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An Efficient, Scalable Process for Benzphetamine Hydrochloride

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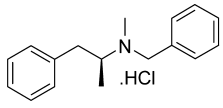
Supporting Information

ABSTRACT: Commercial manufacturing of benzphetamine hydrochloride along with its impurity profiling is disclosed. Deoxygenation of pseudoephedrine is reported with ~100% retention by shielding the amine group as its *tert*-butyl carbamate, which is very straightforward to eliminate at the end. Four unknown process-related impurities are isolated from the samples of final API and characterized on the basis of their NMR and mass spectral analysis. Structures of the isolated impurities are confirmed by independent syntheses and coinjecting with the isolated one.

INTRODUCTION

Benzphetamine (**1**, chemically known as (2*S*)-*N*-benzyl-*N*-methyl-1-phenylpropan-2-amine, figure 1) is an anorectic drug



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Benzphetamine Hydrochloride

Figure 1. Benzphetamine hydrochloride.

marketed under the brand name 'Didrex' in the United States (USA) by Pharmacia.[1] It is used as sympathomimetic appetite suppressants to manage exogenous obesity by stimulating the release of norepinephrine and/or dopamine from storage sites in nerve terminals of the lateral hypothalamic feeding center, thereby producing a decrease in appetite.

Even though the molecule is known for more than half a decade, only a few manufacturing processes have been reported in the literature. The initial synthesis of benzphetamine hydrochloride by Heintzelman et al.[2] in U.S. Patent 2,789,138 (1957) started with *d*-desoxyephedrine (methamphetamine) (**2**) which on N-alkylation with benzyl chloride using anhydrous potassium carbonate as base in solvents like benzene/toluene or xylene under prolonged heating (150 °C) afforded the crude free base (**3**) (Scheme 1). Purification of the crude base by vacuum distillation at high temperature provided pure benzphetamine free base which was transformed to its hydrochloride salt using ethanolic HCl in ethyl acetate followed by crystallization from ether.

The main disadvantages of this process are the extensive high temperature for reactions (150 °C) and vacuum distillation (~127 °C) of the free base and use of ether as solvent during crystallization of salt. Later on Kolota et al.[3] in U.S. Patents 0262268 (2008) and 2,750,187 (2010), reported improved crystallization process of benzphetamine HCl. Tomazi et al.[4] also reported purification methods (U.S. Patents 0124833, 2009 and 0113831, 2010). As a part of our ongoing program towards development for commercially valuable generic drugs, we intended to undertake the synthesis of benzphetamine hydrochloride and come up with a process which would be devoid of all these harsh conditions and afford the product with high purity and yield under milder conditions. We envisaged commercially available ephedrine or pseudoephedrine could be the best suitable starting point for the manufacturing of benzphetamine HCl. Benzylic deoxygenation of ephedrine or pseudoephedrine followed by N-benzylation under mild conditions would give the desired benzphetamine free base, which could be easily converted to its hydrochloride salt. It is noteworthy to mention that ephedrine/norephedrine, methamphetamine, and benzphetamine all are controlled substances (psychotropic), and their uses are restricted.

RESULTS DISCUSSION

In our initial approach, we planned the direct deoxygenation of commercially available ephedrine/pseudoephedrine hydrochloride; for this purpose, among the various methods available in the literature[5] affecting this transformation, we felt hydrogenolysis/deoxygenation with Raney Ni could be the best option for large-scale production instead of using expensive complex and precious metal hydrogenating catalysts. Accordingly, deoxygenation of ephedrine/pseudoephedrine HCl with an excess of Raney Ni in isopropanol was attempted in an autoclave at 50−55 °C (pressure observed up to 2−3 kg); to our satisfaction, the reaction proceeded to completion within 2−3 h and cleanly afforded the desired product (methamphetamine) after filtration of the catalyst. The N-benzylation step was accomplished using benzyl chloride in the presence of K_2CO_3 in toluene which provided benzphetamine free base (**3**) in almost quantitative yield and high purity (Scheme 2). For the hydrochloride salt formation, the free base (oil) was dissolved in ethyl acetate and treated with anhydrous HCl in ethyl acetate (8−10%).

