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Synthesis of enantiomerically pure desmethylzopiclone and determination of its absolute configuration

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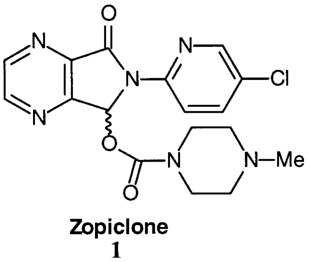
Abstract

Two synthetic methods have been established for the preparation of enantiomerically pure desmethylzopiclone, a metabolite of zopiclone. In Method A, (*S*)-desmethylzopiclone was prepared by demethylation of (*S*)-zopiclone with 1-chloroethyl chloroformate in high yield. Enantiomerically pure zopiclone (>99% ee) was obtained through a highly efficient resolution process in >36% overall yield. In Method B, racemic desmethylzopiclone was resolved with L-*N*-benzyloxycarbonyl phenylalanine (L-ZPA) followed by recrystallization in good yield. The absolute stereochemistry of the (+)-enantiomer was first determined to be the (*S*)-configuration by X-ray crystallography. © 2001 Elsevier Science Ltd. All rights reserved.

Desmethylzopiclone **2** is a metabolite of zopiclone **1** (Fig. 1).[1] Racemic zopiclone is a short-acting hypnotic agent of the cyclopyrrolone class, which has been marketed in Europe for the treatment of insomnia by Rhone–Poulenc Rorer and sold under the brand names Imovane® or Amoban®. Although racemic *N*-desmethylzopiclone was reported in the literature as inac-



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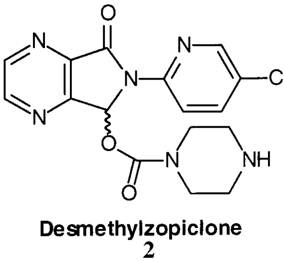

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Figure 1.

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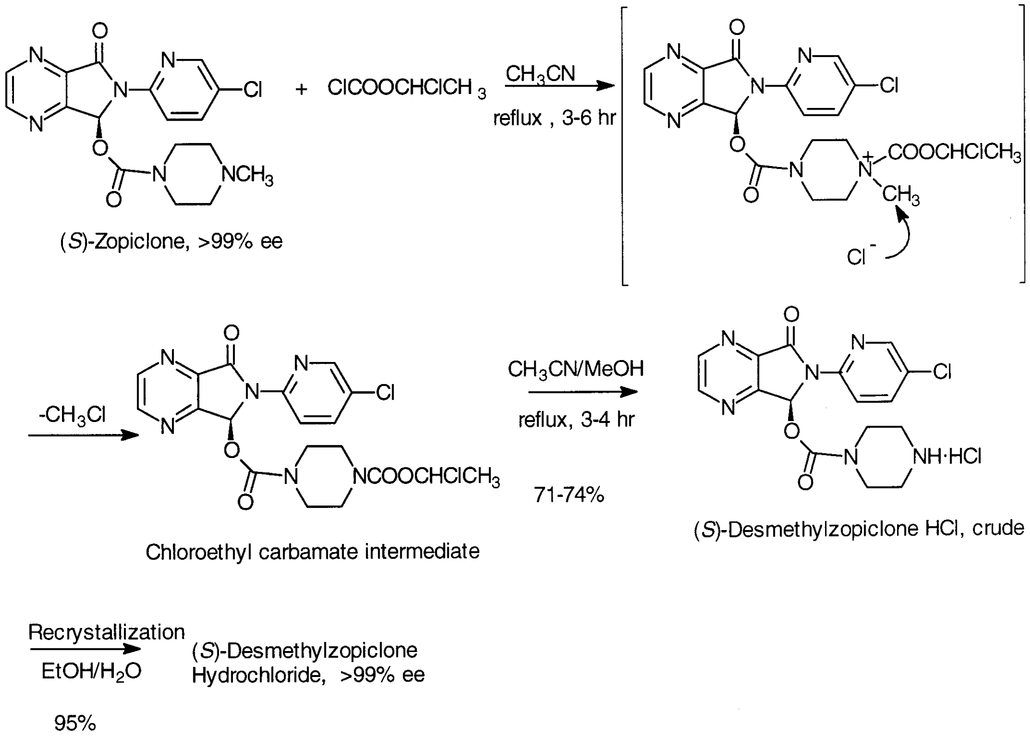
tive,[2] recent studies conducted on the enantiomers by Sepracor showed that enantiomerically pure desmethylzopiclone hydrochloride displayed interesting biological activities in preclinical anxiolytic evaluations.[3] To date, there have been no reported methods in the literature for the preparation of enantiomerically pure *N*-desmethylzopiclone. We report herein two efficient and practical methods for kilogram preparation of enantiomerically pure *N*-desmethylzopiclone (Methods A and B).

