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Process Research and Impurity Control Strategy for Obeticholic Acid, a Farnesoid X Receptor Agonist

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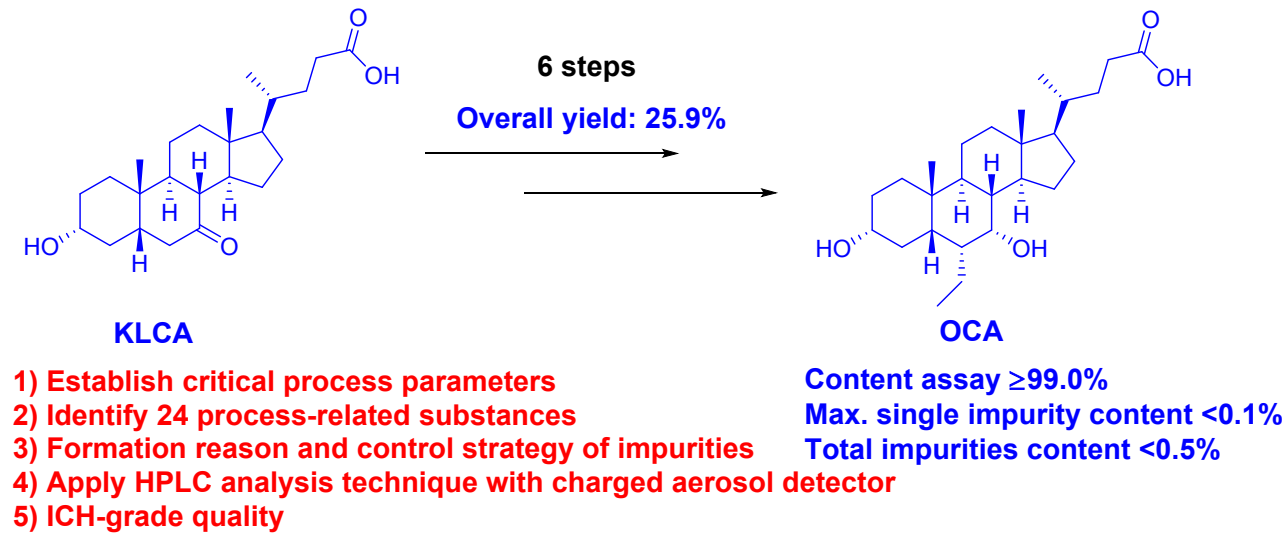
TOC graphic


Quality Controllable and Robust Process for Obeticholic Acid
6 steps
Overall yield: 25.9%
KLCA
OCA
1) Establish critical process parameters
2) Identify 24 process-related substances
3) Formation reason and control strategy of impurities
4) Apply HPLC analysis technique with charged aerosol detector
5) ICH-grade quality
Content assay ≥99.0%
Max. single impurity content <0.1%
Total impurities content <0.5%

ABSTRACT

The process to obtain ICH-grade quality obeticholic acid (OCA) was improved, and the overall yield was 25.9%. The critical process parameters were established to reduce or avoid process-related impurities. The formation reasons, purge pathways and control strategies for these impurities were also discussed for the first time. An HPLC instrument with utilizing the charged aerosol detection (CAD) technique was applied for an impurity content assay in OCA for the first time. The robust process was suitable for manufacturing scale-up.

KEYWORDS

Obeticholic acid, Process, Primary Biliary Cholangitis, Nonalcoholic Steatohepatitis

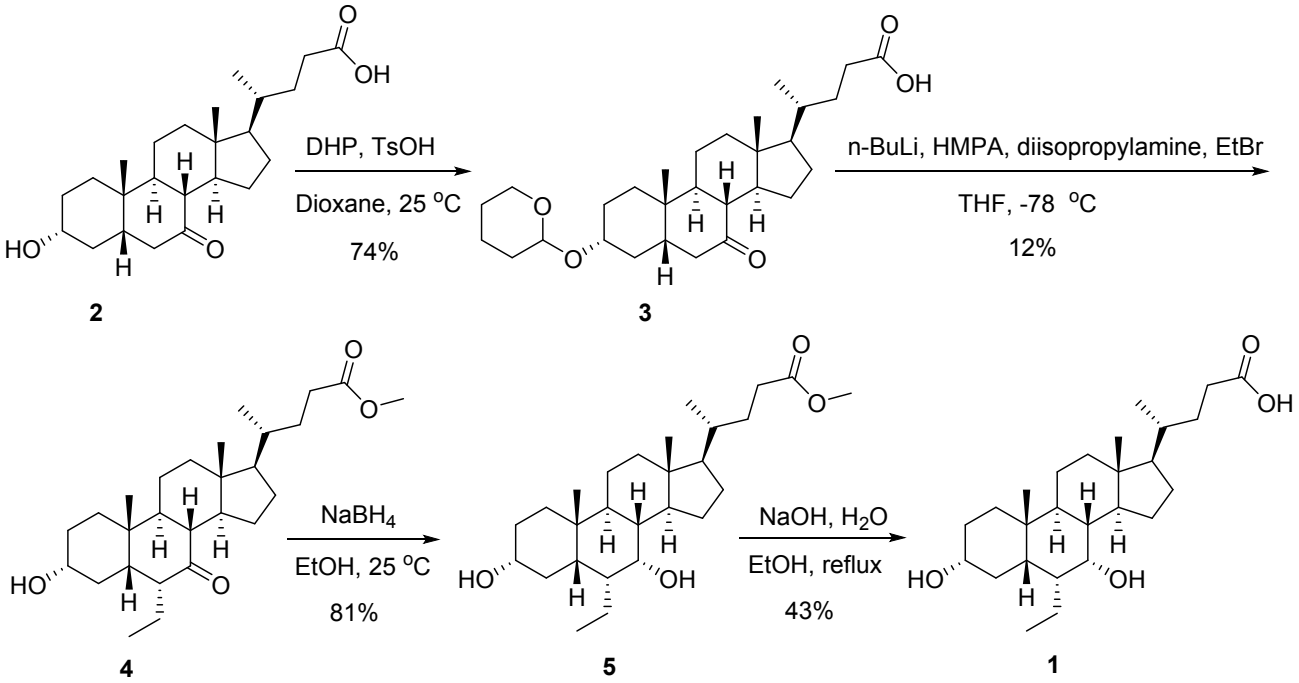
INTRODUCTION

OCA, which has the brand name Ocaliva, is a first-in-class farnesoid X receptor (FXR) agonist that acts as a synthetic chenodeoxycholic acid (CDCA) analogue; Ocaliva was approved by the FDA in May 2016 for the treatment of primary biliary cholangitis (PBC).[1] The new use of OCA for the treatment of patients with noncirrhotic nonalcoholic steatohepatitis (NASH) should be approved in 2020.

The original route[2] for the synthesis of OCA was proposed for the first time by Pellicciari in 2001, as shown in **Scheme 1**. Although this process comprises only 4 steps, it presents a series of drawbacks, such as: (a) in all of the steps, the reaction products are purified on a chromatographic column; (b) the reaction yield for the preparation of **4** is extremely low (12%), while the overall yield is 3.1%; and (c)

hexamethylenphosphonamide (HMPA) is used as a reactant, which is a known carcinogen.