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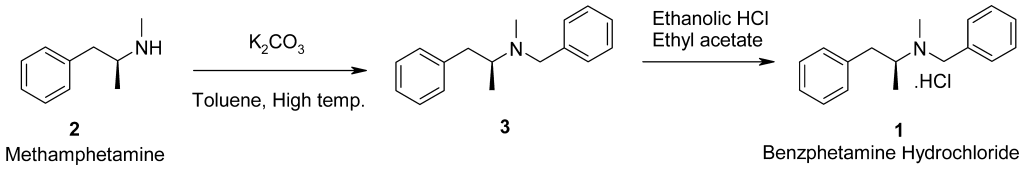
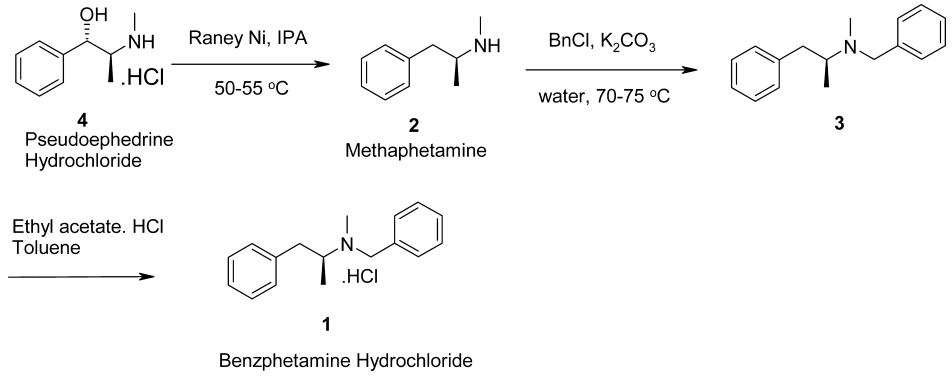
Scheme 1



Scheme 2



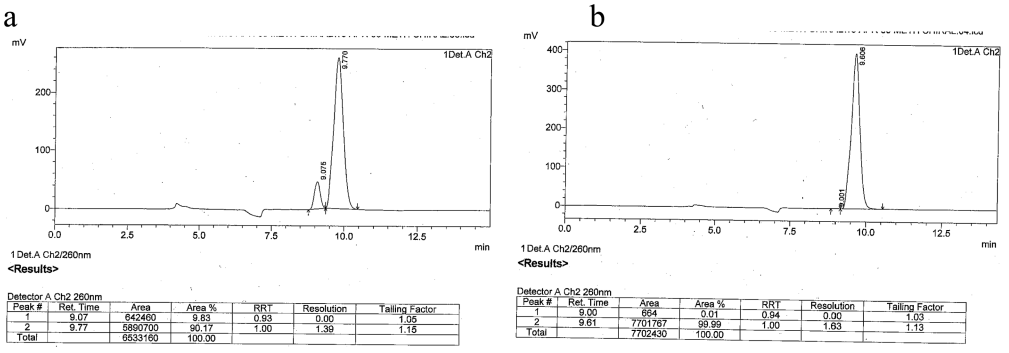
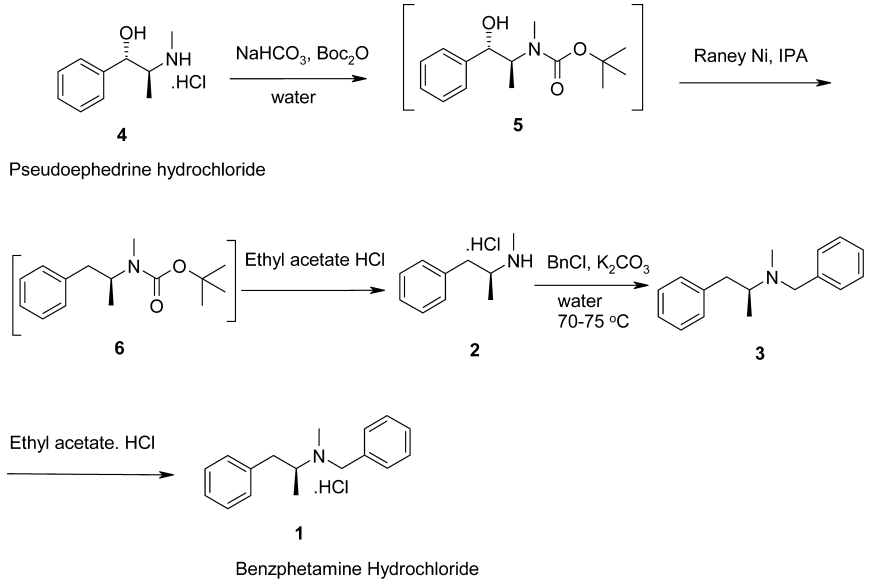


Figure 2. Chiral purity of methamphetamine of initial and new route. (a) Chiral HPLC purity of methamphetamine in initial route. (b) Chiral HPLC purity of methamphetamine in new route.

