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Scalable Ruthenium-Catalyzed Asymmetric Synthesis of a Key Intermediate for the β2-Adrenergic Receptor Agonist

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Supporting Information

ABSTRACT: An enantioselective and robust synthetic process to obtain a useful intermediate for the β2-adrenergic receptor agonist is described. Asymmetric transfer hydrogenation of ketone **1c** by (*S*,*S*)-**3b** (Ms-DENEB) afforded chiral alcohol **2c** in 71% isolated yield and 99% ee. The deprotection completed the synthesis of (*R*)-**5** in 41% overall yield from **1b**, which is readily commercially available.

Respiratory diseases such as asthma and chronic obstructive pulmonary disorder (COPD) are highly prevalent and affect millions of people all over the world.[1] Indacaterol, abediterol, and carmoterol, the most common β2-adrenergic receptor (adrenoreceptor) agonist inhalers, exhibit modest biological activity (Figure 1).[2] Several research programs dealt

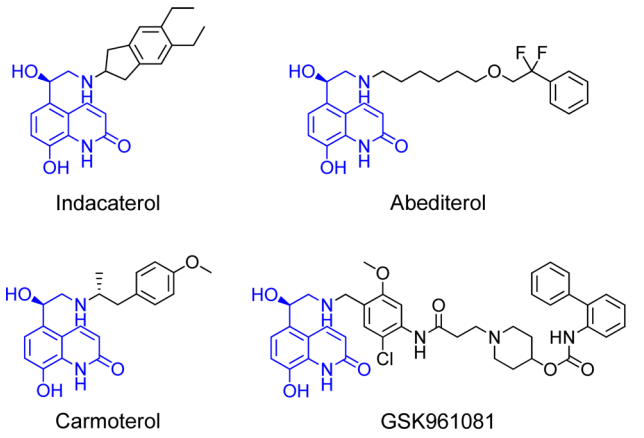
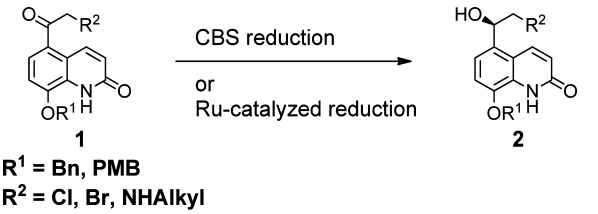


Figure 1. β-Amino-α-hydroxyquinolinones.

with the modification of quinolinone derivatives.[3] This led to the synthesis of several highly biologically active derivatives, including GSK961081, a combination of a β2-adrenergic receptor and a muscarinic receptor antagonist.[4] Chiral β-amino-α-hydroxyquinolinone moieties are essential for biological activity, and we synthesized a series of quinolinone analogues with the same functionalities with the aim of developing drug candidates.

A previous synthesis of a series of hydroxyquinolinones (**2**) was adopted in part from that of ketone **1** by asymmetric reduction (Scheme 1). Asymmetric reductions of ketone intermediates **1**, including Corey–Bakshi–Shibata (CBS) reduction[5] and Ru-catalyzed hydrogenation,[6] have been

Scheme 1. Reported synthetic approach



reported. The CBS method is the most widely applied procedure and affords excellent results for a wide range of ketone substrates. Theravance Inc. has reported the use of CBS reduction to prepare several biphenyl derivatives with β2-adrenergic receptor agonist and muscarinic receptor antagonist activity.[7] GSK961081 has been prepared by CBS reduction of ketone.[8]

Ru-catalyzed asymmetric transfer hydrogenation (ATH) of a ketone has been reported for the preparation of indacaterol and abediterol.[9] The synthetic method for carmoterol was based on reduction using $NaBH_4$ as a reducing agent via internal asymmetric induction.[10] These methods can be developed to prepare useful compounds in excellent yields, but the key asymmetric reduction methods are impractical for manufacturing. In the development of our drug candidates, we wished to avoid using a stoichiometric boron reagent. In addition, due to the limited availability of some substrates, we did not want the progress of the reaction to be limited by the substrate, which has a moiety essential for biological activity.[11] Consequently, we developed an alternative synthetic route to improve the synthesis of the intermediate in terms of safety, environmental friendliness, and robustness. Herein we report a novel efficient synthesis of key intermediate **2** via Ru-catalyzed ATH of ketone **1**.[12]

