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# Sustainable, Short and One-Pot synthesis of a Mirabegron Advanced Intermediate free from Genotoxic compounds and Toxic Reagents

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**Research Article**

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# Sustainable, Short and One-Pot synthesis of a Mirabegron Advanced Intermediate free from Genotoxic compounds and Toxic Reagents

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## Abstract

A sustainable one-pot process for the synthesis of an advanced intermediate of Mirabegron is described. The developed methodology eliminates the isolation of genotoxic intermediates, minimizes solvent usage and avoids the use of hazardous reagents. The process integrates esterification, reductive amination, and nitro reduction into a single reaction pot, thereby simplifying manufacturing operations and improving the process safety. The optimized process affords the advanced intermediate in good overall yield and excellent HPLC purity. Compared with previously reported approaches, the developed route significantly reduced processing steps, solvent consumption, batch cycle time and operational hazards. The strategy represents a greener, safer, cost-effective and industrially viable approach for the large-scale manufacture of Mirabegron intermediate.

## Keywords

One-pot synthesis, Mirabegron, Green chemistry, Process intensification.

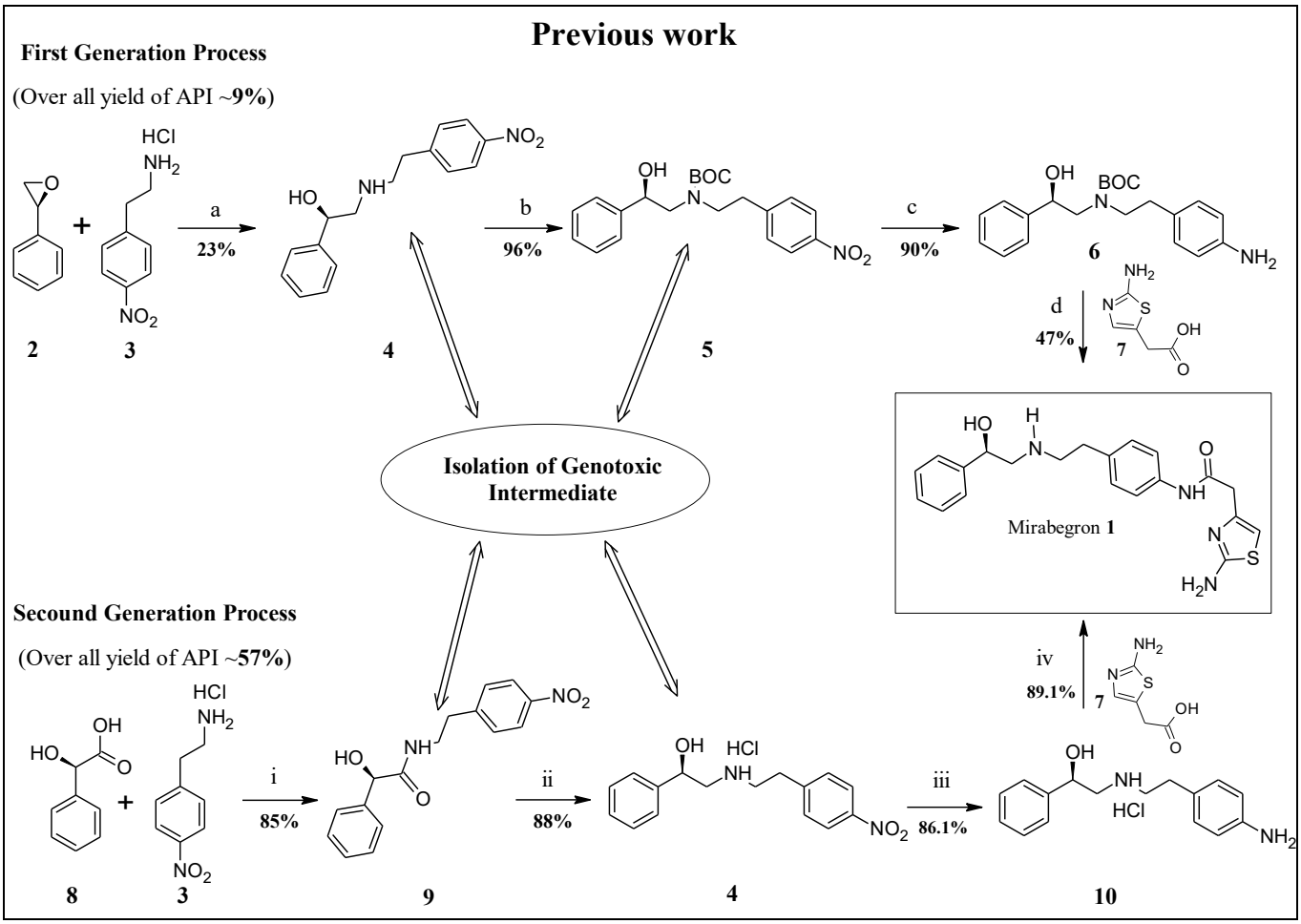
## Introduction:

Genotoxic impurities (GTIs) and their controls are very sensitive topic in the pharmaceutical industries, genotoxic compound are having the potential to damage DNA even at ppm levels. Furthermore, this can lead genetic mutations and induce a cancer. Duirng the synthesis of an active drug substance (API), genotoxic intermediates may arise and therefore required careful control and handling [1-3].

Overactive bladder (OAB) is a chronic urological disorder characterized by urinary urgency, frequency, and urge incontinence, significantly impairing patient quality of life [4]. The ever-increasing global prevalence of lifestyle-associated conditions such as diabetes and obesity has contributed to an increased patient of OAB, with affected individuals often experiencing the need to urinate more than 10-15 times daily [5]. The $\beta_3$-adrenergic receptor agonists, such as mirabegron and vibegron **1**, among these, mirabegron has emerged as an important first-line treatment option owing to its unique mechanism of action and favourable safety profile. Unlike antimuscarinic agents, mirabegron enhances bladder storage capacity without adversely affecting detrusor muscle contractility, making it suitable for long-term therapy [6-9]. Mirabegron was first approved by the United States Food and Drug Administration (USFDA) in 2012 as an extended-release formulation (MYRBETRIQ™, 25 mg and 50 mg) for the treatment of OAB symptoms [10-12].