Scheme 3



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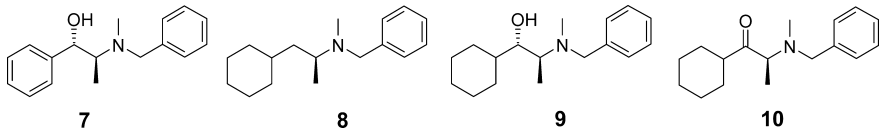


Figure 3. Process-related unknown impurities.

The synthetic sequence was repeated and found to be reproducible on 500-g scale. The final API (benzphetamine HCl) synthesized by this route was highly pure (>99.5% by HPLC), but unfortunately, the optical rotation and chiral purity was found to be fairly low (~10% racemization was observed). We were surprised by this result as we never expected racemization during the deoxygenation reaction using Raney Ni or the N-benzylation step. When we went back to check the optical rotation of the intermediate **2** (methamphetamine) isolated after the deoxygenation step, to our surprise, the SOR was found to be low, indicating that the racemization really happened during this transformation. Also, we developed the chiral HPLC method and found that the chiral purity of methamphetamine (**2**) was low (10% racemization, Figure 2), confirming that the racemization had occurred during the deoxygenation step.

Hence, at this stage we decided to abandon this route and work on alternate process which would avoid this problem. After careful/extensive literature search, it was found that recently Gollapudy et al.[6] disclosed (U.S. Patent 0293971, 2008) an efficient process for methamphetamine involving deoxygenation of protected ephedrine/pseudoephedrine (as amides) without any racemization using Raney Ni. The protecting groups they chose vary from −CO−H, −CO−Me, and −CO−Ph which form the corresponding amides and finally were hydrolyzed after the deoxygenation step under harsh conditions to release the free amine. We planned to investigate the utility of *tert*-butyl carbamate protection (Boc) for this transformation as the Boc deprotection would require milder conditions later in the synthesis. Accordingly, ephedrine/pseudoephedrine HCl was treated with Boc_2O in the presence of $NaHCO_3$ in water (Scheme 3) to afford the Boc-protected compound (**5**) which was subjected to the deoxygenation reaction under our earlier condition of Raney Ni in IPA. The reaction proceeded smoothly to provide clean deoxygenated product (Boc-methamphetamine, **6**), but at this stage we were unaware of the effect on chiral purity. Thus, the Boc group of this intermediate was cleaved using HCl in ethyl acetate to provide the desired methamphetamine HCl (**2**). To our satisfaction, the chiral purity of this was found to be more than 99.9%, and the optical rotation matched with the reported values, indicating no racemization. This transformation was repeated a few times and was scaled up to 0.5 kg scale in the laboratory (it is currently being performed on commercial scale). Once we solved the major problem and were able to avoid/prevent any racemization during the deoxygenation step, we focused our attention on optimizing the N-benzylation step. The benzylation step was attempted using various bases in different solvents; most of the reactions were found to be clean and gave the product in very good yield. Amongst all the conditions for the benzylation reaction, we decided to go with K_2CO_3 as base and water as the solvent (70−75 °C, 10 h) which provided the benzphetamine free base after workup in reasonably good purity and high yield (excess benzyl chloride and benzyl alcohol that formed during the process could be easily removed by acid−base workup).[7] Finally, the hydrochloride salt formation was accomplished using HCl in ethyl acetate (8−10%) which afforded the API (benzphetamine hydrochloride) in >99.8% HPLC as well as >99.9% chiral purity in very good yield. The final API was devoid of any impurity (NMT 0.1%) and satisfied all the ICH guidelines.[8]

