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Development of an Efficient Scale-up Synthesis Method for β_3-Adrenergic Receptor Agonist, Ritobegron Ethyl Hydrochloride

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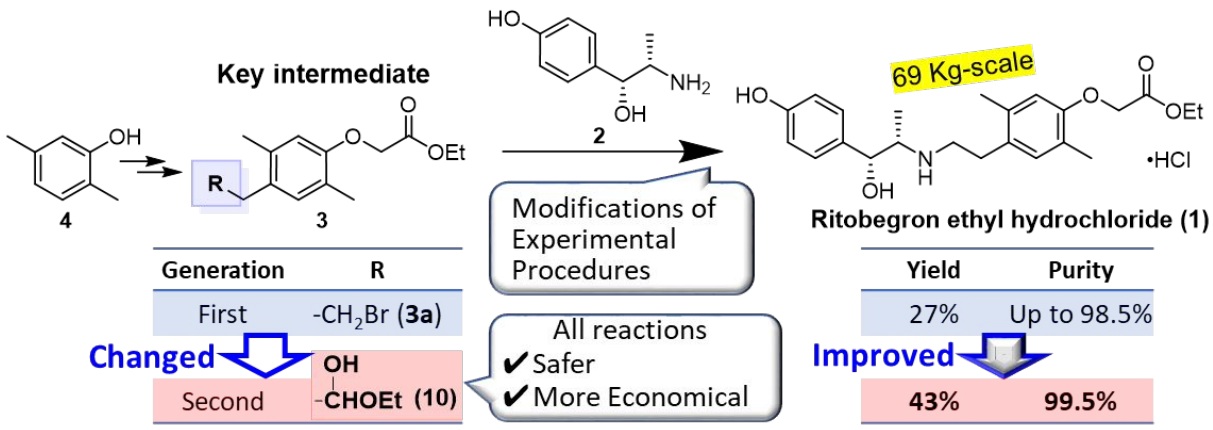


ABSTRACT

An efficient route for the multikilogram synthesis of a selective β_3-adrenergic receptor agonist, ritobegron ethyl hydrochloride (**1**), was developed by changing the coupling method of 4-hydroxynorephedrine (**2**) with phenoxyacetate **3**. This new method successfully overcame several obstacles in the first-generation method via the use of aldehyde **3b** derived from hemiacetal **10** to couple with **2**. The main advantages of the key intermediate, **10** were that it was sufficiently stable to enable handling at large scales, it could be synthesized without an exothermic reaction or excessive use of expensive reagents, and the ability to reduce impurities by purification prior to coupling with **2**. The resulting second-generation method improved the overall yield from 27% to 43%, and the purity from up to 98.5% to 99.5%. Furthermore, it was effective for 69 kg-scale synthesis, representing a major improvement over the hundred-gram scale of the first-generation method.

KEYWORDS: β_3-adrenergic receptor agonist, multikilogram synthesis, ritobegron ethyl hydrochloride, second-generation

Introduction

Adrenergic receptors (ARs) are a class of G protein-coupled receptors that are roughly classified into two groups, α and β, which are further divided into α_1, α_2, β_1, β_2, and β_3 subtypes. Among β-ARs, the β_3-subtype is the predominant receptor in the human bladder, where it mediates the relaxation of the smooth muscles. Thus, β_3-AR agonists have recently attracted attention as potential therapeutic agents for overactive bladder, as they are associated with a reduced risk of side effects, such as dry mouth and constipation, compared to anticholinergics.[1–4] Ritobegron ethyl hydrochloride (**1**; Figure 1) is a prodrug of ritobegron, which is a promising agonist with high selectivity for β_3-ARs that was discovered by Kissei Pharmaceutical Co. Ltd. (Nagano, Japan).[5–6] In order to support the preclinical and clinical development of **1**, a large-scale synthetic method needs to be developed. The basic strategy of synthesis (Scheme 1) includes the coupling of commercially available 4-hydroxynorephedrine (**2**)[7–11] with phenoxyacetate **3**, which can be prepared from 2,5-xylenol (**4**), which is an inexpensive compound.

The first-generation method entailed the coupling of **2** with phenethyl bromide **3a**. The synthesis begins with the *O*-alkylation of **4** with ethyl chloroacetate to obtain phenoxyacetate **5**, followed by Friedel–Crafts acylation with bromoacetyl bromide to yield phenacyl bromide **6**.[12] Reduction of **6** with triethylsilane was conducted to obtain **3a**[12] in crystalline form (73% overall yield) from **4.** The coupling of **3a** with **2**, followed by treatment with hydrogen chloride in ethanol and toluene produced crude salt **1**, which was purified by recrystallizaion from *tert*-butylmethylether–ethanol to obtain pure **1** (47% overall yield) from **2**.

The first-generation method successfully provided a hundred-gram scale of **1**; however, several serious problems regarding safety, economy, and quality hinder its synthesis on a multikilogram

scale. First, an extreme and uncontrollable exotherm and foaming were observed on the scale-up of the Friedel–Crafts acylation. Second, several derivatives are generated by side reactions in the coupling with **2**, such as by overalkylation of **3a** and by β-elimination of **3a**. These impurities induce the generation of other undesired and irremovable compounds with each step. In total, the final compound **1** with only up to 98.5% purity was obtained. Third, an excessive amount (2.5 equiv) of the relatively expensive compound triethylsilane is required for the reduction of **6** to **3a**. Furthermore, only a moderate yield (55%) of the desired crude product was obtained from the coupling of **3a** with expensive **2**. The latter two issues are directly related to the economic problems associated with the first-generation method.

