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One-pot Process for Nalbuphine Hydrochloride and Impurity Control Strategy

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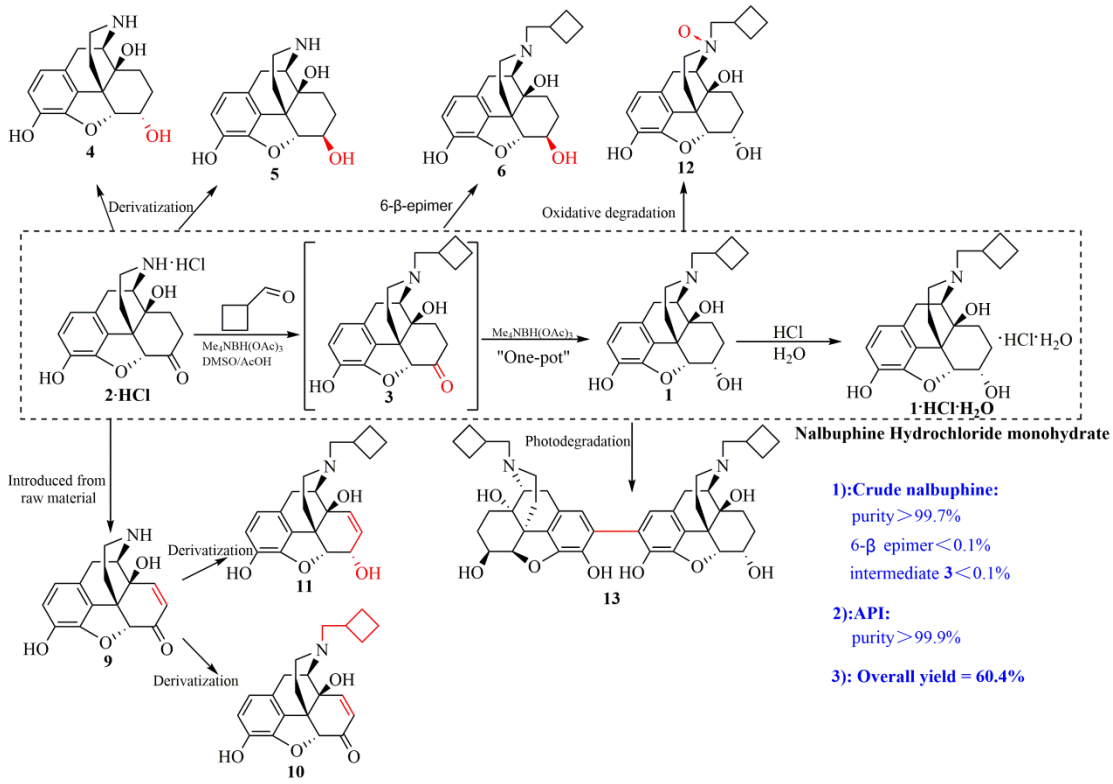


Abstract

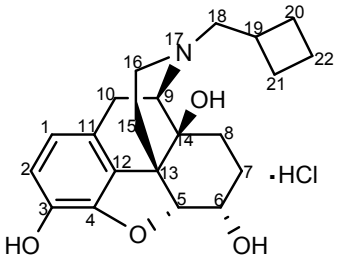
An improved kilogram-scale synthesis of nalbuphine had been developed with critical parameters investigated. Ten process-related impurities were identified, of which the source and control strategy had been elucidated. Moreover, tetramethylammonium triacetoxyborohydride ($Me_4NBH(OAc)_3$) was developed to reduce the imine and ketone in one-pot. As a result, 6-β-epimer was significantly controled to only 0.08% in the crude nalbuphine. The improved process was robust at kilogram-scale in 60.4% overall yield with 99.95% HPLC purity.

Keywords

nalbuphine hydrochloride, process, one-pot synthesis, impurity

Introduction

Nalbuphine hydrochloride is chemically known as (-)-17-(Cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol hydrochloride, a primarily kappa agonist/partial mu antagonist analgesic, which was first approved by the FDA in 1979 under the brand name of Nubain for the treatment of moderate to severe and postoperative pain. Its analgesic potency is essentially equivalent to that of morphine, but exhibits a ceiling effect in dose greater than 30 mg with no further respiratory depression. [1]



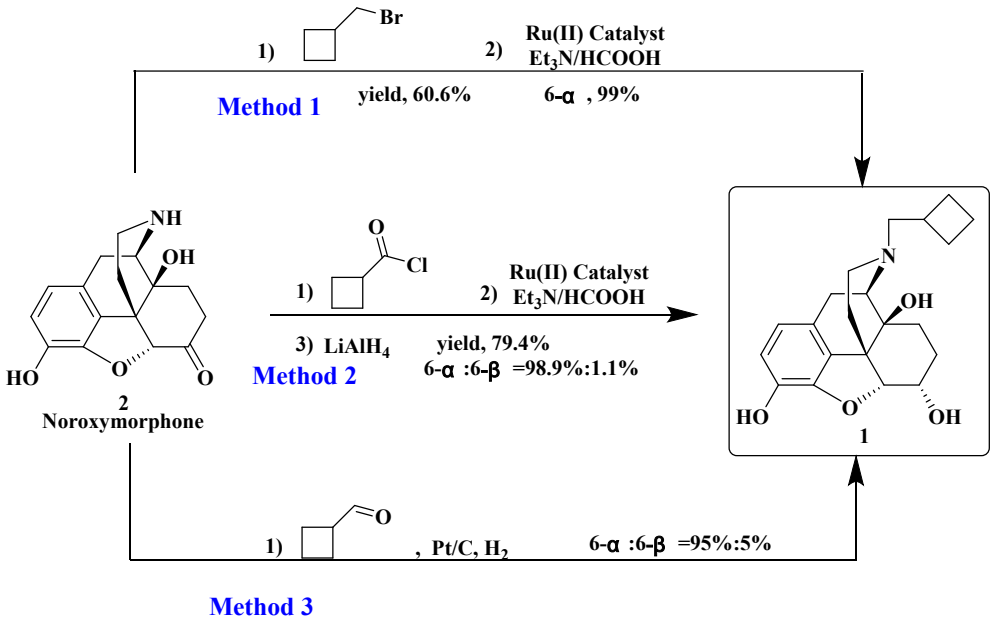
1·HCl
Nalbuphine Hydrochloride

Several synthetic routes of nalbuphine have been reported.[2] It could be synthesized by three methods using noroxymorphone, a semi-synthetic product derived from morphine[3] or thebaine[4] and was commercially available, as starting material (Scheme **1**). Major differences for these three methods are the sources for the introduction of N17-cylcobutylmethyl scaffold of nalbuphine. Method 1 adopted cyclobutylmethyl bromide[2d] as the source to introduce N17-cylcobutylmethyl scaffold through a direct nucleophilic substitution and the reaction needed 15 days for a relatively complete conversion in 73% yield. The downstream reduction step needed a transition metal Ru(II) as the catalyst to produce a result that the content of 6-α hydroxyl was 99%. Unfortunately, chromatographic purification was needed[5], which hampered the further development for scale-up and commercialization. Method 2 adopted cyclobutanecarbonyl chloride[2d] to introduce N17-cylcobutylmethyl scaffold, but three steps were needed to obtain nalbuphine. Such as the additional reduction step to reduce the amide group and the hydrolysis of the excess esterification product of 3-OH position with $LiAlH_4$ were needed.

Method 3 adopted cyclobutanecarboxaldehyde[2g] to introduce N17-cylcobutylmethyl scaffold of nalbuphine directly in one step. However, poorer

stereoselectivity was reported, and the α/β ratio of 6-hydroxyl was only 95/5. Those methods mentioned above suffered from disadvantages such as the usage of $LiAlH_4$, expensive metal catalysts, unsatisfactory stereoselectivity, lower atomic economy, and chromatographic purification. Herein, we wish to develop an improved synthetic process for nalbuphine. Moreover, the impurities generated in a process and the quality control strategy play a more and more important role in researching the quality of a drug substance, as well as helping researchers choose the best synthetic route and conditions. Therefore, we also want to report the impurities generated within this process and the corresponding quality control strategy, which have not yet been reported to the best of our knowledge.