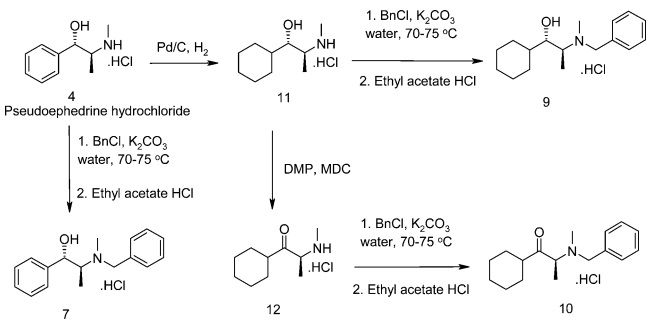
Impurity Profiling. Impurity profile of a drug is very important for its efficiency and safety point of view. To control the process impurities it is very important to isolate and characterize all the impurities present in the drug substance. After developing the process, we turned our attention to impurity profile study and tried to isolate and identify all the possible impurities that could be formed during the process. For this purpose, the ethyl acetate mother liquor after HCl salt formation of the final API was injected in HPLC, and several (six) prominent peaks were observed to the level of 1−5% (HPLC area). From the LC/MS experiment, two of these impurities were confirmed to be pseudoephedrine (m/z 165, SM) and methamphetamine (m/z 149, intermediate) [also confirmed by coinjection]. For identification/characterization and structure confirmation with peaks m/z values 255, 245, 259 and 261, we decided to isolate these impurities. By careful and tedious preparative HPLC, we isolated very small samples of these four impurities and confirmed the structures (**7**, **8**, **9** and **10**) on the basis of mass and ^{1}H NMR (isolated impurity samples were not enough for complete characterization) as in Figure 3.

Hence, we planned to synthesize all these four impurities which would enable us to provide sufficient quantities of these impurities to the analytical group to complete all their activities to include these compounds in the final API as known impurities. Accordingly, we synthesized all these four impurities using a straightforward sequence of reactions (Schemes 4 and 5), and generated working standards of these impurities and completed all the analytical activities including the analytical method validation of the API.

EXPERIMENTAL SECTION

General Procedures. All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian 400 MR spectrometer in $CDCl_3$ and DMSO-d_6, and mass spectra

Scheme 4. Synthesis of impurity 7, 9 and 10



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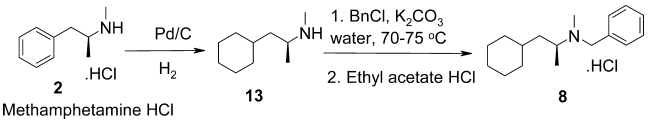
Scheme 5. Synthesis of impurity 8



were determined on an API-2000LCMS mass spectrometer, Applied Biosystems. Elemental Analysis was done in a VarioEL III instrument.

Preparation of Methamphetamine Hydrochloride (2). To a solution of (+)-pseudoephedrine hydrochloride (**4**, 20 kg, 99.0 mol) in water (100 L) at room temperature, was added sodium bicarbonate (18.28 kg, 217 mol) with stirring. Boc anhydride (23.84 kg, 110 mol) was added into the reaction mixture slowly at room temperature, and stirring was continued for the next 12 h. After completion of the reaction (monitored by HPLC), the reaction mixture was extracted with ethyl acetate (2 × 80 L). The combined ethyl acetate layer was washed with water (55 L) and concentrated at below 55 °C under reduced pressure. The residue was redissolved in isopropanol (55 L) and transferred into an autoclave. Raney Ni (40 kg) suspension in isopropanol (55 L) was added into the reaction mixture and heated to 50−55 °C. After completion of the reaction (by HPLC), the reaction mixture was cooled to room temperature and filtered through a Hyflo bed. Filtrate was concentrated at 50−55 °C under reduced pressure to obtain a crude oil. The crude oil thus obtained was dissolved in ethyl acetate and cooled to 0−5 °C. Ethyl acetate HCl (96 L) was added into it, and the reaction mixture was stirred at room temperature for 20 h. Ethyl acetate was removed under reduced pressure at 55−60 °C. To the residue was added ethyl acetate (75 L) and stirred at 10−15 °C for 1 h and filtered. The solid thus obtained was washed with cold ethyl acetate (10−15 °C, 55 L). Material was dried at 50−55 °C under vacuum to obtain **2** (16.5 kg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.73 (bs, 2H), 7.32−7.21 (m, 5H), 3.49 (m, 1H), 3.35 (m, 1H), 2.85 (m, 1H), 2.7 (s, 3H), 1.35 (d, 3H, J = 6.52 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 135.9, 129.1, 128.6, 127.0, 56.9, 39.1, 30.0, 15.2. $C_{10}H_{15}N{\cdot}HCl$, $(M^+)/z$: 149.24, Found: (M + H)/z: 150.0.