Recently, Takasago International Corporation developed new oxo-tethered ruthenium amide complexes, including DENEB.[13] This catalyst exhibited excellent catalytic performance for both ATH and H_2 hydrogenation of acetophenone derivatives without any cocatalysts to give chiral secondary alcohols with high levels of enantioselectivity. In conjunction with the development of our drug candidates, we applied a novel Ru-catalyzed ATH reaction to ketone **1** to produce the chiral alcohol **2**.

In the initial study, we carried out ATH of α-chloroketone **1a** with tethered complex (*R*,*R*)-**3a** (Ts-DENEB) in a mixture of

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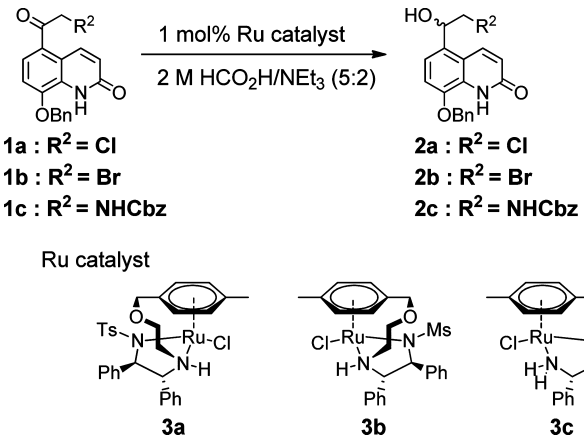
HCO_2H/NEt_3 to give the corresponding chiral alcohol **2a**, which could be transformed to various compounds (Scheme 2).

Scheme 2. ATH of ketones



After screening several cosolvents,[14] we found that $CHCl_3$ led to complete conversion after 2 h at 50 °C, giving the chiral alcohol **2a** in good yield with moderate to good ee (Table 1, entries 1 and 2). ATH using the more bulky substrate **1b** gave miserable yields, but the enantioselectivity was slightly better than for **1a** (entries 3 and 4). In those cases, reduction of the ketone proceeded with the S_N2 substitution on the bromo functional group with HCO_2H, giving a large amount of nucleophilic substitution compounds as major side products.[15] The yield did not change dramatically upon decreasing the reaction temperature (entry 5). To prevent nucleophilic substitution, HCO_2K was used as an insoluble salt, which improved the yield dramatically (entry 6), but it was difficult to avoid nucleophilic substitution of the substrate **1b**. Consequently, asymmetric reduction of *N*-protected α-amino ketone **1c** was conducted using (*S*,*S*)-**3b** (Ms-DENEB) at 50 °C for 2 h to afford the corresponding (*R*)-**2c** in high yield with 92% ee as the desired configuration (entry 7). The Cbz group is a much more practical protecting group for amine in terms of easy deprotection at the subsequent step. The Cbz group can be removed by typical hydrogenation under mild conditions to prevent reduction of the quinolinone double bond. Hydrogenation of the *N*-Bn moiety instead of Cbz gave a troublesome byproduct via olefin reduction.[16] Asymmetric reduction of **1c** with (*R*,*R*)-**3a** proceeded to afford (*S*)-**2c** in quantitative yield, but the ee was lower than that obtained using Ms-DENEB (entry 8). The reduction reactions were carried out at lower temperatures to achieve slightly better enantioselectivity, but the reaction time was longer in each case (entries 9 and 10). However, the use of the typical catalyst (*S*,*S*)-**3c** (RuCl(TsDPEN(*p*-cymene))[6c] gave the product **2c** with very low conversion (entry 11). As a further investigation, the influence of the solvent on the ATH of ketone **1c** was studied.[17] However, no activity was measured when the reaction proceeded in alcohol-like IPA, which also acts as a proton donor and accelerates product release from the reaction intermediate. Among several compounds investigated, the transfer hydrogenation of ketone **1c** without any cosolvent was improved in terms of chemical yield and enantioselectivity by using (*R*,*R*)-**3a** in the presence of a high concentration of hydrogen donor (entry 12). Finally, asymmetric reduction with (*S*,*S*)-**3b** gave the corresponding desired chiral alcohol (*R*)-**2c** in quantitative chemical yield with high enantio purity (entry 13). Incidentally, the reduced olefin byproduct was not observed under the ATH conditions by LC-MS analysis. We also managed to avoid using $CHCl_3$, which is not an environmentally friendly solvent.