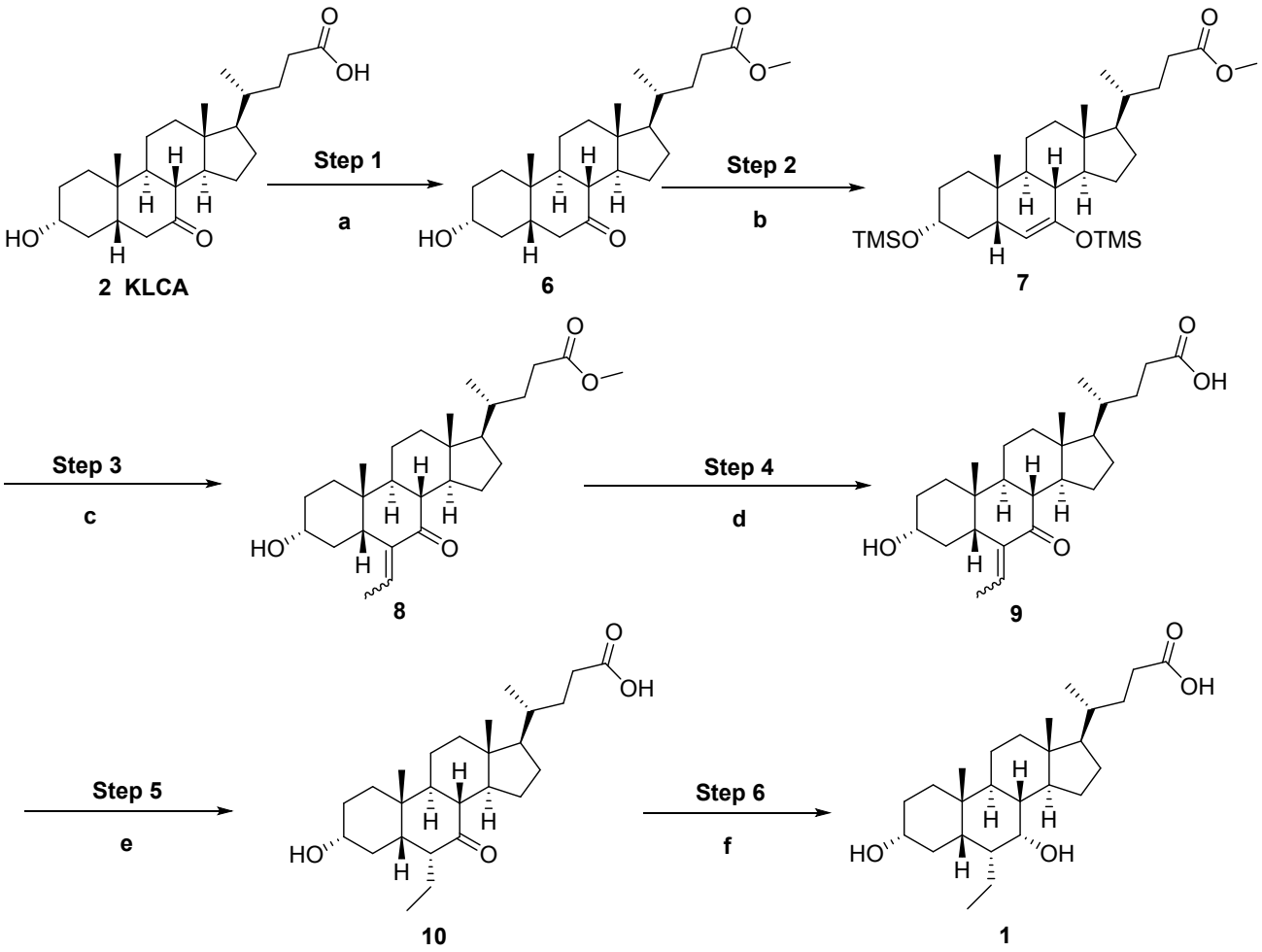
Scheme 1. Original Synthetic Route for OCA



The original commercial synthetic route for OCA was also developed by Pellicciari in 2006,[3] which was further developed by Steiner in 2013.[4] The synthetic process of OCA based on the reported commercial route is further researched by our group, as shown in **Scheme 2**. Some routes[5] similar to the commercial route have been reported as well, and the ethyl of the 6-postion of OCA is constructed by a method similar to the Mukaiyama reaction, which does not have obvious advantages over the above route. The use of different starting materials to prepare OCA, such as cholic acid[6] or hyodeoxycholic acid (HDCA),[7] have also been reported; however, the intermediates in the novel synthetic routes need to be purified by a chromatographic column. Although **Scheme 2** utilizes more steps than **Scheme 1**, the total yield is satisfactory, and the intermediates do not need to be purified by a chromatographic column as previously

reported,[3-4] however, the drug substance OCA with ICH-grade quality is not obtained, and the total yield is only 10%, even though we tried our best to follow the reported procedures.

Scheme 2. Improved Commercial Synthetic Route for OCA[a]



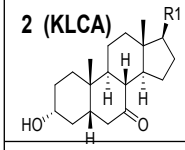
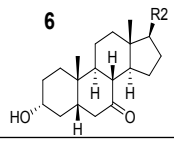
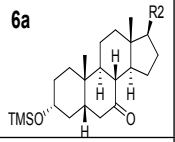
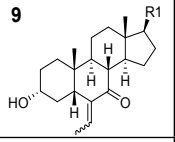
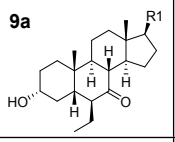
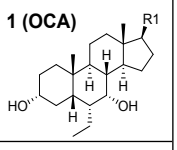
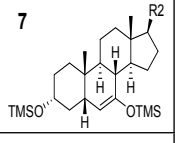
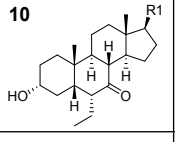
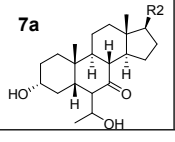
[a]Reagents and conditions: (a) H_2SO_4, MeOH, 50~55 °C, 3 h, 90%; (b) LDA, TMSCl, THF, -60~-65 °C, 5 h, colored substance treated with silica gel adsorbent; (c) BF_3·MeCN, CH_3CHO, DCM, -60~-65 °C, 2.5 h, and then warmed to -5~-10 °C, 2 h; (d) NaOH, H_2O, EtOH, 20~25 °C, 1 h, recrystallized twice with EtOH and H_2O, 52% yield from **6** to **9**; (e) 10 wt% Pd/C, H_2, NaOH, H_2O, 20~25 °C, 10 h, and then heated to 95~100 °C, 2 h, recrystallized twice with EtOH and H_2O, 79%; (f) $NaBH_4$, NaOH, H_2O, 70~75 °C, 6 h, recrystallized twice with n-butyl acetate and n-heptane, 70%.

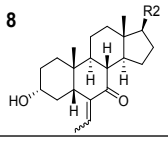
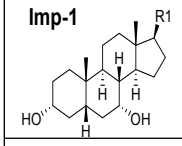
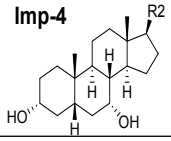
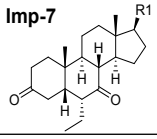
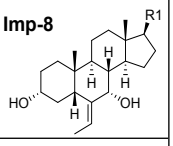
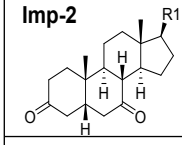
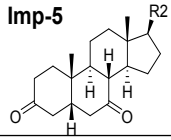
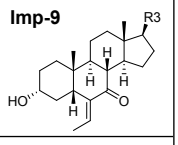
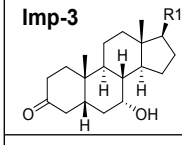
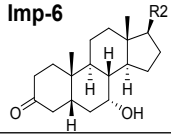
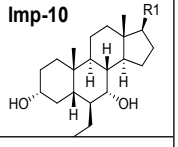
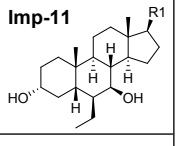
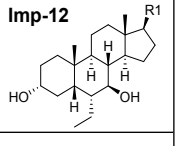
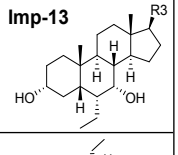
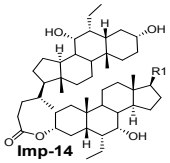
The safety of a drug is dependent not only on the toxicological properties of the bulk drug itself but also on the impurities in the bulk drug, and the presence of these unwanted impurities, even in small amounts, may influence the efficacy and safety of the pharmaceutical product.[8] Therefore, identification, quantification, and control of impurities in the drug substance and drug product are important steps in drug development and regulatory assessment.[9] These unknown impurities (>0.10%) in the drug substance must be identified and characterized according to ICH guidelines.[10] Therefore, developing a practicable process to obtain OCA with ICH-grade quality for commercialization is highly desirable.

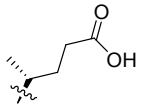
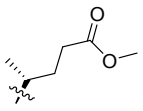
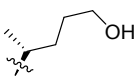
RESULTS AND DISCUSSION

We herein report the quality controllable and robust process for the synthesis of OCA, as shown in **Scheme 2**. The process-related impurity profiles for the preparation of OCA are shown in **Table 1**.

Table 1. Impurity Profiles for **1** (OCA)

Step	0	1	2 and 3	4	5	6
Starting Materials or	**2 (KLCA)** 	**6** 	**6a** 	**9** 	**9a** 	**1 (OCA)** 
			7 		**10** 	
			7a 			

			8 			
Main Byproducts in the Steps	Imp-1 	Imp-4 			Imp-7 	Imp-8 
	Imp-2 	Imp-5 				Imp-9 
	Imp-3 	Imp-6 				Imp-10 
						Imp-11 
						Imp-12 
						Imp-13 
						Imp-14 

Note: R1 =  ; R2 =  ; R3 =  .

Preparation of Methyl 3*α*-Hydroxy-7-keto-5*β*-cholanate (6, Step 1)

The starting material **2** (KLCA, purity>98.5%) was purchased from the supplier, which was synthesized from chenodeoxycholic acid (CDCA), and Imp-1 (CDCA), Imp-2 and Imp-3 (**Table 1**) were detected at approximately 0.46%, 0.44% and 0.36% by HPLC, respectively. The esterification of **2** was carried out smoothly in the

presence of H_2SO_4 and MeOH, and no more than 0.5% of **2** remained, as determined by HPLC. Imp-4 (0.48%), Imp-5 (0.40%) and Imp-6 (0.31%) (**Table 1**) were generated from the esterification of Imp-1, Imp-2 and Imp-3, respectively. These impurities were removed successfully, and no more than 0.1% was found by HPLC through recrystallization using MeOH and H_2O (1.5:1); the purity of **6** was greater than 99.5%.