Preparation of Benzphetamine Hydrochloride. To a solution of methamphetamine hydrochloride (**2**, 11 kg, 59 mol) in water (55 L), at room temperature, was slowly added potassium carbonate (24.5 kg, 177 mol) and stirred for 30 min. Benzyl chloride (9.74 kg, 76.9 mol) was added into the reaction mixture, and the reaction mixture was heated at 70−75 °C for 10 h. After completion of the reaction, it was cooled to room temperature and extracted with toluene (55 L). The toluene layer was acidified with dil HCl (55 L, 6.6 N) at 5−10 °C. The layer was separated; the aqueous layer was washed with toluene (44 L). The aqueous layer was then basified with sodium hydroxide solution (11.78 kg in 11.78 L water) to pH ∼12. The product was then extracted with toluene (3 × 55 L). The combined toluene layers were concentrated at 50−55 °C under reduced pressure to get the benzphetamine free base. The free base was then dissolved in ethyl acetate (6 L) and cooled to 5−10 °C, and to this was added ethyl acetate HCl (32 L, 8−10%), and the reaction mixture was stirred at 25−30 °C for 10 h. The solid thus obtained was filtered and slurry washed with ethyl acetate to obtain API grade benzphetamine hydrochloride (**1**, 15 kg, 93%) after drying at 55−60 °C under vacuum. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 12.56 (bs, 1H), 7.8 (m, 2H), 7.5 (m, 3H), 7.3−7.1 (m, 5H), 4.3−4.2 (m, 2H), 3.9−3.5 (m, 2H), 2.72 (m, 3H), 2.67−2.56 (m, 1H), 1.3−1.2 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 135.8, 135.4, 130.8, 130.7, 129.6, 129.6, 129, 129, 128.9, 128.8, 128.7, 128.5, 128.4, 126.9, 126.8, 60.2, 60.1, 57.34, 55.7, 37.9, 35.8, 36.02, 34.5, 13.4, 11.3. $C_{17}H_{21}N{\cdot}HCl$, $(M^+)/z$: 239.36, Found: (M + H)/z: 240.0; Anal. for $C_{17}H_{21}N{\cdot}HCl$, calcd: C, 73.49; H, 8.71; N, 5.04; Found: C, 73.43; H, 7.93; N, 5.05. HPLC purity >99.8%

Identification of the Impurities by LC/MS. The LC/MS analysis was carried out on hypersil BDS, C8, 250 mm × 4.6 mm, 5 μm particle diameter column. The mobile phase A contained 0.01 M ammonium acetate in purified water, and the pH was adjusted to 4.5 with glacial acetic acid. The mobile phase B consisted of acetonitrile and purified water in the ratio of 9:1 (v/v). The flow rate of the mobile phase was 1.0 mL min^{-1}. The column temperature was kept at 25 °C, and the LC gradient program was set as: time (min)/% solution B: 0/20, 3/20, 30/60, 35/60, 40/90, 45/90, and 46/20, and the detection was monitored at wavelength of 207 nm. The injection volume was 20 μL. A mixture of water and acetonitrile (1:1) was used as diluents. The LC/MS analysis of the impurities were carried out on a triple quadruple mass spectrometer (MDS Sciex model API 2000). The analysis was performed in the positive (+ve) ion mode with electron spray ionization technique (ESI) interface with the following conditions: declustering potential at 40 V, entrance potential at 10 V, focusing potential at 325 V, curtain gas 20 L min^{-1}, ion spray voltage 4500 V, and temperature 450 °C.