Scheme 1. Synthesis of Nalbuphine from Noroxymorphone



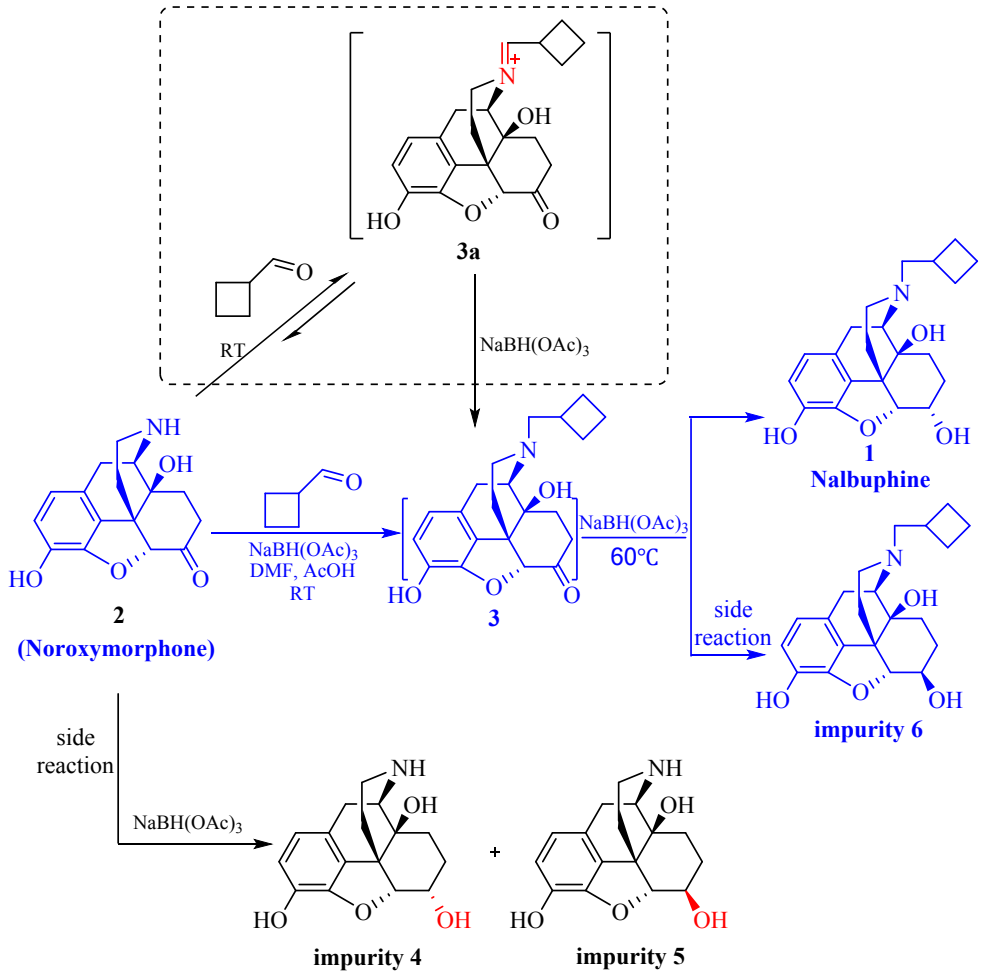
Results and Discussion

Initially we were attracted to the patent applied by the company of Mallinckrodt

(Scheme 2),[2(l)] which described a one-pot process for nalbuphine from noroxymorphone. The reaction of N17-cyclobutylmethyl was installed with cyclobutanecarboxaldehyde in dimethylformamide (DMF), and followed by the reduction of the imine and 6-keto structure with sodium triacetoxyborohydride ($NaBH(OAc)_3$). This process provided a satisfactory result as reported that the content of **1** and β-epimer impurity **6** was 98.9% and 0.1% respectively, with a high yield of 95.5%.

However, it turned out to be unreproducible after three parallel batches trials. There was up to more than 43% unreacted starting material **2** and only 53% of intermediate **3** that could be detected with 1.2 equivalents of $NaBH(OAc)_3$. Then, the second portion of 1.6 equivalent of $NaBH(OAc)_3$ was added. As a result, only 14.9% of nalbuphine was obtained with completely reacted of **2**, and the major product was **3** (83.9%, Table 2, entry 1). Even 4.9 equivalents $NaBH(OAc)_3$ was used, **3** could not be converted into nalbuphine completely (Table 2, entry 1). More importantly, 1.2% of β-epimer impurity **6** was obtained in the incomplete reduction mixture with 22.8% of **3**. Due to the incomplete reduction of **3** with $NaBH(OAc)_3$ and high content of 6-β hydroxyl impurity, the process parameter needs to be optimized adequately with the screening of solvent and suitable reducing agent.

Scheme 2. The One-pot Synthesis of Nalbuphine[a]



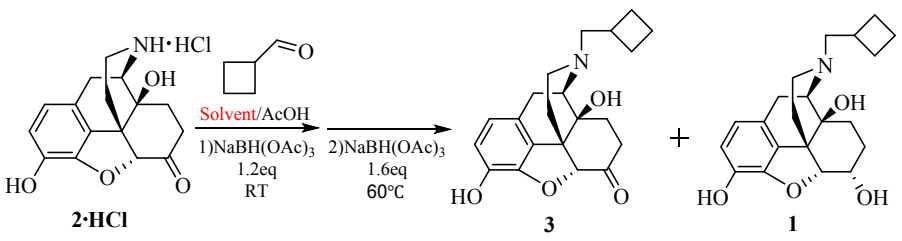
[a]Reagents and Conditions: 1), cyclobutanecarboxaldehyde (1.1 equiv), $NaBH(OAc)_3$ (1.1 equiv), DMF, AcOH, RT; 2), $NaBH(OAc)_3$ (1.6 equiv), 60 ℃; blue marked part.

In terms of mechanism, this one-pot process involves three transformations (Scheme 2). Firstly, compound **2** preferentially reacts with cyclobutanecarboxaldehyde to form the imine intermediate **3a**, which can effectively avoid the reduction of **2** to form the impurity **4** and **5**. Secondly, the imine group is further reduced by $NaBH(OAc)_3$; Thirdly the 6-ketone carbonyl group in compound **3** is reduced to form nalbuphine. (X-ray single-crystal diffraction analysis in supporting information further confirmed the structure of the isomer impurity **4** and **5**)

Different orientation of the hydroxyl group at the C-6 position leads to the formation of β-epimer impurity **6**, a side product which has similar properties with nalbuphine and is hard to avoid and remove.[6] Therefore, the direction of the optimization is to reduce the content of **6** and simultaneously promote the complete transformation of intermediate **3** to the desired product **1** as much as possible.

Synthesis of nalbuphine. First, screening of solvents was studied to increase the conversion of compound **2** to compound **3** and **1**. It was reported that 1,2-dichloroethane (DCE), tetrahydrofuran (THF), and acetonitrile(ACN) were suitable for reductive amination reactions with $NaBH(OAc)_3$.[7] However, the result of solvents screening studies showed that good conversion was obtained using dimethylformamide (DMF) or dimethylsulfoxide (DMSO) as the solvent, while poor conversion for THF, ethanol, dichloromethane (DCM), DCE, methanol and ACN (Table 1). Moreover, for the transformation of 3 to 1, the best conversion was found to be using DMSO as the solvent (Table 1, entry 1 and 8), and the solubility of **2·HCl** in DMSO was advantageous. Therefore, DMSO is determined to be the superior solvent.

Table 1. Screening of the Solvents[a]



entry	solvent	reaction result[b](%)		
		2	**3**	**1**
1	DMF	ND[c]	84.90	15.10
2	THF	97.50	2.33	0.17
3	Ethanol	81.02	17.23	1.75
4	DCM	64.81	30.35	4.84
5	DCE	65.26	20.41	14.32
6	Methanol	53.94	29.93	16.13
7	ACN	97.68	2.23	0.09
8	DMSO	ND	70.31	29.69

[a]Conditions: add 2.8 equiv of $NaBH(OAc)_3$ in 2 portions.

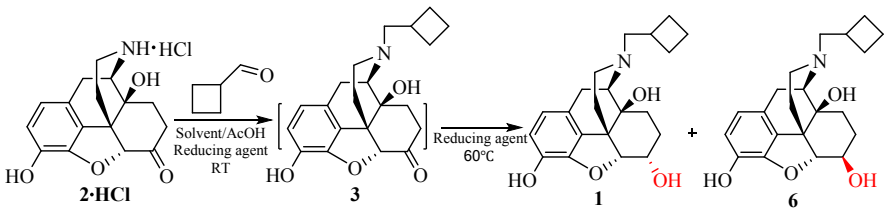
[b]Only peak areas (%) of **2**, **3** and **1** were integrated on HPLC.

[c]ND: Not detected.

