Hz), 6.38 (s, 1H), 3.50 (s, 2H), 3.03 (q, 2H), 2.85 (t, 2H); **^{13}C NMR** (100 MHz, DMSO-d6): δ 168.64, 168.24, 155.92, 146.26, 137.76, 134.52, 129.20, 119.38, 102.98, 77.89, 42.00, 35.33, 28.68. **MS**: (m/z) 277.9 [M+H]$^+$.

Preparation of Mirabegron (1). <u>Method a</u>. The mixture of **9** (500 mg, 0.0001 mol), R-styrene oxide **10** (0.26 mL, 0.002 mol) in isopropanol (5 mL) was stirred at 80-85 °C for 16h. The progress of reaction was monitored by TLC. After completion of starting material, isopropanol was concentrated under reduced pressure. The obtained crude material was purified by column chromatography (on 60-120 mesh silica gel) using 3% MeOH-DCM as eluents to get the desired product as a white solid (216 mg, 27%). **<u>Method b</u>.** Compound **14** (4 g, 9.5 mmol) and ethanol (120 mL) were charged into a round bottom flask at 27 °C and added 1N potassium hydroxide solution (60 mL). The mass was then heated to 78 °C and stirred for 4h at the same temperature. Later, solvent from the reaction mass was evaporated and water was charged to it. Then, the product was extracted with ethyl acetate and ethyl acetate layer was concentrated under vacuum at 50 °C. The resultant crude solid was purified by column chromatography (eluent: DCM/MeOH) to afford title compound, **1** (1.9 g, 50%). **^{1}H NMR** (400 MHz, DMSO-d6): δ 10.05 (br s, 1H), 8.61 (brs, 1H), 7.56 (d, 2H, J = 8.8 Hz), 7.41 - 7.38 (m, 4H), 7.34 - 7.30 (m, 1H), 7.17 (d, 2H, J = 8.4 Hz), 6.88 (brs, 2H), 6.29 (s, 1H), 6.15 (brs, 1H), 4.87 (m, 1H), 3.45 (s, 2H), 3.32 - 3.13 (m, 3H), 3.02 (dd, 1H, 10 Hz, 4.8 Hz), 2.93 – 2.88 (m, 2H). **^{13}C NMR** (100 MHz, DMSO-d6): : δ 31.21,40.53, 48.44, 53.87, 68.60, 104.10, 119.69, 126.33,

128.20, 128.80, 129.30, 132.48, 138.25, 142.26, 167.50, 169.30; **Mass**: *(m/z)* = 396.9 $[M+H]^+$; **HPLC Purity**: 97.9%.

Preparation of (R)-3-(4-nitrophenethyl)-5-phenyloxazolidin-2-one (12). Compound **11** (14 g, 0.05 mol) along with dichloromethane (140 mL) and 1,1'-carbonyldiimidazole (11.9 g, 0.07 mol) were charged into a round bottom flask and stirred at 27 °C for 3 hours. After completion of the reaction, water (100 mL) was added to the reaction mass and stirred for 15 minutes. Then, layers were separated and the organic layer was evaporated under vacuum at 45 °C to give title compound **12** as an orange-red colored solid (13 g, 85.5%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.01 (m, 2H), 3.31 (dd, 1H, J = 10 Hz, 7.2 Hz), 3.60 (m, 2H), 3.82 (t, 1H , J = 8.8 Hz), 5.44 (dd, 1H, J = 9.6 Hz, 6.8 Hz), 7.23 (m, 2H), 7.37 (m, 5H), 8.12 (d, 2H, J = 8.4 Hz); **^{13}C NMR** (100 Hz, $CDCl_3$) : δ 33.69, 44.71, 52.61, 74.24, 123.83, 125.29, 128.87, 129.58, 138.52, 145.85, 146.82, 157.70 ; **MS**: (m/z) = 312.9 [M+H]+ ; **HPLC** Purity: 98.8%.