Isolation and Characterization of the Compounds 7, 8, 9 and 10. The compounds **7**, **8**, **9** and **10** were isolated by preparative HPLC of the crude mass obtained upon concentration of mother liquor of benzphetamine hydrochloride. A Waters autopurification system equipped with binary gradient module (Waters 2545), system fluidics organizer (Waters SFO), photodiode array detector (Waters 2998) and a sample manager (Waters 2767) with Mass lynx data handling system, and a Waters Symmetry C18 (30 mm × 100 mm) preparative column packed with 5 μm was employed for the isolation of impurities. Mobile phase A consisted of 1.0% ammonium acetate pH 4.5 adjusted by acetic acid, and mobile phase B consisted of methanol. Flow rate was kept at 30 mL/min, and UV detection was carried out at 207 nm.The gradient program was as follows. Time (min)/A (v/v): B (v/v), $T_{0.01}$/80:20, $T_{5.00}$/80:20, $T_{25.00}$/40:60, $T_{30.00}$/10:90, $T_{36.00}$/80:20, $T_{40.00}$/80:20. A 500 mg/mL solution was prepared in a mixture of water and acetonitrile (1:1), 900 μL solutions were injected through auto-injector, and the elution was carried out. Initially, one pilot run was carried out for simulation of the auto-fraction collector parameter. Collected fractions were also monitored for the chromatographic purity. In a similar way ∼40 injections were made. All the fractions from the 40 injections of >95% chromatographic purity for a particular impurity were mixed together. The mixed fractions of impurities were concentrated under reduced pressure to remove the solvents, and the product was extracted with dichloromethane under basic conditions. The dichloromethane layer was concentrated and used for further spectral studies. The structure of the isolated compound was confirmed by independent synthesis, and the compound was used for a reference standard for the analysis of the benzphetamine hydrochloride.

Preparation of (1S,2S)-2-(Benzyl(methyl)amino)-1-phenylpropan-1-ol (7). To a solution of (+)-pseudoephedrine hydrochloride (5.0 g, 24.78 mmol) in water (25 mL) were

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added potassium carbonate (6.85 g, 49.56.mmol) followed by benzyl chloride (3.76 g, 29.74 mmol). The reaction mixture was heated at 70−75 °C for 10 h. The reaction mixture was cooled at room temperature. The product was extracted with toluene (30 mL × 2). The toluene layer was washed with DM water (20 mL). Toluene was removed under vacuum at 50 °C to obtain a crude mass. The crude mass was then diluted with ethyl acetate and dil HCl (1 N, 60 mL). The reaction mass was stirred for 15 min, and the layers were separated. The aqueous layer was basified with $NaHCO_3$ and extracted with ethyl acetate (2 × 30 mL). The combined organic layer was concentrated under reduced pressure to obtain a sticky mass. To this anhydrous ethyl acetate HCl (50 mL, 8−10%) was added and stirred at room temperature for 30 min. The reaction mass was concentrated under reduced pressure to obtain **7** (6.6 g, 91%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.17 and 9.48 (br s, 1H), 7.17−7.66 (m, 10H), 6.63−6.79 (m, 1H), 4.11−4.92 (m, 3H), 3.53 and 3.04 (m, 1H), 2.86−2.70 (m, 3H), 1.05−0.94 (m, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 140.5, 139.6, 131.1, 130.6, 129.8, 129.5, 129.2, 129, 128.5, 128.4, 127.2, 127.0, 74.4, 72.8, 63.7, 62.6, 58.2, 56.3, 36.8, 35.0, 11.5, 9.5. $C_{17}H_{21}NO$, $[M^+]^+$ 255.36, Found: (M + H)/z: 256.2.

*Preparation of (S)-1-Cyclohexyl-N-methylpropan-2-amine (**13**).* To a solution of methamphetamine HCl (2.5 g, 13.45 mmol) in water was added 5% Pd/C (0.25 g), and the reaction mixture was hydrogenated at 75−80 psi and at 55 °C for 6 h. After complete consumption of the starting material, the reaction mixture was filtered over a Hyflo bed. Aqueous sodium carbonate was added to the filtrate and stirred for 30 min. The product was extracted with dichloromethane (30 mL × 2). The combined dichloromethane layer was concentrated under reduced pressure at below 45 °C to get the product as free base **13** (1.7 g, 82%); ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.34 (bm, 2H), 3.20 (m, 1H), 2.63 (S, 3H), 1.79−1.7 (m, 7H), 1.6−1.5 (m, 1H), 1.40 (d, J = 6.5 Hz, 3H), 1.29−1.12 (m, 3H), 1.0−0.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 135.9, 129.1, 128.6, 127.0, 96.9, 39.1, 30.0, 15.2. $C_{10}H_{21}N$, MS $m/z[M^+]^+$ 155.29, Found: (M + H)/z: 156.