Preparation of 3*α*-Hydroxy-6-ethylidene-7-keto-5*β*-cholanic Acid (9, Steps 2, 3 and 4)

The alkenyl of the 6-position of **9** was constructed with the Mukaiyama reaction, which was the most critical step and the most difficult to control in the process. The Mukaiyama aldol addition is a type of aldol reaction between a silyl enol ether and an aldehyde or formate, and the reactants allow for a crossed aldol reaction between an aldehyde and a ketone or a different aldehyde without self-condensation of the aldehyde.[11]

Obviously, the formation of silyl enol ethers **7** required low temperature to improve the regioselectivity, and the more reasonable order of addition was that **6** was added slowly to a mixture of TMSCl and LDA at -60~-65 °C. The crude **7** was a dark brown oil that could not be purified by recrystallization, and the colored substance and the impurities with high polarity were brought into the subsequent steps, which led to the recovery rate of the purification of **9** being significantly decreased. Furthermore, the hydrogenation of **9** did not occur completely because the Pd/C catalyst could be poisoned by the colored substance. The colored substance was not adsorbed onto

activated carbon at all. However, it adsorbed well with silica gel in n-heptane, and then, it was filtered and washed with a mixed solvent of n-heptane and ethyl acetate (20:1, v/v). The weights of the silica gel and solvent were only 2 times and 20 times that of **7**, respectively. The in process control (IPC) for preparing **7** was monitored by thin-layer chromatography (TLC), and TMSCl and LDA were added once more in proportion. In this case, the spots of **6** or **6a** (**Table 1**) were still observed by TLC.

Since **7** was not stable in acidic conditions and acetaldehyde (bp: 20.8 °C) could easily volatilize at room temperature, the DCM solution of **7** and acetaldehyde were poured into the mixture of BF_3 and DCM, as described in the patent.[4] Typically, however, the solution of BF_3 would be added slowly to the DCM solution containing **7** and acetaldehyde at -60~-65 °C. **7a** (**Table 1**) was generated from the aldol addition reaction of **7** and acetaldehyde, and **8** was obtained from the elimination of water from **7a**. After the reaction, **6** and **7a** were detected at approximately 3.5% and 0.2% by HPLC, respectively, and **6** was further hydrolyzed to **2** in step 4, while **2** and **7a** would be reduced or removed in the subsequent steps.

Initially, the hydrolyzation of **8** was carried out in a solution of NaOH, H_2O and MeOH at 50 °C for 2 h,[4] and the amounts of **2** increased continually with prolonged time. Consequently, it is indicated that *trans*-**9** was degraded to **2** and *cis*-**9** under alkaline conditions, and the formation mechanism was proposed, as shown in **Scheme 3**. Impurity **2** was likely formed *via* the Michael addition of *trans*-**9** followed by the retro-aldol addition of **9c** in NaOH aqueous solution. **9e** was the rotational conformational isomer of **9b**, which upon retro-Michael addition with hydroxide

would lead to *cis*-**9** and would also produce **10** in a subsequent hydrogenation reaction. There were three sources of impurity **2** in the preparation of **9**; the first source was from the hydrolyzation of impurity **6**, the second source was from the hydrolyzation of **7a** to **9c** followed by the retro-aldol addition of **9c**, and the third source was from the degradation of **9**. Obviously, the degree of degradation of **9** was related to the hydrolytic conditions. The hydrolyzation of high purity **8** was carried out in various conditions to investigate the content changes of impurity **2**, and the results are summarized in **Table 2**. The hydrolyzation of **8** was carried out at 50 °C for 1~2 h, and **2** was greater than 0.2% whether 1.2 equiv. or 1.5 equiv. of NaOH were used (entries 1 and 2), while **2** increased continually with prolonged time (entries 3 and 4). However, **2** was present at no more than 0.2% if the hydrolyzation of **8** was performed at 25 °C for 1 h (entry 5), and product **9** was relatively stable at 25 °C for 8 h (entry 6). Therefore, the hydrolyzation of **8** should be carried out at 25 °C for 1 h. Although crude **9** was recrystallized with EtOH to give high purity **9**, the yield was only 31% from **6** to **9**, even though the weight of the recrystallization solvent was only 2~3 times than that of **9**; furthermore, the recrystallization mixture was too sticky to filter. As expected, **9** was recrystallized twice with a mixture of EtOH and H_2O (1:1), and the yield was 52% from **6** to **9**. Finally, the key impurity **2** was found in quantities of no more than 1.0%, and the purity of **9** was greater than 98.0% by HPLC. Furthermore, the recrystallization mixture was easily filter.

Scheme 3. Proposed Degradation Mechanism of *trans*-**9** in NaOH Aqueous Solution

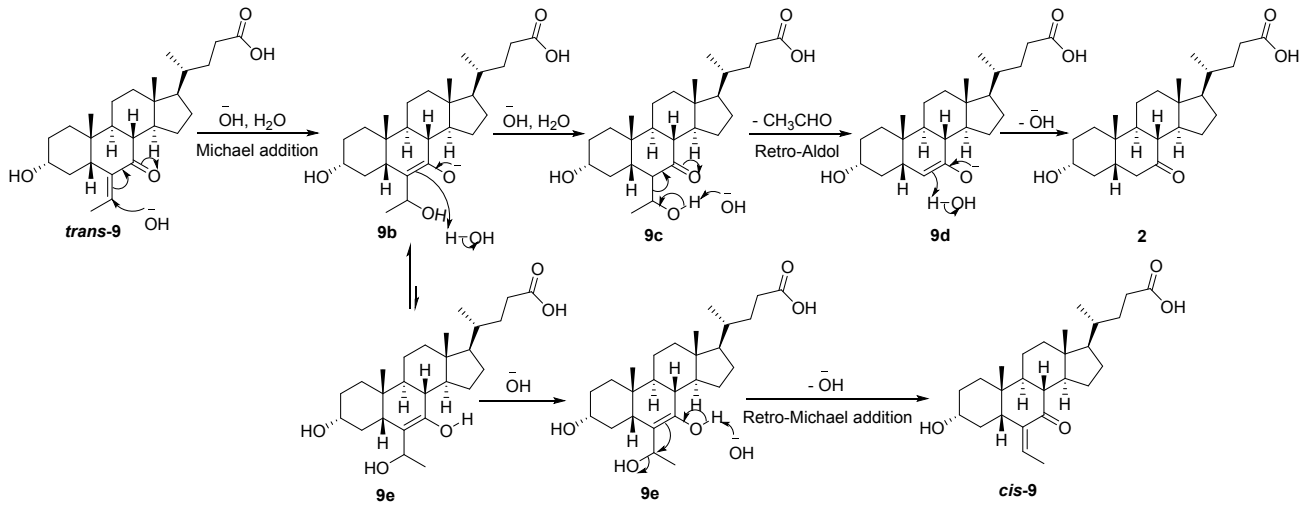
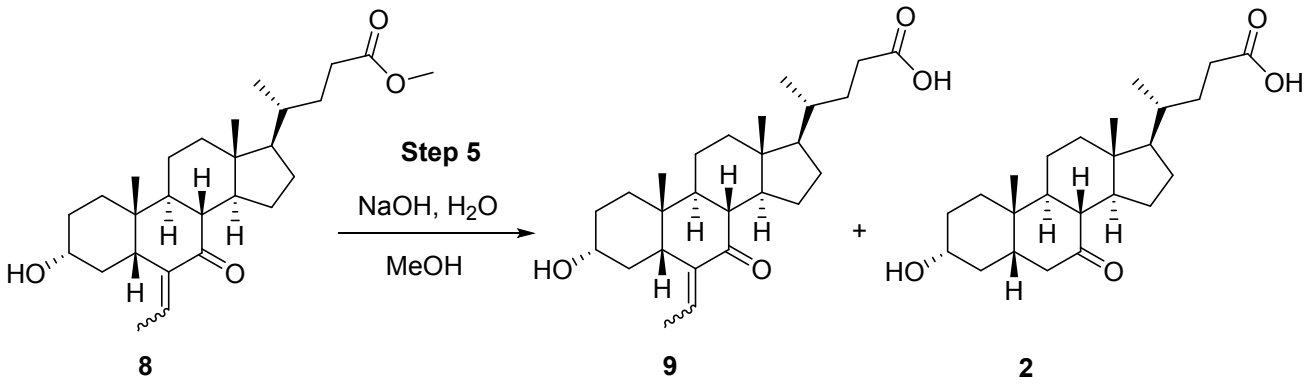


Table 2. Hydrolyzation of High Purity **8** under Various Conditions



			HPLC (%)[b]		
entry[a]	NaOH (equiv.)	T/t (°C/h)	**8**	**2**	**9** (*cis* /*trans*)
1[c]	1.2	50/2	2.60	0.27	97.13
2[d]	1.5	50/1	0.12	0.25	99.63
3	1.5	50/2	0.11	0.61	99.28
4	1.5	50/8	0.12	1.97	97.91
5	1.5	25/1	0.12	0.05	99.83
6	1.5	25/8	0.10	0.15	99.75

