Asymmetric syntheses of both enantiomers of amphetamine hydrochloride *via* bakers' yeast reduction of phenylacetone

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Both enantiomers of amphetamine hydrochloride were stereospecifically synthesised based on bakers' yeast reduction of phenylacetone. A simple and efficient method for the chiral inversion of (S)-1-phenyl-2-propanol **3** to (R)-1-phenyl-2-propanol **8** has been discussed.

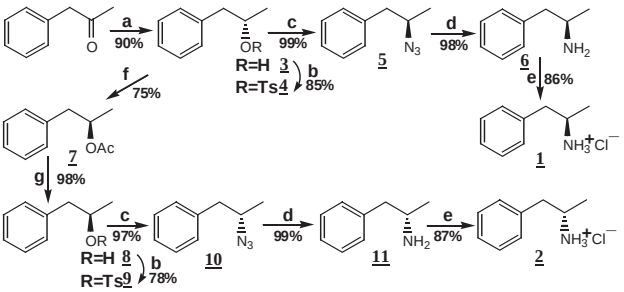
Keywords: asymmetric synthesis, amphetamines, bakers' yeast, chiral inversion.

1-Phenyl-2-propylamine (amphetamine) and its analogues are of pharmacological interest because of their effects on the central nervous system in animals and in humans and their anti-inflammatory activity.[1] Optically-active amphetamine has also been used as a resolving agent in the synthesis of the bidentate chiral ligand, 1,1'-bi-2-naphthol.[2] Syntheses of racemic or enantiomer-enriched amphetamines have been well documented in the literature,[3] but only few syntheses of homochiral amphetamines have been reported.[4] We now report concise asymmetric syntheses of (R)-amphetamine hydrochloride (**1**) and (S)-amphetamine hydrochloride (**2**) based on a bakers' yeast reduction of phenylacetone as well as chiral inversion of (S)-1-phenyl-2-propanol (**3**).

Enzymatic reduction of carbonyl compounds producing chiral alcohols have been extensively explored and applied in organic syntheses.[5] A microbial reduction of phenylacetone and its derivatives has also been mentioned in the literature,[6] but it seems lacking in convenience. We found that phenylacetone can be efficiently reduced by cheap and readily available bakers' yeast using a simple apparatus according to the procedure below. The mixture of phenylacetone, tween-80, sucrose, Mauripan dry yeast and water was well stirred by a mechanical stirrer in a three-necked round-bottom flask at a temperature range of 25–32°C for 6–10 hours. The slurry was extracted with ethyl acetate and the solvent evaporated to afford optically pure (S)-1-phenyl-2-propanol (**3**) after chromatography or distillation. HPLC analysis with a chiral column showed that the ee of the chiral alcohol **3** was more than 99%. Although the concentration of phenylacetone and temperature had almost no impact on the ee value, they had significant effects on yields. The temperature should be kept lower than 35°C and the concentration of phenylacetone should not be higher than 1.5%(w/v).

Starting from the optically pure alcohol **3**, two sequences have been designed and performed for syntheses of (R)-amphetamine hydrochloride **1** and (S)-amphetamine hydrochloride **2** as depicted in the scheme.

The reaction of **3** with 1.5 equivalent of toluenesulfonyl chloride in pyridine using 4-(dimethylamino)pyridine (DMAP) as a catalyst produced the tosylate **4** in 85% yield. Tosylate **4** reacted smoothly with 1.2 equivalent of sodium azide in N,N-dimethylformide (DMF) or dimethylsulfoxide (DMSO) affording an azide **5** in almost quantitative yield *via* a typical S_N2 nucleophilic substitution. The configuration of chiral center changed because of a Walden inversion. Hydrogenation of the azide **5** using palladium on charcoal as a catalyst in an atmosphere of hydrogen gas under a pressure of 1.2 atm gave (R)-amphetamine **6** in 98% crude yield. ^{1}H NMR showed that the crude oily **6** was almost clean, no purification was needed. It could be used as such to react with hydrochloric acid. The reaction of crude **6** with 1.5 equivalent of HCl in ethanol by refluxing for 2 hours finally afforded a white crystalline solid (R)-amphetamine hydrochloride **1** in 86% yield.



Scheme 1 (a) bakers' yeast, tween-80, sucrose, in water, 25–32°C, 6-10h. (b) 1.5 equiv. of toluenesulfonyl chloride, 0.1 equiv. of DMAP, in pyridine, r.t., 3h. (c) 1.2 equiv. of NaN_3, in DMSO, 45°C, 2h. (d) Pd on charcoal, 1.2 atm of H_2, in EtOAc, r.t., 12h. (e) 1.5 equiv. of HCl, in ethanol, refluxing for 2h. (f) 6 equiv. of HOAc, 3 equiv. of Et_3N, 80°C, 2h. (g) 5 equiv. of LiOH, in aqueous methanol, r.t. 3h.