Preparation of (R)-3-(4-aminophenethyl)-5-phenyloxazolidin-2-one (13). Compound **12** (13 g, 0.04 mol) was taken along with ethanol (130 mL) at 27 °C and to that stannous chloride dihydrate (42.2 g, 0.19 mol) was added. The reaction mass was then heated to 70 °C and stirred for 2 hours at the same temperature. After completion of the reaction, solvent was evaporated under vacuum at 55 °C and to the obtained residue added saturated sodium bicarbonate solution (200 mL) till the mass pH reached to basic. The resultant turbid solution was passed through celite bed and the product was extracted with ethyl acetate (4 x 200 mL) and with 10% methanol in dichloromethane (2 x 200 mL). Then, all organic layers were combined and solvent was evaporated under vacuum at 50 °C to yield crude product which on purification using mixture of dichloromethane and n-hexane gave pure compound **13** (10 g, 85%). **^{1}H NMR** (400 MHz, DMSO-d6): δ 2.64 (m, 2H), 3.40 (m, 3H), 3.88 (t, 1H, J = 8.8 Hz), 4.88 (brs, 2H), 5.47 (t, 1H, J = 8.4 Hz), 6.48 (d, 2H, J = 8 Hz), 6.87 (d, 2H, J = 8 Hz), 7.80 (d, 2H), 7.40 (m, 3H); **^{13}C NMR** (100 Hz, CDCl3) : δ 33.13, 45.63, 52.64, 74.34, 115.39, 125.60, 127.96, 128.71, 128.79, 129.49, 138.77, 144.98, 157.77; **MS**: (m/z) = 284 [M+H]+ ; HPLC Purity: 97.13%.

Preparation of (R)-2-(2-aminothiazol-4-yl)-N-(4-(2-(2-oxo-5-phenyloxa zolidin-3-yl)eth yl)phenyl)acetamide (14). Compound **13** (5 g, 0.018 mol), 2-aminothiazol-4-yl-acetic acid, **7** (3.1 g, 0.019 mol) and DMF were charged into a round bottom flask at 27 °C. O-(7-Azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluoro phosphate (6.8 g, 0.018 mol) and diisopropyl ethylamine (3.4 g, 0.026) were charged into the reaction mass and stirred for 3 hours at 27 °C. Then, reaction mass was poured into ice-cold water and the product was extracted with ethyl acetate (4x100 mL). The combined organic layers were dried and concentrated under vacuum at 50 °C. The crude product obtained was purified by column chromatography (eluent: DCM/MeOH) to get the title compound **14** (4.5g, 60%) as solid. **^{1}H NMR** (400 MHz, DMSO-d6): δ 2.77 (t, 2H, *J* = 7.2 Hz), 3.35 (m, 1H), 3.40 (m, 4H), 3.91 (t, 1H, *J* = 9.2 Hz), 5.48 (t, 1H, *J* = 8.4 Hz), 6.30 (s, 1H), 6.89 (brs, 2H), 7.15 (d, 2H, *J* = 8.8 Hz), 7.28 (m, 2H), 7.37 (m, 3H), 7.51 (d, 2H, *J* = 8.8); **13C NMR** (100 Hz, $CDCl_3$): δ 33.25, 40.10, 45.28, 52.48, 74.41, 105.60 120.14, 121.02, 125.47, 125.57, 128.80, 128.83, 128.91, 129.08, 130.31, 133.74, 136.67, 138.59, 144.92, 157.85, 167.56, 168.54; **Mass**: *(m/z)* = 423 $[M+H]^+$; **HPLC Purity**: 95.04%.