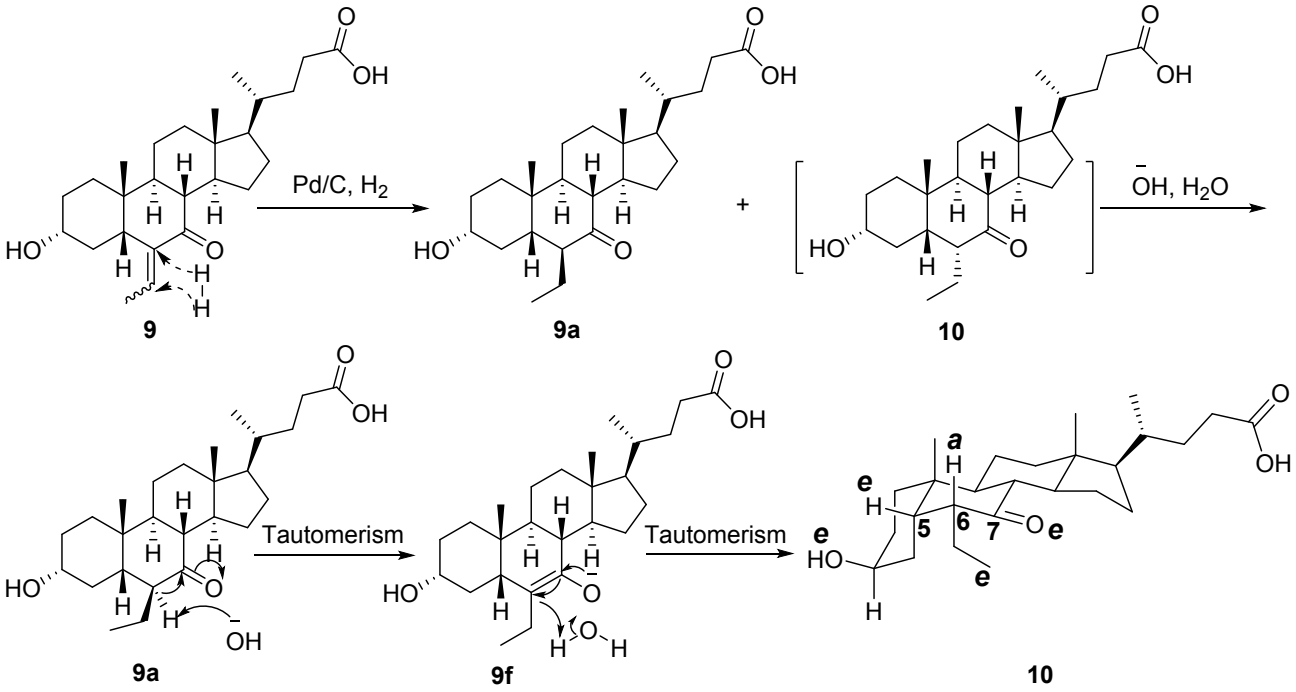
[a]Reaction solvent: EtOH (6 v/w) and H_2O (1 v/w); the purity of **8** is over 99.0%, and impurity **6** is present at quantities of no more than 0.02% by HPLC. [b]Only peak areas (%) of **8**, **2** and **9** were

integrated by HPLC. [c,d]The reaction conditions followed references 4 and 3, respectively.

Preparation of 3*α*-Hydroxy-6*α*-ethyl-7-keto-5*β*-cholanic Acid (10, Step 5)

The reaction mechanism from **9** to **10** was proposed as shown in **Scheme 4**, and **9a** was the main hydrogenated product of **9** due to steric hindrance effect. Compound **10**, with a smaller steric hindrance, was obtained *via* the tautomerism of the *α*-ketone of the 6*β*-ethyl intermediate (**9a**) under strong alkaline conditions. In the spatial stereo structure of **9a**, the conformation of 5*β*-H, 6*β*-ethyl and 7-ketone in *B*-ring was at the equatorial (*e*), axial (*a*) and equatorial (*e*) bond orientation, respectively. However, the conformation of 5*β*-H, 6 *α* -ethyl and 7-ketone in *B*-ring was all at the equatorial (*e*) bond orientation. Obviously, the conformation of **10** was more stable than that of **9a**, and more than 97% **9a** was finally transformed into **10** in NaOH aqueous solution.

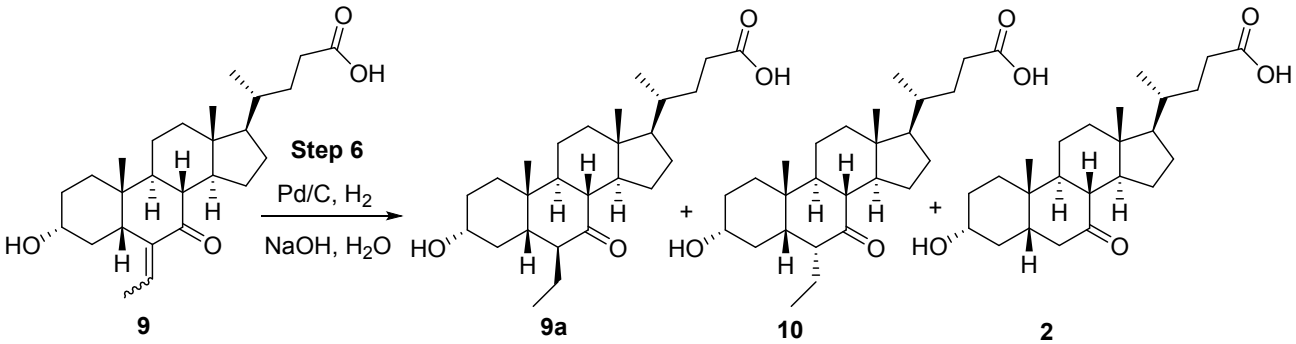
Scheme 4. Proposed Mechanism for the Preparation of **10**



The hydrogenation reduction and configuration inversion from **9** to **10** was performed in NaOH aqueous solution, which was environmentally friendly and safety

without any organic solvent. As mentioned above, **9** was partially degraded in NaOH aqueous solution at high temperature. The hydrogenation of **9** under various conditions was screened, and the results are shown in **Table 3**. The reduction was initially carried out at 25 °C/1 atm with 5% (w/w) Pd/C for 8 h, and 9.93% **9** remained (entry 1). When the reaction time and pressure were increased to 16 h and 3 atm, respectively, and 3.74% **9** still remained (entry 2). When the reaction was carried out at 25 °C/3 atm with 10% (w/w) Pd/C for 10 h, only 0.42% **9** remained (entry 3). Fortunately, impurity **2** from the degradation of **9** was increased to less than 0.1% at 25 °C in 8 h; however, impurity **2** increased over 0.5% by HPLC at 50 °C in 8 h (entries 4 and 5). Although the hydrogenation of **9** was rapid at 75 °C, impurity **2** was increased over 0.7% in 2 h (entry 6). Therefore, the hydrogenation of **9** was performed with 10 wt% Pd/C (10% w/w), NaOH (2 equiv.), H_2O and H_2 (pressure: 3 atm) at 25 °C for 10 h, and the ratio of **9a** to **10** was approximately 50:50, as determined by HPLC.

Table 3. Hydrogenation of **9** under Various Conditions



				HPLC (%)[c]		
entry[a]	T/t (°C/h)	P (atm)	Pd/C[b] (%w/w)	**9**	**2**	**9a&10**
1	25/8	1	5	9.93	0.77	89.30

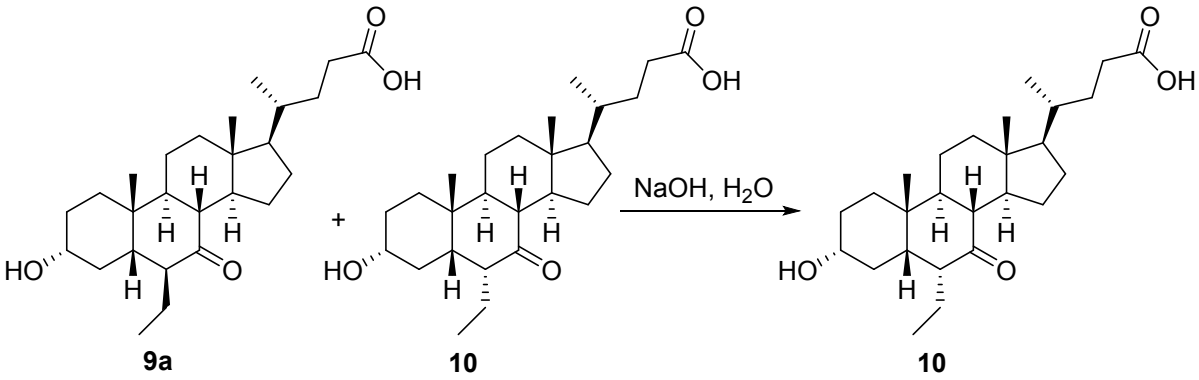
2	25/16	3	5	3.74	0.80	95.46
3[d]	25/10	3	10	0.42	0.85	98.73
4	50/8	3	10	0.30	1.16	98.54
5	50/16	3	10	0.28	1.67	98.05
6	75/2	3	10	0.20	1.59	98.21

[a]Reaction conditions: NaOH (2 equiv.), H_2O (5 v/w); the purity of **9** is 98.5%, and impurity **2** is 0.82% by HPLC. [b]10 wt% palladium on carbon (wetted with ca. 55% water). [c]Only the peak areas (%) of **9**, **2** and **9a** & **10** were integrated by HPLC. [d]The peak areas (%) of **9a** and **10** were 50.02 and 48.71 by HPLC, respectively.