The prior art synthetic routes to mirabegron were reported by Yamanouchi Pharmaceutical (Scheme 1.), utilized (R)-styrene oxide (**2**) as a chiral precursor condensed with 4-nitro phenyl ethyl amine hydrochloride (**3**) in highly basic condition at reflux temperature for 12 hrs to get (1*R*)-2-{[2-(4-nitrophenyl) ethyl] amino}-1-phenyl ethanol (**4**), further amino functionality of **4** was protected with tert-butoxycarbonyl (Boc), to obtain compound **5**, further nitro functionality was reduced in presence of palladium on carbon (Pd/C) furnished compound **6**, finally the acid compound **7** was coupled with compound **6** in presence of EDC.HCl to offer Mirabegron **1.**

The second-generation synthesis of Mirabegron (**1**) (Scheme 1.) involves first the formation of borate ester of D-mandelic acid (**8**) in-situ, condensed with **3** to obtain (2R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide (**9)**. This is followed by the reduction of the amide group using sodium borohydride and iodine in the presence of tetrahydrofuran (THF) yielding **4**, further, the nitro group was reduced using Raney nickel to produce (1*R*)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol **(10)** and finally acid **7** was coupled with **10** in presence of EDC.HCl to afford Mirabegron (**1**).




**Scheme 1.** The first and second generation route of synthesis for Mirabegron **1**.

**First generation approach**: a) Aq.NaOH, IPA. b) $(BOC)_2$, THF. c) Pd/C, $H_2$ gas, EtOH. d) EDC.HCl, Compound 7, con.HCl, Aq. $NH_3$

**Secound generation approach:** (i) B(OMe)3, diisopropylethylamine (DIPEA), ACN. (ii) THF, $NaBH_4$, Iodine, MDC, IPA.HCl . (iii) MeOH, Raney Ni, $H_2$, toluene, IPA. iv) Con.HCl, Compound **7**, EDC.HCl, aqous $NH_3$, *n*-butanol, IPA.

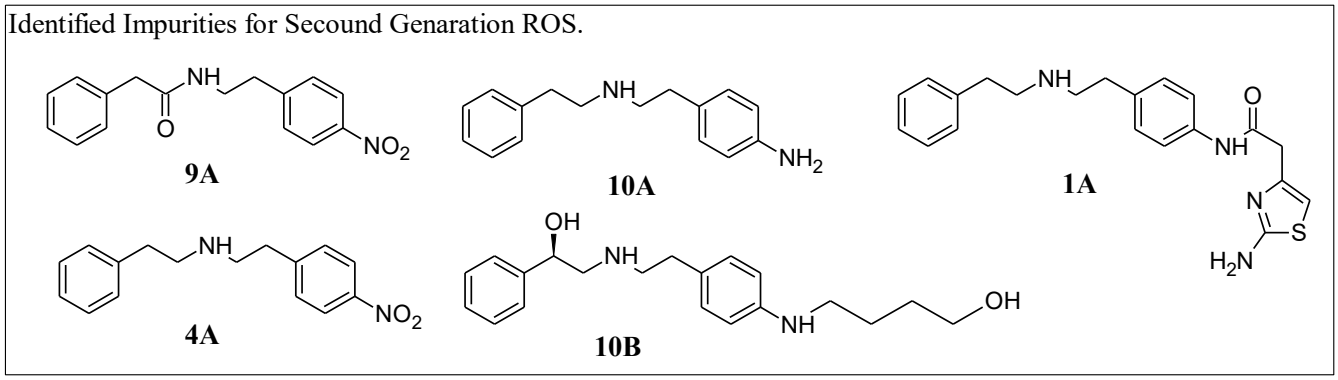
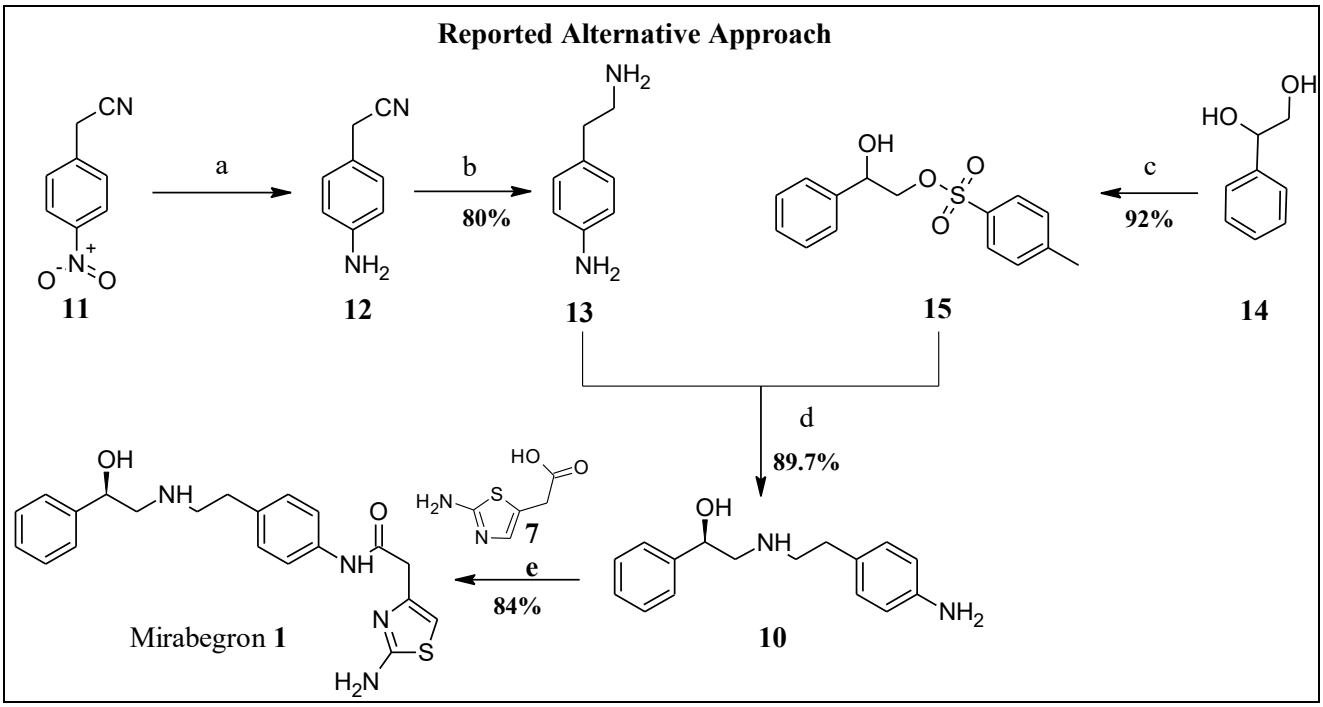