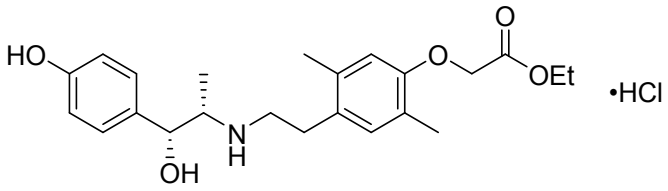
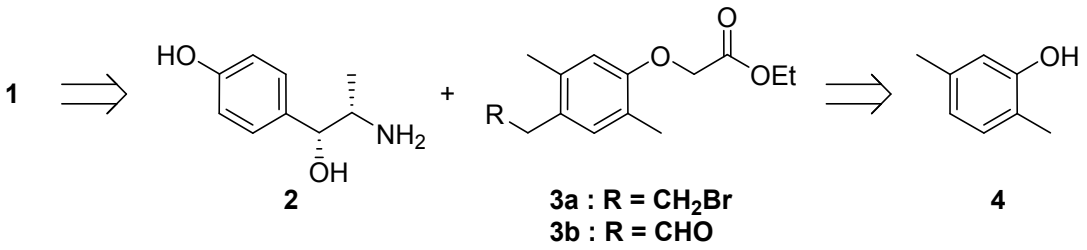
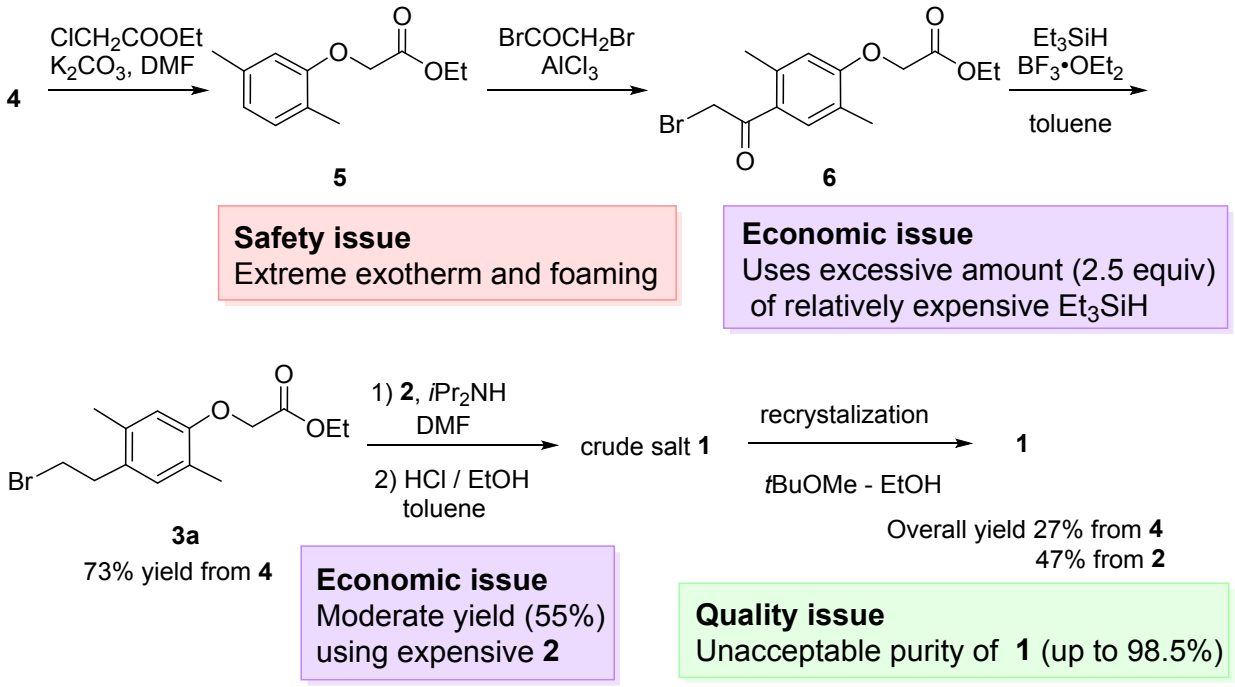


Figure 1. Chemical structure of ritobegron ethyl hydrochloride (**1**)

Scheme 1. Basic Retrosynthetic Strategy for **1**



Scheme 2. The First-Generation Route to **1**



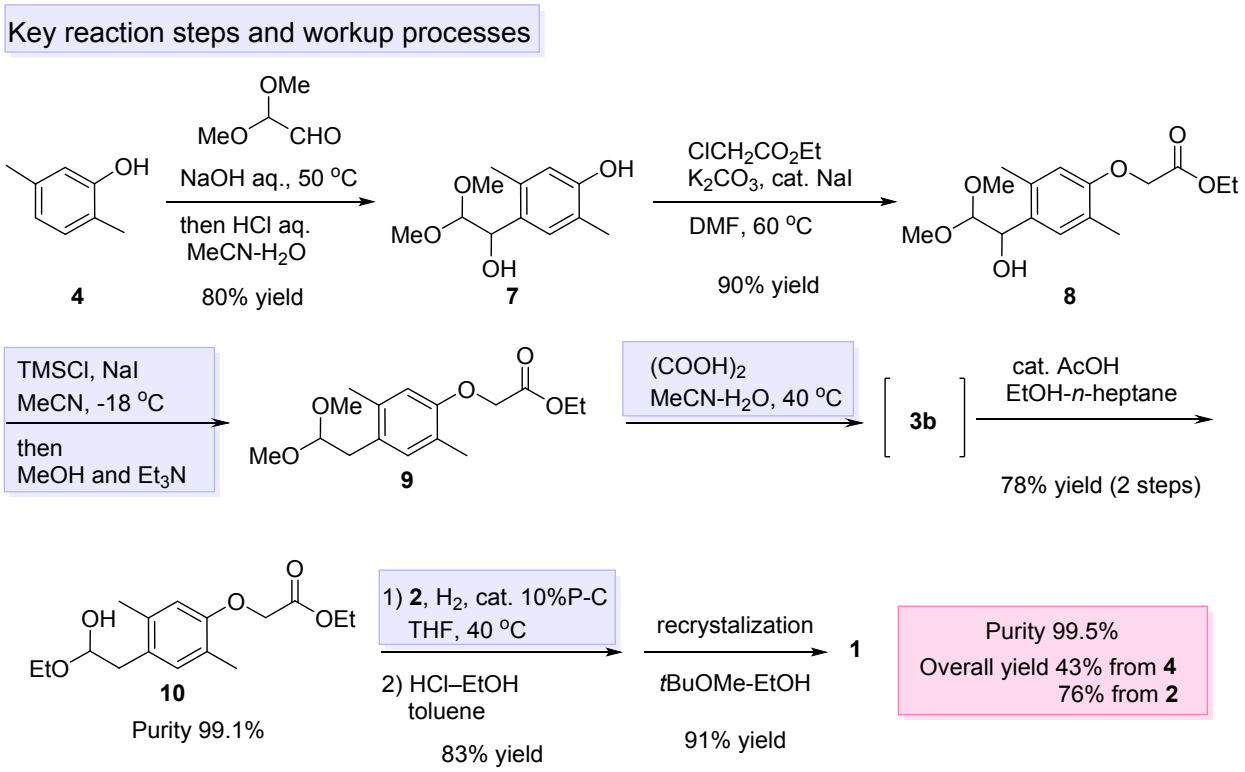
To solve the above problems, an efficient scale-up synthesis of **1** was developed as a second-generation method. We report herein on the improved new process, which uses crystalline hemiacetal **10** to enable the multikilogram-scale production of **1** with higher purity and overall yield than what was obtained using the previous method.

