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Ir/SpiroPAP Catalyzed Asymmetric Hydrogenation of a Key Intermediate of Montelukast: Process Development and Potential Impurities Study

Guo-Liang Zhu,[†] Xiang-Dong Zhang,[†] Li-Jun Yang,[†] Jian-Hua Xie,[‡,§] Da-Qing Che,[†,§] Qi-Lin Zhou,[‡,§] Pu-Cha Yan,*[,†] and Yuan-Qiang Li*[,†]

[†]Zhejiang Jiuzhou Pharmaceutical Co., Ltd., 99 Waisha Road, Jiaojiang District, Taizhou City, Zhejiang Province 318000, P. R. China

[‡]State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, P. R. China

[§]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, P. R. China

Supporting Information

ABSTRACT: An efficient and robust process for the asymmetric hydrogenation of a key intermediate of Montelukast using the highly efficient and selective chiral spiro catalyst Ir/SpiroPAP is reported. The developed process was conducted at mild reaction temperature (30 °C) under a hydrogen pressure of 20 atm with low catalyst loading (S/C = 30 000) and afforded the desired chiral alcohol intermediate in 99.5% ee. This process currently has been carried out at 30 kg scale. The process-related impurities (impurities **I**–**V**) were also identified, synthesized, and characterized by LC-MS and NMR techniques.

INTRODUCTION

Montelukast sodium (Singulair) is a leukotriene receptor antagonist (LTRA) developed by Merck & Co which is used for the maintenance treatment of asthma and to relieve symptoms of seasonal allergies.[1] It acts as a selective antagonist of the leukotriene D4 receptor which leads to the reduction of bronchoconstriction and results in less inflammation.

The first and conventional process for production of montelukast sodium (**1**) exploits commercially available alcohol **2** and thiol carboxylic acid **3** as starting materials (Scheme 1).[2] Although its structure and consequently its synthesis is complex, montelukast sodium has only a single stereocenter, which is usually installed via asymmetric reduction of the bulky and highly functionalized ketone **4**. Various reduction methodologies have been developed for the preparation of optically pure alcohol **5**, including (−)-DIP-Cl[3] or (*R*)-Me-CBS/borane[4] reduction, transition metal catalyzed asymmetric hydrogenation[5] or transfer hydrogenation,[6] and enzymatic or biomimetic methods.[7] The multiple functional groups in ketone **4** are labile or sensitive to metal hydrides and/or hydrogenation conditions. The widely used production process applied (−)-DIP-Cl as the reduction reagent primarily because of its mild reaction condition and selectivity. However, there are still shortcomings associated with (−)-DIP-Cl reduction, such as corrosivity and moisture sensitivity of the reagent, as well as poor atom economy, tedious workup procedure, and heavy burden on the waste treatment (at least 1.5−1.8 equiv is needed). Recently, a KetoREDuctase (KRED) method with very high enantioselectivity was developed as an alternative economical and simple process to the (−)-DIP-Cl reduction.[7f]

The transition metal catalyzed asymmetric hydrogenation has proved to be an efficient and economically feasible method for preparing chiral compounds.[8] However, there is still no efficient large-scale process for asymmetric hydrogenation of ketone **4**. Researchers at Lonza[5a] used the [(*R*)-BINAP-$RuCl_2$-(*R*)-DAIPEN] system (up to S/C = 5000) to achieve the desired transformation in 86% yield and up to 96.9% ee, though chlorobenzene was used as the cosolvent. They also showed that, under certain ruthenium- or iridium-catalyzed asymmetric hydrogenantion conditions, the olefin-reduced compound is the major product. A Ru-catalyzed asymmetric hydrogenation of a related montelukast intermediate was reported by Fox et al. earlier this year. Catalyst ((*R*)-Xyl-BINAP)((*R*,*R*)-DPEN)-$RuCl_2$ afforded an enantioselectivity of 99% ee in the hydrogenation step on a multigram lab scale at S/C = 5000.[9] Herein, we developed an economical and suitable for scale-up process by applying a highly efficient, selective, and stable catalyst Ir/SpiroPAP[10] to obviate many previous problems and limitations. Furthermore, a comprehensive study has been undertaken to identify, synthesize and characterize five impurities present in the hydrogenation of ketone **4** using spectroscopic and spectrometric techniques.