**Figure 1.** Reported impurities in second generation route of synthesis for Mirabegron 1.

The intermediate **4**, **5**, and **9** were evaluated using Quantitative Structure Activity Relationship (QSAR) methodologies DEREK Nexus (rule base QSAR) and SARAH Nexus (statistical QSAR) and founds potential mutagenic/genotoxic as per ICH M7 guideline [13].

The synthetic strategies outlined in Scheme 1. exhibits several notable limitations. First, both process involves challenges of three isolation operations for intermediates. Notably, two of these are potential genotoxic intermediate, which raises significant safety risk to human health, during the operations such as centrifugation (loading/ unloading of wet material), drying (loading/ unloading), milling and packaging, operator directly in contact with genotoxic compounds, though the operator used proper personal protective equipment's (PPEs). Second, these all-isolation operations, directly impact in increase the batch cycle time, processing cost of product and scalability. Third, first generation process has overall yield was approximately 9%, which made the process inefficient and non-scalable. In second generation, process, the overall yield of the route was approximately 57%, although this route affords a moderate yield, but it utilizes seven solvents, including four Class 2 solvents (acetonitrile, dichloromethane, toluene and THF). These are relatively expensive, toxic and pose environmental concerns. In addition, THF is potential risk of peroxide formation (Class B) creating potential safety risk during storage and handling. The second generation process involves the reduction of amide by $NaBH_4$/ Iodine in THF, iodine is highly corrosive, toxic and expensive, however, during amide reduction, over reduction of nitro group was done, presence of THF leads to formation of THF opening impurity **10B**, also hydroxy group was knocked out due to iodine, that could generate the deshydroxy impurity **9A**, further this impurity could mimic the same reaction sequence to form deshydroxy impurities of corresponding intermediate up to API (Fig. 1) that tend to add load of extra purification to eliminate these impurities, this activity not only decreases the yield but also increases the processing cost [14]. the process utilized Hunig's base diisopropylethylamine (DIPEA), it could be precursor of corresponding potentially carcinogenic N-nitrosamines, which make the process unsafe, expensive and limits its suitability for large industrial manufacturing. Furthermore, the second-generation process involves reduction of nitro group by pyrophoric Raney nickel under hydrogen pressure, and dependence on the pressure reactors and include handling of highly explosive hydrogen pressure, making the process unsafe and dependent on the pressure reactors causes the higher process cost and less throughput of production. Collectively, these limitations reveal the shortcomings of the reported methodology and highlight the need for the development of robust, safer, greener, inexpensive and simple viable synthetic route for Mirabegron [15,17].

An alternative strategy reported by Xu et al. the synthesis route started from (4-nitrophenyl) acetonitrile **(11)**, two-step reduction performed in an autoclave, with catalyst Pd/C to provide (4-aminophenyl)acetonitrile **(12)** followed by reduction of nitrile functionality in presence of Raney nickel and hydrazine hydrate to offer 4-(2-aminoethyl)aniline **(13)** as intermediate. The side chain 2-hydroxy-2-phenylethyl 4-methylbenzenesulfonate **(15)** was produced from 1-phenylethane-1,2-diol **(14)** with chemo selective conversion of alcohol functionality into good leaving group by using $(C_4H_9)SnO$ and *p*-toluene sulfonyl chloride, further compounds **13** and **15** were subsequently condensed to offer aniline compound **10**, the resulting amine compound **10** was subsequently coupled with acid **7** to offer Mirabegron **1** (Scheme 3.).