Table 1. ATH of ketones catalyzed by (*R*,*R*)-3a, (*S*,*S*)-3b, or (*S*,*S*)-3c[a]

entry	ketone	cat.	temp (°C)	time (h)	HPLC area %	% ee[b]
1	**1a**	**3a**	50	2	94	70 (*S*)
2	**1a**	**3b**	50	2	94	90 (*R*)
3	**1b**	**3a**	50	2	36	75 (*S*)
4	**1b**	**3b**	50	2	56	92 (*R*)
5	**1b**	**3b**	25	24	67	95 (*R*)
6[c]	**1b**	**3b**	25	24	94	94 (*R*)
7	**1c**	**3b**	50	2	99	92 (*R*)
8	**1c**	**3a**	50	2	99	69 (*S*)
9	**1c**	**3a**	25	24	99	75 (*S*)
10	**1c**	**3b**	25	24	99	95 (*R*)
11	**1c**	**3c**	25	24	53	90 (*R*)
12[d]	**1c**	**3a**	50	26	98	83 (*S*)
13[d]	**1c**	**3b**	50	6	99	95 (*R*)

[a]Standard reaction conditions: ruthenium catalyst (1 mol %), 2 M HCO_2H/NEt_3 (5:2), and 0.5 M $CHCl_3$. [b]The ee was determined by HPLC analysis using DAICEL CHIRALPAK AS-RH, 5 μm, 4.6 × 150 mm column. [c]10 equiv of HCO_2K and 5 equiv of HCO_2H in place of HCO_2H/NEt_3. [d]0.25 M HCO_2H/NEt_3 (5:2) without 0.5 M $CHCl_3$,

From the point of view of enantioselectivity, a promising result was obtained with the oxo-tethered ruthenium amide complex (*S*,*S*)-**3b** in comparison with (*R*,*R*)-**3a**. As reported by Takasago group, the Ms-analogue provided a better result than the Ts-analogue in view of the ATH enantioselectivity of 1-acetophenone derivatives.[13] Our results support the conclusion that the oxo-tethered ruthenium complex shows remarkable catalytic performance for both ATH and hydrogenation of ketones. As reported by Wills's group,[18] the structure of the substrate might also influence enantioselectivity due to both the arene/aryl interaction and potential repulsive interaction. ATH of the Cbz moiety of **1c** takes place through a transition state via the well-established arene/aryl interaction, preventing steric interactions (Figure 2).

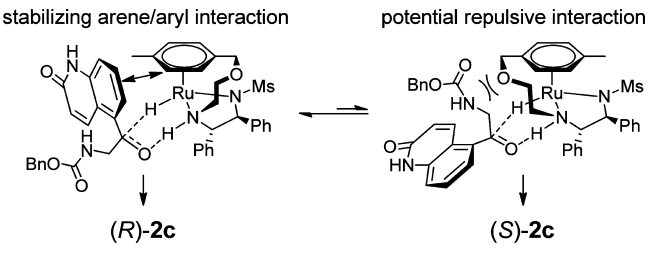


Figure 2. Predicted reduction of ketone **1c**.