RESULTS AND DISCUSSION

The iridium catalysts with chiral tridentate spiro ligands, SpiroPAP, have proved to be extremely efficient for the asymmetric hydrogenation of ketones, especially for the acetophenone derivatives; the TON is up to 4 550 000.[10a]

Asymmetric Hygrogenation of 4. We initially carried out the hydrogenation of **4** under similar conditions previously optimized for the reaction of acetophenone (S/C = 2000, 0.04 equiv base, 15 atm H_2, 30 °C). As indicated in Table 1, the effects of ligands, solvents, and other reaction parameters on reactivity and enantioselectivity were screened. Through a preliminary comparison of various chiral SpiroPAP ligands, it was found that introduction of an alkyl group at the 6- position of the pyridine ring of the ligand reduced the enantioselectivity

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Scheme 1. Structure of Montelukast Sodium (1) and Installation of the Stereocenter

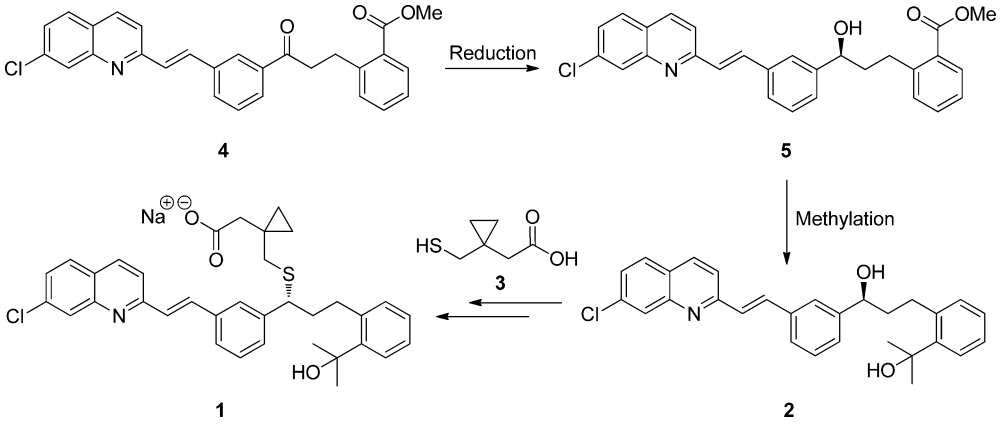
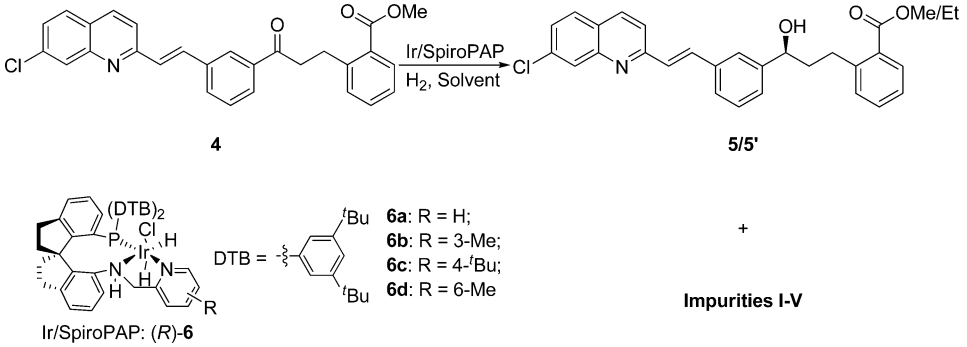


Table 1. Asymmetric Hydrogenation of Ketone 4 with Optimizing Reaction Conditions[a]