*Preparation of (S)-N-Benzyl-1-cyclohexyl-N-methylpropan-2-amine (**8**).* To a solution of **13** (5.0 g, 32.19 mmol) in water was added potassium carbonate (8.9 g, 64.39 mmol), followed by benzyl chloride (4.89 g, 38.63 mmol). The reaction mixture was heated to 70−75 °C for 10 h and then cooled to room temperature. The product was extracted with toluene (25 mL × 2). The combined toluene layers were washed with DM water (20 mL). Toluene was removed at below 50 °C under reduced pressure to obtain a crude mass. The crude mass was then diluted with ethyl acetate and dil HCl (1 N, 70 mL). The reaction mass was stirred for 15 min and layer was separated. The aqueous layer was basified with $NaHCO_3$ and extracted with ethyl acetate (2 × 30 mL). The combined organic layer was concentrated under reduced pressure to obtain sticky mass. To this anhydrous ethyl acetate HCl (50 mL, 8−10%) was added and stirred at room temperature for 30 min. Reaction mass was concentrated under reduced pressure to obtain **8** (5.68 g, 62%) as white solid. Molecular formula: ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.30−7.20 (m, 5H), 3.50 (ABq, 2H, J = 13.3 Hz), 2.82 (m, 1H), 2.11 (s, 3H), 1.48−1.40 (m, 2H), 1.3−1.1 (4H), 1.0 (d, J = 6.5 Hz 3H), 0.88 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 140.6, 128.7, 128.1, 126.6, 57.7, 54.4, 41.7, 41.6, 36.3, 36.3, 34.5, 33.6, 26.8, 26.4, 13.61, 13.4. $C_{17}H_{27}N$, MS m/z $[M^+]^+$ 245.41, Found: (M + H)/z: 246.

*Preparation of (1S,2S)-1-Cyclohexyl-2-(methylamino)-propan-1-ol (**11**).* To a solution of (+)-pseudoephedrine hydrochloride (**4**, 5.0 g, 24.8 mmol) in water (50 mL) was added Pd/C (1.0 g, 5% w/w), and the mixture was hydrogenated under pressure (75−80 psi) at 55 °C for 6 h. After completion of the reaction, the reaction mixture was degassed with nitrogen and was filtered over a Hyflo bed. The filtrate was diluted with aqueous sodium carbonate and stirred for 30 min. The product was extracted with dichloromethane (2 × 30 mL). The combined dichloromethane layer was concentrated under reduced pressure at below 45 °C to obtain a crude mass. To this crude mass, anhydrous ethyl acetate HCl (30 mL, 8−10%) was added and stirred for 30 min. The reaction mixture was then concentrated under reduced pressure to yield **11** (4.0 g, 94%) as hydrochloride salt. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 3.0 (m, 1H), 2.5 (m, 1H), 2.4 (s, 3H), 1.8 (m, 2H), 1.6 (m, 3H), 1.5−1.1 (m, 6H), 1.0 (d, 2H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 77.9, 56.6, 39.6, 32.8, 30.7, 26.7, 26.4, 26.3, 25.5, 15.2. $C_{10}H_{21}NO$, $(M^+)/z$: 171.28, Found: (M + H)/z: 172.1.

*Preparation of (1S, 2S)-2-(Benzyl(methyl)amino)-1-cyclohexyl-propane-1-ol (**9**).* To a solution of **11** (3.5 g, 20.5 mmol) in water (20 mL) was added potassium carbonate (5.64 g, 40.86 mmol), followed by benzyl chloride (3.1 g, 24.5 mmol) at room temperature. The reaction mixture was heated at 70−75 °C for 8 h. After completion of the reaction, it was cooled at room temperature and extracted with toluene (2 × 20 mL). The combined toluene layers were washed with water (20 mL). Toluene was removed under reduced pressure at below 50 °C to obtain a crude mass. The crude mass was then diluted with ethyl acetate and dil HCl (1 N, 50 mL). The reaction mass was stirred for 15 min, and the layer was separated. The aqueous layer was basified with $NaHCO_3$ and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was concentrated under reduced pressure to obtain a sticky mass. To this anhydrous ethyl acetate HCl (20 mL, 8−10%) was added and stirred at room temperature for 30 min. The reaction mass was concentrated under reduced pressure to obtain **9** (5.2 g, 86%) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.31−7.25 (m, 5H), 3.68 and 3.39 (ABq, J = 13 Hz, 2H), 3.26 (m, 1H), 2.72 (m, 1H), 2.13 (s, 3H), 1.8−1.15 (m, 11H), 0.93 (d, 3H, J = 6.6 Hz), ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 138.9, 128.8, 128.3, 127.0, 74.8, 59.5, 57.8, 39, 35.8, 31.5, 27.0, 26.5, 26.4, 24.5, 7.6. $C_{17}H_{27}NO$, $(M^+)/z$: 261.41, Found: (M + H)/z: 262.2.