The screening and optimization of reducing agent was studied in DMSO. The

reaction, which was conducted with more than 4.0 equivalents of $NaBH(OAc)_3$, gave a result that only 56.60% of **1** was obtained with still 42.62% of unreacted intermediate **3** in the mixture, but further decreased the content of β-epimer impurity contrast with that in DMF (Table 2, entry 2). Both potassium Tri-sec-butylborohydride ($KBH(s\text{-}Bu)_3$)[8] and sodium borohydride gave unattractive results (Table 2, entries 3-4). The result of tetramethylammonium triacetoxyborohydride ($Me4NBH(OAc)_3$) showed a distinct advantage that it gave a higher conversion from compound **2** to **1** with 99.47% of **1**, 0.11% of **3** and 0.12% of **6** detected in reaction mixture (Table 2, entry 8). Then, the feeding mode of $Me_4NBH(OAc)_3$ was investigated. It was found that, for the same amount of reducing agent, the more portions added in, the better experimental result obtained (Table 2, entries 5-9). Adding 4.0 equivalents of $Me_4NBH(OAc)_3$ in five portions generated 99.79% of **1** with only 0.08 % of **6** and 0.05% of **3** detected, while the reaction of adding $Me_4NBH(OAc)_3$ in one portion achieved the result that 98.53% of **1**, 0.17% of **6** and 0.76% of **3** were detected (Table 2, entry 9 and 5). Owing to further decreased of **6**, adding 4.0 equiv of $Me_4NBH(OAc)_3$ in five portions is preferred.

Table 2. Screening and Optimization of the Reducing Agent[a]



entry	reducing agent	solvent	amounts (eq)		reaction result[c] (%)			
					2	3	6	1
1	$NaBH(OAc)_3$	DMF	4.9	1.2	43.89	52.96	0.02	0.14
				1.6	ND	83.88	0.18	14.94
				1.0	ND	53.64	0.55	44.83
				1.1	ND	22.84	1.16	75.05
2	$NaBH(OAc)_3$	DMSO	4.0	1.2	31.97	62.78	0.02	0.27
				1.6	ND	69.89	0.17	29.47
				0.8	ND	50.80	0.29	48.47
				0.4	ND	42.62	0.37	56.60
3[b]	$NaBH_4$	DMSO	2.3	2.3	-	ND	20.65	79.35
4[b]	$KBH(s\text{-}Bu)_3$	DMSO/ THF	2.3	2.3	-	52.44	-	47.56

5	$Me_4NBH(OAc)_3$	DMSO	4.0	4.0	ND	0.76	0.17	98.53
6	$Me_4NBH(OAc)_3$	DMSO	4.0	1.2	ND	87.67	0.04	12.12
				2.8	ND	0.62	0.16	99.04
7	$Me_4NBH(OAc)_3$	DMSO	4.0	1.2	ND	87.01	0.04	12.68
				2.0	ND	0.90	0.12	98.87
				0.8	ND	0.38	0.13	99.35
8	$Me_4NBH(OAc)_3$	DMSO	4.0	1.2	ND	90.89	0.05	8.85
				1.6	ND	6.12	0.12	93.55
				0.8	ND	0.41	0.13	99.19
				0.4	ND	0.11	0.12	99.47
9	$Me_4NBH(OAc)_3$	DMSO	4.0	1.0	7.22	91.98	ND	0.65
				1.0	ND	33.32	0.05	66.59
				1.0	ND	2.95	0.07	96.88
				0.5	ND	0.25	0.08	99.55
				0.5	ND	0.05	0.08	99.79

[a]A total of 4.0 equivalent (4.9 equivalent in entry 1) of reducing agent was added in portions, and the first portion of reducing agent was used to the reduction of imine to produced compound **3**, and the other subsequent portions acted on the reduction of 6-keto carbonyl to **1**.

[b]Prepared from intermediate **3**, and only peak areas (%) of **3, 6** and **1** were integrated on HPLC.

[c] Measured by HPLC (area %).

A less good result in the repeatability experiments was captured that another source of $Me_4NBH(OAc)_3$ gave a bad result of stereoselective reduction with more than 3.03% of **6** (Table 3, entry 1). As $Me_4NBH(OAc)_3$ was commercially manufactured using sodium borohydride as the starting material (Scheme 3)[9], we proposed that the residual sodium borohydride in $Me_4NBH(OAc)_3$ caused the poor stereoselectivity. Therefore, we studied the effect of different amounts of sodium borohydride present in the stereoselective reduction reaction. It was shown that the more sodium borohydride in $Me_4NBH(OAc)_3$, the worse stereoselectivity achieved (Table 3, entries 1, 3-7). The results displayed that the content of $Me_4NBH(OAc)_3$ exceeds 98% could afford the satisfactory replication with the content of impurity **6** less than 0.2% (Table 3, entries 5-7). In addition, although the content of $Me_4NBH(OAc)_3$ was only 91.3%, the impurity **6** could be greatly reduced from 3.03% to 0.63% with adding reducing agent in more portions (Table 3, entries 1-2). This result further indicated that adding the reducing agent in portions would contribute to the control of β-epimer impurity **6**.

Scheme 3. The Synthesis of $Me_4NBH(OAc)_3$

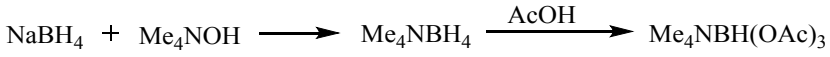


Table 3. The Effect of the Content of Reducing Agent on Stereoselective Reduction Reaction[a]

entry	$Me_4NBH(OAc)_3$		reaction result[c] (%)	
	lot No.	Content[b] (%)	**6**	**1**
1	T1-0340	91.3	3.03	96.00
2[d]	T1-0340	91.3	0.63	98.30
3	HT0401180327	95.9	1.93	97.88
4	HT-20180426	96.2	0.44	99.36
5	HT-20180412	98.1	0.18	99.73
6	HT-20180423	98.4	0.15	99.71

7	HT-20180505	99.9	0.11	99.55

[a]Conditions: add 4.0 equiv of $Me_4NBH(OAc)_3$ in 4 portions.

[b]Content was detected by QNMR (Quantitative nuclear magnetic resonance) in $CDCl_3$ with 1,2,4,5-tetrachlorobenzene as an internal standard.

[c] Measured by HPLC (area %).

[d]Add 4.0 equiv of $Me_4NBH(OAc)_3$ in 6 portions.

As known, acetic acid is often used to catalyze the formation of the imine in reductive amination reactions of ketones， but not needed in most reactions of aldehydes.[7, 10] We examined the transformation of substrate in the absence of acetic acid, and got a result that the compound **2** was completely converted to intermediate **3** and finally generated 75.09% of **1** with 24.18% of **3** (Table 4, entry 1). While in the presence of acetic acid, further transformation from **3** to **1** was observed by HPLC, and the more acetic acid was given, the higher conversion rate was achieved, with a decreased of **3** from 24.18% to 0.05% (Table 4, entries 1-5). Entry 4, with the 4.2 v/w of acetic acid, was preferred with just 0.08% of **3**. It could be concluded that the addition of acetic acid was not essential for the formation of the imine intermediate, but could greatly enhance the ability of $Me_4NBH(OAc)_3$ to reduce 6-ketone carbonyl to alcohol.

Table 4. Screening of the Amount of AcOH for Conversion from **3** to **1**

entry	AcOH (v/w)[a]	reaction result[b]	
		3	1
1	0	24.18%	75.09%
2	1.4	2.65%	96.99%
3	2.1	0.56%	98.82%
4	4.2	0.08%	99.69%
5	7.6	0.05%	99.34%

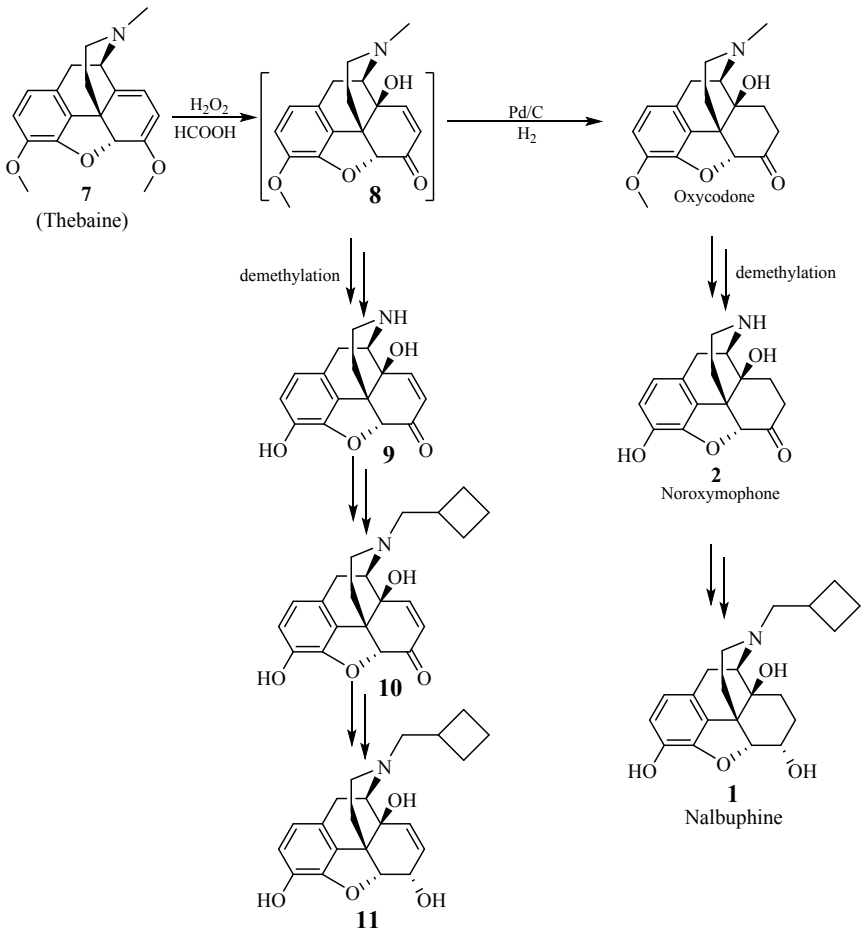
[a]The ratio between the volume of AcOH and the weight of **2·HCl**.