entry	(*R*)-**6**	S/C[b]	solvent (V/V)	(**5** + **5**′):**I**:(**II** + **III**):**IV**:**V** (%)[c]	time (h)	ee[d] (%)
1	**6a**	2000	EtOH	95.2:0:0.7:0.1:4.0	1	99.1
2	**6b**	2000	EtOH	95.8:0:0.3:0.1:3.8	0.5	99.6
3	**6c**	2000	EtOH	95.6:0:0.6:0.1:3.7	1	99.5
4	**6d**	2000	EtOH	95.3:0:0.9:0.1:3.7	1	98.9
5	**6b**	2000	MeOH	99.3:0:0.3:0:0.4	0.5	97.0
6	**6b**	2000	EtOH/DMF (5/1)	91.4:2.2:2.0:0.1:4.3	0.5	97.3
7	**6b**	2000	EtOH/Tol (5/1)	93.8:1.7:0.4:0:4.1	0.5	98.2
8	**6b**	2000	EtOH/DCM (5/1)	87.7:0.2:4.1:0.2:7.8	0.5	95.0
9[e]	**6b**	2000	EtOH	90.2:0.5:5.5:0.6:3.2	0.5	99.2
10[f]	**6b**	2000	EtOH	88.6:1.2:6.4:0.1:3.7	0.5	99.0
11[g]	**6b**	10000	EtOH	96.0:0:0.3:0.1:3.6	2	99.6
12[g]	**6b**	30000	EtOH	95.6:0.1:0.5:0.1:3.7	5	99.5

[a]Reaction conditions unless otherwisely noted: 2.0 mmol scale, solvent (8.0 mL), 15 atm H_2, 30 °C. [b]Substrate to catalyst ratio. [c]Determined by HPLC analysis on a XDB-C8 column. [d]Determined by HPLC analysis on a chiral AS-H column. The absolute configuration of **5** is *S* by comparing the specific rotation with reported data. [e]Reaction temperature was 50 °C. [f]Reaction temperature was 70 °C. [g]P_{H2} = 20 atm, 100 mmol scale.

(compare entry 4 with entry 1); however, the presence of an alkyl group at either the 3- or 4-position of the pyridine ring could increase the enantioselectivity (compare entries 2 and 3 with entry 1). The catalyst (*R*)-**6b** was the most efficient and enantioselective catalyst; full conversion was obtained within 30 min and gave the product in 99.6% ee. We were pleased to find that the byproducts with over reduction of the ethylene bridge could be controlled to <1%. As the solubility of ketone **4** in ethanol was extremely poor (~1.4 g/L), other solvent systems were tried in order to reduce the volume of solvent. Although the solubility of ketone **4** in methanol was better than in ethanol, the enantiomeric excess was reduced to 97% (Table 1, entry 5). When cosolvent was used, the depression of enantioselectivity had also been observed, and the impurities increased (Table 1, entries 6–8). Solvent screening showed that ethanol gave the best enantioselectivity. When the reaction was performed at higher temperature, such as 50 or 70 °C, the product was obtained with only a slightly lower enantiomeric excess, but more impurities could be detected in the reaction solution (Table 1, entries 9 and 10). When the catalyst loading was lowered to 0.01 mol % (S/C = 10000), the hydrogenation product (*S*)-**5**/**5**′ still could be obtained in 99.6% ee with full conversion within 2 h under a hydrogen pressure of 20 atm (Table 1, entry 11). Lowering the catalyst loading further to 0.0033 mol % (S/C = 30000), the reaction was completed within 5 h, providing the product (*S*)-**5**/**5**′ in 99.5% ee (Table 1, entry 12).

During our initial development work, we were plagued with inconsistent conversion under nominally identical conditions. After some investigation, we find that this process is sensitive to

