Enantioselective Synthesis of Both Enantiomers of Cathinone via the Microbiological Reduction of 2-Azido-1-phenyl-1-propanone

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Cathinone, 1a, or (−)-(2S)-2-amino-1-phenyl-1-propanone is the main active constituent of the products extracted from the fresh leaves of Catha edulis (Khat) which is found in several countries of East Africa and the Arabian peninsula. The biological activity of cathinone is analogous to that of amphetamines, especially on the cardiovascular system and the metabolism of dopamine.‡ Berrang et al.† have reviewed all the previous studies and racemic syntheses of cathinone. They have also discussed the puzzling results obtained for the physical constants of the natural 1a and presented a synthesis of both enantiomers of cathinone.4

We have shown, in previous work on the microbiological reduction of α-azido ketones,5,6 that by the appropriate choice of the microorganism, all the chiral isomers of the corresponding β-azido alcohols can be obtained with excellent enantiomeric excesses. A fast and effective synthesis of both enantiomers of 1 was envisaged using the β-azido alcohol 2 from the microbiological reduction of the corresponding azido ketone, thus avoiding the problem of the resolution of a racemic mixture. In this paper, we describe the preparation of the optically pure synth 2 by microbiological reduction as well as its conversion into both enantiomers of 2-amino-1-phenyl-1-propanone (1).

Results and Discussion

Microbiological Reduction of 2-Azido-1-phenyl-1-propanone (4). The microbiological reduction of 2-azido-1-phenyl-1-propanone, 4, was studied in order to prepare the corresponding azido alcohols, 2. Ketone 4 was obtained by treatment of the corresponding bromo ketone 3 with sodium azide following a method described previously7(Scheme 1).

The study of the microbiological reduction of 4 was realized with the same microorganisms as those previously used for the reduction of α-azido ketones:6 the yeasts (Saccharomyces cerevisiae and Rhodotorula glutinis), the fungi (Beauveria sulfurescens, Cunninghameella elegans, Geotrichum candidum, Mortierella isabellina and Sporotrichum exile) and the bacterium Lactobacillus kefir. The bakers' yeast (S. cerevisiae) was used freeze-dried under nonfermenting conditions, i.e. suspended in water without added sugar. The bioconversions with the other microorganisms were done with washed resting cells, except R. glutinis. Growing cells were used for this microorganism.

First, a rate study was conducted with each microorganism. The results showed that all the microorganisms reduced 4 after an incubation time of 24 h, except C. elegans and S. exile, which subsequently were not used for quantitative assays. The percent conversion of α-azido ketone was determined by studying the residue from the bioconversion by GC, but the diastereomeric azido alcohols gave a single peak regardless of the GC conditions. The proportions of each isomer were determined, in consequence, by the use of 1H NMR spectroscopy, which distinguished clearly between the syn and anti diastereomers of 2.

Quantitative assays were carried out for an incubation time of 24 h with all the microorganisms which reduced 4. However, separation of the two diastereoisomers required their derivatization with TBDMS-triflate.8 Silyl ether formation was quantitative, and the syn 5a and anti 5b diastereoisomers could be separated by semi-preparative HPLC (Table 1).

Only L. kefir and M. isabellina yielded an alcohol with the (S) absolute configuration. But both diastereoisomers exhibited medium enantiomeric excesses of 44% for the syn and 61% for the anti isomer with L. kefir, and very low with M. isabellina. All the other microorganisms gave the (R) alcohol and in all cases, the anti diastereoisomers were optically pure. Bakers' yeast and R. glutinis were the only microorganisms yielding the syn diastereoisomer with an excellent enantiomeric excess. The indicated chemical yields are those of the TBDMS-protected azido alcohols after purification. The low yields obtained with bakers' yeast and L. kefir were due to the recovered quantity of α-azido ketone which did not react (60 and 30%, respectively). In all other cases, the reduction was complete and the yields were good or even excellent as with R. glutinis (92%).

Determination of the enantiomeric excess of each diastereoisomer required the initial hydrolysis of the silyl group and the use of 1H NMR on the azido alcohol in the presence of the chiral europium derivative: Eu(tfc)3. Under these conditions, preferential shielding of the methyl group located at 1.15 ppm was observed, and the proportion of each enantiomer could be determined from their integration. The only disadvantage of this method is its precision (5%), and so an optically pure compound is noted as ee ≥95%.