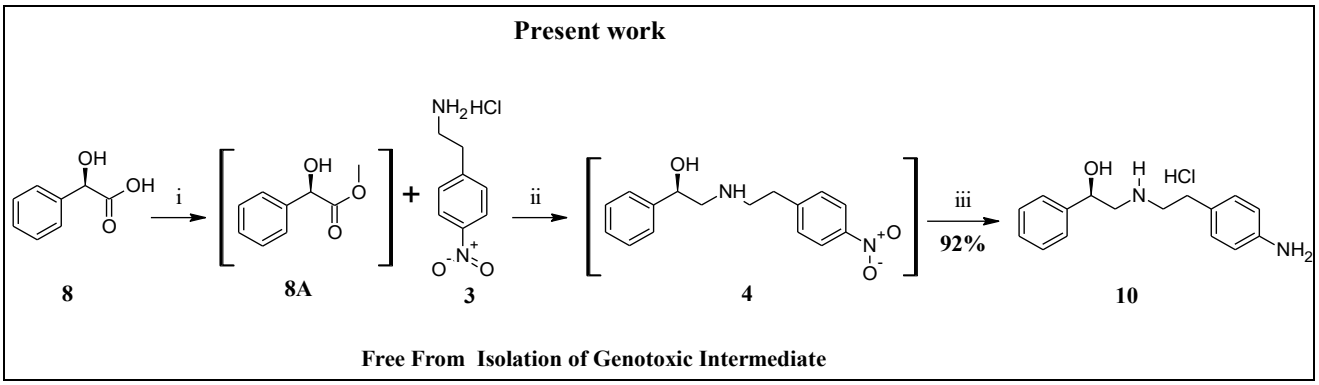

**Scheme 3**. An alternative synthesis for Mirabegron **1** is reported by Xu et al.

a) Pd/C, $H_2$ gas, $N_2H_4.H_2O$, ethanol. b) Raney Ni, $H_2$ gas, $N_2H_4.H_2O$, ethanol. c) p-Toluene sulphonyl chloride, DCM, TEA, $(C_4H_9)_2SnO$. d) Acetonitrile, *n*-hexane. e) HATU, Diisopropylethylamine, DMF, Compound 7, dichloromethane (DCM), methanol: water.

Though the overall yield is moderate (~60%) but this process also having limitation, first limitation is utilization of commercially unavailable and expensive starting material **14,** pyrophoric and expensive catalyst palladium and Raney nickel increase overall raw material cost of product, secondly the requirement of special equipment i.e., autoclave which leads to dependability on it also increase the process cost of product and decreases the throughput of production. Third, this process involves

explosive, toxic, carcinogenic hydrazine hydrate, also process utilized highly corrosive *p*-toluene sulfonyl chloride, expensive reagent $(C_4H_9)SnO$ and triethyl amine probable precursor for *N*-nitrosamine of diethyl amine (NDEA). All above concerns made the process unsafe and expensive, considering all limitation of reported alternative approach [18].

The present work describes the development and optimization of multistage telescoping one-pot process (three steps in one-pot) for advanced intermediate **10** followed by API. This approach offers significantly improved overall yield, while eliminating the isolation of GTIs intermediates. The number of solvents were reduced with complete avoidance of peroxide forming solvent THF. Unlike formation of reported impurities like deshydroxy impurity effectively suppressed by avoiding the use of iodine and THF. The one-pot process also eliminated the autoclave operation and hydrogen pressure handling, thereby enhanced operational simplicity and process safety with acceptable quality of compound **10**/API. Furthermore, Acid compound **7** is coupled with compound **10** in presence of EDC.HCl to get Mirabegron **1**. Now mirabegron is synthesis only in two steps from **8** (scheme 3.) with excellent HPLC purity and good overall yield. These improvements collectively provide a sustainable, short, one-pot process which is safer, greener, efficient and commercially scalable suitable for large-scale manufacturing.




**Scheme 4**. Present work for synthesis of Mirabegron **1**.

Present work: (i) Methanol, $H_2SO_4$, 50-55 $^oC$, 4h. And $NaCO_3$ (ii) Compound **3,** $NaBH_4$/MeOH, -5-0 $^oC$, 2h (iii) $Na_2S$/IPA/IPA. HCl, Ethyl acetate, 60-65 $^oC$, 6h.

## Results and Discussion:

In our work, we aimed at a unique one-pot process, which effectively overcomes the disadvantage of reported multistep process. Our studies mainly focused on following three aspects: (a) to convert

compound **8** to methyl (R)-2-hydrxoy-2-phenylacetate **8A**. (b) ester **8A** to nitroaryl amine **4** and (c) nitroaryl amine to aniline **10** as shown in scheme 4. The cost-contributing key starting material **3** was identified for yield and mole ratio calculation.

**a) The conversion of D-mandelic acid (8) to methyl (R)-2-hydrxoy-2-phenylacetate (8A):**

The synthesis of methyl (R)-2-hydrxoy-2-phenylacetate (8A) involves the esterification of D-mandelic acid (**8**). To optimize the esterification conditions, we evaluated the different reaction parameters such as moles ratio of sulphuric acid, time, temperature and volume of methanol as shown in in table 1. Based on our optimization studies, we found that entry no. 4, molar ratio of sulphuric 0.015 at temperatures 50-55 °C with five volumes of methanol, provide 99.0% conversion in 4 hours. Lower and higher mole ratio, volumes and temperature did not give additional benefits.

**Table 1: Optimization of methanol volume, mole equivalence of Sulfuric acid and temperature for the synthesis of methyl (R)-2-hydrxoy-2-phenylacetate 8A.**

| Entry No. | Sulfuric acid (mole ratio) w.r.t 8 | Time in hours. | Temp (°C) | Solvent MeOH (vol.) | HPLC Purity of 8A (%) |
|---|---|---|---|---|---|
| 1 | 0.5 | 2 | 25-30 | 10 | 98.90 |
| 2 | 0.1 | 1.5 | 50-55 | 5 | 98.92 |
| 3 | 0.05 | 2.5 | 50-55 | 5 | 98.80 |
| 4 | 0.015 | 4 | 50-55 | 5 | 99.00 |
| 5 | 0.015 | 9 | 25-30 | 5 | 99.00 |