Results and Discussion

In the second-generation method, the hemiacetal form of aldehyde **3b** was used in the coupling process of **2** (Scheme 3), as the undesired issues in the first-generation method stem primarily from the synthetic and treatment processes used for phenethyl bromide **3a**. The hemiacetal form of aldehyde **3b**, compound **10**, could be synthesized while avoiding the exothermic Friedel–Crafts acylation using a Lewis acid and an excessive quantity of relatively expensive triethylsilane. Furthermore, the condensation of the primary amine of **2** with the aldehyde **3b** derived from hemiacetal **10** under reductive conditions could be more reactive than the *N*-

alkylation of **2** with phenethyl bromide **3a**. Our expectation of the instability of aldehyde **3b** led us to prepare the related hemiacetal or acetal form as its equivalent. The synthesis began with the aqueous base-promoted hydroxyalkylation of **4** with glyoxal dimethylacetal[13] to result in 80% yield of **7** with high regioselectivity (para:ortho = 97:3). *O*-alkylation of **7** with ethyl chloroacetate successfully enabled the production of benzyl alcohol **8** with 96.8area% purity and 90% yield.

Scheme 3. Second-Generation Route to **1**



The reduction of benzyl alcohol **8** was the first difficulty to overcome, as various catalytic hydrogenations with W-4 Raney Ni, Pt/C, Rh/alumina, Rh/C, $Pd(OH)_2$, $Pd/BaSO_4$, and Rh/Pt/C, as well as reduction with triethylsilane, were unsuccessful. The only condition for producing a satisfactory, laboratory-scale yield (ca. 80%) of dimethylacetal **9** was that which used three equiv

of TMSCl–NaI–MeCN reagents[14–16] at −10 °C. Further optimization was necessary to increase the yield of the scale-up synthesis and to reduce impurities, such as aldehyde **3b** and styryl ether **13**[17] (Scheme 4). Overreaction of **8** was predicted to generate the intermediate **11** under this condition,[14,18] which could easily be converted to the relatively unstable **3b** or undesired **13** in the presence of water or a base, respectively, during the workup process. The formation of these impurities was effectively suppressed by the addition of methanol[19] during the workup process, due to the quick conversion of the intermediate **11** into dimethyl acetal **9** with the use of methanol, resulting in a quantitative yield of **9** in the first plant operation. However, another impurity, methyl ester **12**,[20] was generated due to transesterification with methanol under the acidic conditions that arose from the excess of TMSCl. Undesired **12** persisted throughout all steps of drug synthesis, and was difficult to remove because it possesses chemical properties that are almost identical to those of the desired ethyl ester **9**. The formation of **12** can be suppressed by the rapid addition of triethylamine in toluene solution while controlling the heat of neutralization (Table 1). The yield of **12** increased as the batch scale expanded from 700 g (Table 1, entry 1) to 85 kg (Table 1, entry 2). We further optimized the process to reduce the production of **12** by controlling the addition time of the trimethylamine-toluene solution and the internal temperature. We found that the yield of **12** increased in a temperature- (Table 1, entries 3–5 and entries 6/7) and time-dependent (Table 1, entries 3/6 and 4/7) manner. Additional experiments (Table 1, entries 8 and 9) also supported that the rapid addition of a base might be more effective than maintaining low temperature. Moreover, the calculated adiabatic temperature rise of 13 K[21] for this reaction indicated the feasibility to add all at once below 0 °C by pre-cooling of trimethylamine-toluene. Finally, the amount of undesired **12** was suppressed below 0.10% at 57 kg-scale production by the addition of triethylamine-toluene which was pre-cooled to -15 °C

for 25 min after the reaction (Table 1, entry 10). The successful condition resulted in only an 8 degree internal temperature rise, from −17 to −9 °C.

Scheme 4. Role and Influence of Methanol during the Workup Process

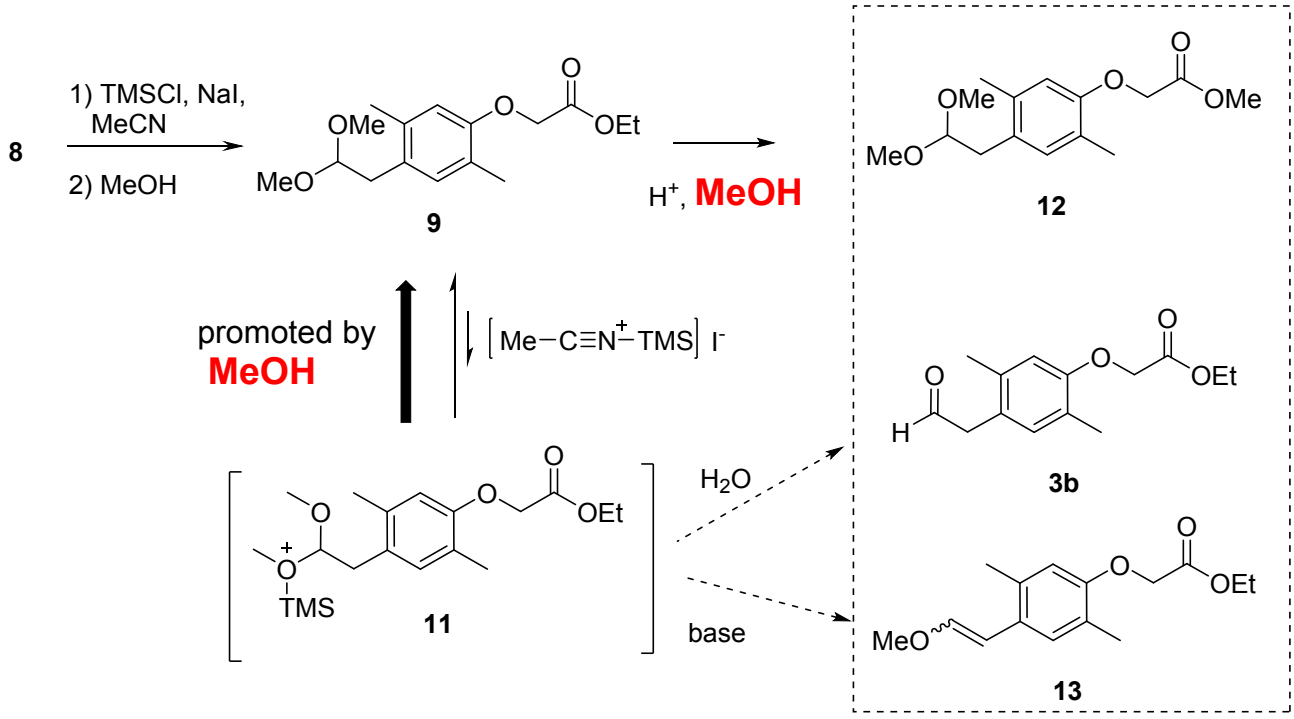


Table 1. Optimization of the Workup Process by Control of Methyl Ester **12** Generation

Entry	*Internal Temperature (°C)*	*Time for addition of Et_3N/toluene (min.)*	*Yield of Methyl ester **12***	*Scale*
1	−16 to −13	120	0.21%	700 g
2	−14 to −13	255	0.62%	85 kg
3	−15	180	0.58%	10 g