Absolute configurations were determined by comparing the azido alcohols coming from the microbiological reduc-

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(4) The synthesis of both enantiomers of 1, as their hydrochlorides, was based on the resolution of (±)-norephedrine, with O(D)-dibenzoyl-tartaric acid. A three-step sequence of N-protection, oxidation to the ketone, and N-deprotection yielded the natural cathinone and its enantiomer.
Notes

Scheme 1*

Scheme 2

Table 1. Microbiological Reduction of 2-Azido-1-phenyl-1-propanone (4)

<table>
<thead>
<tr>
<th></th>
<th>syn TBDMs derivatives</th>
<th></th>
<th>anti TBDMs derivatives</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[α]D</td>
<td>ee, %</td>
<td>config</td>
<td>[α]D</td>
</tr>
<tr>
<td>Rhodotorula glutinis</td>
<td>−139</td>
<td>≥95</td>
<td>(1R,2R)</td>
<td>−60</td>
</tr>
<tr>
<td>Bakers' yeast</td>
<td>−139</td>
<td>≥95</td>
<td>(1R,2R)</td>
<td>−60</td>
</tr>
<tr>
<td>Geotrichum candidum</td>
<td>−28</td>
<td>20</td>
<td>(1R,2R)</td>
<td>−60</td>
</tr>
<tr>
<td>Beauveria sulfurescens</td>
<td>+14</td>
<td>10</td>
<td>(1S,2S)</td>
<td>+12</td>
</tr>
<tr>
<td>Mortierella isabellina</td>
<td>+9</td>
<td>6</td>
<td>(1S,2S)</td>
<td>+32</td>
</tr>
<tr>
<td>Lactobacillus kefir</td>
<td>+61</td>
<td>44</td>
<td>(1S,2S)</td>
<td></td>
</tr>
</tbody>
</table>

* Reaction conditions: (a) i) TBDMS-triflate, ii) HPLC.

During this synthesis, it was observed that the diastereoisomers of a racemic mixture of N-Boc and O-TBDMs protected amino alcohols, one of the intermediates, could be separated easily by column chromatography on silica gel. Thus a new synthetic pathway was envisaged, starting directly from the diastereomeric mixture of 2a and 2b coming from the microbiological reduction of 4 (Scheme 3).

We considered it prudent to convert the azide group into a protected amine, before oxidizing the alcohol to the ketone, as it has been shown that cathinone, 1, is prone to racemization if the amine is free. The method of Saito et al. constituted a very convenient one-pot protocol for the direct conversion of the azido group to the N-Boc amino group. Treatment of the diastereomeric mixture (2a and 2b) with di-tert-butyl dicarbonate (Boc2O) in a suspension of 10% Pd/C in ethyl acetate under a hydrogen atmosphere gave the compounds 9a and 9b in a 92% yield. They were separated by column chromatography on silica gel. Oxidation of each isomer, 9a and 9b, was done following the method of Cossio et al., who used pyridinium chlorochromate (PCC). Compounds 10a and 10b were obtained in a 86% yield and were characterized by their NMR spectra, specific rotations, and their elemental analyses. Hydrolysis with 3 N hydrochloric acid of 10a or 10b gave, in the last step, the two optically


(10) 5a or 5b was treated with (Boc)2O under a hydrogen atmosphere according to Saito et al., and the compounds obtained were oxidized with PDC in the presence of SiMesCl according to Cossio et al. Hydrolysis in acidic medium (3 N HCl) led to 1a and 1b with a 24 and 30% yield, respectively.


Gas phase chromatography (GC) analyses were performed by using a 25m x 0.32 mm capillary column coated with Carbowax 20 M. Reactions were monitored by TLC using silica gel Kieselgel 60 PF plates and the purification of products was performed on silica gel Merck 60 (70-230 μm) with mixtures of pentane and Et2O as the mobile phase.