The other sequence leading to (S)-amphetamine hydrochloride **2** was almost the same as above, but employing (R)-1-phenyl-2-propanol **8** instead of (S)-1-phenyl-2-propanol **3**.

The transformation of the fermentation product (S)-1-phenyl-2-propanol **3** into (R)-1-phenyl-2-propanol **8** was a crucial problem. We first tried the Mitsunobu reaction with compound **3**.[7] Unfortunately it only gave a low yield. We then tried the nucleophilic substitution of tosylate **4** using sodium acetate or potassium acetate as a nucleophile in DMF or DMSO.[8] but an elimination occurred and 1-phenyl-1-propene was detected by GC analysis and became the major product. We observed that a buffer dramatically reduced the elimination reaction and significantly enhanced the yield of nucleophilic substitution as shown in Table 1. The mixture of acetic acid and sodium acetate or potassium acetate gave a good yield and a high ee value, although partial racemisation occurred. Optimisation of the reaction condition has also been done. The mixture of 2 molar of acetic acid and 1 molar of triethylamine gave the best yield and stereoselectivity. Hydrolysis of ester **7** with 5 equivalent of lithium hydroxide in aqueous methanol afforded **8** in 98% yield with 93% ee. Compound **8** was then transformed into the tosylate **9** by reacting with toluenesulfonyl chloride in pyridine in the presence of catalytic DMAP. Fortunately recrystallisation of **9** in hexane gave the optical pure **9** in 78% yield with 99% ee. The nucleophilic substitution of **9** with sodium azide produced compound **10**, and then hydrogenation of compound **10** yielded crude (S)-amphetamine **11** which was exposed to hydrochloric acid to afford (S)-amphetamine hydrochloride **2**.

In summary, asymmetric syntheses of (R)-amphetamine hydrochloride **1** and (S)-amphetamine hydrochloride **2** starting from fermentation product (S)-1-phenyl-2-propanol **3** are described in this paper. A practical procedure for bakers'

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Table 1 Reaction of tosylate **4** with acetate anion.

Conditions	Yield(%)	ee(%)[a]
NaOAc in DMF, 90°C, 2h	8	–[b]
NaOAc in DMSO, 90°C, 2h	7	–[b]
NaOAc in HOAc, 95°C, 2h	68	91
KOAc in HOAc, 95°C, 2h	66	91
Et_3N in HOAc, 95°C, 2h	72	93
Et_3N in HOAc, 80°C, 3h	75	93

[a]ee was determined by HPLC with a Chiralcel column. [b]not identified.

yeast reduction of phenylacetone were developed. A simple and efficient method for the chiral inversion of alchol **3** to (R)-1-phenyl-2-propanol **8** has also been studied.

Experimental

NMR spectra were acquired on Bruker AM-500 in $CDCl_3$ using TMS as internal standard. IR spectra were recorded on Nicolet Magna IR-550. Mass spectra were recorded on HP5989A. Optical activities of chiral compounds were measured on WZZ-1S polarimeter. Melting points were determined by using a sulfuric acid bath and were not corrected. All chemicals were analytically pure and were used as received without purification prior to use. Bakers' yeast was imported from Mauripan Yeast Co. Ltd. in Australia.

Reduction of phenylacetone by Bakers' Yeast: Water (400ml), phenylacetone (5g) and Tween 80 (10g) were added to a three-necked flask(1000ml) equipped with a mechanical stirrer and a water bath. The temperature of the bath was adjusted to 25–32°C. A milk-like solution formed after stirring for 15 min. Mauripan dry instant yeast (100g) and of sucrose (100g) were well mixed, and the mixture was then added gradually to the above milk-like solution over a period of one hour. After the addition was finished, a viscous slurry formed and was stirred for 6–10h. TLC showed that the reaction was complete. The viscous slurry was then extracted three times with ethyl acetate. The extracts were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crude oil which was purified by chromatography to afford (S)-1-phenyl-2-propanol(**3**) 4.5g (90% yield). $[\alpha]_D^{20}$ +41°(c 2.0, benzene). ^{1}H NMR δ 1.22(d, *J*=6.2Hz, 3H), 2.68(dd, *J*=7.8Hz; 13.4Hz, 1H), 2.75(dd, *J*=5.1Hz; 13.5Hz, 1H), 3.96–4.01(m, 1H), 7.18–7.24(m, 3H), 7.27–7.32(m, 2H). IR(neat) 700, 745, 940, 1085, 1215, 1460, 2925, 2990, 3415cm^{-1}(br).