As indicated in Table 1, a highly enantiopure product, (*R*)-**2c**, was obtained, but the enantiopurity (95% ee) was not sufficient for our drug candidate study. Therefore, we have developed an efficient method for achieving an improvement in enantiopurity (>99% ee). Among the compounds tested, we found that the addition of *i*-PrOH to the reaction mixture directly as an antisolvent gave the desired product (*R*)-**2c** in 73% isolated yield with >99 area% and 99% ee at a relatively low catalyst concentration (Scheme 3). This process is concise

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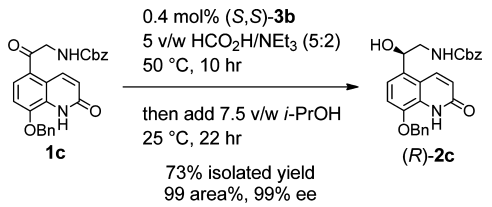
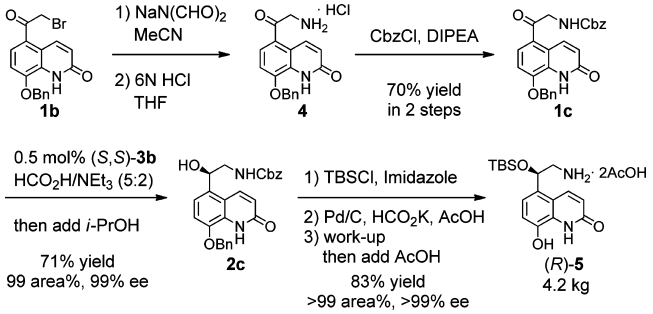
Scheme 3. Improvement of enantiopurity by crystallization



and straightforward for manufacturing operations. Interestingly, the enantiopurity of the mother liquor was much higher than that of the solid when alternative antisolvents such as acetonitrile, dichloromethane, and EtOAc were used (see Supporting Information).

A high-yielding synthesis of the *N*-Cbz-protected ketone **1c** from the commercially available compound **1b** via amidation and Cbz protection was developed (Scheme 4). With

Scheme 4. Synthesis of key intermediate (*R*)-5



compound **1c** in hand, we proceeded with ATH to give the desired chiral alcohol **2c** in good isolated yield with high ee. The results were consistent with previous lab-scale trials, and these process conditions were successfully demonstrated in a reproducible manner to give the product on a multikilogram scale. The chiral secondary alcohol of **2c** was protected by a TBS group, which allowed easy deprotection. The resulting TBS-protected product, without further isolation, was treated under hydrogenation conditions, involving simultaneous deprotection of the *N*-Cbz and *O*-Bn groups. Preliminary results showed that reduction by hydride methods using hydrogen gave unsatisfactory selectivity, with reduction of the double bond of the quinolinone moiety.[19] Among the various conditions examined, transfer hydrogenation with Pd/C/HCO_2K gave the product **5** with manageable levels of the side product. After aqueous workup, the desired (*R*)-**5** was isolated as an acetate salt in 83% yield, with >99% purity and >99% ee by the addition of AcOH to the organic layer.[20] Downgrading of the enantiopurity of **2c** did not occur in subsequent steps under the conditions used. The resulting chiral alcohol (*R*)-**5** was converted to several drug candidates.[21]

In conclusion, an efficient and scalable enantioselective synthesis of the intermediate (*R*)-**5** for a β2-adrenergic receptor agonist has been developed. This synthesis features an enantioselective reduction of α-amino-1-acetophenone derivative **1c** using the novel chiral ruthenium catalyst Ms-DENEB. Effective transfer hydrogenation of the chiral alcohol afforded the primary amine (*R*)-**5** in >99% ee. Starting from the commercially available quinolinone derivative **1b**, the key scaffold of β2-adrenergic receptor agonists was prepared in 41% yield over four steps. This synthetic method is applicable to the preparation of various analogues of (*R*)-**5** on a multikilogram scale.