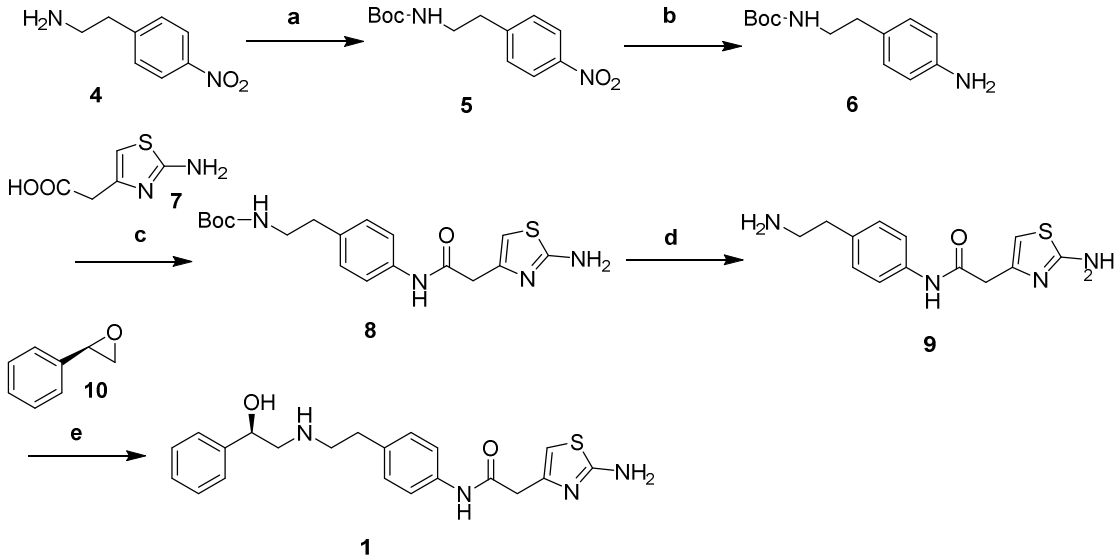
Preparation of (R)-2-[[2-(4-nitrophenyl)-ethyl]amino]-1-phenylethanol (11). <u>Method a</u>. 4-Nitrophenyl ethylamine hydrochloride, **4** (30.3 g, 0.15 mol) was taken along with dichloromethane (100 mL) and treated with 8N aqueous sodium hydroxide solution (30 mL) at 25 °C. The obtained layers were separated and organic layer was dried and solvent was evaporated. To the resulting residue, 2-propanol (150 mL) and (R)-styrene oxide, **10** (15 g, 0.12 mol) were added under stirring successively and the mixture was maintained at reflux for 24 hours. After completion of the reaction, solvent was evaporated under vacuum and the obtained residue was purified by column chromatography on silica gel (eluent: DCM followed by n-hexane/EtOAc). The resultant product was further recrystallized in ether at -10 °C and dried to give 9 g (21%) of compound **11**. **<u>Method b</u>.** Compound **16** (3.0 g, 0.021 mol), tetrahydrofuran (60 mL) and triethylamine (3.4 g, 0.03) were stirred at 26 °C for 15 minutes. Later, 4-nitrophenyl ethyl bromide, **17** (5.0 g, 0.022 mol) was added and heated to 52 °C. After 16 hours stirring at 52 °C, water (35 mL) followed by ethyl acetate (30 mL) were charged to the reaction mass under stirring. Organic layer was separated and aqueous layer was washed with ethyl acetate (2 x 20 mL). The ethyl acetate layers were dried and concentrated under reduced pressure at 45 °C. The resulted crude product was purified by column chromatography (eluent: DCM/MeOH) to give compound **11** (1.9 g, 29%). **<u>Method c</u>.** To the mixture of compound **21** (16.5 g, 0.10 mol) and dichloromethane (82.5 mL) at 30 °C compound **16** (20.8 g, 0.15 mol) was added and stirred for 10 minutes. Then, sodiumcyanoborohydride (12.5 g, 0.20 mol) was added to the reaction mass at 30 °C and stirred for 30 minutes. Later, methanol (33 mL) was added in 15 minutes at 30 °C and stirred for 3 hours. Then, water (165 mL) and dichloromethane (82.5 mL) were added to the reaction mass and stirred for 5 minutes at 30 °C. The organic and aqueous layers were separated and the aqueous layer was extracted with DCM (41.5 mL). The combined organic layer was washed with brine solution, dried and concentrated under vacuum at 30 °C. The crude product was dissolved in ethyl acetate (165 mL) and water (165 mL). The pH of the solution was adjusted to 2 by adding