[b] Measured by HPLC (area %).

An unknown impurity was found in nalbuphine when another source of noroxymorphone, which was prepared from thebaine, was used as the starting material. This impurity was difficult to remove during the synthetic process of nalbuphine hydrochloride. The molecular weight was detected as 355 (the molecular weight of nalbuphine is 357). The content of this impurity could be decreased from 0.58% to 0.24% after the hydrogenation reaction, which indicated the existence of the carbon-carbon double bonds. In the second step of the synthetic route of the

noroxymorphone, palladium-catalyzed hydrogenation was used for the reduction of the carbon-carbon double bond of intermediate **8** (Scheme 4). A small amount of unreacted compound **8** would convert to compound **9** as an impurity coexisted with noroxymorphone after the demethylation reactions. Compound **9** would convert to impurities **10** and **11** through the synthetic process of nalbuphine (Scheme 4). These three impurities were synthesized from compound **8** and confirmed by NMR and HPLC (see the supporting information).

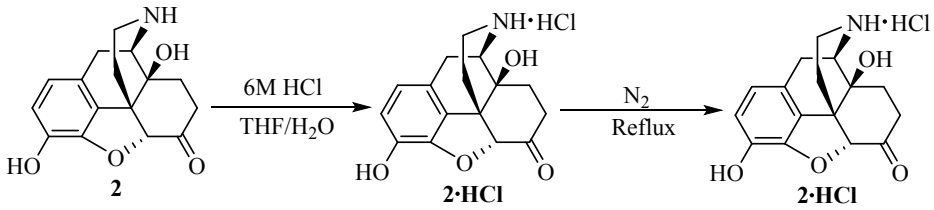
Scheme 4. Preparation of Impurity **9**, **10** and **11**



To decrease the content of key impurity **9**, the purification of initial material is

essential. Noroxymorphone suspended in THF/H_2O with 6M HCl and then slurried at reflux temperature under nitrogen atmosphere, and gave a satisfactory result that the content of impurity **9** in **2·HCl** decreased from 0.14% to 0.05% and the yield of **2·HCl** is 93.2% (Table 5, entry 1 and 5), and the further generation of nalbuphine contained 0.05% of impurity **11** accordingly, with no detected of **9** and **10**.

Table 5. The Purification of **2·HCl**[a]



entry	*T*(℃)	THF/H_2O (v/v)	THF (v/w)[b]	yield (%)	impurity **9**[c] (%)
1[d]	-	-	-	-	0.14
2	reflux	20:1	11	95.9	0.09
3	reflux	15:1	11	87.6	0.05
4	reflux	10:1	11	74.4	0.05
5	reflux	15:1	8	93.2	0.05
6	reflux	15:1	6	94.3	0.06

[a]Reagents and conditions: 6 mol/L hydrochloric acid solution (1.5eq), nitrogen

atmosphere, under reflux temperature for 10-15min.

[b]The ratio between the volume of THF and the weight of **2**.

[c] Measured by HPLC (area %).

[d]Content of **9** in raw material **2.**

Finally, $Me_4NBH(OAc)_3$ was added in portions after the purified noroxymorphone hydrochloride reacted with cyclobutanecarboxaldehyde in DMSO and acetic acid. A grayish solid of crude nalbuphine was achieved in a yield of 86.3% on the kilogram-scale process. As the purity of crude nalbuphine was up to 99.79%, and the maximum single impurity is less than 0.1%, no additional operation was required except for the color removal with activated carbon prior to recrystallization, which was performed in methanol/water.[6] A off-white solid was obtained with the yield of 90.0%, and the purity was up to 99.9%.

Synthesis of nalbuphine hydrochloride. The solvent of ethanol/water,[2g] tetrahydrofuran/water,[2c] and water,[6] had been studied in the synthesis of nalbuphine hydrochloride. The mixture solvent of THF/H_2O gave a better removal capacity of impurity and a higher yield. However, a low stability of nalbuphine in THF had been detected by HPLC analysis, and 0.65% of impurity **12** was generated increasingly during 12 hours, which might be generated from nalbuphine by the oxidation with the peroxides in the solvent of THF (**Figure 1**).[11] The other study on the stability of nalbuphine hydrochloride showed that about 1.26% of an unknown impurity had been

generated in THF (H_2O as the cosolvent) under light for four days, while just 0.12% detected in H_2O (**Figure 2**). After separation and characterization, it was confirmed as impurity **13**. Nalbuphine, as reported by Frank Diana,[12] has the structure characteristic of a phenolic group at the 3-position in 4,5-epoxymorphinans, which is sensitive to light, and could primarily degrade to 2,2'-dimer impurity **13**.[13] To control and decrease the generation of **13**, the precautions should be taken to avoid the exposure of light in the step of recrystallization and the salt-formation process. In the end, we selected water instead of THF as the solvent, and nalbuphine hydrochloride was produced with no detection of compound **12** and **13** under strictly exclusion of light. To increase the recovery of product, partial solvent evaporation was performed after the filtration and removal of activated carbon, and meanwhile made part of crystals precipitate. In order to improve the purity of product and maintain the same crystal form, the suspension was heated to reflux for complete dissolution, and recrystallized by a slow cooling to 0-10 ℃.

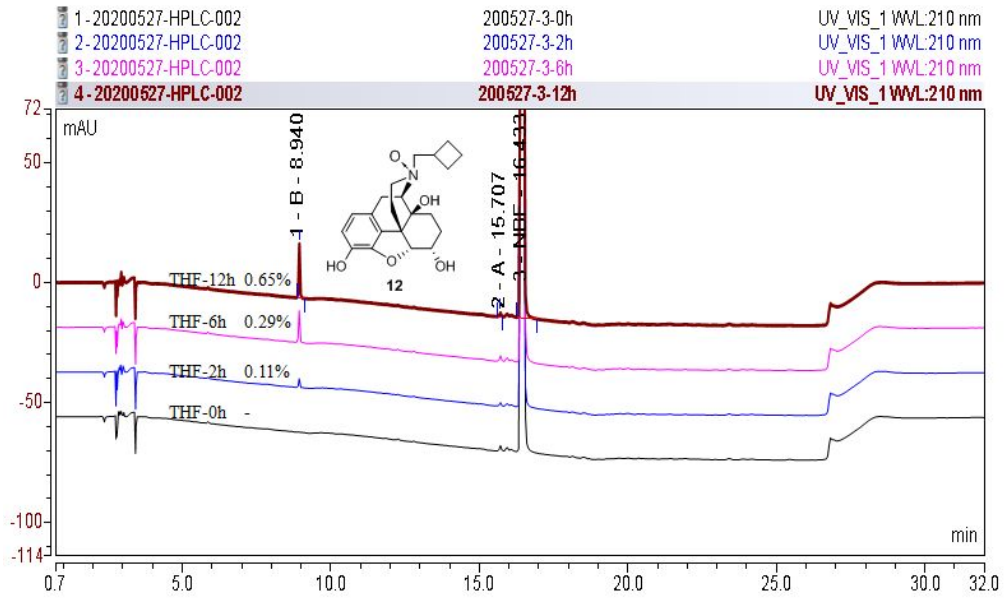


Figure 1. The Stability of Nalbuphine in THF. Original **1** (black), Two hours later(blue), Six hours later(pink), Twelve hours later(red).