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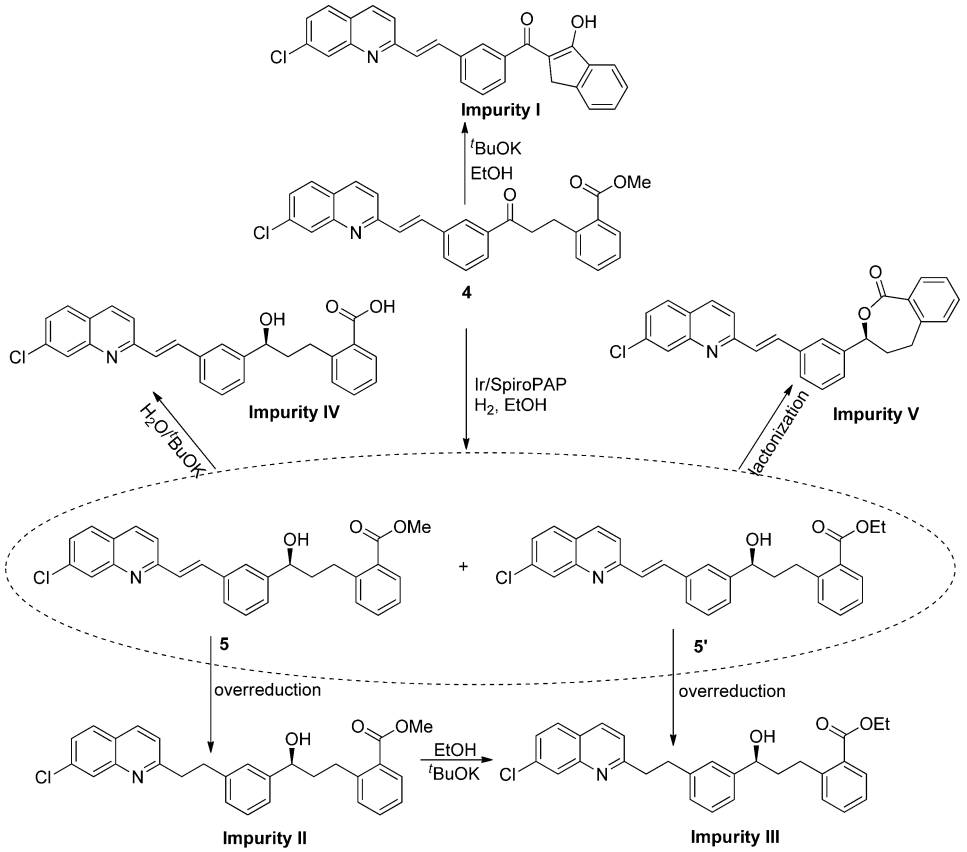
Scheme 2. Formation and Structure of Potential Impurities



the purity of the substrate ketone **4**, especially depends on the remaining traces of palladium in ketone **4** from the former coupling reaction.[3a] And careful refinement of ketone **4** was necessary to ensure reproducibility of the hydrogenation reaction.[11] Therefore, we chose to conduct the large scale experiments at S/C = 30 000 to ensure acceptable quality was achieved. Further optimization of this step should focus on reduction of the catalyst loading. The developed asymmetric hydrogenation condition was applied on the large-scale production for multiple batches (from 25 kg to a maximum of 75 kg), and all gave the same results as from the lab scale.

Formation of Potential Impurities. In the aforementioned optimized reaction conditions, ethanol was the best reaction solvent. The base ^{t}BuOK is known to be critical as an additive in the Ir/SpiroPAP catalyzed asymmetric hydrogenation of ketone and ketone esters.[10]

Under the optimized reaction condition of asymmetric hydrogenation of **4**, it was found that the product was a mixture of methyl and ethyl esters (**5** and **5′**) due to the occurrence of ester exchange between the substance and the solvent. It was obvious that the ratio of **5**/**5′** was dependent on the reaction time, and the measured enantiomeric excess of **5** and **5′** was almost the same. If the hydrogenation proceeded slowly, in parallel to the hydrogenation, ketone **4** was subjected to undesired reaction, namely, a intramolecular condensation reaction that leads to impurity **I** (Scheme 2). In the ^{1}H NMR spectrum of this impurity, the singlet signal appearing at δ 3.56 ppm with two proton integration was evidence for the presence of CH_2 group in the indenol moiety. This was further substantiated by the DEPT spectrum, which displayed a methylene carbon signal (negative signal) at δ 33.97 ppm. Overreduction of **5** and **5′** leaded to the ethane bridged analogues impurity **II** and impurity **III**. The compounds **5** and **5′** were hydrolyzed to the corresponding acid (impurity **IV**) under the basic condition when water existed.[12] Another critical impurity **V** was observed which lactonized from hydrogenation products **5** and **5′**. Although the reaction mixture seemed to be complicated, it was pleasing to find that impurity **V** could be transformed to product **5′** in the following workup steps. We also examined the mixture of **5**, **5′**, and impurity **V**; all of these compounds could react with MeMgCl to provide the same product **2** in high yield. Typically, the hydrogenation reaction was judged to be complete according to the HPLC analysis of an aliquot, the total area % of **5**, **5′**, and impurity **V** was usually >99%. After crystallization from an aqueous ethanol solvent system, the monohydrates of (*S*)-**5** and **5′** were obtained in 90−95% yield, >99.9% ee, and 99% chemical purity, which were used to make Montelukast API (50 g), and the quality was proved up to the USP 35 standard.