dilute hydrochloric acid. The layers obtained were separated and the pH of the aqueous layer was adjusted to 12 by adding aqueous sodium hydroxide. Product was extracted with dichloromethane (82.5 mL) and the organic layer was evaporated to obtain the product **11**. **^{1}H NMR** ($CDCl_3$): δ 2.75 (dd, 1H, J = 12 Hz, 8.8 Hz), 2.91 (m, 3H), 2.99 (m, 2H), 4.70 (dd, 1H, J = 9.2 Hz, 4 Hz), 7.27 (m, 1H), 7.34 (m, 6H), 8.15 (d, 2H, J = 8.8 Hz); **^{13}C NMR** (100 MHz, DMSO-d6): δ 31.20, 35.78, 48.41, 53.88, 68.59, 105.24, 119.75, 126.32, 128.18, 128.80, 129.33, 132.68, 134.43, 138.07, 142.26, 166.49, 170.02 ; **MS** (FAB) m/z: 287 (MH^+).

RESULTS AND DISCUSSION

In our studies, we focused on alternate approaches and improvements on reported procedures for the synthesis of **1** to avoid cross reactions due to the participation of other functional groups on which the reaction sequence is not planned. We were interested in exploring two strategies which involve the installation of the chiral hydroxyl group in **1** using (R)-Styrene epoxide either at the beginning or at a late stage.

In the first approach, the introduction of the chiral hydroxyl group was planned at the later stage (Scheme 1). Accordingly, 2-(4-nitrophenyl)ethyl amine **4** was protected as the Boc-derivative **5**, followed by the reduction of the nitro group using stannous chloride to furnish corresponding aniline **6**. Alternate reducing conditions such as hydrogenation in the presence of 10% Pd-C were also provided the desired **6** in good yield. Amide coupling of the aniline **6** with 2-(2-aminothiazol-4-yl) acetic acid **7** in the presence of EDC, HOBt/DIPEA furnished the desired amide **8**. Interestingly, lower reactivity of 2-aminothiazole precluded any self-coupling of **7**.

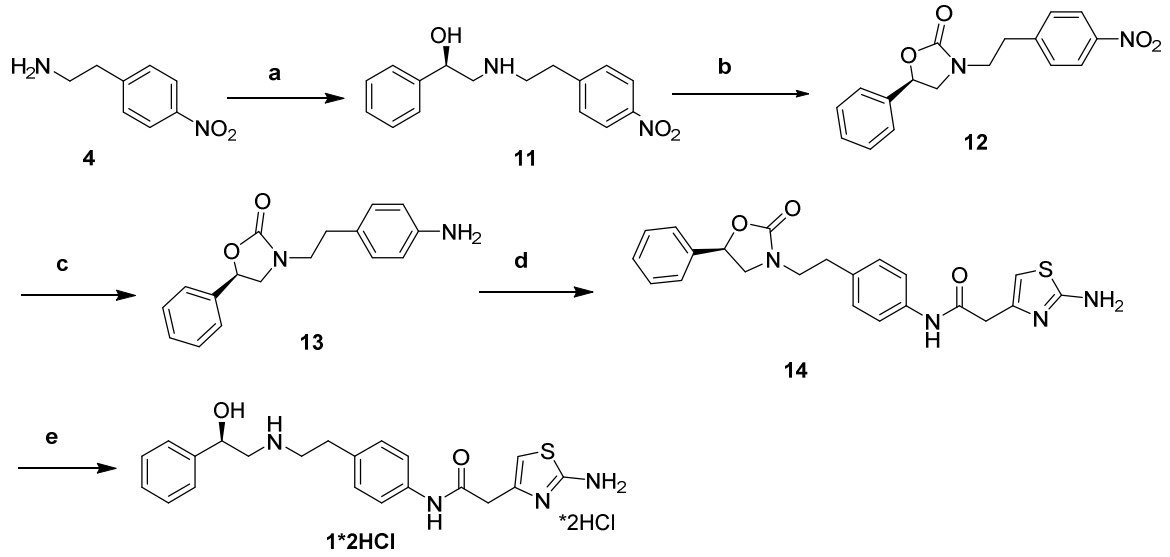


Scheme 1. Reagents and conditions: (a) $(Boc)_2O$, 2*N* NaOH, rt, 3h, 71%; (b) 10% Pd-C (50% wet), H_2(1 atm.), MeOH, rt, 16h, 85%; (c) EDC, HOBt, DIPEA, DMF, rt, 2h, 76%; (d) TFA, 0 °C, 3h, 81% (e) IPA, 85 °C, 16h, 27%