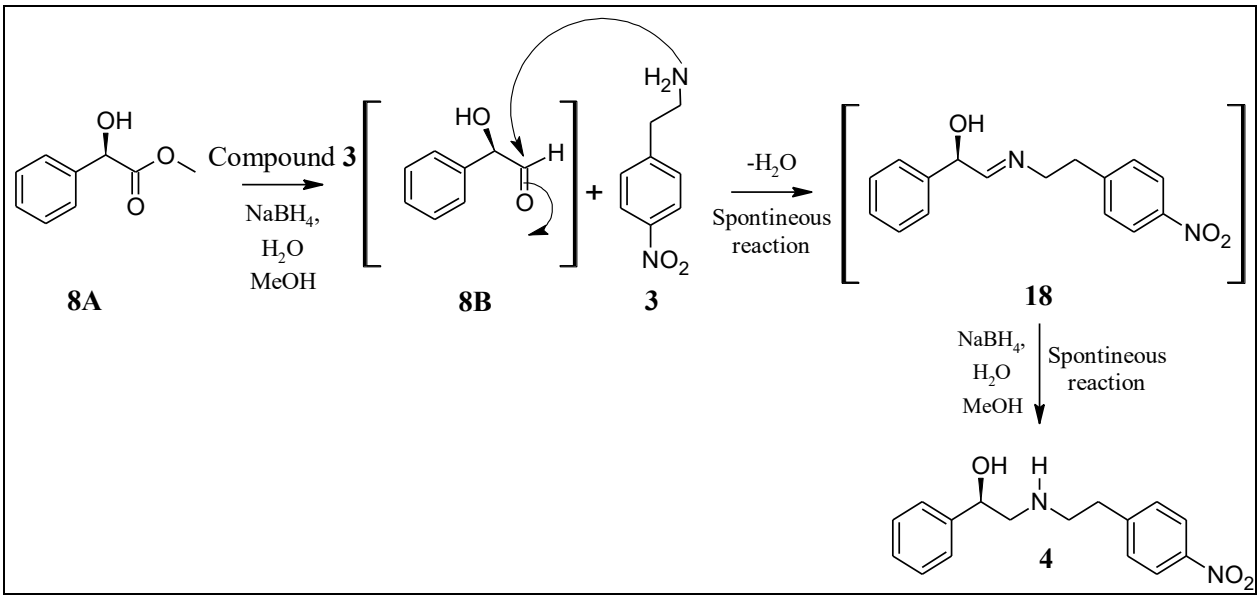
**Note: mole ratio is calculated considering Key starting material i.e., compound 8.*

**b) Methyl ester 8A to (1R)-2-{[2-(4-nitrophenyl)ethyl]amino}-1-phenylethanol (4):**

The synthesis of in-situ intermediate **4** was accomplished via a one-pot reductive amination, eliminating formation of genotoxic amide intermediate **9**. This transformation represented the most critical and challenging step, as esters are generally not amenable to direct reductive amination due to their inability to readily form imine intermediates; such processes typically require aldehyde precursors [19,21].

Initially one-pot process was designed at -15 to -10 °C, the thought behind was ester might be reduced to corresponding aldehyde, once the aldehyde generated it would be available to react with

amine compound **3** to offer its imine. The experiments were conducted wherein starting material amine **3** was added to a solution of ester 8A at -15 to -10 °C, followed by slow addition of sodium borohydride. Reaction progress was monitored by HPLC. Surprisingly, analysis revealed that there is direct formation of nitroaryl amine compound **4** as the major product, with only trace levels of amide compound **9** (less than 0.10%) and 9-15% formation of diol **14** by HPLC, the diol **14** is process related impurity classified as non-genotoxic as predicted by DEREK Nexus and SARAH Nexus evaluations. The impurity originates from over-reduction of methyl mandelate **8A** which is subsequently controlled in intermediate **10** not more than 0.10%. Also, verified its impact on further reactions and isolation, it was concluded that diol **14** do not take part in reaction and purge out effectively during filtration, being highly soluble in methanol, IPA and ethyl acetate. Now, as results demonstrated the successful one-pot conversion of ester **8A** to nitro aryl amine **4**, a plausible reaction pathway shows evident of the transient formation of aldehyde **8B** through partial reduction of methyl mandelate **8A**. which is immediately trapped by amine **3** to generate an imine **18** intermediate, further which undergoes in-situ reduction by sodium borohydride to furnish nitroaryl amine **4**. The negligible formation of amide intermediate **9** and absence of detectable aldehyde accumulation support the proposed reaction pathway. The proposed mechanism is illustrated in Scheme 7.




**Scheme 7.** Probable reaction mechanism of ester to substituted amine.

Notably, the developed one-pot process enables the direct conversion of acid **8** to substituted amine **4** without isolation of genotoxic intermediates.

To optimize the one-pot conversion of ester compound **8A** to compound **4**, the key reaction parameters including reaction temperature, mole ratios of $NaBH_4$ and compound **8A** with respective compound **3** were systematically screened as shown in table 2. We found that entry no. 5, each 2-molar ratio of $NaBH_4$ and compound **8A** at temperature -5 to 0 °C gave 82.25% conversion with minimum impurity load during reaction monitoring.

**Table 2: Optimization of mole ratio of sodium borohydride, compound 8A and temperature for the synthesis of intermediate 4.**

| Entry No. | $NaBH_4$ Mole ratio# | 8A Mole ratio# | Temp (°C) | Reaction monitoring by HPLC (%) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Purity of 4 | 9 | 8A | 3 | Diol |
| 1 | 1 | 1 | -5 to 0 | 68.22 | 0.01 | ND | 19.75 | 10.04 |
| 2 | 1.5 | 2 | -5 to 0 | 74.21 | 0.00 | ND | 8.20 | 12.50 |
| 3 | 2 | 2 | 0 to 5 | 79.50 | 0.01 | 0.02 | ND | 16.34 |
| 4 | 2 | 2 | 5 to10 | 80.13 | 0.01 | 0.03 | ND | 12.09 |
| 5 | 2 | 2 | -5 to 0 | 82.25 | ND | 0.11 | 0.02 | 9.85 |
| 6 | 2.5 | 2 | -5 to 0 | 78.5 | 0.00 | 0.09 | 0.02 | 10.05 |
| 7 | 2 | 3 | -5 to 0 | 81.5 | 0.01 | 0.09 | 0.02 | 15.56 |

**Note: # mole ratio is calculated considering Key starting material i.e., compound 3.*

The final chemical conversion of one-pot sequence involved the reduction of nitroaryl amine **4** to aniline **10**. Sodium sulfide was selected as an inexpensive, readily available, and operationally safe reducing agent, eliminating the need for pyrophoric catalysts or pressurized hydrogenation systems. Notably, the reaction medium (methanol–water) exhibited a pH of ~10–12, which is favorable for nitro reduction under conditions analogous to the Zinin process [22].