■ CONCLUSION

In conclusion, we have developed an efficient and robust process for the asymmetric hydrogenation of a key intermediate **4** of Montelukast using the highly efficient and selective chiral spiro catalyst Ir/SpiroPAP. The finalized process was conducted at mild temperature (30 °C) under a hydrogen pressure of 20 atm with low catalyst loading (S/C = 30 000) and afforded the desired product **5** and **5′** in 99.5% ee. After crystallization from an aqueous ethanol solvent system, the monohydrates of (*S*)-**5** and **5′** were obtained in 90−95% yield, >99.9% ee, and 99% chemical purity, which were used to make Montelukast API (50 g), and the quality was proved up to the

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USP 35 standard. Additionally, a comprehensive study has been undertaken to identify, synthesize, and characterize five impurities present in the hydrogenation of ketone **4**. Further optimization of this process should focus on reduction of the catalyst loading.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus spectrometer at 400 and 100.6 MHz, respectively. Chiral separations for ee determinations of the hydrogenation products **5** and **5′** were conducted on Chiracel AS-H, 4.6 mm × 250 mm × 5 μm column on an Agilent 1200 series instrument. Mass spectra were recorded on Agilent 6530 Accurate-Mass Q-TOF LC/MS spectrometer with ESI resource. An in-house HPLC (gradient mode) method was developed for the analysis of the desired product and its potential impurities (Agilent 1200 series HPLC device with DAD detector) according to the following conditions: column XDB-C8, 4.6 mm × 150 mm × 5 μm; eluent A, 0.2% (v/v) acetic acid in purified water; eluent B, acetonitrile; flow rate, 1.0 mL/min; wavelength, 343 nm; column temperature, 30 °C; injection volume, 10 μL; at t = 0 min, 60% eluent B; at t = 22 min, 82% eluent B; at t = 26 min, 98% eluent B; at t = 33 min, 98% eluent B; at t = 35 min, 60% eluent B, and this composition was held to the end (overall time 40 min). Anhydrous MeOH and EtOH was freshly distilled from magnesium. All reagents and solvents were used as received without further purification unless otherwise noted.

Scale-up Hydrogenation Representative Procedure of Ketone 4. To a 500 L autoclave was charged ketone **4** (30 kg, 65.8 mol) and anhydrous ethanol (240 L). To the resulting slurry was added a solution of ^{t}BuOK (295.3 g, 2.6 mol) in anhydrous ethanol (5.2 L) over 5 min, maintaining a temperature less than 20 °C. Nitrogen purging was done twice, and the solution was stirred with N_2 bubbling through for a total of 15 min. Then the catalyst (*R*)-**6b** (2.2 g, 2.2 mmol) was transferred by Schlenk techniques as a solution in anhydrous ethanol (100 mL) into the autoclave. The autoclave was then purged with hydrogen (0.3 MPa, 5 times) and then pressurized with hydrogen to 2.0−2.2 MPa. The reaction was agitated at 25 ± 5 °C until the hydrogen uptake ceased (8−10 h), signifying reaction completion. After releasing the hydrogen pressure, the mixture was purged with N_2. The reaction mixture was added 1 M HCl (2.6 L, 2.6 mol) at 10 °C to adjust the pH to 7. The solution was heated to 60 ± 5 °C, and water (120 L) was added slowly, during which time the product crystallized. The resultant slurry of product **5** and **5′** was cooled to 20 ± 5 °C and aged for 3 h before filtration. The cake was washed with two bed volumes of 1:2 mixture of water/ethanol. After drying, 29.6 kg of product **5** and **5′** were obtained as monohydrate in 94% yield, 99.9% ee as a pale yellow solid. Chiracel AS-H, *n*-hexane/IPA = 85:15, 0.8 mL/min, 40 °C, 287 nm UV detector, t_R = 23.63 min for (*S*)-**5** and t_R = 18.14 for (*R*)-**5**; t_R = 15.68 min for (*S*)-**5′** and t_R = 14.91 for (*R*)-**5′**. **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12−8.09 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 7.74−7.64 (m, 4H), 7.53 (d, J = 7.2 Hz, 1H), 7.47−7.26 (m, 7H), 4.75 (t, J = 6.2 Hz, 1H), 3.90 (s, 3H), 3.19−3.06 (m, 3H), 2.14−2.08 (m, 2H); **5′**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08−8.05 (m, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.70−7.60 (m, 4H), 7.50 (d, J = 7.2 Hz, 1H), 7.45−7.24 (m, 7H), 4.73 (t, J = 6.2 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 3.37 (s, 1H), 3.18−3.06 (m, 2H), 2.14−2.07 (m, 2H), 1.38 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 156.9, 148.5, 145.6, 143.7, 136.3, 136.1, 135.5, 135.3, 132.1, 131.1, 130.7, 129.7, 128.8, 128.7, 128.4, 128.0, 127.0, 126.5, 126.3, 126.0, 125.6, 124.8, 119.5, 73.1, 61.1, 41.4, 30.5, 14.3 ; HRMS (ESI) calcd for $[M + H, C_{29}H_{27}ClNO_3]^+$: 472.1679, Found 472.1686.