4	−10	180	0.89%	10 g
5	−5	180	1.09%	10 g
6	−15	120	0.46%	10 g
7	−10	120	0.63%	10 g
8	−8	60	0.14%	50 g
9	0	50	0.21%	10 g
10	−17 to −9	25	0.08%	57 kg

After we had produced **9**, the hydrolysis reaction was optimized by the use of various acids and reaction conditions (Figure 2)[22] to obtain the relevant aldehyde **3b**, which was allowed to crystallize in order to ensure high purity. Perchloric acid hydrolyzed the acetal **9** immediately with high reaction conversion; however, the reaction produced undesired products, such as the related carboxylic acid, resulting in a reduction in purity (Figure 2, run 1). Other conditions, such as the use of 1.5 equiv of sulfuric acid, oxalic acid, or phosphoric acid and 0.5 equiv of sulfuric acid at 20 °C or 40 °C, also gave rise to unsatisfactory results (Figure 2, runs 2–6). Hydrolysis with 0.5 equiv of oxalic acid at 40 °C was the most appropriate condition, with the reaction reaching the desired end point (over 99%) and the purity remaining over 94.5% for 2 h (Figure 2, run 7).

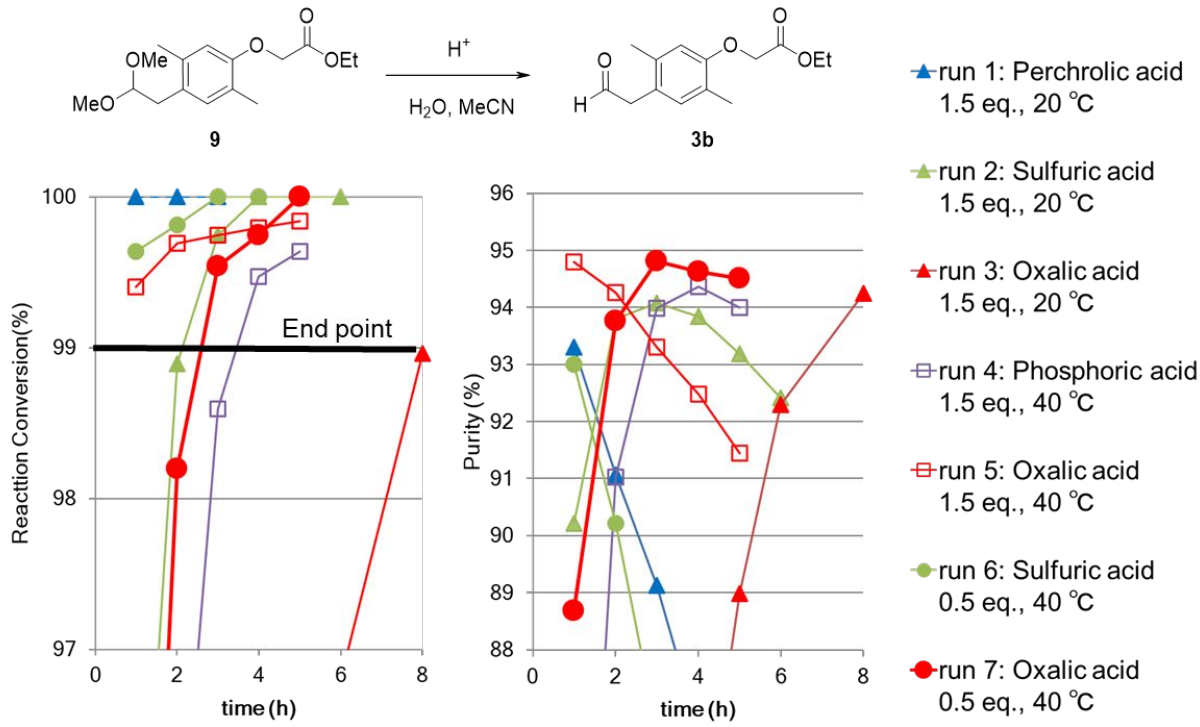
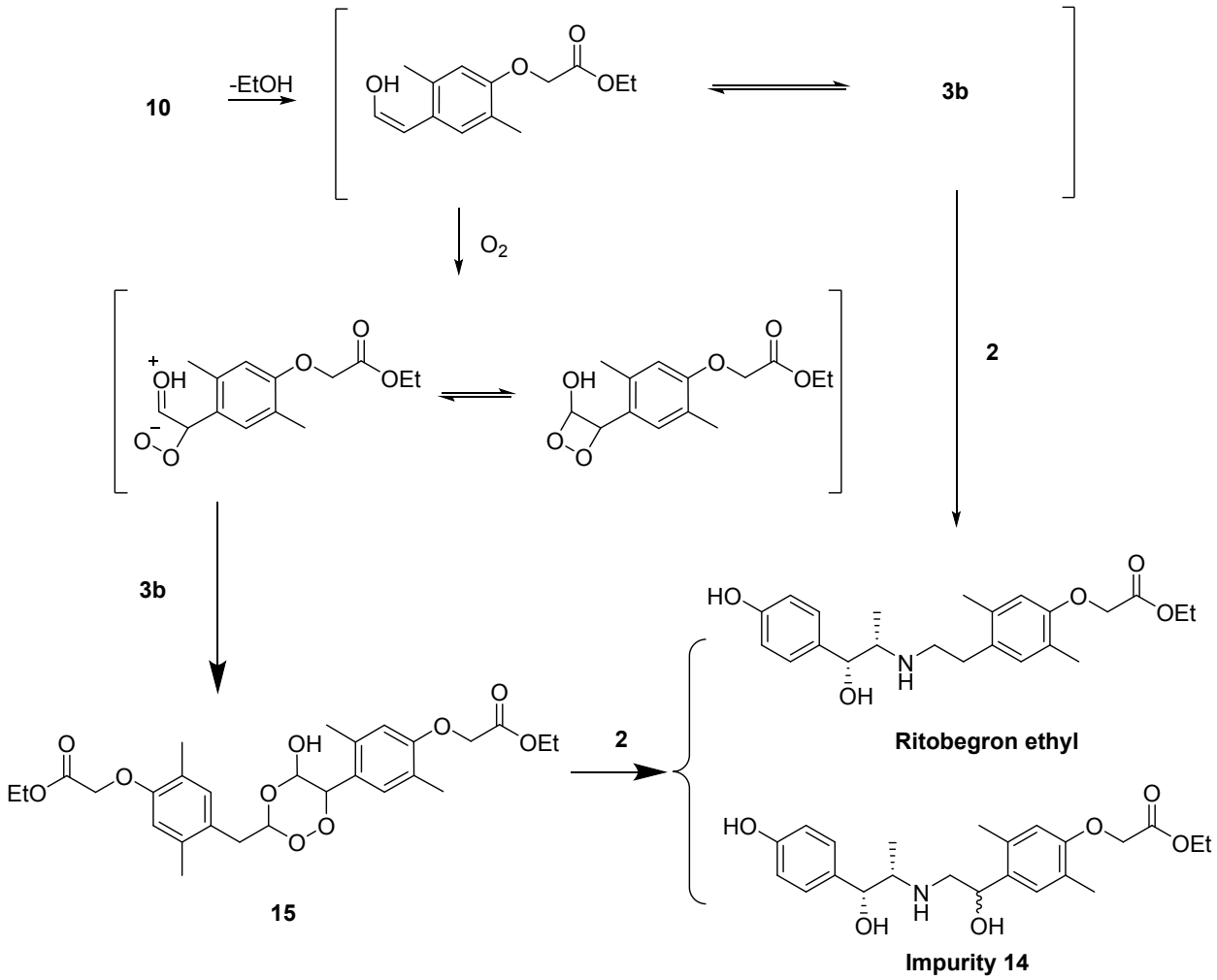