To optimize the reduction of nitro compound **4** to aniline compound **10**, the key reaction parameter's reaction temperature and mole ratio of sodium sulfide with respective compound **3** were systematically studied as shown in table 3. We found that entry no. 3, 2.6 mole ratio of sodium sulphide at 60-65 °C gave best quality 99.75% purity by HPLC and 92% yield, the used of higher and lower mole ratio of sodium sulphide did not gives any additional benefits and at lower temperatures reaction progress get pause.

**Table 3: Optimization of mole equivalence of sodium sulfide and temperature for the compound 10.**

| Entry No. | Sodium sulfide mole ratio# | Temp (°C) | Isolated solid Relative substance by HPLC (%) | | | Yield (%) |
|---|---|---|---|---|---|---|
| | | | Compound 10 | Compound 4 | SMUI | |
| 1 | 2 | 40-55 | 32.39 | 61.38 | 1.03 | PNI |
| 2 | 2.4 | 60-65 | 99.05 | 0.049 | 0.105 | 88 |
| 3 | 2.6 | 60-65 | 99.75 | ND | 0.064 | 92 |
| 4 | 3 | 60-65 | 99.70 | ND | 0.071 | 92 |

**Note: # mole ratio is calculated considering Key starting material i.e., compound 3. PNI means product not isolated, SMUI means single maximum unknown impurity.*

**Preparation for Mirabegron 1:**

The coupling of compound **10** with acid compound **7**, the reaction conditions were optimized as shown in table 4. As per our study, the best results were obtained from entry no. 3, wherein 1.05 mole ratio of compound **7** with 1.15 mole ratio of EDC·HCl gave 99.85% purity by HPLC and 87% yield.

**Table 4: Optimization of EDC.HCl, and compound 7 for the synthesis of Mirabegron 1:**

| Entry No. | Compound 7 Mole ratio# | EDC.HCl Mole ratio# | Purity by HPLC (%) | | | | Yield (%) |
|---|---|---|---|---|---|---|---|
| | | | Purity | 11 | 7 | SMUI | |
| 1 | 1.1 | 1.1 | 99.34 | 1.28 | 0.8 | 0.64 | 80 |
| 2 | 1.1 | 1 | 99.50 | 4.8 | 2.61 | 0.87 | 82 |
| 3 | 1.15 | 1.05 | 99.65 | 0.03 | 0.36 | 0.22 | 87 |
| 4 | 1.2 | 1.05 | 99.65 | 0.08 | 0.10 | 0.47 | 86 |

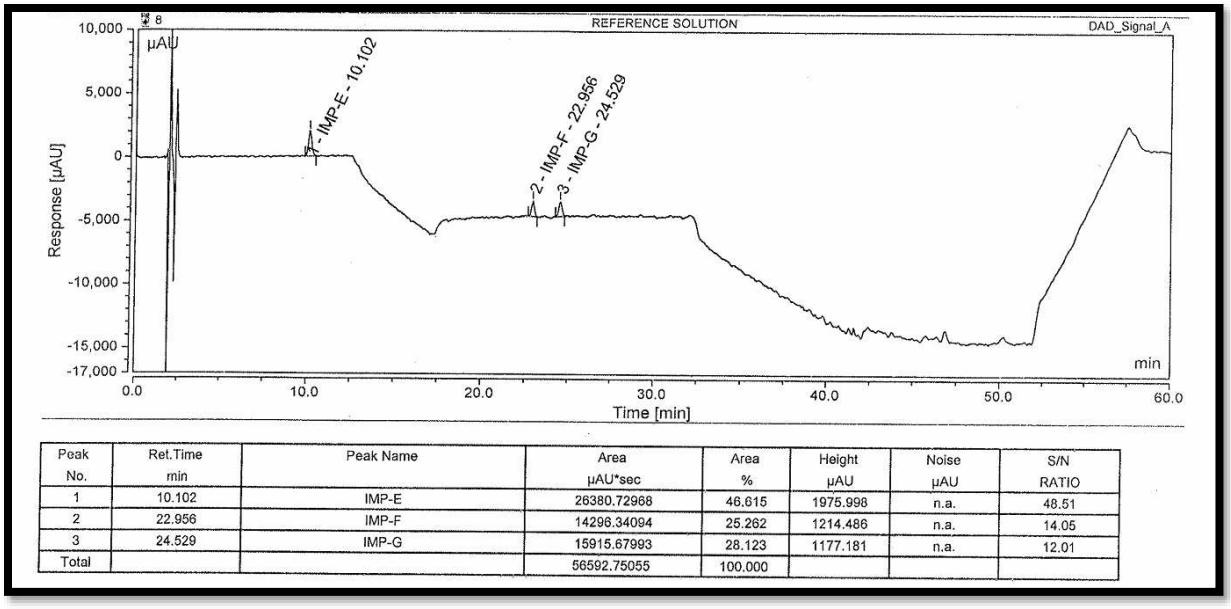
**Note: # mole ratio with respective compound 10. SMUI means single maximum unknown impurity.*

**Overview of One-pot process:** The novel developed One-pot process offers significant advantages over the reported process, including higher yield, milder conditions and less Batch cycle time (BCT).