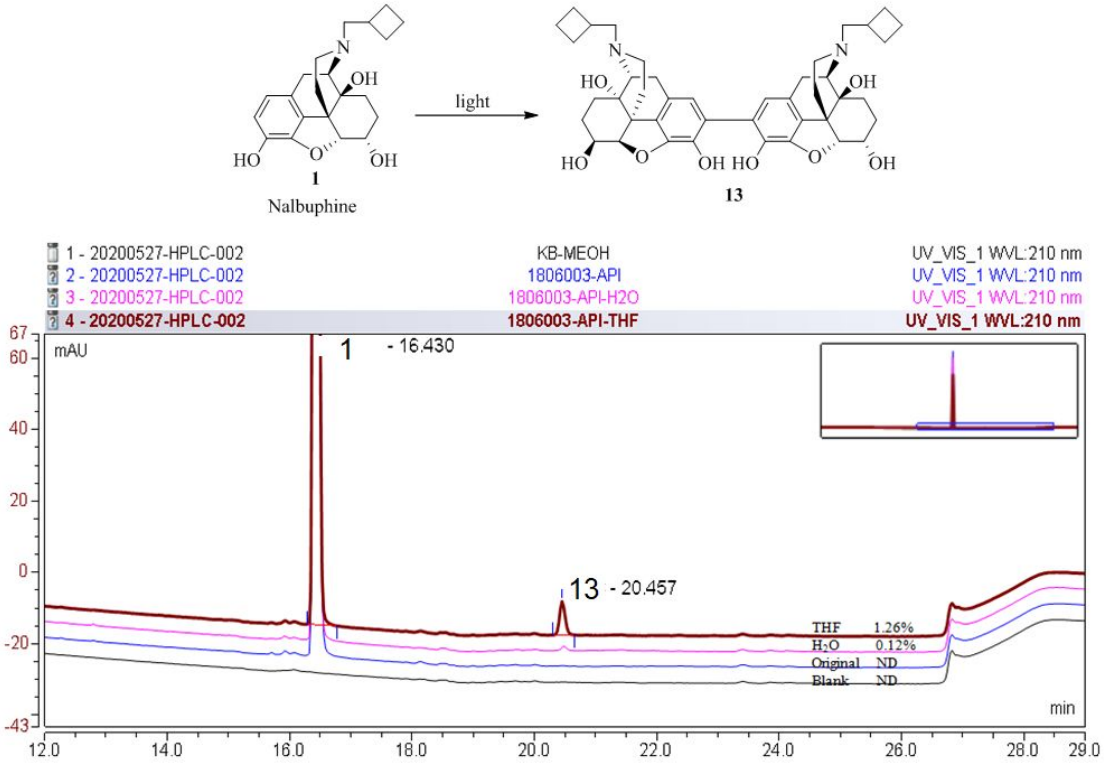


Figure 2. The Formation of Impurity **13** in Nalbuphine Hydrochloride. Blank(black), Original **1** (blue), Water(red), THF(red).

There are polymorphic forms for nalbuphine hydrochloride, and form C, as mentioned by Jason[14], is a stable monohydrate which could be transformed from an unstable dihydrate form B at 60 ℃. In order to obtain the stable crystal form, the study on the crystal form was conducted next. The crystals precipitated from water were classified as form B by X-ray powder diffraction (XRPD), and in order to obtain

the stable form C, the drying temperature was increased to 85 ℃, under which temperature the dihydrate form B transformed into monohydrate form C entirely. Nalbuphine hydrochloride monohydrate was generated as white solid in a yield of 83.4% with 99.95% purity.

In summary, the improved synthesis of nalbuphine hydrochloride has been optimized on the kilogram scale (Scheme 5). The starting material **2·HCl** was purified through reslurrying in THF/H_2O at reflux temperature. $Me_4NBH(OAc)_3$ was added in portions to reduce the imine and ketone group successively, and the white solid of nalbuphine hydrochloride was prepared from the grayish solid of crude nalbuphine through the decolorization treatment with activated carbon during recrystallization in methanol/water and salt-forming process in water. The final product, nalbuphine hydrochloride monohydrate, was obtained with 99.95% purity and 60.4% overall yield. Three batches of validation results showed that the optimized process parameters, which were obtained from the lab-scale experiment, could be applied in pilot scale with the scale-up strategy (Table 6).

Scheme 5. The Improved Synthesis of Nalbuphine Hydrochloride

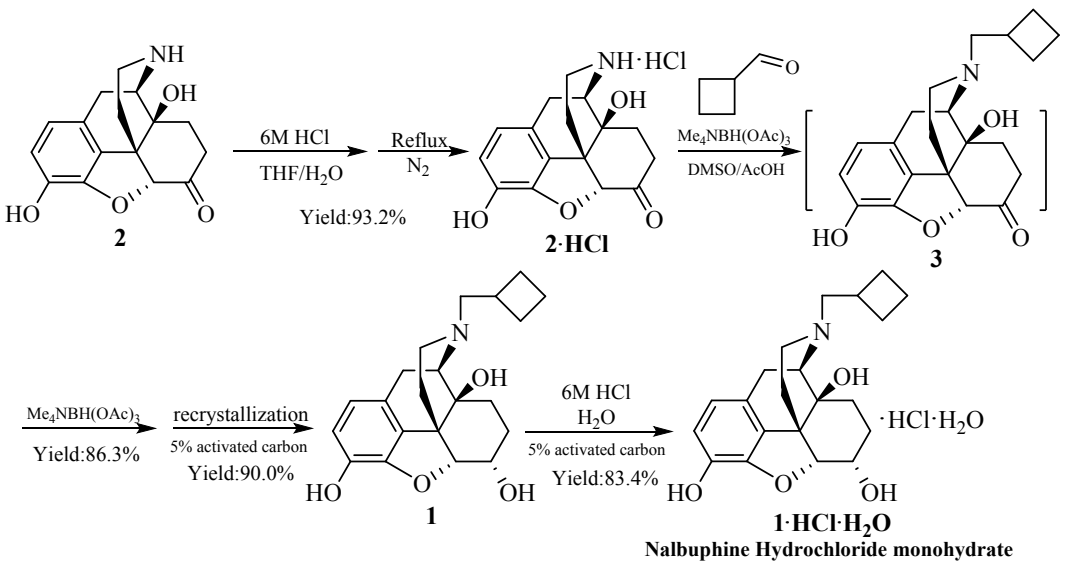


Table 6. Validation Result of Kilogram Scale Batches

batch	**2** (kg)	**1·HCl ·H_2O** (kg)	yield (%)	result[a] (%)										
				1	**2**	**3**	**4**	**5**	**6**	**9**	**10**	**11**	**12**	**13**
1	2.0	1.73	60.4	99.95	ND[b]	ND	ND	ND	ND	ND	ND	0.05	ND	ND
2	2.0	1.71	59.7	99.92	ND	ND	ND	ND	0.02	ND	ND	0.05	ND	ND
3	2.0	1.73	60.4	99.94	ND	ND	ND	ND	0.01	ND	ND	0.05	ND	ND

[a] Measured by HPLC (area %).

[b]Not detected.

Control Strategy and Result of Process-Related Impurity in Nalbuphine

hydrochloride. The optimized process made the nalbuphine hydrochloride reliable in quality control. The process parameters were investigated in details and improved well as described above. The process-related impurities are illustrated in Scheme **6**, and the control strategy and result of these impurities are shown in Table **7**.

Scheme 6. Process Related Impurities in Nalbuphine

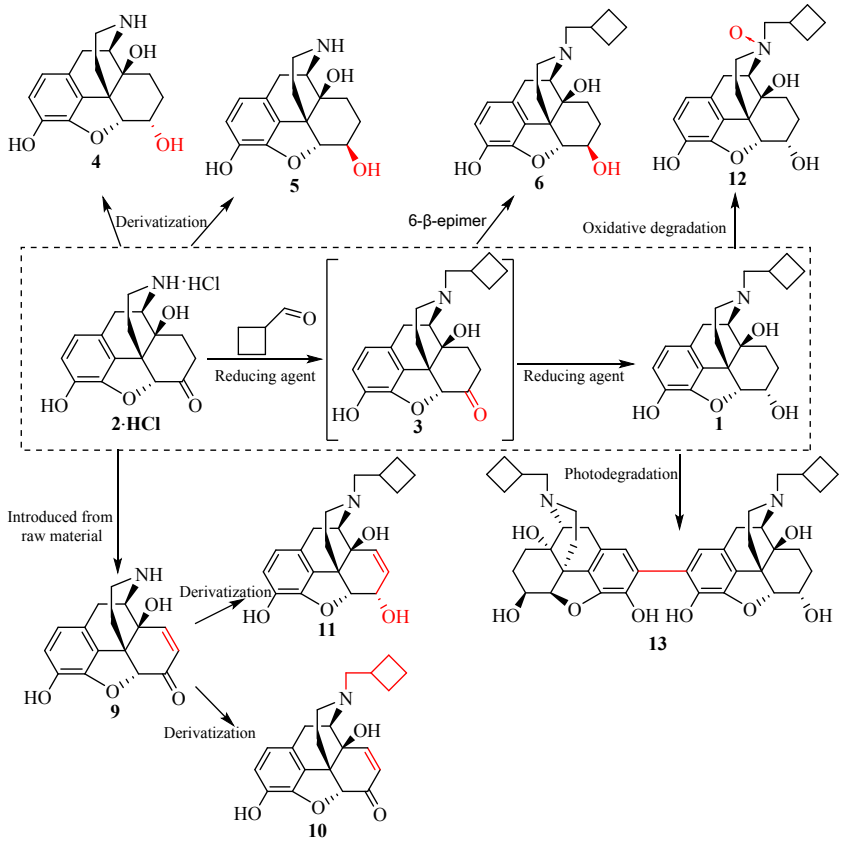


Table 7. Control Strategy and Result of Process-Related Impurity in Nalbuphine Hydrochloride

impurities	source	control strategy	impurity limit	Result (%)