The configuration inversion from **9a** to **10** was carried out in NaOH aqueous solution, and the conversion rate was related to the temperature, as shown in **Table 4**. **9a**, and was greater than 3.0% by HPLC when the temperature was below 50 °C for 16 h (entries 1 and 2); 2.87% **9a** remained at 75 °C for 5 h (entry 3). The amount of **9a** remaining was 2.78% at 95 °C after only for 2 h (entry 4), and 2.75% **9a** still remained even though the time was prolonged to 8 h (entry 5). Interestingly, approximately 2.7% **9a** was detected by HPLC even though the high purity (>99.5%) **10** was used in the presence of NaOH (2, 3 or 4 equiv.) aqueous solution at 95 °C for 2 h, and this result indicated that the configuration inversion from **9a** to **10** was an equilibrium reaction. Initially, the emission of hydrogen was performed immediately after the hydrogenation of **9** considering safety; then, the configuration inversion of **9a** was carried out at 95 °C for 2 h. Approximately 10% of an unknown impurity was detected by HPLC, and it increased with prolonged time. The impurity was identified by MS and NMR, and the structure of the impurity is shown in **Table 1** (Imp-7). To the best

of our knowledge, it has not yet been reported that the oxidation of a hydroxyl group to a ketone carbonyl was carried out in the presence of Pd/C, air and NaOH aqueous solution. Despite that, the reduction of Imp-7 with $NaBH_4$ would produce the final product **1** in the next step, and the recovery yield of **10** was decreased because Imp-7 was easily removed in the crystallization process of crude **10**. Therefore, the coexistence of Pd/C with air should be avoided for the configuration inversion from **9a** to **10** after completing hydrogenation. To prevent the coexistence of Pd/C and air, two approaches could be used: first, the configuration inversion process could be performed in a hydrogen atmosphere, and second, the Pd/C filtered off prior to the reaction. Obviously, the former was performed easily in a pilot plant.

Table 4. Screening of the Temperature and Time for Configuration Inversion from **9a** to **10**



9a **10** **10**

			HPLC (%)[b]	
entry[a]	T (°C)	t (h)	**9a**	**10**
1	25	16	12.43	87.57
2	50	16	3.01	96.99
3	75	5	2.87	97.13
4	95	2	2.78	97.22
5	95	8	2.75	97.25

[a]Reaction conditions: NaOH (2 equiv.), H_2O (5 v/w); the initial ratio of **9a** to **10** was approximately 50:50 by HPLC. [b]Only the peak areas (%) of **9a** and **10** were integrated on the HPLC.

Approximately 0.8% **2**, 0.5% **9** and 2.8% **9a** were detected by HPLC in crude **10** (HPLC purity: 91.2%), and these impurities would lead to the generation of new impurities (**Table 1**: Imp-1, Imp-8, Imp-9, Imp-10 and Imp-11) in step 6. The above impurities in crude **10** have already been controlled well in the hydrogenation reaction, and **10** was further recrystallized twice using a mixture solution of EtOH and H_2O (1:1). Approximately 0.3% **2**, 0.3% **9** and 0.5% **9a** were detected in intermediate **10** (HPLC purity: 97.3%).

Preparation of 3*α*,7*α*-Dihydroxy-6*α*-ethyl-5*β*-cholanic Acid (1, Step 6)

OCA (**1**) was obtained by the reduction of **10** with $NaBH_4$ in NaOH aqueous solution.[4] The reaction mechanism from **10** to **1** was proposed as shown in **Scheme 5**, and the 7-ketone of **10** was reduced by hydride ion more easily from *β*-plane to *α*-plane due to the 6*α*-ethyl of **10** with high steric hindrance in *α*-plane. The reduction reaction of **10** with $NaBH_4$ in various conditions is shown in **Table 5**, and a large amount of the starting material **10** remained when it was carried out at 25 or 50 °C for 24 h (entries 1 and 2), while 0.68% of the starting material remained with increasing the reaction temperature to 75 °C (entry 3). Despite the reduction reaction being performed at 95 °C for 3 h (entry 4), Imp-12 was produced, resulting in a content greater than 3.0%, as determined by HPLC. The amounts of Imp-12, Imp-13 (**Table 1**) and **10** were almost unchanged despite the different stoichiometry of NaOH in the reduction reaction (entries 4, 5 and 6). To summarize the above results, the optimized

reaction conditions were carried out with $NaBH_4$ (1.1 equiv.), NaOH (2 equiv.) and H_2O at 75 °C for 6 h.

Scheme 5. Proposed Mechanism for the Preparation of **1**

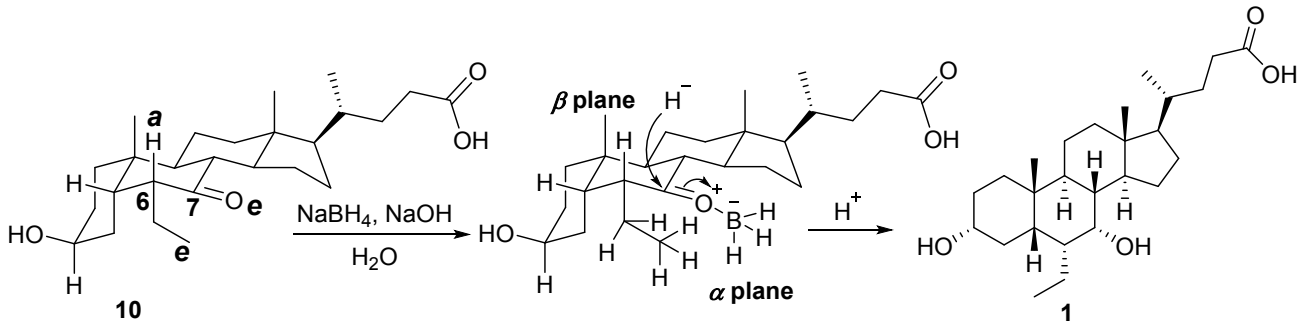
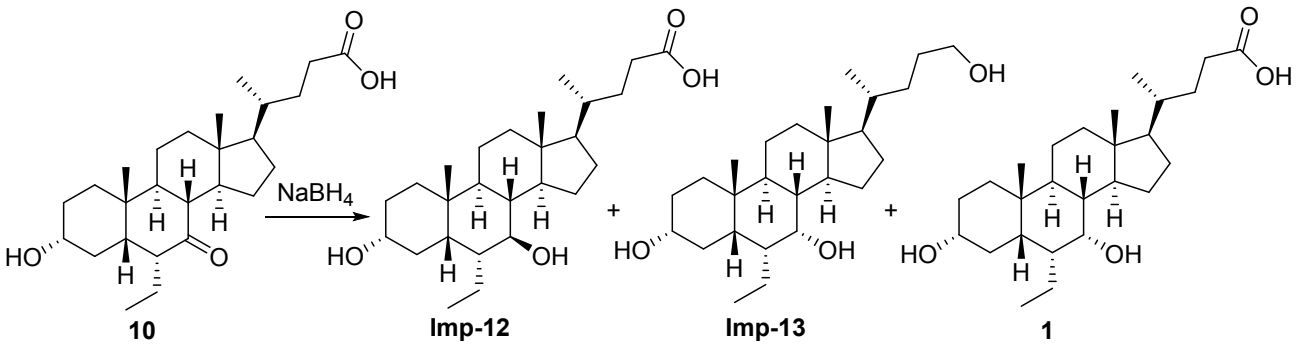


Table 5. Reduction Reaction of **10** with $NaBH_4$ under Various Conditions



			HPLC (%)[b]			
entry[a]	NaOH (equiv.)	T/t (°C/h)	Imp-12	Imp-13	**10**	**1**
1	2	25/24	0.75	ND	80.69	18.56
2	2	50/24	2.24	ND	12.96	84.80
3	2	75/6	2.97	0.05	0.68	96.30
4	2	95/3	3.61	0.06	0.62	95.71
5	3	95/3	3.53	0.05	0.57	95.85
6	4	95/3	3.65	0.07	0.72	95.56

[a]Reaction conditions: $NaBH_4$ (1.1 equiv.), H_2O (8 v/w). [b]Only the peak areas (%) of Imp-12, Imp-13, **10** and **1** were integrated on the HPLC.

The dimeric impurity Imp-14 (**Table 1**) was generated from the self-esterification of

10 in acidic conditions, which was removed by usual recrystallization with difficulty. The level of Imp-14 had been controlled well and was no more than 0.1% in the final product, and HOAc aqueous solution, rather than diluted hydrochloric acid, was used to adjust the alkaline reaction mixture until the pH=3~4. Imp-1 was almost not removed at all by recrystallization using the usual solvents except for n-butyl acetate. The recrystallization recovery yield of crude **1** was only 60% even though the weight of n-butyl acetate was only 2~3 times than that of **1**, and the amount of Imp-1 was only reduced by half at every recrystallization according to the spiking/purge studies of the impurity. Furthermore, the recrystallization mixture was too sticky to filter, and the drawback was that some of the mother liquor containing the impurities remained in the crystals. The crude **1** was recrystallized twice with n-butyl acetate and n-heptane (1:1, v/v), which provided a good yield (~70%) of OCA with ICH-grade quality, and the recrystallization mixture was filtered smoothly.