Figure 2. Optimization of Hydrolysis Conditions (Left: Reaction Conversion, Right: Purity of **3b**)

Crystallization is a preferred purification method for obtaining the desired compound with high purity in multikilogram synthesis. Unfortunately, it was not easy to get **3b** as a crystal probably due to the low melting point.[23] In addition, the instability of **3b** required low-temperature drying and refrigerated storage. Several attempts to recrystallize **3b**[23] serendipitously led us to find an ideal intermediate, i.e., treatment with ethanol containing *n*-heptane. The resulting hemiacetal **10** was in a relatively stable crystalline form, which provided the advantages of easy handling at large scales, and the ability to control the purity by recrystallization. The hemiacetalization of **3b** was accelerated in the presence of a catalytic amount of acetic acid to obtain **10** with 99.1area% purity and 78% yield from **8**.

The reductive amination of **10** with 1.0 equiv of **2** at 40 °C proceeded smoothly, as anticipated. However, an unexpected side reaction led to the production of alcohol **14**[24] (Scheme 5) (in less than 1% yield). It should be noted that the starting material **10** was very pure without contamination by benzyl alcohol **8**, which might be converted into **14**. Further investigation indicated that the yield of **14** was dependent on the stirring time before hydrogen introduction. The resulting imine required to be consumed by the reduction as soon as possible to avoid the formation of **14**, although we have no clear reasons. Meanwhile, the formation of trioxane **15**[25] was observed during the stability assessment of **10** in the ethanol solution. **15** could be related to the formation of **14**, since the amount of **14** was increased by the addition of **15** into the reaction of **10** with **2**. Taking all of this together, a possible reaction mechanism for **14** is proposed as shown in Scheme 5. The enolate of **3b** derived from **10** was partially oxidized in the presence of oxygen. The resulting peroxide was coupled with aldehyde **3b** to obtain **15**, which could be transformed to both the desired ritobegron ethyl and undesired **14**.

Scheme 5. A Possible Mechanism of Impurity **14** generation



Several effective processes were discovered during our efforts aimed at suppressing the generation of impurity **14**; these included the following: (1) removal of O_2 from the solution by multiple nitrogen purge with vacuum manner and compressed manner (refer to Experimental section) to mitigate oxidization; (2) decreasing the solubility of **10** by cooling below −13 °C before starting the reaction to minimalize the imine formation; and (3) heating immediately after the completion of all raw material charging at −13 °C to rapidly consume the resulting imine (Figure 3). The obtained ritobegron ethyl was treated with hydrogen chloride solution to produce

crude salt **1**, which was recrystallized from *tert*-butyl methyl ether-ethanol. As a result, 69 kg of **1** was obtained from **2** with 99.5area% purity and 76% yield.