The microorganisms were all laboratory-grown except freeze-dried bakers’ yeast, which was a commercial product (ANCEL S. A. Strasbourg). Preculture and culture conditions as well as bioconversion conditions have been described elsewhere.6

2-Azido-1-phenyl-1-propanone (4). To a solution of 2.1 g (10 mmol) of 2-bromo-1-phenyl-1-propanone6 in 3 mL of CH2-OH, with stirring and cooling at 0°C, was added 0.650 g (10 mmol) of NaN3. After stirring overnight at room temperature, the methanol was evaporated under vacuum. The residue was diluted with H2O and extracted three times with EtO. The organic phase was dried over anhydrous MgSO4. After evaporation of Et2O, the pure azido ketone (1.6 g) was obtained in a 85% yield. 1H NMR (CDCl3) δ: 1.59 (d, 3H, J = 7 Hz); 4.73 (q, 1H, J = 7 Hz); 7.25-7.35 (m, 5H); 7.35-7.45 (m, 1H); 7.86-8.05 (m, 2H). 13C NMR δ: 16.5; 55.8; 128.7; 129.0; 134.0; 134.4; 196.8. Anal. Calcd for C8HgON3: C: 61.70; H: 5.18; N: 23.98. Found: C: 61.70; H: 5.20; N: 23.90.

Microbiological Reduction of 2-Azido-1-phenyl-1-propanone (4). Incubation time was 24 h. GC oven temperature was 170°C. After isolation of the diastereomeric azido alcohols 2, the alcohol functionality was protected by TBDMS, according to the described method, in order to separate the two diastereoisomers by HPLC.

2-Azido-1-(tert-butylmethyisilyl)-1-phenylpropane (5). To an ice-cold solution of 715 mg of dry and freshly distilled pyridine (2.0 equiv) and 800 mg (1 equiv, 4.5 mmol) of 2 in 4.5 mL of dry CH2Cl2 was added slowly 1.56 mL (1.5 equiv, 6.8 mmol, 1.80 g) of TBDMS-triflate. After 30 min, the reaction mixture was diluted with Et2O and added into a saturated solution of NaHCO3 (10 mL). After several extractions with EtO, the organic extracts were dried over anhydrous MgSO4 and evaporated under vacuum. The residue was purified by column chromatography (eluent: pentane) and gave 1.25 g (95% yield) of the alcohol functionality was protected by TBDMS, according to the described method, in order to separate the two diastereoisomers 5a and 5b were separated by semipreparative HPLC by using a Nucleosil 5 pm column. The eluent was isooctane, 2 mL/min.

Results obtained with Rhodotorula glutinis. From ten flasks, 45% (−)-(1R,2S)-5a and 55% (−)-(1R,2R)-5b were obtained. Yield: 92%.

Results obtained with Bakers’ yeast (S. cerevisiae). From seven flasks, 60% 2-azido-1-phenyl-1-propanone (4), 20% (−)-(1R,2S)-5a, and 20% (−)-(1R,2R)-5b were obtained. Yield: 35%.

Results obtained with Geotrichum candidum. From five flasks, 65% (−)-(1R,2S)-5a and 35% (−)-(1R,2R)-5b were obtained. Yield: 72%.

Experimental Section

Methyl points are uncorrected. Optical rotations were recorded at the mercury J line (λ = 578 nm) in CHCl3 solution. NMR spectra were recorded in CDCl3 or CD3OD at 400 MHz (1H) and 100.61 MHz (13C). Chemical shifts are relative to CDCl3 or CD3OD. All reaction solvents were distilled before use.
(-)-(1R,2R)-2-azido-1-(tert-butyldimethylsilyloxy)-1-phenylpropane (2b).  

(-)-(1R,2R)-2-azido-1-(tert-butyldimethylsilyloxy)-1-phenylpropane (5b): 0.150 g; [α]D25 = −60 (c 0.03, CHCl3); ee = 95%. 

(-)-(1R,2S)-2-azido-1-(tert-butyldimethylsilyloxy)-1-phenylpropane (6a): 0.150 g; [α]D25 = −14 (c 0.05, CHCl3); ee = 10%. 

Results obtained with Mortierella isabellina. From six flasks, 50% (+)-(1S,2R)-5 and 55% (+)-(1S,2S)-5 were obtained. Yield: 75%. 