Preparation of Impurity I. To the suspension of ketone **4** (9.1 g, 20 mmol) in 75 mL ethanol was added ^{t}BuOK (3.4 g, 30 mmol) at 0 °C, and the reaction mixture was stirred for 24 h. The resultant slurry was filtrated. The cake was washed with 2 bed volumes ethanol and dried at 35 °C to afford impurity **I** as a yellow solid in 85% yield. ^{1}H NMR (400 MHz, DMSO): δ 8.38 (d, J = 8.8 Hz, 1H), 8.10−7.89 (m, 5H), 7.66−7.56 (m, 3H), 7.46−7.22 (m, 6H), 3.56 (s, 2H). ^{13}C NMR (100 MHz, DMSO): δ 182.1, 157.0, 148.1, 145.4, 144.8, 136.5, 135.9, 134.2, 129.7, 129.3, 128.1, 127.9, 127.3, 127.2, 127.1, 126.5, 125.5, 125.5, 124.4, 121.1, 120.4, 106.3, 34.0; HRMS (ESI) calcd for $[M + H, C_{27}H_{19}ClNO_2]^+$: 424.1104, Found 424.1110.

Preparation of Impurity II. To a 300 mL autoclave was charged methyl ester **5** (9.2 g, 20 mmol) and anhydrous THF (100 mL). To the resulting solution was added Raney-Ni (4.0 g, wet) and then purged with hydrogen (0.3 MPa, 3 times) and then pressurized with hydrogen to 0.6−0.8 MPa. The reaction was agitated at 30 ± 5 °C until the hydrogen uptake ceased, signifying reaction completion. After releasing the hydrogen pressure, the mixture was filtered over Celite to remove Raney-Ni, and the filtrate mother liquors was concentrated to dryness in vacuo. The residual product thus obtained was purified by crystallization from $MeOH/H_2O$ = 7/3 (v/v, 100 mL). After drying at 50 °C, 8.2 g impurity **II** was obtained as monohydrate in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.44−7.38 (m, 2H), 7.27−7.17 (m, 6H), 7.11 (d, J = 7.2 Hz, 1H), 4.67−4.63 (m, 1H), 3.85 (s, 3H), 3.27−3.23 (m, 2H), 3.14−3.09 (m, 3H), 3.02−2.98 (m, 2H), 2.07−1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 163.0, 148.2, 145.0, 144.0, 141.3, 136.0, 135.2, 132.2, 131.1, 130.8, 129.3, 128.7, 128.4, 127.8, 127.5, 126.8, 126.1, 126.0, 125.1, 123.7, 121.8, 73.4, 52.1, 41.3, 40.8, 35.8, 30.5; HRMS (ESI) calcd for $[M + H, C_{28}H_{27}ClNO_3]^+$: 460.1679, Found 460.1691.

Preparation of Impurity III. To a stirred solution of impurity **II** (2.8 g, 6 mmol) and ethanol (30 mL) was added ^{t}BuOK (337 mg, 3 mmol), and the reaction mixture was heated to 50 °C for 3 h. The reaction mixture was cooled to 25 °C and then concentrated to dryness in vacuo. The residual product thus obtained was purified through column chromatography using ethyl acetate and hexanes (1:3, v/v) as eluent to afford impurity **III** in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.44−7.39 (m, 2H), 7.27−7.17 (m, 6H), 7.11 (d, J = 7.2 Hz, 1H), 4.66−4.63 (m, 1H), 4.34 (q, J = 7.2 Hz, 2H), 3.27−3.23 (m, 2H), 3.14−3.10 (m, 3H), 3.05−2.98 (m, 2H), 2.04−1.95 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 163.0, 148.2, 145.0, 143.8, 141.3, 136.0, 135.2, 132.1, 131.1, 130.7, 129.7, 128.7, 128.4, 127.8, 127.5, 126.8, 126.0, 126.0, 125.1, 123.6, 121.8, 73.3, 61.1, 41.3, 40.8, 35.8, 30.4, 14.3; HRMS (ESI) calcd for $[M + H, C_{29}H_{29}ClNO_3]^+$: 474.1836, Found 474.1844.