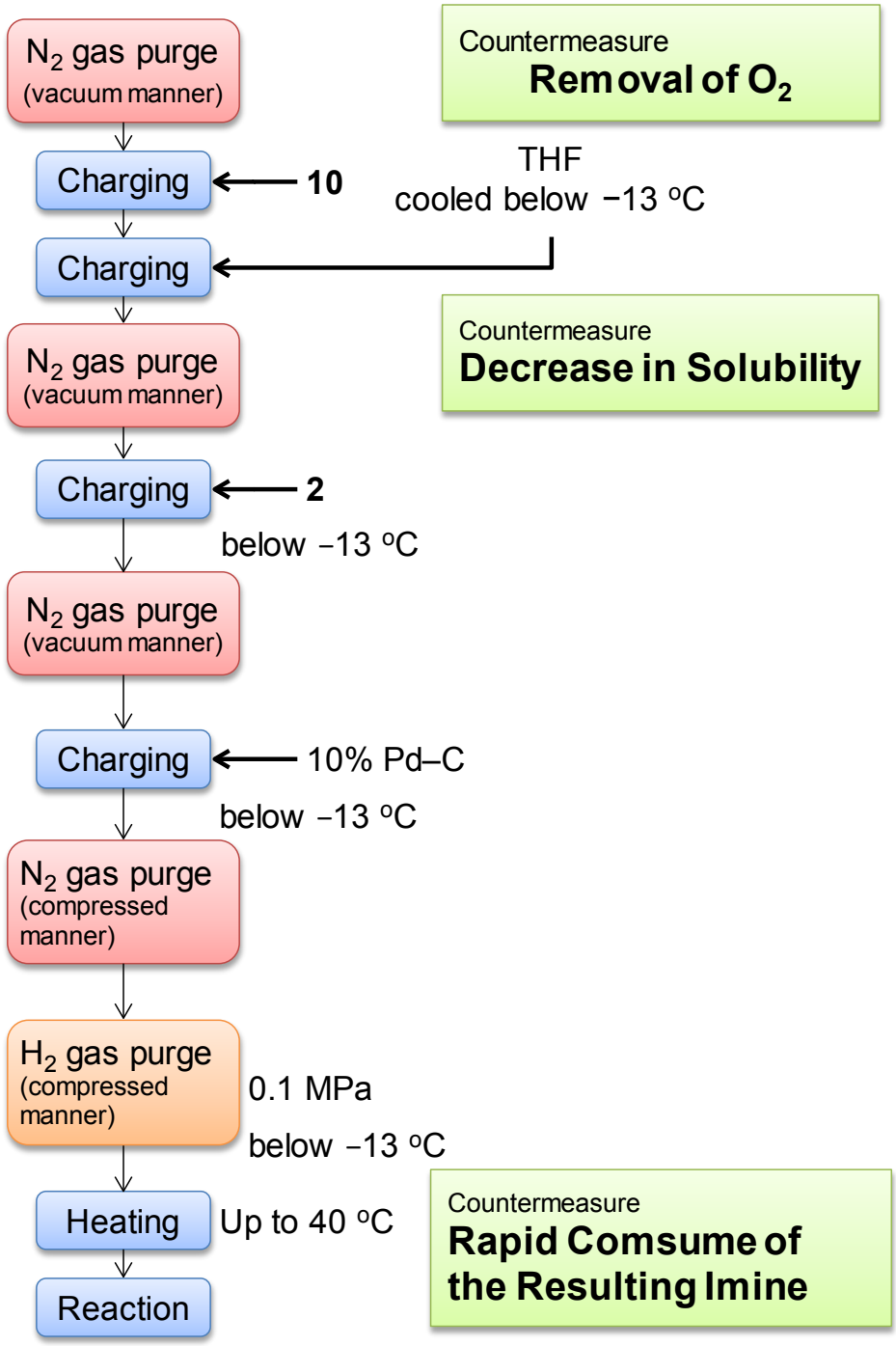


Figure 3. Production Flow for Suppressing Impurity **14**

Conclusion

In summary, the efficient scale-up synthesis method for ritobegron ethyl hydrochloride (**1**) was established. The new process overcomes the main issues encountered in the first-generation process by changing the intermediate to crystalline hemiacetal **10** and optimizing the reaction conditions. It also enables the multikilogram production of **1** with improved overall yield and higher purity (Table 2). Finally, 69 kg of **1** for clinical study was obtained from **4** in six steps, with 99.5area% purity and 76% overall yield.

Table 2. Comparison between the First-Generation Process and the New Process

Item	*First Generation* ➡ *Second Generation improved*	
Total Number of Steps	5	6
Overall yield from **4**	27%	43% (1.6 times)
Overall yield from **2**	47%	76% (1.6 times)
Area% purity of **1** by HPLC	Up to 98.5%	99.5% (1 point increase)

Experimental Section

General. All air- and moisture-sensitive manipulations were performed under a nitrogen atmosphere. All substrates, reagents, and solvents were purchased from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Burker AVANCE 400M (400 MHz) or AVANCE DRX500 (500 MHz) spectrometer using tetramethylsilane as the internal standard in the indicated solvents. High-resolution mass spectra (HRMS) were measured on an Agilent Technologies Q-TOF 6520 mass spectrometer. Elemental

analysis was conducted on an Elementar Analysensysteme GmbH vario EL III elemental analyzer.

Analytical HPLC method A for measuring the purity of **7**: XbridgeC18 column (4.6 x 250 mm, 5 μm); mobile phase A: 20 mM KH_2PO_4; mobile phase B: acetonitrile; UV detection at 225 nm; flow rate: 1.0 mL/min; column temperature: 55 °C; gradient initial conditions: A-70%:B-30%; hold at A-70%:B-30% from 0−5 min; linear ramp to A-40%:B-60% from 5−20 min.

Analytical HPLC method B for measuring the purity of **8**: XbridgeC18 column (4.6 x 250 mm, 5 μm); mobile phase A: 20 mM KH_2PO_4; mobile phase B: acetonitrile; UV detection at 225 nm; flow rate: 1.0 mL/min; column temperature: 55 °C; gradient initial conditions: A-65%:B-35%; hold at A-65%:B-35% from 0−10 min; linear ramp to A-35%:B-65% from 10−30 min; hold from 30−60 min.

Analytical HPLC method C for measuring the purity of **10**: Intertsil ODS-P column (4.6 x 250 mm, 5 μm); mobile phase A: 20 mM H_3PO_4 (pH 2.3); mobile phase B: acetonitrile; UV detection at 225 nm; flow rate: 1.0 mL/min; column temperature: 40 °C; gradient initial conditions: A-55%:B-45%; hold at A-55%:B-45% from 0−15 min; linear ramp to A-30%:B-70% from 15−25 min; hold from 25−45 min.

Analytical HPLC method D for measuring the purity of **1**: Intertsil ODS-3 column (4.6 x 250 mm, 5 μm); mobile phase A: 20 mM H_3PO_4 (pH 3.0); mobile phase B: acetonitrile; UV detection at 225 nm; flow rate: 1.0 mL/min; column temperature: 40 °C; gradient initial conditions: A-74%:B-26%; hold at A-74%:B-26% from 0−20 min; linear ramp to A-30%:B-70% from 20−50 min; hold from 50−60 min.

4-(1-Hydroxy-2,2-dimethoxyethyl)-2,5-dimethylphenol (7) A 60% aqueous solution of glyoxal dimethylacetal (235 kg, 1350 mol, 1.5 equiv) was steadily added to a mixture of sodium

hydroxide (36.0 kg, 900 mol, 1.0 equiv), water (875 L), and 2,5-xylenol (**4**) (110 kg, 900 mol) at 50 °C; the reaction mixture was stirred at this temperature for 8 h. The conversion was monitored by HPLC analysis. After acetonitrile (96.8 kg) was added at 0 °C, 7.5% hydrochloric acid (139 kg) was steadily added over a duration of 1 h, and compound **7** (80 g) were added as a seed crystal. The mixture was stirred for 1 h between −5 and 10 °C to precipitate the product. Additional 7.5% hydrochloric acid (278 kg) was steadily added over a duration of 2 h between −5 and 10 °C and the suspension was stirred for 2 h, and then filtered. The resulting cake was washed with a mixed solvent of acetonitrile (8.8 kg) and water (275 L), and dried at 60 °C under reduced pressure to obtain **7** (163 kg, 97.2area% purity). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 2.06 (s, 3H), 2.16 (s, 3H), 3.08 (s, 3H), 3.35 (s, 3H), 4.24 (d, 1H, J = 6.8 Hz), 4.55 (dd, 1H, J = 4.3, 6.8 Hz), 4.93 (d, 1H, J = 4.3 Hz), 6.49 (s, 1H), 7.04 (s, 1H), 8.94 (br s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 14.2, 17.3, 52.2, 53.6, 67.4, 106.5, 114.2, 118.8, 127.9, 128.8, 132.1, 152.3. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{18}O_4Na$, 249.1097; found, 249.1091. Retention time (analytical HPLC method A): 4.8 min.