(S)-1-Phenyl-2-(toluenesulfonoxy)-propane **(4)**: (S)-1-Phenyl-2-propanol (4.8g, 35.2mmol), pyridine (15ml) and DMAP(215mg, 1.76mmol) were placed in a flask (100ml). The mixture was stirred and cooled to 0°C by an ice bath. Toluenesulfonyl chloride (10.1g, 53.0mmol) was then added slowly. After the addition was complete, the ice bath was removed. the reaction was continued at 30°C for 3h and monitored by TLC. Water (70ml) was added dropwise and off-white solid precipitated. The solid was collected and dried. Recrystallisation of the crude product from hexane gave a white solid **4** (8.7g, 30.0mmol) in 85% yield. M.p. 75–76°C. $[\alpha]_D^{20}$ +28.5° (c 4.0, benzene). ^{1}H NMR δ 1.30(d, *J*=6.3Hz, 3H), 2.41(s, 3H), 2.77(dd, *J*=6.5Hz; 13.8Hz, 1H), 2.91(dd, *J*=6.6Hz; 13.8Hz, 1H), 4.71–4.77(m, 1H), 7.02–7.05(m, 2H), 7.16–7.22(m, 5H), 7.60–7.65(m, 2H). MS(*m/z*) 290 (M^+). IR(KBr film) 895, 915, 1180, 1340, 1598, 2985cm^{-1}. Anal. Calcd. for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 65.90; H, 6.12%.

(R)-1-Phenyl-2-azido-propane **(5)**: Sodium azide (1.56 g, 24.0 mmol) was added to the solution of tosylate **4** (5.81g, 20.0mmol) in DMSO (20ml). The solution was then warmed to 45°C. Stirring was continued for 2h. After the reaction was complete, water (80ml) was added, the aqueous solution was extracted twice with hexane (50ml×2). The extracts were combined and dried over anhydrous magnesium sulfate. Evaporation gave a crude oil which was chromatographied to produce compound **5** (3.21g, 19.9mmol) in 99.6% yield. $[\alpha]_D^{20}$ –64°(c 2.5, $CHCl_3$). ^{1}H NMR δ1.25(d, *J*=6.4Hz, 3H), 2.72(dd, *J*=6.5Hz; 13.7Hz, 1H), 2.83(dd, *J*=7.3Hz; 13.6Hz, 1H), 3.64–3.72(m, 1H), 7.18–7.21(m, 2H), 7.22–7.26(m, 1H), 7.29–7.33(m,2H). MS(m/z) 161(M^+). IR(neat) 700, 750, 1120, 1255, 1460, 2120, 2920, 2980cm^{-1}. Anal. Calcd. for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.40; H, 6.87; N, 26.42%.

(R)-1-Phenyl-2-propylamine **(6)**: A solution of compound **5** (3.6g, 22.3mmol) in ethyl acetate (40ml) was put into a three-necked flask which was equipped with an outlet of air and an inlet of hydrgenation. Palladium on charcoal (350mg, 10%) was added. Air in the flask was removed by a vacuum pump and replaced by hydrogen gas. The reaction mixture was then rapidly stirred at room temperature for 12h under an atmosphere of hydrogen gas. After the reaction was complete, the reaction was filtered through a thin layer of Celite to remove the catalyst. Evaporation of the solvent gave a colourless oil **6** (2.96g, 21.9mmol) in 98% yield. $[\alpha]_D^{20}$ –33°(c 2.6, CH_3OH). ^{1}H NMR δ 1.03(d, *J*=6.5Hz, 3H), 1.19(s, 2H, NH_2), 2.43(dd, *J*=8.1Hz; 13.2Hz, 1H), 2.62(dd, *J*=5.3Hz; 13.2Hz, 1H), 3.04–3.11(m, 1H), 7.08–7.14(m, 3H), 7.18–7.23(m, 2H). IR(neat) 700, 745, 820, 1460, 1495, 1600, 2925, 2950cm^{-1}.