			(%)	
2	Incomplete reaction of noroxymorphone	Keep the cyclobutanecarboxaldehyde excessive	0.1	ND
3	Incomplete reduction the intermediate **3**	Add 4.0 equiv of reducing agent in five portions	0.1	ND
4	Reduction of the unreacted **2**	Keep the Cyclobutyl formaldehyde excessive	0.1	ND
5	Reduction of the unreacted **2**	Keep the Cyclobutyl formaldehyde excessive	0.1	ND
6	The reduction at 6-keto of compound **3** in β-orientation	Add 4.0 equiv of reducing agent in five portions, and keep the content of $Me_4NBH(OAc)_3$ greater than 98%	0.1	ND
9	Derive from the residual compound **8**	Purification of **2·HCl**	0.1	ND

10	Intermediate of the reaction from **9** to **11**	Purification of **2·HCl**	0.1	ND
11	Derive from the **9**	Purification of **2·HCl**	0.1	0.05
12	Oxidizing degradation of nalbuphine	Exclude the use of tetrahydrofuran	0.1	ND
13	Photodegradation of nalbuphine	Avoid light during the dissolution process and storage	0.1	ND

Conclusions

A one-pot synthesis method of nalbuphine from noroxymorphone, a commercially available starting material, was developed and optimized. DMSO/AcOH was selected as the solvent due to the better conversion and solubility. The $Me_4NBH(OAc)_3$, added 4.0 equivalents in five portions, gave a higher conversion rate and a better stereoselectivity in the reduction of 6-keto group, and the crude nalbuphine was obtained with 0.05% of impurity **3** and 0.08% of impurity **6**. The stable crystalline form of nalbuphine hydrochloride was then further formed after being dried at 85 ℃. The source and control strategy of the process-related impurities in nalbuphine were

studied subsequently. The experimental validation on the kilogram scale generated the title compound with 99.95% purity in 60.4% overall yield.

Experimental section

General procedure

All of the reagents and solvents were obtained from commercial sources and used without further purification. The Nuclear magnetic resonance (NMR) spectra were recorded by a Bruker 400 MHz or 600 MHz instrument in DMSO-d_6 or CD_3OD with Me_4Si (TMS) as an internal reference. Mass spectra were recorded with a Waters Q-TOF micro mass spectrometer by electrospray ionization (ESI). Thermo gravimetric analysis (TGA) was performed on a TA Q500 analyzer under a nitrogen atmosphere with a heating rate of 10 °C/min. X-ray single crystal diffraction data were recorded on a Bruker SMART APEX-II instrument. X-ray Powder Diffraction (XRPD) data were recorded on a Bruker D8 Advance instrument. Chemical purity was analyzed by HPLC (normalized area percentage) on a Dionex UItiMate 3000 chromatograph system with UV detector. Mobile phase: (A) phosphate-buffered saline (0.01mol/L Na_2HPO_4 aqueous solution, adjusted to pH 8 with Phosphoric acid) - acetonitrile (95:5) and (B) acetonitrile. Column: Waters X-Bridge (C18, 4.6 mm × 250 mm, 3.5 μm). Column temperature: 30 °C, with a flow rate of 1.0 mL/min at 210 nm. The HPLC analyses were accomplished with a gradient elution program (time (min)/% B: 0/0, 16/70, 24/70, 24.1/0, and 32/0). LC/MS was performed on an Agilent LC/MS system which was consist of an Agilent 1260 LC system and electrospray

ionization (ESI) interface. HPLC purity is reported in area percentage.

Preparation of (-)-4,5α-Epoxy-3,14-Dihydroxymorphinan-6-one Hydrochloride (2·HCl):

A suspension of noroxymorphone (2.0 kg, 7.0 mol, 1.0 equiv) in THF (16 L) and water (1.1 L) was stirred under an atmosphere of nitrogen. The mixture was heated to reflux for 10-15min after 6M HCl (1.74 L, 10.4 mol, 1.5 equiv) was added slowly, and then cooled to the room temperature. The solid was collected by filtration, washed with THF (6 L) , and dried at 50 ℃ under vacuum to give intermediate **2·HCl** as a off-white solid (2.1 kg, yield, 93.2%; HPLC purity, 99.48%).^{1}H NMR (400 MHz, DMSO-d_6): δ 9.72 (s, 1H), 9.48 (s, 1H), 6.68 (d, J = 8.1 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 6.53 (s, 1H), 4.95 (s, 1H), 3.69 (d, J = 5.8 Hz, 1H), 3.30 (d, J = 19.1 Hz, 1H), 3.12-2.90 (m, 3H), 2.59 (td, J = 12.9, 4.4 Hz, 1H), 2.49-2.39 (m, 1H), 2.16-2.04 (m, 1H), 2.00-1.90 (m, 1H), 1.50-1.35 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 207.84, 143.65, 140.17, 127.97, 120.96, 119.67, 118.10, 88.82, 68.66, 56.48, 48.90, 36.38, 35.04, 30.40, 27.28, 26.19. MS (ESI+): m/z, (287.93 $[M + H]^+$).

Preparation of 17-(Cyclobutylmethyl)-4,5α-Epoxymorphinan-3,6α,14-triol (1)

Intermediate **2·HCl** (2.1 kg, 6.5 mol, 1.0 equiv) was dissolved in DMSO (21 L) at room temperature. The mixture was stirred for 0.5-1.0 hour after cyclobutanecarboxaldehyde (0.65 kg, 7.8 mol, 1.2 equiv) was added. $Me_4NBH(OAc)_3$ (1.7 kg, 6.5 mol, 1.0 equiv) was added to the above reactor followed by addition of acetic acid (8.4 L) . The reaction was stirred at room temperature for 1 hour and then

heated to 60 ℃ after the twice portion of $Me_4NBH(OAc)_3$ (1.7 kg, 6.5 mol, 1.0 equiv), keep the same temperature, the third portion of $Me_4NBH(OAc)_3$ (1.7 kg, 6.5 mol, 1.0 equiv), fourth portion of $Me_4NBH(OAc)_3$ (0.86 kg, 3.3 mol, 0.5 equiv), fifth portion of $Me_4NBH(OAc)_3$ (0.85 kg, 3.3 mol, 0.5 equiv), were added every 1 hour interval. The formed suspension was stirred at 60 ℃ for another 1 hour after water (21 L) and then aqueous ammonia (21 L) were added, and then cooled down to room temperature, adjusted pH to 9 with aqueous ammonia (6 L), continued to stir for 1 hour and filtered, washed with water (5 L), and dried at 50 ℃ under vacuum to give crude nalbuphine as a grayish solid. (2.0 kg, yield, 86.3%; HPLC purity, 99.79%)

Then recrystallization of the crude nalbuphine (2.0 kg) in methanol (40.0 L) and water (2.0 L) with activated carbon (100 g, 5.0%) was performed, gave nalbuphine as an off-white solid (1.8 kg, yield, 90.0%; total yield, 77.7%; HPLC purity, 99.91%).