Control Strategy and Impurity Limit of Process Related Impurity in OCA Drug Substance

Our primary goal was not only to obtain the high quality drug substance but also to develop a quality controllable and robust process. The process parameters were optimized and improved well as above described. The structures and physical properties of process-related impurities, intermediates and **1** are very similar to each other; therefore, the purification of crude **1** to obtain high-purity OCA was a highly challenging task. The control strategy and impurity limit of process related impurities were proposed, as shown in **Table 6**.

Table 6. Control Strategy and Impurity Limit of Process Related Impurity

Intermediate	Crude product	Control strategy	Impurity limit
9[a]	**2** (3.5%)	Recrystallized twice with EtOH/H_2O:	**2**≤1.0%
		(1) **2**≤1.5%;	
		(2) **2**≤1.0%.	
10[a]	**2** (0.8%)	Recrystallized twice with EtOH/H_2O:	**2**≤0.3%
	9 (0.5%)	(1) **2**≤0.6%; **9**≤0.4%; **9a**≤1.5%;	**9**≤0.5%
	9a (2.8%)	(2) **2**≤0.3%; **9**≤0.3%; **9a**≤0.5%.	**9a**≤0.5%
1[b]	**2** (ND)[c]	Recrystallized twice with n-butyl acetate/	**2**<0.10%
	9 (ND)	n-heptane:	**9**<0.10%
	9a (ND)		**9a**<0.10%
	10 (0.61)	(1) **10**≤0.20%; Imp-1≤0.15%; Imp-10≤0.25%;	**10**<0.10%
	Imp-1 (0.32%)	Imp-12≤0.10%; Imp-8(ND); Imp-9(ND);	Imp-1<0.10%
	Imp-8 (0.23%)	Imp-11(ND); Imp-13(ND); Imp-14(ND);	Imp-8<0.10%
	Imp-9 (0.04%)		Imp-9<0.10%
	Imp-10 (0.43%)	(2) **10**(ND); Imp-1<0.10%; Imp-10<0.10%;	Imp-10<0.10%
	Imp-11 (0.27%)	Imp-12 (ND).	Imp-11<0.10%
	Imp-12 (2.82%)		Imp-12<0.10%
	Imp-13 (0.02%)		Imp-13<0.10%
	Imp-14 (0.04%)		Imp-14<0.10%

[a]Content assay of impurities in crude **9** and **10** using peak area normalization method. [b]Content assay of impurities in crude **1** using the main component self-compare method. [c]No detected on HPLC.

As discussed above, Imp-1, Imp-8, Imp-9, Imp-10 and Imp-11 were generated from the $NaBH_4$ reduction of **2**, **9** and **9a** in intermediate **10**, and the key of quality control of these impurities was to control the contents of **2**, **9** and **9a**. Imp-1 mainly originated from steps 1, 2, 3 and 4, and impurity **2** was no more than 3.5% in intermediate **9** on HPLC, and the impurity limits of **2** must be set in a strict quality specification so as to ensure that the content of Imp-1 no more than 0.1%. Imp-8 and Imp-9 were generated from **9**, and therefore the control strategy of Imp-8 and Imp-9 was that the content of **9** should be controlled no more than 0.5% in step 5. Impurity **9a** is a diastereomer of **10**,

and Imp-10 and Imp-11 are diastereomers of OCA which generated from **9a**, and therefore the control strategy of Imp-10 and Imp-11 was that the content of **9a** should be controlled no more than 0.5% in step 5. In step 6, Imp-1, Imp-10 and 10 should be controlled no more than 0.15%, 0.25% and 0.20% after the first recrystallization, respectively, and the content of all these impurities was no more than 0.1% after the second recrystallization. Imp-12, Imp-13 (<0.05%) and Imp-14 (<0.05%) were the byproducts of the preparation of **10**, Imp-12 is a diastereomer of OCA, which removed easily by recrystallization twice.

As shown in the supporting information, the content assay of the process-related impurities of OCA calculated them to be no more than 0.1% using the main component self-compare HPLC method, and the drug substance of OCA was prepared by our improved process. However, the content assay of the three known impurities in the original drugs (from Intercept Pharmaceuticals Inc.) calculated content of these impurities to be over 0.1%.

CONCLUSION

In conclusion, we have developed a quality controllable, reproducible, and industrially scalable synthetic process for OCA. The high purity intermediate **6** was obtained smoothly, and the maximum impurity in **6** was less than 0.1%. The Mukaiyama reaction from **6** to **8** was performed well in a reasonable order of addition at the given temperature. The hydrolyzation of intermediate **8** was carried out under the optimized reaction conditions to reduce the generation of **2**. Impurity **2** was also controlled well in the hydrogenation reduction of intermediate **9**, and diketone

impurity Imp-7 content was no more than 1.0% in the improved configuration inversion conditions from **9a** to **10**. The $NaBH_4$ reduction of **10** was carried out in an appropriate temperature to reduce the generation of Imp-12 and Imp-13. Three intermediates with stable transient states (**6a**, **7a** and **9a**) and fourteen process-related impurities were confirmed and characterized by HRMS and NMR. The formation mechanisms/reasons, purge pathways and control strategies for the process-related substances were discussed in detail. The purification processes of **7**, **9**, **10** and **1** were efficient, which were reported for the first time. The limits and control strategy for these impurities were set strictly according to their origination along with the spiking/purge studies of the impurities. Finally, OCA with ICH-grade quality was successfully obtained, and the overall process yield was 25.9%.

EXPERIMENTAL SECTION

All solvents and reagents were purchased from suppliers and were used without further purification. NMR spectra were recorded on a Bruker Avance III instrument operated at 400 MHz or 600 MHz for ^{1}H NMR and 100 MHz or 150 MHz for ^{13}C NMR with Me_4Si (TMS) as an internal standard. High-resolution mass spectrometry (HRMS) measurements were recorded on a Bruker Daltonics Solarix 7.0T. Melting points (MP values) were measured on a WRS-1B apparatus. The TLC method was carried out to monitor steps 2 and 3 using the ethanol solution of 10% phosphomolybdic acid as the chromogenic agent and n-heptane and ethyl acetate (1:1 or 8:1, v/v) as the developing solvent. Three HPLC methods were developed to

monitor the reactions and to detect the impurities. (a) The HPLC method was carried out to monitor steps 1 and 6 and to detect the purity of **6**, which was performed on a Dionex UltiMate 3000 HPLC instrument using a Waters XBridge C18 column (250 mm × 4.6 mm, 3.5 μm) at 30 °C with a flow rate of 1 mL/min and detection at 192 nm for 20 min or 50 min. The mobile phase involved a mixture of 50% aqueous solution (pH adjusted to 2.6 by using phosphoric acid) and 50% MeCN with isocratic elution. (b) The HPLC method was carried out to monitor steps 4 and 5 and to detect the purities of **8**, **9** and **10**, which was performed on a Dionex UltiMate 3000 HPLC instrument using a Waters XBridge C18 column (250 mm × 4.6 mm, 3.5 μm) at 30 °C with a flow rate of 1 mL/min and detection at 200 nm for 35 min. The mobile phase involved an aqueous solution (pH adjusted to 2.6 by using phosphoric acid) as phase A and MeCN as phase B. The HPLC analyses were accomplished with a gradient elution program (time (min)/% B: 0/40, 25/60, 35/90, 35/40, and 40/40). (c) The content assay of the related impurities of OCA was performed using the main component self-compare HPLC method. The HPLC method was carried out on a Dionex UltiMate 3000 HPLC instrument with Corona CAD using a Waters Cortecs Shield RP18 column (150 mm × 4.6 mm, 2.7 μm) at 35 °C with a flow rate of 1 mL/min for 60 min. The mobile phase involved an aqueous solution (0.1% formic acid) as phase A and MeCN as phase B. The HPLC analyses were accomplished with a gradient elution program (time (min)/% B: 0/35, 35/95, 50/95, 50.1/35, and 60/35).