**Table 5: One-pot advantages over reported process**

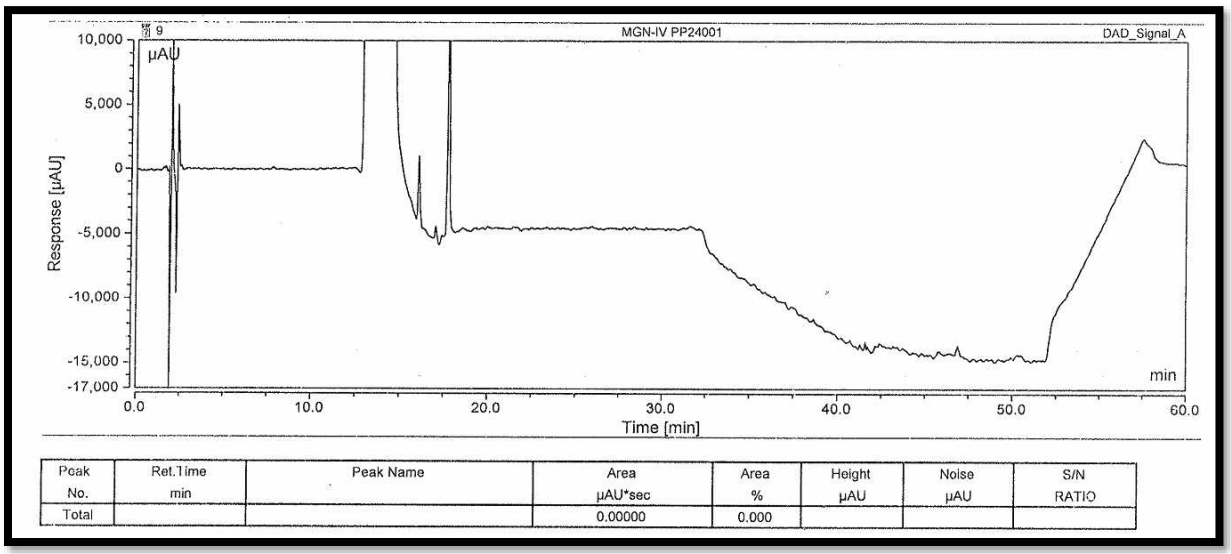
| Parameter | Reported Second Generation Approach | Present Approach |
|---|---|---|
| Overall Yield | 57% | 80% |
| Solvents Used | 9 | 4 |
| Class 2 Solvents | 4 | 0 |
| GTI isolation | Yes | No |
| Hydrogenation | Yes | No |
| Batch Cycle Time | 21 Days | 8 Days |
| Drying Operations | 5 | 2 |
| Hazardous Chemicals | $B(OMe)_3$, DIPEA, $I_2$ and Raney Ni/$H_2$ | Completely Avoided |

A key advantage of the present methodology is its superior impurity profile. The process consistently generated material free from identified genotoxic impurity as well as reported in European pharmacopeia specified Mirabegron impurities E, F and G (compound **3**, **9** and **4** respectively). Moreover, des-hydroxy impurities like **1A, 4A, 9A, 10A** and THF opening impurity **10B** (shown in Fig. 1), which were prevalent in earlier iodine-mediated protocols. These attributes collectively render the route practical, sustainable, and economically attractive for commercial manufacture, aligning well with modern principles of green chemistry and process intensification.




| Peak No. | Ret.Time min | Peak Name | Area μAU*sec | Area % | Height μAU | Noise μAU | S/N RATIO |
|---|---|---|---|---|---|---|---|
| 1 | 10.102 | IMP-E | 26380.72968 | 46.615 | 1975.998 | n.a. | 48.51 |
| 2 | 22.956 | IMP-F | 14296.34094 | 25.262 | 1214.486 | n.a. | 14.05 |
| 3 | 24.529 | IMP-G | 15915.67993 | 28.123 | 1177.181 | n.a. | 12.01 |
| Total | | | 56592.75055 | 100.000 | | | |

**Figure 2**. HPLC chromatogram of genotoxic impurities (GTIs) reference standards corresponding to Mirabegron.




| Peak No. | Ret.Time min | Peak Name | Area μAU*sec | Area % | Height μAU | Noise μAU | S/N RATIO |
|---|---|---|---|---|---|---|---|
| Total | | | 0.00000 | 0.000 | | | |

**Figure 3**. HPLC chromatogram of final process sample demonstrating the absence of genotoxic impurities (GTIs) in Mirabegron.

## Conclusion

The present work reports first telescoped one-pot process for the synthesis of a key advance intermediate (**10**) of Mirabegron through the integration of esterification, reductive amination and nitro reduction unit process. This process offers Mirabegron **1** free from genotoxic impurities.

A novel and sustainable, short one-pot process for the synthesis of a key advance intermediate of Mirabegron **1** has been successfully developed. Thereby eliminating the isolation of genotoxic intermediates and reducing process complexity. The process provides the advanced intermediate >92% yield and 99.75% HPLC purity and affords Mirabegron in an overall yield of approximately >80%. Compared with previously reported routes, the process minimizes solvent consumption, eliminates hazardous reagents and peroxide forming solvents, avoids hydrogen-pressure operations and significantly reduces batch cycle time. Owing to its safety, efficiency, scalability and environmental benefits, the process represents an attractive alternative for the commercial manufacture of Mirabegron and its advanced intermediates.