(+)-(1S,2S)-2-azido-1-(tert-butyldimethylsilyloxy)-1-phenylpropane: 0.170 g; [α]D25 = +12 (c 0.02, CHCl3); ee = 22%. 

(+)-(1S,2R)-2-azido-1-(tert-butyldimethylsilyloxy)-1-phenylpropane: 0.205 g; [α]D25 = +9 (c 0.03, CHCl3); ee = 6%. 

Results obtained with Lactobacillus kefiri. From six flasks, 30% 2-azido-1-phenyl-1-propanone (4), 20% (+)-(1S,2R)-5, and 50% (+)-(1S,2S)-5 were obtained. Yield: 45%. 

(+)-(1S,2R)-2-azido-1-(tert-butyldimethylsilyloxy)-1-phenylpropane: 0.070 g; [α]D25 = +32 (c 0.01, CHCl3); ee = 61%. 

(+)-(1S,2S)-2-azido-1-(tert-butyldimethylsilyloxy)-1-phenylpropane: 0.165 g; [α]D25 = +61 (c 0.04, CHCl3); ee = 44%. 

Synthesis of Enantiomers of 2-Amino-1-phenyl-1-propanone Hydrochloride from 2-Azido-1-phenyl-1-propanol (2). After the preparation and growth of the Rhodotorula glutinis for 60 h at 27 °C as previously described, the substrate, ketone 4, was added to the culture (50 μL of culture) of six flasks, 45% (+)-(1S,2R)-5 and 55% (+)-(1S,2S)-5 were obtained. Yield: 75%. 

(+)-(1S,2R)-2-Amino-1-phenyl-1-propanone Hydrochloride (1). From six flasks, 30% 2-azido-1-phenyl-1-propanone (4), 20% (+)-(1S,2R)-5, and 50% (+)-(1S,2S)-5 were obtained. Yield: 45%. 

(+)-(1S,2R)-2-Amino-1-phenyl-1-propanone Hydrochloride (1): 0.170 g; [α]D25 = +12 (c 0.02, CHCl3); ee = 22%. 

(+)-(1S,2R)-2-Amino-1-phenyl-1-propanone Hydrochloride (2b).  

(-)-(2S)-2-Amino-1-phenyl-1-propanone Hydrochloride (2b).  

(+)-(1R,2R)-2-Amino-1-phenyl-1-propanone Hydrochloride (9): mp 70–72 °C. [α]D25 = +48 (c 0.02, CHCl3); ee = 95%. 

2-N-Boc-Amino-1-phenyl-1-propanone (10). To a suspension of FCC (1.19 mmol, 255 mg) in 10 mL of CH2Cl2 (freshly distilled from P2O5) was added a solution of 200 mg (0.8 mmol) of 9a or 9b in 2 mL of CH2Cl2 and the dark-brown reaction mixture was stirred at room temperature for 1.5 h. A volume of 10 mL of ether was added and the mixture was filtered through a Florisil column. The black deposit was washed with dry Et2O and filtered as well. The filtrate was concentrated under vacuum to 170 mg (86% yield) of 10. 

(−)-(2S)-2-N-Boc-Amino-1-phenyl-1-propanone (10a): mp 70–72 °C. [α]D25 = +48 (c 0.02, CHCl3); ee = 95%. 

2-Amino-1-phenyl-1-propanone Hydrochloride (1). A suspension of 100 mg (0.40 mmol) of 10a or 10b in 3 mL of a mixture of 3 N HCl in EtOAc (3 N HCl/EtOAc 1:2) was stirred vigorously at room temperature for 30 min. The mixture was evaporated to dryness, and the residue was recrystallized from i-PROH–Et2O. After the sample was dried overnight, 75 mg of 1-HCl was obtained (95% yield). 


(−)-(2R)-2-Amino-1-phenyl-1-propanone Hydrochloride (1b.HCl). Overall yield = 40%. mp 181–182 °C. Same NMR spectra as its (2S) enantiomer. [α]D25 = −48 (c 0.02, H2O); lit.1 [α]D25 = +47.3 (c 1, H2O).