*Preparation of (S)-1-Cyclohexyl-2-(methylamino)propan-1-one (**12**).* To a solution of **11** (1.5 g, 8.8 mmol) in dichloromethane (15 mL) was added Dess−Martin periodinane (3.9 g, 9.2 mmol) at 5−10 °C. The reaction mixture was stirred for 4 h at room temperature. After completion of the reaction, it was quenched with aqueous sodium sulfite (20 mL) and stirred for 1 h. The product was then extracted with dichloromethane (2 × 20 mL). The combined organic layer was washed with water (20 mL) and concentrated under reduced pressure at below 40 °C to obtain a crude mass. To this crude mass, anhydrous ethyl acetate HCl (20 mL, 8−10%) was added and stirred for 30 min. The reaction mixture was then concentrated under reduced pressure to yield **12** (1.0 g, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 9.67 (br s, 2H), 4.17 (q, 1H, J = 7.2 Hz), 2.72 (s, 3H), 2.59−2.52 (m, 1H), 2.0−1.9 (m, 2H), 1.8−1.7 (m, 4H), 1.67 (d, 3H, J = 7.2 Hz),

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1.5−1.4 (m, 1H), 1.4−1.16 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 208.0, 60.5, 47.0, 30.8, 28.8, 27.3, 25.4, 25.3, 24.7, 13.8; $C_{10}H_{19}NO$, MS $m/z[M^+]^+$ = 169.27, Found: (M + H)/z: 170.1, (M + Na)/z: 192.3.

*Preparation of (S)-2-(Benzyl(methyl)amino)-1-cyclohexylpropan-1-one (**10**).* To a solution of **12** (1.0 g, 5.90 mmol) in water (10 mL) was added potassium carbonate (1.63 g, 11.81 mmol) followed by benzyl chloride (0.9 g, 7.09 mmol). The reaction mixture was heated at 70−75 °C for 8 h. The reaction mixture was cooled at room temperature and was extracted with toluene. The combined toluene layers were washed with water (20 mL) and concentrated under reduced pressure at below 40 °C to obtain a crude mass. The crude mass was then diluted with ethyl acetate and dil HCl (1 N, 20 mL). The reaction mass was stirred for 15 min, and the layer was separated. The aqueous layer was basified with $NaHCO_3$ and extracted with ethyl acetate (2 × 25 mL). The combined organic layer was concentrated under reduced pressure to obtain a sticky mass. To this anhydrous ethyl acetate HCl (20 mL, 8−10%) was added and stirred at room temperature for 30 min. The reaction mass was concentrated under reduced pressure to obtain **10** (1.2 g, 69%) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.34−7.24 (m, 5H), 3.55−3.38 (m, 2H), 3.47 (q, J = 6.7 Hz, 1H), 2.96−2.91(m, 1H), 2.2 (s, 3H), 1.8−1.7 (m, 5H), 1.4−1.18 (m, 5H), 1.1 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 215.7, 139.4, 128.7, 128.3, 127.1, 64.2, 58.8, 47.0, 37.9, 29.6, 28.1, 26.1, 25.9, 25.5, 7.9. $C_{17}H_{25}NO$, MS $m/z[M^+]^+$ 259.39, Found: (M + H)/z: 260.3.

CONCLUSION

A practical, efficient and scalable process for the manufacture of benzphetamine hydrochloride has been described. The process is mild, industrially reliable and capable for delivering high quality API with high enantimeric excess even in multi kg scale. The process is presently being used for the commercial production in our organization.

ASSOCIATED CONTENT

Supporting Information

Spectral data of selected intermediates and final compound. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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