Methyl 3*α*-Hydroxy-7-keto-5*β*-cholanate (6) A 3-L reactor was charged with **2** (300.0 g, 0.77 mol) and MeOH (1.5 L) under an atmosphere of nitrogen. H_2SO_4 (2 g,

20.4 mmol) was added slowly to the stirring mixture at 20~25°C. The reaction mixture was then heated to 50~55 °C for 3 h. The reaction was monitored by HPLC and deemed complete when **2** was less than 0.5%. $NaHCO_3$ (3.4 g, 40.8 mmol) aqueous solution (0.5 L) was added slowly to the reaction mixture at 20~25 °C over 30 min. The mixture was stirred at 5~10 °C for 1 h until good precipitation appeared. Another portion of water (0.5 L) was added slowly at 5~10 °C over 30 min. After stirring for 1 h, the solid product was isolated by filtration, washed twice with a mixture of MeOH and H_2O (1:2, 0.5 L × 2) and then dried in an air-drying oven at 55~60 °C to yield the title compound as a white solid (279.7 g, yield: 90%, HPLC purity>99.5%, water content<1.0%). Mp 88.8 ~ 99.1 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.49 (d, *J* = 3.2 Hz, 1H), 3.57 (s, 3H), 2.90 (dd, *J* = 4 Hz, 8.4 Hz, 1H), 2.44 (t, *J* = 7.6 Hz, 1H), 2.31-2.35 (m, 1H), 2.18-2.23 (m, 1H), 2.03-2.09 (m, 1H), 1.92 (dt, *J* = 2.4 Hz, 6.4 Hz, 1H), 1.78-1.84 (m, 2H), 1.66-1.73 (m, 4H), 1.00-1.51 (m, 14 H), 1.14 (s, 3H), 0.89-0.94 (m, 1H), 0.87 (d, *J* = 4.4 Hz, 3H), 0.61 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 211.94, 174.21, 69.55, 54.69, 51.69, 49.26, 49.05, 45.85, 45.54, 42.65, 39.03, 37.89, 35.24, 35.19, 34.33, 31.11, 30.83, 30.30, 28.31, 24.87, 23.27, 21.68, 18.66, 12.35. HRMS *m/z* $[M+Na]^+$ Calcd for $C_{25}H_{40}NaO_4$: 427.2824; found: 427.2822.

Methyl 3*α*-Trimethylsiloxy-7-keto-5*β*-cholanate (7) The water and MeOH in intermediate **6** (250.0 g, 0.62 mol) were removed by azeotropic distillation with THF at normal pressure until the water content was no more than 0.05% (Karl Fischer titration). A 10-L reactor was charged with LDA (1.86 L, 3.72 mol, 2 mol/L) and THF (1 L) at -60~-65 °C under an atmosphere of nitrogen. TMSCl (336.8 g, 3.10 mol) was

added slowly to the stirring mixture at -60~-65 °C over 20 min. The mixed solution of **6** and THF (total volume of approximately 1.2 L) was added slowly to the 10-L reactor at -60~-65 °C over 1.5 h, and then, the mixture was stirred at -60~-65 °C for another 3 h. The reaction was monitored by TLC and deemed complete when the spots of **6** and **6a** disappeared when using n-heptane and EA (1:1 and 8:1, v/v) as the developing solvent. The reaction mixture was warmed to -5~0 °C and diluted with EA (2 L), and then, citric acid aqueous solution (260 g citric acid in 2 L water) was added slowly to the mixture over 1 h at -5~0 °C. After the addition, the aqueous phase was separated and discarded, the organic solvent was evaporated, and it was replaced twice with n-heptane (1 L × 2) under reduced pressure at 40~45 °C. The oily residue was added to n-heptane (2.5 L) and 300~400 mesh silica gel (500 g) and then stirred for another 30 min. The mixture was filtered and then washed with a mixture of n-heptane and EA (20:1, v/v, 2.5 L), and the organic solvent in the filtrate was evaporated and replaced twice with DCM (1 L × 2) under reduced pressure at 35~40 °C. Water in intermediate **7** was removed by azeotropic distillation with DCM at normal pressure until the water content was no more than 0.05% (Karl Fischer titration). The mixed solution of **7** and DCM (total volume of approximately 2.5 L) was directly used for the next step. A small analytical sample of **7** was purified by a chromatographic column. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (dd, J = 1.6 Hz, 6 Hz, 1H), 3.66 (s, 3H), 3.47-3.55 (m, 1H), 2.31-2.39 (m, 1H), 2.18-2.26 (m, 1H), 1.51-2.00 (m, 10H), 0.99-1.44 (m, 12 H), 0.92 (d, J = 6.4 Hz, 3H), 0.61 (s, 3H), 0.68 (s, 3H), 0.16 (s, 9H), 0.10 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.76, 151.80, 108.90, 71.63, 54.95, 54.20, 51.53, 44.49,

42.77, 41.10, 41.05, 40.45, 40.23, 35.39, 34.76, 33.08, 31.18, 31.14, 30.78, 28.79, 27.19, 22.65, 21.05, 18.55, 12.37, 0.47, 0.35.

Methyl 3*α*-Hydroxy-6-ethylidene-7-keto-5*β*-cholanate (8) A 5-L reactor was charged with the mixed solution of **7**, DCM (2.5 L) and acetaldehyde (68.3 g) at -60~-65 °C under an atmosphere of nitrogen. BF_3 (663.4 g, 1.86 mol, 19 wt% solution in MeCN) was added slowly to the stirring mixture at -60~-65 °C over 1.5 h, and then, the mixture was stirred at -60~-65 °C for another 1 h. The reaction was monitored by TLC and deemed complete when the spot of **7** disappeared when using n-heptane and EA (8:1, v/v) as the developing solvent. The reaction mixture was warmed to -5~-10 °C for 1 h and stirred at -5~-10 °C for another 1 h. The reaction was monitored by TLC and deemed complete when the spot of **7a** disappeared when using n-heptane and EA (1:1, v/v) as the developing solvent. The reaction mixture was added slowly to NaOH aqueous solution (75 g of NaOH in 1 L of water) over 30 min at -5~0 °C, and then, the aqueous phase was separated and discarded; the organic solvent was evaporated and replaced twice with EtOH (1 L × 2) under reduced pressure at 35~40 °C. The mixed solution of **8** (HPLC purity > 90.0%) and EtOH (total volume of approximately 1.7 L) was directly used for the next step. A small analytical sample of **8** was purified by a chromatographic column. ^{1}H NMR (400 MHz, CD_3OD) δ 6.11 (q, J = 6.8 Hz, 14 Hz, 1H), 3.67 (s, 3H), 3.58-3.66 (m, 1H), 2.70 (dd, J = 4 Hz, 12.8 Hz, 1H), 2.23-2.43 (m, 4H), 1.10-2.11 (m, 24H), 1.06 (s, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 205.63, 174.49, 143.51, 128.53, 69.10, 54.07, 50.17, 50.15, 48.30, 45.01, 42.85, 38.87, 38.41, 36.53, 34.70, 33.93, 33.57,

30.41, 30.01, 28.63, 27.57, 25.17, 21.41, 20.60, 17.08, 10.92, 10.65. HRMS *m/z* $[M+H]^+$ Calcd for $C_{27}H_{43}O_4$: 431.3136; found: 431.3161.

3*α*-Hydroxy-6-ethylidene-7-keto-5*β*-cholanic Acid (9) A 5-L reactor was charged with the mixed solution of **8** and EtOH (1.7 L) under an atmosphere of nitrogen. NaOH (37.2 g, 0.93 mol) aqueous solution (0.25 L of H_2O) was added and stirred at 20~25 °C. After stirring for 1 h, the reaction was monitored by HPLC and deemed complete when **8** was less than 0.5%. The reaction mixture was diluted with water (1.17 L), and then, hydrochloric acid (37%, 80 mL) was added slowly to the mixture until the pH = 3~4. The mixture was refluxed to form a clear solution within 30 min and then cooled naturally to 60~62 °C before the crystal seeds (0.2 g) were added to the solution. After adding the crystal seeds, the mixture was stirred at 60~62 °C for 1 h. The mixture was cooled naturally to 20~25 °C within 1.5 h and stirred for another 2 h. The solid was isolated by filtration, washed twice with a mixture of EtOH and H_2O (1:2, 0.5 L × 2), and dried in an air-drying oven at 55~60 °C to yield crude **9** (157.5 g). A 3-L reactor was charged with the crude product (157.5 g), EtOH (1.57 L), and H_2O (1.57 L). The mixture was refluxed to form a clear solution within 30 min and then cooled naturally to 20~25 °C within 1.5 h, followed by stirring for another 2 h. The solid was isolated by filtration and washed twice with a mixture of EtOH and H_2O (1:2, 0.3 L × 2) and then dried in an air-drying oven at 55~60 °C to give the title compound as an off-white solid (134.3 g, 52% yield from **6** to **9**, HPLC purity > 98.0%). Mp 187.8 ~ 190.7 °C. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.96 (s, 1H), 5.97 (q, *J* = 4.8 Hz, 9.6 Hz, 1H), 4.54 (d, *J* = 2.8 Hz, 1H), 3.42-3.47 (m, 1H), 2.58 (dd, *J* =

2.8 Hz, 8.4 Hz, 1H), 2.17-2.30 (m, 3H), 2.08-2.13 (m, 1H), 1.95 (dt, *J* = 2 Hz, 8.4 Hz, 1H), 1.86-1.91 (m, 1H), 1.78-1.83 (m, 2H), 1.66-1.71 (m, 1H), 1.65 (d, *J* = 4.8 Hz, 3H), 1.55-1.57 (m, 1H), 1.32-1.45 (m, 5H), 1.04-1.27 (m, 8H), 0.94 (s, 3H), 0.89 (d, *J* = 4 Hz, 3H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 204.16, 175.35, 144.15, 128.88, 69.04, 54.49, 50.71, 48.64, 45.35, 43.53, 39.06, 38.94, 38.02, 35.20, 34.67, 34.50, 31.20, 30.06, 28.46, 26.13, 23.07, 21.33, 18.77, 12.80, 12.33. HRMS *m/z* $[M+H]^+$ Calcd for $C_{26}H_{41}O_4$: 417.3005; found: 417.3004.