(R)-amphetamine hydrochloride **(1)***:* To a solution of **6** (2.96g, 21.9mmol) in ethanol(20ml), concentrated hydrochloric acid (2.7ml, 32.4mmol) was added. The solution was heated to reflux for 2h. Solvents were removed by a rotavapor in a vacuum. Anhydrous ethanol (20ml) was added and then was removed again to dryness. Ethyl acetate (50ml) was added and the solution was vigorously stirred for half an hour. A white crystalline solid precipitated. The white solid was filtered off and dried to give (R)–(–)–amphetamine hydrochloride **1**(3.25g, 18.9mmol) in 86% yield. $[\alpha]_D^{20}$ –27°(*c* 3.0, H_2O). ^{1}H NMR(CD_3OD) δ 1.25(d, *J*=6.5Hz, 3H). 2.79(dd, *J*=8.4Hz; 13.5Hz, 1H), 2.99(dd, *J*=6.1Hz; 13.6Hz, 1H), 3.48–3.55(m, 1H), 7.24–7.30(m, 3H), 7.33–7.37(m, 2H). IR(neat) 700, 745, 1098, 1215, 1395, 1460, 1500, 1615, 2050, 2750-3200cm^{-1}(br).

*(R)-1-Phenyl-2-acetoxy-propane***(7)**: Acetic acid (10.8g, 180mmol) was placed in a flask which was equipped with a magnetic stirring bar, a thermometer and an ice bath. Triethylamine(9.1g, 90mmol) was dropwise added. After stirring for half an hour, a clear solution was obtained. Tosylate **4** (8.7g, 30.0mmol) was then added. The ice bath was removed and the reaction mixture was heated to 75–80°C. The internal temperature was not allowed to exceed 80°C. The reaction was continued at this temperature for 3h and monitored by TLC. The reaction mixture was cooled down to room temperature. Water(100ml) and benzene(100ml) were added. Organic layer and aqueous layer were separated. The aqueous solution was extracted again with benzene (50ml). The combined extracts were washed with saturated aqueous solution of sodium bicarbonate and dried over anhydrous magnesium sulfate. Evaporation of solvent gave a crude oil which was purified by chromatography to afford compound **7** (4.01g, 22.5mmol) in 75% yield. HPLC analysis with a chiral column showed that ee% of **7** was 93.3%. $[\alpha]_D^{20}$ –10.2°(*c* 4.5, benzene). ^{1}H NMR δ 1.21(d, *J*=6.3Hz, 3H), 1.98(s, 3H), 2.74(dd, *J*=6.5Hz; 13.6Hz, 1H), 2.92(dd, *J*=6.7Hz; 13.6Hz, 1H), 5.06–5.15(m, 1H), 7.17–7.23(m, 3H), 7.25–7.30(m, 2H). MS(*m/z*) 179(M^++1). IR(neat) 700, 750, 965, 1065, 1245, 1375, 1465, 1735, 2920, 2980cm^{-1}.

(R)-1-phenyl-2-propanol **(8)**: Lithium hydroxide monohydrate (4.72g, 112.5mmol) was added to a well stirred solution of **7** (4.01g, 22.5mmol) in aqueous methanol (20ml, CH_3OH:H_2O=8:2). The reaction mixture was then stirred at room temperature for 3h. TLC showed that the reaction was complete. Water (60ml) was added. The aqueous solution was extracted three times with dichloromethane (50m×3). The extracts were combined and dried over anhydrous sodium sulfate. Evaporation of solvent gave a colorless oil which was purified by chromatography to afford compound **8**(3.0g, 22.0mmol) in 98% yield. $[\alpha]_D^{20}$ –38°(*c* 2, benzene). ^{1}H NMR δ 1.22(d, *J*=6.3Hz, 3H), 2.68(dd, *J*=7.8Hz; 13.4Hz, 1H), 2.75(dd, *J*=5.1Hz; 13.5Hz, 1H), 3.96–4.00(m, 1H), 7.18–7.24(m, 3H), 7.27–7.32(m, 2H). IR(neat) 700, 750, 940, 1080, 1215, 1460, 2925, 2985, 3415cm^{-1}(br).

(R)-1-Phenyl-2-(toluenesulfoxy)-propane **(9)**: The same procedure as that for **4** was followed. Recrystallisation of the crude product in hexane gave a white solid **9** in 78% yield. M.p. 74–75°C. $[\alpha]_D^{20}$ –29.0° (*c* 3.0, benzene).

(S)-1-Phenyl-2-azido-propane **(10)**: Compound **10** was obtained in 97% yield according to the same procedure as that for **5**. $[\alpha]_D^{20}$ +64.5°(*c* 2, $CHCl_3$).

(S)-1-Phenyl-2-propylamine **(11)**: Compound **11** was obtained in 99% yield according to the same procedure as that for **6**. $[\alpha]_D^{20}$ +33°(*c* 3.5, CH_3OH).

(S)-Amphetamine hydrochloride **(2)**: (S)-(+)-amphetamine hydrochloride **2** was obtained in 87% yield according to the same procedure as that for (R)–(–)–**1**. $[\alpha]_D^{20}$ +28°(*c* 3.5, H_2O).

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