EXPERIMENTAL SECTION

General Information. All reaction carried out under nitrogen. Asymmetric transfer hydrogenation generates CO_2 gas, so the reactor should be vented. Melting points (m.p.) were measured using a Yanaco MP-S3 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL-400 (400 and 100 MHz) as noted. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (Hz), integrationm and major or minor of rotamers. Optical rotations were obtained using JASCO P-1020 with a 1 mL cell and a 0.1 dm path length. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were obtained from Tharmo Nicolet AVATAR 320. High-resolution mass spectra were obtained from SHIMADZU LCMS-IT-TOF. Data for residual ruthenium were recorded on Rigaku EDXL300.

General Procedure of Asymmetric Transfer Hydrogenation. *Entries 1–5 and 7–11.* To compound **1a**, **1b**, or **1c** (200 mg) and ruthenium catalyst (1 mol %) were added $CHCl_3$ (0.5 M), HCO_2H/TEA (5:2, 2 M) under N_2 atmosphere. The resulting slurry was agitated at any temperature.

Entries 6. To compound **1b** (200 mg, 0.537 mmol), (*S*,*S*)-**3b** (3.1 mg, 0.0054 mmol)m and HCO_2K (452 mg, 5.37 mmol) were added $CHCl_3$ (1.07 mL) and HCO_2H (124 mg, 2.69 mmol) under N_2 atmosphere. The resulting slurry was agitated at 25 °C for 24 h.

Entries 12, 13. To compound **1c** (200 mg, 0.452 mmol) and (*R*,*R*)-**3a** (*S*,*S*)-**3b** (0.0045 mmol) was added HCO_2H/TEA (5:2, 1.81 mL) under N_2 atmosphere. The resulting slurry was agitated at 50 °C.

*Preparation of 5-(2-Aminoacetyl)-8-(benzyloxy)-1,2-dihydroquinolin-2-one Hydrochloric Acid Salt (**4**).* To a 300 L glass lined vessel was added 8-(benzyloxy)-5-(2-bromoacetyl)-1,2-dihydroquinolin-2-one (**1b**, 8.43 kg, 22.6 mol), $NaN(CHO)_2$ (2.77 kg, 28.3 mol), and acetonitlile (66.3 kg) under N_2 atmosphere. The resulting slurry was warmed to 65 °C for 50 min and agitated at 65–68 °C for 10 h until >99.0% conversion was achieved by HPLC. The batch was allowed to cool to 10 °C for 10 h. To the resulting slurry was added THF (75.6 kg) and 6 N HCl (18.4 kg) under N_2 atmosphere. The resulting slurry was warmed to 65 °C for 70 min and stirred at 65–68 °C for 6 h until >99.0% conversion was achieved according to HPLC analysis (refer to the HPLC method in the Supporting Information). The batch was allowed to cool to 23 °C for 15 h and then cooled to 5 °C for 55 min. After aging at 0–5 °C for 1 h, the solid was collected by filtration. The wet cake of compound **4** was washed with THF (60.0 kg) and obtained as a white solid (9.80 kg).

A sample of compound **4** was purified for NMR analysis by recrystallization from EtOH/H_2O. The purified compound **4** gave the NMR data as follows. ^{1}H NMR (DMSO, 400 MHz): δ = 11.15 (br s, 1H), 8.71 (d, J = 10.2 Hz, 1H), 8.30 (br s, 3H), 7.87 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 6.8 Hz, 2H), 7.38 (t, J = 7.3 Hz, 2H), 7.35–7.29 (m, 2H), 6.72 (d, J = 10.2 Hz, 1H), 5.45 (s, 2H), 4.54 (s, 2H). ^{13}C NMR (DMSO, 100 MHz): δ = 193.8, 160.6, 148.3, 137.1, 135.9, 130.3, 128.4, 128.1, 127.9, 126.6, 124.8, 123.0, 117.5, 110.8, 70.1, 45.6; HRMS calculated for $C_{18}H_{17}N_2O_3$ (M + H): 309.1234, found: 309.1227. The melting point is 222 °C (degradation).