Preparation of 17-(Cyclobutylmethyl)-4,5α-Epoxymorphinan-3,6α,14-triol Hydrochloride, Monohydrate (1·HCl·H_2O)

A 50 L reactor was charged with nalbuphine (1.8 kg, 5.0 mol, 1.0 equiv) and water (34.2 L), and the suspension was then heated to 60 ℃. The 6M HCl (1.3 L, 7.6 mol, 1.5 equiv) was added slowly to form a clear solution, and activated carbon (90.0 g, 5.0%) was added in 45 ℃ and stirred for 0.5-1.0 hour. Then the activated carbon was removed through rapid filtration, and the filtrate was evaporated to remove water under calculation to keep volume of the residual solvent at 5-8 v/w. Then the mixture was refluxed to form a clear solution and cooled naturally to room temperature, followed by stirring for another 6 hours in 0-10 ℃. The crystalline solid was isolated by filtration, washed with cold water, dried to constant weight at 50 ℃ under vacuum

and continue to dried at 85 ℃ for 2-3 hours under vacuum to give the monohydrate form of nalbuphine hydrochloride as a white solid (1.73kg, yield, 83.4%; HPLC purity, 99.95%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.23 (s, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 6.38 (s, 1H), 4.69 (s, 1H), 4.51 (d, J = 4.5 Hz, 1H), 4.19 – 4.02 (m, 1H), 3.50 (d, J = 6.6 Hz, 1H), 3.36 (dt, J = 13.1, 8.2 Hz, 1H), 3.33-3.27 (m, 1H), 3.08 (ddd, J = 10.1, 6.1, 3.4 Hz, 1H), 3.02 – 2.90 (m, 2H), 2.79 – 2.69 (m, 1H), 2.65 (qd, J = 13.0, 3.8 Hz, 1H), 2.44 (td, J = 13.4, 5.0 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.09 – 2.01 (m, 1H), 1.94 – 1.72 (m, 5H), 1.57-1.51 (m, 1H), 1.48(dd, J = 10.2, 2.4 Hz, 1H), 1.34 (ddd, J = 14.3, 8.1, 3.7 Hz, 1H), 1.05-0.95 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 146.66, 139.31, 129.68, 121.91, 118.88, 118.50, 89.44, 70.04, 65.07, 61.68, 57.65, 46.36, 45.47, 30.77, 30.33, 28.69, 27.38, 25.63, 23.83, 23.10, 18.58. MS (ESI+): m/z, (358.10 $[M + H]^+$).

Preparation of 6-Ketonalbuphine hydrochloride (3·HCl):

To a stirred solution of compound **2·HCl** (5.0 g) in DMSO (50 mL), cyclobutane carboxaldehyde (1.42 g) was added. After stirring for 30 min at room temperature, $Me_4NBH(OAc)_3$ (4.1 g) and acetic acid (7 mL) were added. After reacting for 50 min, $Me_4NBH(OAc)_3$ (0.4 g) was added. After 20 min, water (100 mL) and aqueous ammonia (30 mL) were added and stirred over night. Subsequently, the crude product was obtained by filtration and washed by water. Isopropanol was added, and after the crude product was fully dissolved, concentrated hydrochloric acid was added to form the hydrochloride. The precipitate was collected by filtration and dried under vacuum at 50 ℃ to give impurity **3·HCl** (4.1 g, 67.6% yield, chemical purity: 96.4%) as a off-white solid. ^{1}H NMR (400 MHz, DMSO- d_6) δ 9.51 (s, 1H), 7.03 (s, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.62 (d, J = 8.1 Hz, 1H), 5.01 (s, 1H), 3.44-3.36 (m, 1H), 3.33-3.27 (m, 1H), 3.14-2.91 (m, 4H), 2.80-2.61 (m, 2H), 2.50-2.40 (m, 2H), 2.21-1.99 (m, 4H), 1.98-1.78 (m, 4H), 1.52-1.40 (m, 2H).^{13}C NMR (101 MHz, DMSO- d_6) δ 207.73, 143.52, 140.15, 127.80, 120.52, 119.82, 118.05, 88.55, 69.73, 61.00, 56.98, 48.40, 46.51, 34.98, 30.51, 30.31, 27.14, 26.74, 25.13, 22.87, 18.13.

Preparation of 6-α-noroxymorphinol hydrochloride (4·HCl):

In a 250 mL reactor, compound **2·HCl** (10 g) and DMSO (100 mL) were placed and stirred to dissolved, and then $Me_4NBH(OAc)_3$ (12 g) and acetic acid (3 mL) were added. After heated for 60 min at 50 ℃, $Me_4NBH(OAc)_3$ (12 g) and acetic acid (3 mL) were added. After 3 h, $Me_4NBH(OAc)_3$ (6 g) was added. After 1h, water (40 mL) and aqueous ammonia (50 mL) were added. Subsequently, the reaction mixture was adjusted to acidity, and forced out by acetonitrile and collected by filtration to obtained **4·HCl**. (4.18 g, 41.6% yield, chemical purity: 99.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.64 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 4.48 (d, *J* = 4.5 Hz, 1H), 4.10-4.00 (m, 1H), 3.53 (d, *J* = 5.3 Hz, 1H), 3.17-2.95 (m, 3H), 2.64 (td, *J* = 12.8, 3.6 Hz, 1H), 2.34 (td, *J* = 13.2, 4.8 Hz, 1H), 1.66-1.40 (m, 3H), 1.36-1.25 (m, 1H), 1.05-0.94 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 146.55, 138.99, 129.98, 122.43, 119.23, 118.50, 89.57, 68.89, 65.18, 57.35, 45.82, 36.40, 29.24, 28.39, 28.13, 23.10. MS (ESI+): m/z, (290.03 $[M + H]^+$).

Preparation of 6-β-noroxymorphinol hydrochloride (5·HCl):

NaOH aqueous solution (6.4 g NaOH (8 eq) + 130 mL water) was prepared. Compound **2·HCl** (6.5 g) and water (65 mL) were stirred in a reactor, and a small amount of NaOH aqueous solution was added to this mixture to make it alkaline. Then thiourea dioxide (8.7 g, 4 eq) was added to the remaining NaOH aqueous solution, which was added by partial to the reaction solution after it was fully dissolved. After heated for 2h at 85 ℃ under nitrogen atmosphere, a solution of thiourea dioxide (4.5g, 2 eq) in NaOH (3.2 g, 4 eq) aqueous solution was added to the reaction solution and continued to react for 1h. After adjusting to about pH=9 with concentrated hydrochloride acid, the mixture was stirred for 30 min under ice cooling and then filtrated to isolate the solid. Subsequently, the solid and THF were placed in a reactor and stirred, and then 6M HCl aqueous solution was added dropwise to adjust pH=2~3. After stirring for 3.5 h at room temperature, the precipitate was collected by filtration, washed with THF, and dried under vacuum at 50 ℃ to give impurity **5·HCl**

(2.9 g, 44% yield, chemical purity: 99.1%) as white solid. ^{1}H NMR (400 MHz, DMSO- d_6) δ 9..05-9.85 (m, 2H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 5.78 (s, 1H), 5.14 (d, *J* = 4.0 Hz, 1H), 4.26 (d, *J* = 6.5 Hz, 1H), 3.53 (d, *J* = 5.4 Hz, 1H), 3.31 (d, *J* = 18.9 Hz, 1H), 3.14 (d, *J* = 5.1 Hz, 1H), 3.07-2.83 (m, 2H), 2.42 (td, *J* = 12.6, 3.2 Hz, 1H), 2.31 (td, *J* = 12.7, 4.1 Hz, 1H), 1.85-1.67 (m, 1H), 1.60 (d, *J* = 13.6 Hz, 1H), 1.50-1.40 (m, 1H), 1.32 (d, *J* = 10.1 Hz, 1H), 1.16 (t, *J* = 12.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO- d_6) δ 142.59, 141.09, 130.41, 120.81, 118.67, 117.78, 94.49, 71.02, 68.66, 56.98, 45.62, 36.49, 28.77, 27.28, 26.33, 26.18. MS (ESI+): m/z, (289.92 $[M + H]^+$).

Preparation of 6β-hydroxy-17-cyclobutylmethyl -4,5α-epoxy- 3,14-dihydroxymorphinan hydrochloride (6·HCl):

NaOH aqueous solution (3.3 g NaOH (8 eq) + 72 mL water) was prepared. Compound **3** (3.6 g) and water (46 mL) were stirred in a reactor, and a small amount of NaOH aqueous solution was added to this mixture to make it alkaline. Then thiourea dioxide (4.4 g, 4 eq) was added to the remaining NaOH aqueous solution, which was added to the reaction solution after it was fully dissolved. After heated for 2h at 85 ℃, a solution of thiourea dioxide (2.2 g, 2 eq) in NaOH (1.6 g, 4 eq) aqueous solution was added to the reaction solution and continued to react for 1h. After adjusting to about pH=9 under ice cooling, the mixture was filtrated, and the filter cake was made to salt of hydrocloride in THF. The precipitate was collected by filtration and dried to give 6β-hydroxy-17-cyclobutylmethyl-4,5α-epoxy-3,14-dihydroxymorphinan hydrochloride **(6·HCl)** (2.2 g, 55.1% yield, chemical purity 95.9%). ^{1}H NMR (400 MHz,CD_3OD) δ 6.73 (d, J = 8.2 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H), 4.39 (d, J = 6.5 Hz, 1H), 3.49 (d, J = 5.7 Hz, 1H), 3.43-3.32 (m, 3H), 3.19-3.04 (m, J = 25.8, 12.5, 7.0 Hz, 3H), 2.81-2.72 (m, 1H), 2.68 (dd, J = 12.7, 3.6 Hz, 1H), 2.57 (td, J = 13.1, 4.5 Hz, 1H), 2.30-2.11 (m, 2H), 2.07-1.85 (m, 5H), 1.73 (d, J = 14.0 Hz, 1H), 1.69-1.60 (m, 1H), 1.39-1.58 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 143.97, 142.67, 131.19, 121.69, 120.71, 119.41, 95.80, 73.20, 71.40, 64.40, 58.90,

48.52, 47.18, 32.09, 30.57, 28.98, 28.20, 26.62, 26.54, 24.43, 19.37. MS (ESI+): m/z, (358.15 $[M + H]^+$).