Preparation of Impurity IV. To the stirred suspension of ester **5** and **5′** (9.2 g, 20 mmol) in 50 mL MeOH was added 5 M NaOH (2.0 g, 50 mmol in 10 mL water) at 0 °C, and the reaction mixture was heated to 50 °C and stirred for 5 h. The reaction mixture was cooled to 25 °C and then concentrated to dryness in vacuo. The resulting solid was resolved in CH_2Cl_2 and acidified with 3 M HCl inducing crystallization of the

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impurity **IV**, which was collected by filtration and rinsed with further portion MeOH/water. After drying at 50 °C under vacuum, the impurity **IV**, 7.8 g, was obtained as a yellow solid in 88% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 8.95 (d, J = 8.8 Hz, 1H), 8.43 (d, J = 8.8 Hz, 1H), 8.32−8.19 (m, 3H), 7.88−7.85 (m, 2H), 7.82 (s, 1H), 7.72 (d, J = 6.4 Hz, 1H), 7.58−7.42 (m, 4H), 7.30−7.25 (m, 2H), 4.74 (t, J = 6.4 Hz, 1H), 3.16−3.08 (m, 1H), 3.04−2.97 (m, 1H), 2.07 (q, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 171.2, 155.5, 147.9, 147.3, 146.2, 144.9, 141.8, 140.0, 135.9, 133.0, 132.1, 131.9, 131.5, 131.3, 130.8, 130.4, 128.7, 127.5, 127.4, 127.1, 120.7 (d), 119.7, 74.3, 42.2, 31.8; HRMS (ESI) calcd for $[M + H, C_{27}H_{23}ClNO_3]^+$: 444.1366, Found 444.1360.

Preparation of Impurity ***V***. Impurity **IV** (6.7 g, 15 mmol) and DMAP (3.7 g, 30 mmol) were charged to a round bottle, followed by CH_2Cl_2 (100 mL). After the solution was stirred for 15 min, DCC (4.1 g, 20 mmol) was added, and the reaction mixture was stirred overnight at 25 °C. The undissolved material was filtered off, followed by concentration of the filtrate mother liquors to dryness in vacuo. The residual product was purified through column chromatography using ethyl acetate and hexanes (1:3, v/v) as eluent to afford impurity **V** as an off-white solid in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12−8.06 (m, 2H), 7.79 (d, J = 7.2 Hz, 1H), 7.74−7.70 (m, 3H), 7.63−7.54 (m, 3H), 7.46−7.30 (m, 6H), 5.13 (dd, J = 12.0, 4.4 Hz, 1H), 3.24−3.15 (m, 1H), 2.94−2.88 (m, 1H), 2.51−2.43 (m, 1H), 2.33−2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 156.6, 148.6, 139.6, 137.6, 136.7, 136.2, 135.5, 134.5, 132.9, 131.7, 130.2, 129.1, 129.0, 128.8, 128.7, 128.2, 127.6, 127.2, 127.1, 126.5, 125.7, 125.0, 119.7, 79.4, 36.5, 30.0; HRMS (ESI) calcd for $[M + H, C_{27}H_{21}ClNO_2]^+$: 426.1261, Found 426.1268.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00339.

Copies of relevant NMR spectra and chromatograms (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*Telephone: +86 571 87000701. Fax: +86 571 87000702. E-mail: pcyan@zbjz.cn.

*E-mail: yqli@zbjz.cn.

Notes

The authors declare no competing financial interest.

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(11) When the substrate with palladium was used, an incomplete reaction and more impurities happened. In order to alleviate this issue, the residual palladium in the substrate should be <10 ppm.

(12) When denature EtOH was used, the reaction proceeded slowly or incompletely. Less than 0.1% water can be tolerated.

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