Removal of Boc-group in **8**, set the stage for the critical step of introducing the chiral hydroxyl by means of stereo-controlled ring opening of the chiral (R)-styrene epoxide **10**. Epoxide opening reaction of **10** was initially attempted with amine **9** in the presence of Et_3N in MeOH as the solvent. Alternatively, epoxy opening was also performed under simple isopropanol reflux condition to get the desired **1**. The desired product **1** was isolated in 27% yield after purification by column chromatography. This is due to the formation of N-alkylated derivatives of **1** by undesired reaction of **10** with amino functionalities of **1**. However, the inefficiency of the epoxide opening reaction precluded a high purity of final product, Mirabegron **1**. Since it is not practical to embark on repeated purifications at the last stage (which leads to poor yields), this route was not pursued for further optimization.

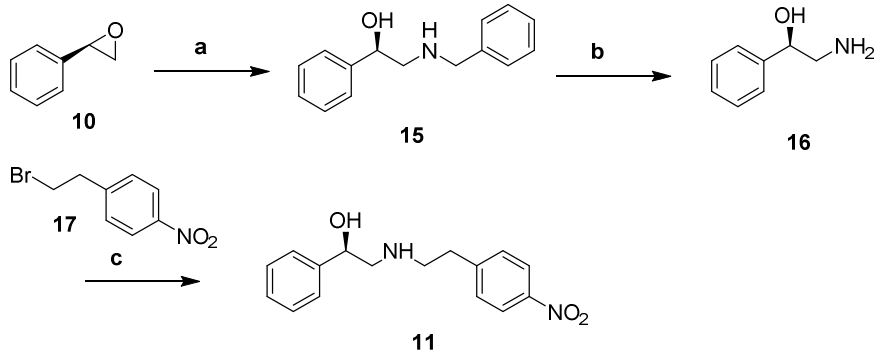
We therefore decided to examine the alternate possibility of introducing the chiral hydroxyl group early, and studied the reaction of 2-(4-nitrophenyl)ethylamine **4** with (R)-Styrene epoxide **10**. Similar to the earlier observations with compound **9**, epoxide-opening reaction of **10** with amine **4** proceeded with higher yields, and with the desired regioselectivity. Various conditions were screened for the epoxide opening, and IPA/reflux was observed to be the best amongst them. The innovator route to Mirabegron involved Boc-protection of the secondary amine in **11**, and subsequent elaboration to **1**. However, there are concerns regarding possible deoxygenation of the unprotected benzylic group during nitro reduction under catalytic hydrogenation conditions or unwanted side-reactions when reductive conditions such as $SnCl_2$ or Fe/AcOH. This prompted us to explore a strategy where-in both the amine and chiral benzylic hydroxyl could be protected in one-pot. Oxazolidine group was the clear possibility and we

performed the simultaneous masking of both secondary amine and the benzylic hydroxyl in **11** using CDI to obtain **12**. Subsequently, Reduction of the nitro group in **12** could be conveniently carried out using $SnCl_2$ to obtain **13** in 85% yield. Later, amidation with **7** in the presence of HATU/DIPEA in DMF furnished **14** in 60% yield. We observed similar yields when the amidation was performed in the presence of a relatively cheaper carbodiimide such as EDC. Base-hydrolysis of the oxazolidinone in **14** furnished **1** as the free base with >99% ee, and was further converted to its dihydrochloride salt using EtOH-HCl.