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*Preparation of Benzyl N-{2-[8-(benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-oxoethyl} Carbamate (**1c**).* To a 600 L glass-lined vessel was added wet compound **4** (9.80 kg, <22.6 mol) and THF (59.8 kg) under N_2 atmosphere. To the slurry was added CbzCl (4.25 kg) at 4 °C for 2 min, and the resulting mixture was aged at 0−4 °C for 30 min. The solution of DIPEA (7.33 kg) and THF (8.82 kg) was charged over 75 min at 0−3 °C. The resulting slurry was stirred at 2−5 °C for 40 min until the reaction was deemed complete (Refer to HPLC method in Supporting Information). The reaction was quenched by addition of the solution of methanol (30.0 kg) and deionized water (37.8 kg) at 2−10 °C for 35 min. The resulting slurry was stirred at 6−10 °C for 18.5 h followed by stirring at −4 to 3 °C for 1 h. The solid was collected by filtration and washed with the solution of methanol (30.0 kg) and ion-exchanged water (37.8 kg) followed by methanol (46.5 kg). Drying in vacuum at 50 °C afforded compound **1c** as a white solid (6.99 kg, 69.7% from **4**, 99.7% purity).

^{1}H NMR (DMSO, 400 MHz): δ = 11.02 (br s, 1H), 8.51 (d, J = 10.0 Hz, 0.9H, major), 8.36 (d, J = 10.0 Hz, 0.1H, minor), 7.78 (d, J = 8.6 Hz, 0.9H, major), 7.72 (d, J = 8.3 Hz, 0.1H, minor), 7.63 (t, J = 5.9 Hz, 0.9H, major), 7.61−7.56 (m, 2.1H), 7.42−7.20 (m, 9H), 6.65 (d, J = 10.0 Hz, 0.9H, major), 6.57 (d, J = 10.0 Hz, 0.1H, minor), 5.41 (s, 2H), 5.04 (s, 1.8H, major), 4.99 (s, 0.2H, minor), 4.44 (d, J = 5.9 Hz, 2H). ^{13}C NMR (DMSO, 100 MHz): δ = 197.6, 160.7, 156.6, 147.4, 137.4, 137.0, 136.0, 130.2, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 125.1, 124.8, 124.2, 117.4, 110.7, 70.0, 65.4, 48.7; HRMS calculated for $C_{26}H_{23}N_2O_5$ (M + H): 443.1601, found: 443.1598. The melting point is 170−172 °C.

*Preparation of Benzyl N-[(2R)-2-[8-(Benzyloxy)-2-oxo-1,2-dihydroquinolin-5-yl]-2-hydroxyethyl]carbamate (**2c**).* To a 300 L glass lined vessel was added degassed HCO_2H (17.3 kg, 378.3 mol) under N_2 atmosphere. Triethylamine (15.3 kg) was charged at 6−10 °C for 2 h. (***Caution!! Generating gas***!) The resulting solution was evacuated and backfilled with N_2 (3 cycles) and aged for 19 h. To the solution was added compound **1c** (6.99 kg, 15.8 mol) and (*S*,*S*)-Ms-DENEB (0.0457 kg, 0.0158 mol) at 13 °C. The resulting slurry was degassed twice more. The slurry warmed to 50 °C for 1 h and agitated at 50−54 °C for 6 h until >99.5% conversion was achieved according to HPLC analysis (***Caution!! Vigorous gas evolution!*** Refer to HPLC method in the Supporting Information). To the reaction mixture was charged IPA (41.0 kg) and the seed of compound **2c** (ca. 0.1% to the product) at 27−53 °C and the resulting mixture aged at 25 °C for 16 h until the crystallization was complete. The solid was collected by filtration and washed twice with cooled IPA (−15 °C, 31.0 kg +14.0 kg). Drying in vacuum at 50 °C afforded compound **2c** as a white solid (5.00 kg, 71.2%, 99.7% chemical purity, 98.6% ee).