3*α*-Hydroxy-6*α*-ethyl-7-keto-5*β*-cholanic Acid (10) A 2-L hydrogenation reactor was charged with NaOH (24.8 g, 0.62 mol) and H_2O (0.65 L) and cooled to 20~25 °C. **9** (130 g, 0.31 mol) and Pd/C (10 wt%, 13 g) were added to the stirring mixture at 20~25 °C, and then, the reactor was flushed three times with nitrogen (2 atm) and three times with hydrogen (2 atm). A hydrogen pressure of 3 atm was applied for 10 h until hydrogen absorption was no longer noted. The reaction was monitored by HPLC and deemed complete when **9** was less than 0.5%. The hydrogen pressure was adjusted to 1 atm, and the reaction mixture was heated up to 95~100 °C for 2 h. The reaction was monitored by HPLC and deemed complete when **9a** was less than 3.0%. The reaction mixture was cooled to 40~50 °C, Pd/C was filtered off, and it was washed with water twice (65 mL × 2). The filtrate (approximately 0.95 L) and EtOH (0.78 L) were transferred into a 2-L reactor, and citric acid monohydrate (52 g, 0.25 mol) was added in batches to the mixture over 10 min. The mixture was refluxed to form a clear solution within 30 min and then cooled naturally to 58~61 °C before the crystal seeds (0.1 g) were added to the solution. After adding the crystal seeds, the mixture was

stirred at 58~61 °C for 1 h. The mixture was cooled naturally to 20~25 °C within 1.5 h and stirred for another 2 h. The solid was isolated by filtration, washed twice with a mixture of EtOH and H_2O (1:2, 0.3 L × 2), and dried in an air-drying oven at 55~60 °C to yield crude **10** (113.9 g). A 2-L reactor was charged with the crude product (113.9 g), EtOH (0.68 L) and H_2O (0.68 L). The mixture was refluxed to form a clear solution within 30 min and then cooled naturally to 60~63 °C before the crystal seeds (0.1 g) were added to the solution. After adding the crystal seeds, the mixture was stirred at 60~63 °C for 1 h. The mixture was cooled naturally to 20~25 °C within 1.5 h and stirred for another 2 h. The solid was isolated by filtration and washed twice with a mixture of EtOH and H_2O (1:2, 0.2 L × 2) and then dried in an air-drying oven at 55~60 °C to give the title compound as an off-white solid (103.5 g, yield: 79%, **HPLC** purity >97.0%). Mp 189.3 ~ 193.7 °C. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.95 (br, 1H), 4.47 (d, *J* = 3.2 Hz, 1H), 3.25-3.32 (m, 1H), 2.74 (q, *J* = 4.0 Hz, 8.8 Hz, 1H), 2.42 (t, *J* = 7.6 Hz, 1H), 2.21-2.26 (m, 1H), 2.02-2.13 (m, 2H), 1.92 (dt, *J* = 2.0 Hz, 6.4 Hz, 1H), 1.78-1.85 (m, 1H), 1.73-1.77 (m, 1H), 1.65-1.71 (m, 3H), 1.53-1.60 (m, 1H), 1.46-1.49 (m, 2H), 1.31-1.43 (m, 4H), 1.17 (s, 3H), 0.98-1.27 (m, 8H), 0.90-0.92 (m, 1H), 0.88 (d, *J* = 4.4 Hz, 3H), 0.74 (t, *J* = 4.8 Hz, 3H), 0.62 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d6) δ 212.69, 175.35, 69.73, 54.83, 51.54, 50.41, 49.48, 49.34, 43.66, 42.67, 39.09, 35.80, 35.21, 34.42, 32.16, 31.18, 30.20, 28.35, 24.70, 23.72, 21.88, 19.08, 18.70, 12.40, 12.33. HRMS *m/z* $[M+H]^+$ Calcd for $C_{26}H_{43}O_4$: 419.3161; found: 419.3157.

3*α*,7*α*-Dihydroxy-6*α*-ethyl-5*β*-cholanic Acid (Obeticholic acid, 1) A 2-L reactor

was charged with **10** (100 g, 0.24 mol), NaOH (19.2 g, 0.48 mol) and H_2O (0.7 L) under an atmosphere of nitrogen. The mixture of $NaBH_4$ (9.8 g, 0.26 mol), NaOH (1 g) and H_2O (0.1 L) was added to the stirring mixture at 20~25 °C over 10 min, and then, the mixture was stirred at 70~75 °C for another 6 h. The reaction was monitored by HPLC and deemed complete when **10** was less than 0.5%. The reaction mixture was cooled to 35~40 °C. Acetic acid aqueous solution (53.3 g of HOAc and 0.2 L of H_2O) was added slowly to the reaction mixture over 30 min. The mixture was combined with n-butyl acetate (0.6 L). The aqueous layer was discarded, and the organic layer was washed with NaCl aqueous solution (5% of NaCl, 0.1 L). The organic layer was transferred into a 2-L reactor and heated to 70~75 °C, and n-heptane (0.6 L) was added slowly to the mixture over 30 min to form a clear solution; then, the solution was cooled naturally to 58~60 °C before the crystal seeds (0.1 g) were added to the solution. After adding the crystal seeds, the mixture was stirred at 58~60 °C for 1 h. The mixture was cooled naturally to 20~25 °C within 1.5 h and stirred for another 2 h. The solid was isolated by filtration, washed twice with a mixture of n-butyl acetate and n-heptane (1:2, 0.2 L × 2), and dried in an air-drying oven at 55~60 °C to yield crude **1** (81.4 g). A 2-L reactor was charged with the crude product (81.4 g), n-butyl acetate (0.49 L) and n-heptane (0.49 L). The mixture was heated to 70~75 °C and formed a clear solution within 30 min and then cooled naturally to 60~62 °C before the crystal seeds (0.1 g) were added to the solution. After adding the crystal seeds, the mixture was stirred at 60~62 °C for 1 h. The mixture was cooled naturally to 20~25 °C within 1.5 h and stirred for another 2 h. The solid was isolated by

filtration and washed twice with a mixture of n-butyl acetate and n-heptane (1:2, 0.16 L × 2) and then was dried in an air-drying oven at 55~60 °C to give the title compound as an off-white solid (70.6 g, yield: 70%, content assay >99.5%). Mp 104.5 ~ 106.2 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 3.55-3.57 (m, 1H), 3.18-3.24 (m, 1H), 2.21-2.26 (m, 1H), 2.07-2.12 (m, 1H), 1.90 (dt, *J* = 2.4 Hz, 8.4 Hz, 1H), 1.62-1.85 (m, 7H), 1.18-1.51 (m, 13H), 0.97-1.12 (m, 3H), 0.88-0.93 (m, 1H), 0.87 (d, *J* = 4.0 Hz, 3H), 0.82 (s, 3H), 0.81(t, *J* = 4.8 Hz, 3H), 0.60 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.76, 71.81, 69.79, 55.97, 50.28, 45.58, 42.36, 41.77, 40.17, 39.67, 35.40, 35.39, 35.27, 33.14, 33.04, 30.96, 30.60, 29.88, 27.90, 23.20, 22.41, 22.13, 20.61, 17.45, 10.88, 10.69. HRMS *m/z* $[M+Na]^+$ Calcd for $C_{26}H_{44}NaO_4$: 443.3137; found: 443.3130.

ASSOCIATED CONTENT

Supporting information

Analytical spectrograms and data of compounds **2**, **6**, **6a**, **7**, **7a**, **8**, **9**, **9a**, 1**0**, **1**(OCA), the original drugs of OCA, Imp-1, Imp-2, Imp-3, Imp-4, Imp-5, Imp-6, Imp-7, Imp-8, Imp-9, Imp-10, Imp-11, Imp-12, Imp-13 and Imp-14 (PDF).

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

OCA, Obeticholic Acid; ICH, The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; CAD, Charged Aerosol Detection; FXR, Farnesoid X Receptor; CDCA, Chenodeoxycholic Acid; PBC, Primary Biliary Cholangitis; NASH, Nonalcoholic Steatohepatitis; HMPA, Hexamethylenphosphonamide; HDCA, Hyodeoxycholic Acid; KLCA, Keto-lithocholic Acid; MeOH, methanol; LDA, Lithium Diisopropylamide; TMSCl, Trimethyl Chlorosilane; THF, Tetrahydrofuran; MeCN, Acetonitrile; DCM, Dichloromethane; EtOH, Ethanol; NMR, Nuclear Magnetic Resonance; HRMS, High-Resolution Mass Spectrometry; Mp, Melting Point; THF, Tetrahydrofuran; EA, Ethyl Acetate; HOAc, Acetic Acid; IPC, In Process Control; equiv., Equivalent.

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