3-Methoxy-17-methyl-7,8-didehydro-4,5α-epoxymorphinan-6α,14-diol (9):

The DL-methionine (3.4 g) dissolved in methanesulfonic acid (40 mL) and the solution was maintained at 15 ℃, followed by adding compound **8** (4.0 g) to the mixture and the reaction was heated to 53 ℃ for 7 days. Then quenched with methanol (60 mL) and water (120 mL), and the pH was adjusted to 9 with 20% NaOH aqueous solution at below 20 ℃. The product was extracted with dichloromethane and ethyl acetate and concentrated to obtain a yellow solid. This crude solid was then dissolved in chloroform (30 mL), and potassium carbonate (6.0 g) was added to the reaction, followed by ethylchloroformate (8.0 g) dissolved in chloroform (10.0 mL). The mixture was heated to reflux and stirred for 10h. After the work-up procedure, the product hydrolyzed by sulfuric acid, and gave compound 9 as off-white solid through column chromatography (1.2 g, 33.0% yield, chemical purity 99.1%).

^{1}H NMR (400 MHz, CD_3OD) δ 6.90 (d, *J* = 10.2 Hz, 1H), 6.68 (q, *J* = 8.2 Hz, 2H), 6.15 (d, *J* = 10.2 Hz, 1H), 4.77 (s, 1H), 3.95 (dd, *J* = 4.9, 1.8 Hz, 1H), 3.27-3.14 (m, 3H), 2.93 (td, *J* = 13.3, 4.3 Hz, 1H), 2.73 (td, *J* = 13.3, 5.0 Hz, 1H), 1.84 (dd, *J* = 13.4, 3.6 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 195.48, 147.87, 144.65, 141.66, 134.46, 130.31, 122.42, 121.55, 119.97, 87.47, 67.45, 58.25, 47.81, 38.49, 28.86, 26.96. MS (ESI+): m/z, (286.08 $[M + H]^+$).

17-(Cyclobutylmethyl)-7,8-didehydro-4,5α-epoxymorphinan-6-keto-3, 14-diol (10):

Synthesized via the synthesis process of impurity **3** using compound **9** (0.4 g) as starting material to afford an off-white solid **10** (0.2 g, 40.4% yield, chemical purity 97.3%)

^{1}H NMR (400 MHz, CD_3OD) δ 6.94 (d, *J* = 10.2 Hz, 1H), 6.69 (s, 2H), 6.16 (d, *J* = 10.2 Hz, 1H), 4.79 (s, 1H), 3.81 (d, *J* = 6.1 Hz, 1H), 3.54-3.39 (m, 2H), 3.24-3.13 (m, 2H), 3.03 (dd, *J* = 19.8, 6.3 Hz, 1H), 2.89 (td, *J* = 12.7, 3.4 Hz, 1H), 2.83-2.70 (m, 2H), 2.35-2.13 (m, 2H), 2.11-1.90 (m, 4H), 1.89-1.81 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 195.29, 147.63, 144.53, 141.66, 134.59, 130.17, 122.01, 121.69, 119.98, 87.23, 68.45, 62.90, 59.07, 48.60, 47.59, 32.03, 28.14, 28.07, 26.58, 24.22, 19.41. MS (ESI+): m/z, (354.16 $[M + H]^+$).

17-(Cyclobutylmethyl)-7,8-didehydro-4,5α-epoxymorphinan -3,6α,14-triol (11)

Synthesized via the synthesis process of nalbuphine using compound **9** (0.4 g) as starting material to afford an off-white solid **11** (0.3 g, 60.2% yield, chemical purity 98.3%)

^{1}H NMR (400 MHz, CD_3OD) δ 6.52 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 8.1 Hz, 1H), 5.79 (dt, *J* = 9.6, 1.6 Hz, 1H), 5.48 (dd, *J* = 9.9, 3.2 Hz, 1H), 4.75 (dd, *J* = 6.4, 1.2 Hz, 1H), 4.55 (ddd, *J* = 6.3, 3.2, 1.9 Hz, 1H), 3.15-3.05 (m, 2H), 2.60-2.45 (m, 5H), 2.42 (td, *J* = 12.4, 3.2Hz, 1H), 2.32 (td, *J* = 12.4, 5.0 Hz, 1H), 2.16-2.01 (m, 2H), 2.02 -1.81 (m, 2H), 1.79-1.64 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 146.56, 140.12, 138.38, 133.51, 130.59, 126.36, 120.23, 118.11, 91.50, 70.35, 66.72, 63.37, 61.60, 48.61, 45.06, 35.05, 32.98, 28.10, 27.70, 24.01, 19.60. MS (ESI+): m/z, (356.19 $[M + H]^+$).

Preparation of Nalbuphine-*N*-oxide (12):

In a 100 mL reaction flask, DCM (50 mL) and Nalbuphine were placed and stirred, and then M-CPBA (3.7 g, 1.5 eq) was added. After 3 h, the reaction was complete. The oily substances were obtained through column chromatography (DCM : MeOH= 10: 1). And then the oily substances were vigorously stirred in isopropyl ether and then filtrated to give Nalbuphine-N-oxide as solid **(12)** (2.7 g, 51.9% yield, chemical purity 99.1%).^{1}H NMR (400 MHz, CD_3OD) δ 6.69 (d, *J* = 8.1 Hz, 1H), 6.57 (d, *J* = 8.1 Hz, 1H), 4.64 (d, *J* = 4.6 Hz, 1H), 4.22-4.13 (m, 1H), 3.77-3.64 (m, 1H), 3.46 (d, *J*

= 6.2 Hz, 1H), 3.37 (d, *J* = 19.9 Hz, 1H), 3.27-3.02 (m, 5H), 2.87 (td, *J* = 13.3, 4.2 Hz, 1H), 2.24-2.05 (m, 2H), 2.04-1.88 (m, 3H), 1.87-1.76 (m, 1H), 1.70-1.55 (m, 3H), 1.55-1.43 (m, 1H), 1.10-1.01 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 147.46, 140.12, 131.77, 122.73, 120.56, 119.58, 91.23, 74.97, 74.67, 72.92, 67.01, 60.44, 48.17, 31.83, 30.57, 29.72, 29.29, 29.02, 28.72, 24.01, 20.04. MS (ESI+): m/z, (374.17 $[M + H]^+$).

Preparation of 2,2'-Bisnalbuphine (13):

Nalbuphine (8.0g) was dissolved in 0.1% phosphoric acid solution (500 mL) under oxygen atmosphere. The mixture exposed to light for 90 days, and adjusted pH to 9 with aqueous ammonia, the obtained solid was purified through column chromatography (DCM : MeOH = 20:1) to give compound **13** as yellow solid (0.7 g, 8.8% yield, chemical purity 97.8%)

^{1}H NMR (400 MHz, CD_3OD) δ 6.56 (s, 2H), 4.49 (d, *J* = 4.2 Hz, 2H), 4.10-4.00 (m, 2H), 3.16 (d, *J* = 18.8 Hz, 2H), 3.01 (d, *J* = 6.3 Hz, 2H), 2.84-2.62 (m, 8H), 2.61-2.48 (m, 4H), 2.30 (td, *J* = 12.6, 4.8 Hz, 2H), 2.17-2.01 (m, 4H), 1.98-1.92 (m, 2H), 1.90-1.82 (m, 2H), 1.80-1.69 (m, 4H), 1.65-1.40 (m, 8H) 1.23-1.08 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 149.71, 141.52, 133.08, 129.97, 122.96, 122.78, 91.37, 71.51, 67.78, 64.33, 61.05, 47.99, 45.92, 34.01, 33.62, 30.21, 28.19, 27.28, 24.53, 24.21, 19.55.MS (ESI+): m/z, (713.47 $[M + H]^+$).

Associated Content

Supporting Information

HPLC, NMR, and MS data of the impurity **2, 3, 4, 5, 6, 9, 10, 11, 12, 13**; X-ray powder diffraction(XRPD), thermo gravimetric analysis (TGA), MS and NMR data of nalbuphine hydrochloride; X-ray single crystal diffraction data of **nalbuphine hydrochloride**, impurity **4** and **5**; HPLC data of crude **nalbuphine** and **API** in three

batches of kilogram-scale experiment; Process Related Impurities of Nalbuphine in HPLC Chromatogram.

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Notes

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