^{1}H NMR (DMSO, 400 MHz): δ = 10.66 (br s, 1H), 8.25 (d, J = 10.0 Hz, 0.9H, major), 7.93 (d, J = 10.0 Hz, 0.1H, minor), 7.57 (d, J = 7.1 Hz, 2H), 7.43 (t, J = 5.6 Hz, 1H), 7.40−7.00 (m, 10H), 6.55 (d, J = 10.0 Hz, 0.9H, major), 6.20 (d, J = 10.0 Hz, 0.1H, minor), 5.54 (d, J = 4.2 Hz, 1H), 5.28 (s, 2H), 5.10−4.94 (m, 3H), 3.26−3.18 (m, 1H), 3.09−3.00 (m, 1H). ^{13}C NMR (DMSO, 100 MHz): δ = 160.9, 156.4, 143.3, 137.2, 136.7, 136.5, 132.2, 129.2, 128.3, 127.9, 127.8, 127.7, 127.6, 122.0, 119.3, 116.8, 112.0, 69.8, 68.1, 65.2, 48.3; HRMS calculated for $C_{26}H_{25}N_2O_5$ (M + H): 445.1758, found: 445.1772. The melting point is 143−145 °C. Residual ruthenium is 4.1 ppm.

$[\alpha]_D^{22} = +18.4 \quad (c = 2.10, \text{DMSO})$

*Improvement Enantiopurity of Compound **2c** in Filtrate from the Mother Liquor and Isolation of Racemate.* IPA was evaporated from 800 mL of the mother liquor of **2c** under reduced vacuum pressure. To the resulting solution (148 g, 83% ee) was added EtOAc (200 mL) and stirred for 30 h at room temperature. The resulting slurry was stirred in ice bath for 4 h. The solid was collected by filtration and washed with the solution of EtOAc (15 mL) and heptane (15 mL) followed by cooled EtOAc (40 mL). The collected compound racemic-**2c** as a white solid (1.46 g, 3.5%, 0.82% ee), and the enantio purity in the mother liquor was higher than the original (95.5% ee). The melting point is 168 °C.

*Preparation of 5-[(1R)-2-Amino-1-[(tert-butyldimethylsilyl)oxy]ethyl]-8-hydroxy-1,2-dihydroquinolin-2-one diacetic acid salts ((R)-**5**).* To a 600L glass lined vessel was added compound **2c** (5.00 kg, 11.3 mol), Imidazole (1.55 kg, 22.8 mol), DMF (23.6 kg) and iPrOAc (11.0 kg) under N_2 atmosphere. To the solution was added 50 wt % TBSCl in EtOAc (6.78 kg, 22.6 mol) at 9−15 °C for 5 min. The solution heated to 75 °C for 33 min and aged at 75−82 °C for 4 h until >99.0% conversion was achieved according to HPLC analysis (refer to HPLC method in the Supporting Information). The batch was cooled to 9 °C and quenched by addition of deionized water (25.0 kg) and iPrOAc (22.0 kg) at 9−17 °C. The organic layer containing TBS protected compound **2c** was separated and washed twice with deionized water (25.0 kg + 25.0 kg). The organic layer was allowed to remain for 18 h under N_2 atmosphere below 17 °C.