**Experimental section.**

**General Methods:**

Melting points were determined on an Analab melting point apparatus using open capillary tubes and are uncorrected. $^{1}$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a SA-Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as internal standard. Deuterated chloroform ($CDCl_3$) and deuterated dimethyl sulfoxide (DMSO-$d_6$) were used as solvents unless otherwise specified. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using potassium bromide (KBr) pellets. Elemental analyses were performed on a Hosli CH-Analyzer and results were within ±0.3% of theoretical values. Liquid-chromatography mass spectra (LC-MS) were obtained with a Shimadzu GC-MS QP system operating at 70 eV ionization potential. Reaction progress was monitored by thin-layer chromatography (TLC) on silica gel 60F254 plates (Merck) visualized under UV light (254 and 366 nm) or by HPLC analysis on an Agilent Technologies 1200 series system. Residual solvents were analyzed by gas chromatography using an Agilent Technologies 7683B with headspace sampler. Commercial reagent-grade chemicals were used as received or prepared according to literature procedures.

All raw materials, solvents, reagents, and catalysts used for the process development studies were used as received, without further purification, unless otherwise specified.

**Synthesis of (R)-2-((4-Aminophenethyl) amino)-1-phenylthan-1-ol (compound 10)**

To a stirred solution of D-mandelic acid **8** (14.92 kg, 98.0 mol) in methanol (50.0 L) was added concentrated sulfuric acid (1.440 kg, 1.47 mol) at ambient temperature. The reaction mixture was heated to 50-55 °C and maintained for 4 h. Completion of esterification was confirmed by TLC. The reaction mass was cooled to 05-10 °C, and solid sodium carbonate was added portion wise until effervescence ceased and the pH reached 7-8. The mixture was stirred for an additional 30 min and used directly in the next step. To the cooled solution of methyl mandelate **8A** was added p-nitrophenylethylamine hydrochloride **3** (10.0 kg, 49.3 mol), followed by dropwise addition of an aqueous solution of sodium borohydride (3.708 kg, 98.0 mol and 6 L water) over 45 min, maintaining the temperature -05 to 0 °C. The reaction mixture was stirred for 2h at -05 to 0 °C. After conversion to intermediate **4**, MeOH (56.0 L) is added at RT, the reaction mass was heated to 60-65 °C and sodium sulfide (9.94 kg, 127.4 mol) was added in 10 equal portions at 10 min intervals. The reaction mixture was stirred for 6 h at 60-65 °C. TLC confirmed formation of compound **10**. The mixture was cooled to ambient temperature, and methanol was distilled under vacuum at 50 °C. The residue was stripped twice with ethyl acetate (2 × 20.0 L), and the product was extracted into ethyl acetate (50.0 L). The organic layer was washed with water (2 × 25.0 L), dried over sodium sulfate, and treated with IPA (20.0 L). The pH of the solution was adjusted to 3 using IPA.HCl at 05-20 °C. The resulting precipitate was filtered, washed with a mixture of ethyl acetate: IPA (4:1, 10.0 L), and dried under reduced pressure. The crude product was recrystallized from a methanol-water mixture to afford compound **10** as a solid. Purity by HPLC 99.80%. Yield: 13.40 kg (92.47%). MS m/z = 257 $[M + 1]^+$. $^1$H NMR (DMSO-*d*$_6$, 400 MHz): δ 2.76-2.88 (m, 2H), 2.96-3.15 (m, 4H), 4.97-5.02 (m, 1H), 5.11 (s, 2H), 6.19-6.20 (d, 1H), 6.52-6.54 (d, 2H), 6.88-6.90 (d, 2H), 7.28-7.34 (m, 1H), 7.36-7.44 (m, 4H), 8.87 and 9.28 (s, 2H). $^{13}$C NMR (DMSO-*d*$_6$, 400 MHz): δ 147.03, 141.89, 129.03, 128.37, 127.37, 125.92, 124.21, 114.29, 68.18, 53.55, 48.59, 30.65.

**Synthesis of 2-(2-Amino-1, 3-thiazol-4-yl)-N-[4-(2-{[(2S)-2-hydroxy-2-phenyl ethyl] amino} ethyl) phenyl] acetamide (Compound 1)**

To the solution of compound **10** (10.0 kg, 34.15 mol) and compound **7** (5.67 kg, 35.84 mol) in con. HCl (100.0 L) was added EDC.HCL (7.529 kg, 39.27 mol) at 25 °C in 10 lots within a 10 min time interval, reaction mass maintained at room temperature for 3 hrs. After completion of reaction by TLC, *n*-butanol (120.0 L) was added and pH was adjusted 8-10 using the sodium carbonate solution (10% solution in water), the organic layer was separated and keep side aqueous layer was extracted by *n*-butanol 20.0 L, both *n*-butanol layer was mix and distil out under vacuum up to solid precipitation further IPA was added and stirred for 30 min at 60-65 °C, cool to room temperature and the reaction mixture was filtered to isolate the crude solid, which was subsequently washed with IPA to remove residual impurities. The wet solid was then subjected to hot slurry treatment in IPA (80.0 L), and the resulting purified solid was dried under reduced pressure to afford compound Mirabegron (**1**). Purity by HPLC 99.85%. Yield: 11.8 kg (87.3%). MS m/z = 397 $[M + 1]^+$, $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 1.63 (s, 1H), 2.49-2.65 (m, 4H), 2.66-2.77 (m, 2H), 3.44 (s, 2H), 4.57-4.61 (m, 1H), 5.21-5.22 (s, 1H), 6.29 (s, 1H), 6.90 (s, 2H), 7.10-7.12 (d, 2H), 7.18-7.27 (m, 1H), 7.29-7.32 (m, 4H), 7.48-7.50 (d, 2H). , 10.00 (s, 1H). $^{13}$C NMR (DMSO-$d_6$, 400 MHz): δ 168.24, 167.80, 145.88, 144.63, 137.17, 135.12, 128.78, 127.90, 126.74, 125.86, 118.98, 102.58, 71.48, 57.57, 50.79, 39.50, 35.40.

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## Conflict of Interest

The author declares no conflict of competing financial interest or personal relationships that could have appeared to influence the work reported in the manuscript.

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