Ethyl 2-[4-(1-hydroxy-2,2-dimethoxyethyl)-2,5-dimethylphenoxy]acetate (8) A mixture of **7** (40.8 kg, 180 mol), potassium carbonate (32.4 kg, 234 mol, 1.3 equiv), sodium iodide (0.81 kg, 5 mol, 0.03 equiv) and DMF (99.2 kg) was charged. A solution of ethyl chloroacetate (25.4 kg, 207 mol, 1.15 equiv) in DMF (17.6 kg) was added at 60 °C; the reaction mixture was stirred at this temperature for 3 h. The reaction completion was confirmed by HPLC analysis. After toluene (326 kg) and water (163 L) were added, the upper layer was collected. The organic layer was successively washed with 15% sodium chloride aqueous solution (122 kg) and water (163 L), and concentrated under reduced pressure. The residue was dissolved at 60 °C by adding *n*-heptane (326 kg) and toluene (39.9 kg) and then stirring the mixture for 1 h each at 30 °C and

0 °C, followed by filtration. The resulting cake was washed twice with *n*-heptane (94 kg) and dried under reduced pressure for 12 h at 30 °C, 15.5 h at 50 °C to obtain **8** as white powder (50.7 kg, 96.8area% purity). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.29 (t, 3H, *J* = 7.1 Hz), 2.26 (s, 3H), 2.31 (s, 3H), 2.60 (br s, 1H), 3.21 (s, 3H), 3.49 (s, 3H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.32 (d, 1H, *J* = 6.6 Hz), 4.60 (s, 2H), 4.79 (d, 1H, *J* = 6.6 Hz), 6.48 (s, 1H), 7.24 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 14.2, 15.9, 19.5, 55.1, 56.4, 61.2, 65.8, 70.1, 108.5, 113.3, 124.7, 129.3, 130.5, 135.0, 155.4, 169.2. HRMS (*m/z*): $[M+NH_4]^+$ calcd for $C_{16}H_{28}O_6N$, 330.1911; found, 330.1911; $[M+Na]^+$ calcd for $C_{16}H_{24}O_6Na$, 335.1465; found, 335.1465. Retention time (analytical HPLC method B): 12.8 min.

Ethyl 2-[4-(2,2-dimethoxyethyl)-2,5-dimethylphenoxy]acetate (9) A solution of **8** (56.8 kg, 182 mol) in acetonitrile (80 L) was steadily added at −19 to −18 °C for 53 min to the suspension of sodium iodide (84.5 kg, 564 mol, 3.1 equiv), trimethylsilyl chloride (61.2 kg, 564 mol, 3.1 equiv), and acetonitrile (364 L). After stirring for 30 min, methanol (5.83 kg, 182 mol, 1.0 equiv) was added, and a mixed solution of triethylamine (27.6 kg, 273 mol, 1.5 equiv) and toluene (227 L), which was pre-cooled to -15 °C, were charged for 25 min at −17 to −9 °C. A solution of sodium erythorbate (51.1 kg) and potassium carbonate (19.9 kg) in water (460 L) was steadily added for 10 min at −9 to 7 °C, and the mixture was stirred for 1 h at 15 °C to obtain the organic layer. The obtained layer was successively washed with water (114 L) and 20% sodium chloride aqueous solution (102 L) twice, and concentrated under reduced pressure. Acetonitrile (364 L) was added to the residue, and the mixture was concentrated under reduced pressure again. Acetonitrile (292 L) was added to obtain the acetonitrile solution of **9** [53.9 kg (theoretical amount)]. The sample for analysis of **9** was obtained by the concentration of the acetonitrile solution. ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 1.29 (t, 3H, *J* = 7.1 Hz), 2.23 (s, 3H), 2.27 (s, 3H), 2.82

(d, 2H, J = 5.6 Hz), 3.32 (s, 6H), 4.26 (q, 2H, J = 7.1 Hz), 4.47 (t, 1H, J = 5.6 Hz), 4.59 (s, 2H), 6.50 (s, 1H), 6.96 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ): 12.4, 13.9, 18.0, 34.5, 51.8, 59.3, 64.2, 103.6, 111.6, 122.6, 126.4, 131.0, 133.1, 152.8, 167.5. HRMS (*m/z*): $[M+NH_4]^+$ calcd for $C_{16}H_{28}O_5N$, 314.1962; found, 314.1961, $[M+Na]^+$ calcd for $C_{16}H_{24}O_5Na$, 319.1516; found, 319.1516.

Ethyl 2-[4-(2-ethoxy-2-hydroxyethyl)-2,5-dimethylphenoxy]acetate (10) Oxalic acid (8.2 kg, 91 mol, 0.5 equiv) and water (216 L) were added to a acetonitrile solution of **9** (53.9 kg [theoretical amount], 182 mol). The reaction mixture was stirred for 3 h at 42 °C and reaction completion was confirmed by HPLC analysis. 7% potassium carbonate aqueous solution (180 kg), toluene (59 L), and *t*-butylmethylether (271 kg) were added to the mixture at 26 to 30 °C. The organic layer was separated, washed with 7% potassium carbonate aqueous solution (180 kg), 5% sodium bicarbonate aqueous solution (164 kg), and 10% sodium chloride aqueous solution (162 kg) twice, and dried over anhydrous sodium sulfate (38 kg). After the removal of sodium sulfate, the filtrate was concentrated below 50 °C under reduced pressure. After the residual oil was solved in ethanol (70 L) and *n*-heptane (108 kg), acetic acid (0.54 kg, 9 mol, 0.05 equiv) and compound **10** (5.4 g) was successively added as a seed crystal. The mixture was stirred for 2 h at 20 °C to achieve a suspension of **10**. *n*-Heptane (443 kg) was steadily added over a duration of 1.5 h at the same temperature; the suspension was stirred for 1 h at 20 °C and for 2 h at −2 to 8 °C, and then filtered. The resulting cake was washed with *n*-heptane (108 kg) twice and dried at 0 to 10 °C under reduced pressure to obtain **10** (42.2 kg, 99.1area% purity). ^{1}H NMR (DMSO-d_6, 400 MHz, δ): 1.06 (t, 3H, J = 7.1 Hz), 1.21 (t, 3H, J = 7.1 Hz), 2.12 (s, 3H), 2.20 (s, 3H), 2.62 (dd, 1H, J = 6.0, 13.9 Hz), 2.71 (dd, 1H, J = 5.0, 13.9 Hz), 3.28 (dq, 1H, J = 7.1, 9.6 Hz), 3.66 (dq, 1H, J = 7.1, 9.6 Hz), 4.16 (q, 2H, J = 7.1 Hz), 4.57–

4.66 (m, 1H), 4.71 (s, 2H), 5.91 (d, 1H, J = 7.6 Hz), 6.59 (s, 1H), 6.93 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz, δ): 14.5, 15.7, 16.0, 19.2, 40.2, 61.0, 61.5, 65.5, 97.3, 113.5, 123.1, 129.1, 133.1, 135.1, 154.4, 169.5. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{18}O_4$, 251.1278; found, 251.1276 detected as aldehyde **3b**. Retention time (analytical HPLC method C): 13.8 min (detected as aldehyde **3b**).