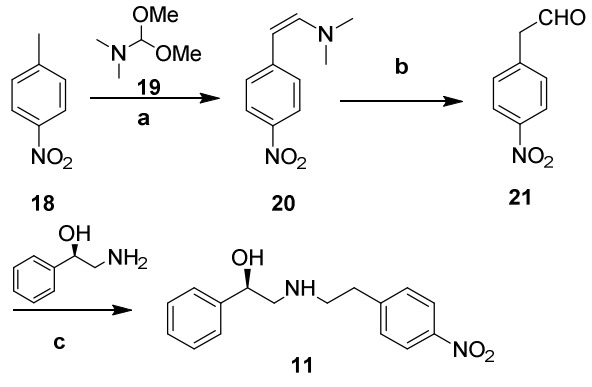


Scheme 2. Reagents and conditions: (a) 10, Isopropanol, reflux, 24 h, 24%; (b) CDI, CH_2Cl_2, rt, 3h, 86%; (c) $SnCl_2.2H_2O$, 75 °C, 2 h, 85%; (d) 7, HATU, DIPEA DMF, rt, 2h, 60%; (e) aq. 1N KOH, EtOH, 5h, 38%; EtOH-HCl, 0 °C, 1h, 85%

In order to develop an improved process for the key intermediate **11** and address the efficiency of the epoxide ring opening, **10** was reacted with a readily accessible benzylamine in isopropanol at reflux temperatures to afford chiral N-benzyl-hydroxyethylamine derivative **15** (Scheme 3). The isolated yields were much better and this reaction could be offered a quick access to the key chiral beta-amino alcohol **16,** after N-debenzylation using catalytic hydrogenation with 10% Pd-C. Two strategies were envisaged for the attachment of a 4-nitrophenylethyl segment to the amine in **16**. In the first approach, controlled alkylation with 4-nitrophenylethyl bromide gave **11** in 24% yield.



Scheme 3. Reagents and conditions: (a) $PhCH_2NH_2$, 2-propanol, reflux, 37%; (b) H_2, 10% Pd-C, MeOH, 94%; (c) 17, NEt_3, THF, 20%



Scheme 4. Reagents and conditions: (a) 19, DMF, 120°C, MeOH 60%; (b) 30% H_2SO_4, $CHCl_3$, 25 °C, 50%; (c) $NaCNBH_3$, MeOH, 25 °C, 40%

In the second approach, reductive amination of amine **16** with 4-nitrophenyl acetaldehyde **21** in the presence of sodium cyanoborohydride as the reducing agent furnished desired nitro intermediate **11** of mirabegron. Aldehdye **21** was conveniently prepared from 4-nitrotoluene **18** *via* enamine **20**, followed by hydrolysis using reported procedure.[4]

CONCLUSION

In conclusion, we have delineated an improved synthesis of Mirabegron which is based on stereo controlled and economical process and is better suited for industrial application.

Acknowledgements
We thank the management of Dr. Reddy's Institute of Life Sciences and Dr. Reddy's Laboratories Ltd. for supporting this work.

REFERENCES

§ Dr. Reddy's communication number: IPDO IPM-00384
[1] (a) P Tyagi; V Tyagi, *I Drugs*, **2010**, 13(10), 713-722. (b) P Tyagi; V Tyagi; M Chancellor, *Expert Opin Drug Saf.*, **2011**, 10(2), 287-294. (c) WF Stewart; JB Van Rooyen; GW Cundiff; P Abrams; AR Herzog; R Corey; TL Hunt; AJ Wein, *World Journal of Urology*, **2003**, 20(6), 327–336. (d) I Milsom; P Abrams; L Cardozo; RG Roberts; J Thuroff; AJ Wein, *BJU Int.*, **2001**, 87(9), 760–766. (e) V Khullar, *European Urology Supplements*, **2011**, 10.2, 278-279. (f) P Tyagi; V Tyagi, *I Drugs*, **2010**, 13(10), 713-722. (g) National Association for Continence. Accessed May 29, 2012. http://www.nafc.org/media/media-kit/facts-statistics.
[2] (a) M Hayakawa; T Kimizuka; T Maruyama; T Matsui; H Moritomo; K Onda; T Suzuki, WIPO Patent 1999020607A1, **1999**. (b) T Maruyama; T Suzuki; K Onda; M Hayakawa; H Moritomo; T Kimizuka; T Matsui, U.S. Patent 6,346,532, **2012**.
[3] S Kawazoe; K Sakamoto; Y Awamura; T Maruyama; T Suzuki; K Onda; T Takasu, WIPO Patent 2003037881 A1, **2003**.
[4] L Dai; J Yu; Y Chen; S Yu, *Synth. Commun.*, **2011**, 41, 3078–3084.