To the solution of TBS protected compound **2c** (<11.3 mol) was added 2-Me-THF (51.9 kg) and methanol (15.8 kg) under N_2 atmosphere. To the reaction mixture was charged HCO_2K (3.79 kg, 45.2 mol), 5% Pd/C 50% wet (0.50 kg, 0.11 mol), and AcOH (2.70 kg, 45.2 mol) at 8−10 °C. The slurry was warmed to 30 °C and aged at 30−36 °C for 4 h until >99.0% conversion was achieved according to HPLC analysis (refer to the HPLC method in the Supporting Information). To the slurry of Pd/C and the desired compound was added deionized water (40.0 kg) and the desired compound was dissolved by stirring at 25−37 °C for 30 min. The organic layer was separated and filtered through Celite (3 kg) to remove Pd/C. The filter cake was washed with 2-Me-THF (16.6 kg) through the line. The combined filtrate containing the desired compound was allowed to remain for 16 h under N_2 atmosphere below 23 °C. To the solution was added AcOH (1.00 kg, 17.0 mol) and the seed of (*R*)-**5** (ca. 0.1% to the product) at 31 °C. The resulting mixture was stirred at 31−35 °C for 1 h to initiate crystallization. To the slurry was added AcOH in five portions (0.47 kg + 0.47 kg + 0.47 kg + 0.47 kg + 0.47 kg) every 1 h at 32−35 °C. The resulting mixture was aged for 18 h at 18−33 °C and cooled to 6 °C for 1 h, followed by stirring at 3−6 °C for 1 h. The solid was collected by filtration and washed with iPrOAc (36.1 kg). Drying in vacuum at 50 °C afforded (*R*)-**5** as a white solid (4.25 kg, 83.1%, 99.7% purity, 99.2% ee). The overall yield was 41.3% over four steps from **1b**.

^{1}H NMR (DMSO, 400 MHz): δ = 8.23 (d, J = 10.0 Hz, 1H), 7.88 (br s, 4H), 6.99 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.50 (d, J = 10.0 Hz, 1H), 5.08 (dd, J = 4.9, 2.2 Hz, 1H), 2.81−2.70 (m, 2H), 1.86 (s, 6H), 0.81 (s, 9H), 0.03 (s, 3H), −0.19 (s, 3H). ^{13}C NMR (DMSO, 100 MHz): δ = 172.5, 160.7, 143.8, 136.8, 128.8, 128.7, 121.5, 120.5, 116.7, 113.9, 73.1, 49.0, 25.7, 21.7, 17.9, −4.9; HRMS calculated for

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$C_{26}H_{25}N_2O_5$ (M + H): 335.1785, found: 335.1774. The melting point is 140 °C (degradation). Residual ruthenium is not detected. $[\alpha]_D^{22} = -37.7$ (c = 2.02, DMSO).

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR, IR, MS, and HPLC spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

M.K. and T.I. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(11) Indacaterol is prepared via epoxide intermediate with low selectivity, and the diversity of the side chain is subject to restrictions by the synthetic approach of abediterol. See: ref 9.

(12) We also screened a number of enzymatic agents for preliminary investigation of the reaction using Codex KRED screening kit containing 24 ketoreductases that is a commercially available from Codexis (http://www.codexis.com).

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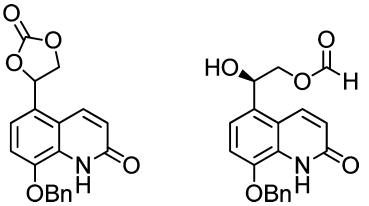
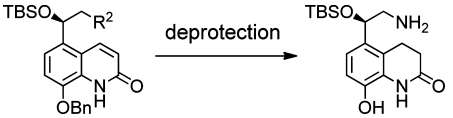
(14) Several solvents such as toluene, $CHCl_3$, *i*-PrOAc, 2-Me-THF, 1,2-dimethoxyethane, MeCN, DMF, DMSO, water, anisole, and *i*-PrOH were investigated. Among them, $CHCl_3$ and anisole gave a better reaction conversion. Especially, $CHCl_3$ was a preferable solvent for the ATH.

(15) The predicted major byproducts via nucleophilic substitution are as shown below (by LC-MS analysis).



(16) The deprotection of *N*-Bn group has a critical issue on preventing the production of byproduct **6** via the reduction of a double bond.



R^2 = NHBn 4.0 area%
R^2 = NHCbz 0.1 area%

(17) Several solvents such as anisole, MeOH, and *i*-PrOH were investigated.

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(19) It should be avoided to produce the side product **6** that is an extremely difficult to remove by crystallization.

(20) No residual ruthenium in (*R*)-**5** was detected by XRF (X-ray fluorescence analysis).

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