Ritobegron ethyl hydrochloride (1) (Ethyl [4-(2-{[(1*R*,2*S*)-1-hydroxy-1-(4-hydroxyphenyl)propan-2-yl]amino}ethyl)-2,5-dimethylphenoxy]acetate monohydrochloride) After charging THF (320 L) to a sub reactor under reduced pressure, the pressure was released with nitrogen gas followed by cooling THF below −13 °C. Separately, **10** (63.5 kg, 212 mol, 1.0 equiv, 99.1% purity) was added to a main reactor that was purged by decompression and release with nitrogen gas to reduce oxygen below 0.5% (vacuum manner), and then cooled THF was added to a main reactor. After the above-mentioned nitrogen gas purge, (1*R*,2*S*)-2-amino-1-(4-hydroxyphenyl)-1-propanol (**2**) (35.5 kg, 212 mol) and THF (39 L) were successively added to a main reactor below −13 °C. After the same nitrogen gas purge again, the suspension of 10% Pd-C (ca. 50% water content) (11.9 kg) in THF (39 L) without gas purge were added below −13 °C. The reactor was purged by repeating compression up to 0.5 MPa with nitrogen gas and release three times to reduce oxygen below 0.5% (compressed manner) followed by the hydrogen gas purge in the same manner. The reaction mixture was stirred at 40 °C with 0.1 MPa of hydrogen gas for 3 h, and its conversion was monitored by HPLC analysis. After the removal of palladium by filtration using celite, the filtrate was concentrated below 50 °C under reduced pressure; THF (39 L) and toluene (288 L) were added to the residue. Water (284 L) to the residue, the organic layer was separated and successively washed with 1% sodium bicarbonate aqueous solution (180 kg) and 18% sodium chloride

aqueous solution (217 kg), and then dried over anhydrous sodium sulfate (36 kg). After removal of sodium sulfate, the filtrate was concentrated below 50 °C under reduced pressure, and toluene (206 L) was added to the residue. The solution was concentrated below 50 °C under reduced pressure, and then toluene (132 L) and ethanol (34.5 kg) were added to the residue. A 20% hydrogen chloride solution in ethanol (35.0 kg, 212 mol, 1.0 equiv) was steadily added at 0 to 9 °C, and the mixture was stirred for 1 h at 3 to 8 °C. Toluene (213 L) was added, the suspension was stirred for 1 h at the same temperature range, and then filtered. The resulting cake was washed with the mixed solvent of ethanol (13 kg) and toluene (146 L) twice, and dried below 50 °C under reduced pressure to give crude compound of **1** (76.9 kg).

The obtained crude **1** (76.9 kg) was dissolved in ethanol (538 L) at 78 °C, the insoluble materials was removed by filtration and washed with ethanol (77 L). The seed compound **1** (3.8 g) were added to the ethanol solution at 55 °C, *t*-butylmethylether (300 kg) was added at 46 to 48 °C, and the suspension was then stirred for 1 h at 46 °C. *t*-Butylmethylether (300 kg) was added at 25 °C and the mixture was stirred for 1 h, settled for 5 h, and stirred for 3 h at 0 to 6 °C. After filtration, the obtained cake was successively washed with the solvent mixture consisting of *t*-butylmethylether (192 kg) and ethanol (48 L), followed by *t*-butylmethylether (231 kg), and then dried below 70 °C under reduced pressure to obtain **1** (68.6 kg, 99.5% purity). ^{1}H NMR (DMSO-d_6, 500 MHz, δ): 0.98 (d, 3H, J = 6.7 Hz), 1.22 (t, 3H, J = 7.1 Hz), 2.15 (s, 3H), 2,27 (s, 3H), 2.92–3.12 (m, 4H), 3.26–3.38 (m, 2H), 4.17 (q, 2H, J = 7.1 Hz), 4.75 (s, 2H), 5.13 (m, 1H), 5.95 (d, 1H, J = 3.9 Hz), 6.68 (s, 1H), 6.78 (d, 2H, J = 8.6 Hz), 6.97 (s, 1H), 7.18 (d, 2H, J = 8.6 Hz), 9.09 (br s, 2H), 9.45 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz, δ): 9.8, 14.5, 16.0, 19.4, 29.0, 45.5, 59.1, 61.0, 65.5, 69.7, 114.0, 115.4, 123.9, 127.4, 128.4, 131.2, 131.7, 134.9, 154.9, 157.1, 169.4. Elemental Analysis: Calcd for $C_{45}H_{28}N_4O_7Cl$: C, 63.08; H, 7.36; N,

3.20; Cl, 8.10. Found: C, 62.98; H, 7.29; N, 3.15; Cl, 8.01. Retention time (analytical HPLC method D): 19.6 min.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://

Copies of NMR spectra of compounds **1**, **7**–**10**, **12**, **14**, and **15**, synthetic scheme for hydrochrolic acid of one isomer among impurity **14**, and HRMS of **15**. (PDF)

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(17) It was estimated as an *E*/*Z* mixture of styryl ether **13** according to specific peaks of *E*-isomer (6,77 ppm, 5.84 ppm [*J*= 12.8 Hz]) and *Z*-isomer (6.10 ppm, 5.22 ppm [*J*= 7.2 Hz])

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(19) Ethanol did not effectively suppress the production of impurities.

(20) The structure was confirmed by HPLC with alternatively synthesized **12** from dimethyl acetal **9** by treatment with sodium methoxide in methanol. The analytical data refers to supporting data. The retention time of **12** was 17.2 min and that of **9** was 24.4 min with analytical HPLC method C (refer to Experimental section).

(21) Reaction calorimetry was measured with Mettler Toledo MultiMax RB04-50 Reaction Calorimeters. The adiabatic temperature was calculated based on 2.00 J/(g K) as the specific heat of the reaction mixture and 1.71 J/(g K) as the specific heat of the triethylamine/toluene solution

(22) The reaction with other strong acids, such as hydrochloric acid, gave a similar result to that with sulfuric acid. The use of weak acids, such as acetic acid, did not promote hydrolysis.

(23) The following solvent systems were attempted: *t*-butylmethylether, *t*-butylmethylether–*n*-hexane, diisopropyether, diisopropyether–*n*-hexane, toluene–*n*-hexane, *n*-hexane, ethyl acetate–*n*-hexane, ethanol–*n*-hexane, *n*-heptane, and ethyl acetate–cyclohexane. Solid was obtained from ethanol–*n*-hexane and diisopropylether; however, the latter easily melted around 20 °C.

(24) Impurity **14** is a mixture of diastereomers and each isomer has a respective retention time of 12.7 and 13.1 min based analytical HPLC method D (refer to Experimental section). One isomer, which is minimally removed and has a retention time of 13.1 min, was isolated from ritobegron ethyl hydrochloride by preparative liquid chromatography and was synthesized as hydrochloride salt. The structure was ascertained with ^{1}H NMR and MS measurement (refer to supporting data); however, the absolute configuration of the hydroxyl group has not been determined.

(25) Impurity **15** has a retention time of 27.3 min under analytical HPLC method C (refer to Experimental section). It was isolated by filtration of insoluble materials in the mixture. The mixture was prepared by adding ethanol and water into the residue after the concentration of the

aqueous acetonitrile solution of hemiacetal **10** with catalytic acetic acid, which was stirred for two weeks at ambient temperature and for 1 day at 50 °C. The structure was determined with ^{1}H NMR, ^{13}C NMR, HMQC, HSQC, and HRMS (refer to supporting data).