In Method A, enantiomerically pure zopiclone was treated with a demethylation reagent to form enantiomerically pure *N*-desmethylzopiclone with retention of absolute configuration. By modification of a literature procedure using D-malic acid,[4] a scalable resolution process was developed to produce enantiomerically pure (*S*)-zopiclone in >99% ee and >36% overall yield. The literature procedure using 0.5 equivalent of D-malic acid as resolution agent was not reproducible in our hands at larger scale (>20 g scale provided variable de from 5 to 95% in the first crystallization). Significant improvement in the D-malic acid resolution process has been achieved and >99.9% ee (*S*)-zopiclone has been manufactured at pilot plant scale.[5] The initial demethylation of (*S*)-zopiclone was effected using diethyl azodicarboxylate (DEAD).[6] This method proved to be inefficient for (*S*)-zopiclone and difficulties were encountered on multi-gram scale preparation. Two major problems were associated with this protocol: (1) low overall yield was obtained (5–28% yields were obtained depending on the scale, with larger scale affording lower yield); and (2) high levels of by-products were formed (up to 80% by HPLC) requiring a tedious isolation and purification protocol to purify the product. Multiple chromatographic steps were used in the purification. Therefore, a practical and scalable process was desirable to produce larger quantities of enantiomerically pure *N*-desmethylzopiclone.

A new demethylation method (Method A) for the demethylation of zopiclone was established using 1-chloroethyl chloroformate as the dealkylating reagent.[7] 1-Chloroethyl chloroformate was chosen because it has two unique properties: (1) it reacts with (*S*)-zopiclone to form a very active chloroethyl carbamate intermediate, which enables a selective hydrolysis by MeOH on the chloroethyl piperidinyl carbamate moiety with minor effect on the other piperidinyl carbamate moiety in the molecule; and (2) it generates one equivalent of HCl in situ, which reacts with (*S*)-desmethylzopiclone spontaneously to form the HCl salt. Since the (*S*)-desmethylzopiclone HCl salt is insoluble in the reaction medium (CH_3CN/MeOH 5:1, v/v), it crystallizes, thereby avoiding future hydrolysis under the strong acidic conditions (pH 0–1) generated during the decarboxylation with MeOH. The isolation is straightforward, requiring a simple filtration. All reaction by-products, including CH_3Cl, CO_2 and $CH_3CH(OMe)_2$ are volatile, and are easily removed during the process. The crude product was further purified by recrystallization from EtOH/H_2O, affording pure (*S*)-desmethylzopiclone hydrochloride with high purity in good yield (two steps, overall yield 65%, Scheme 1).

Other commonly used demethylation reagents, such as vinyl, isopropyl, phenyl, and benzyl chloroformates are not suitable for this reaction.[8,9] Much harsher conditions are required to hydrolyze the carbamate intermediates derived from these chloroformates and (*S*)-zopiclone. These conditions include aqueous HCl, HBr, HOAc, concentrated NaOH solution or catalytic hydrogenation and are not compatible with the functionalities in desmethylzopiclone molecule.

Resolution of racemic desmethylzopiclone is an alternate method for the preparation of enantiomerically pure desmethylzopiclone (Method B). Racemic desmethylzopiclone can be obtained by either demethylation of racemic zopiclone described above or known literature procedures.[10] Through reagent screening, L-*N*-benzyloxycarbonyl phenylalanine (L-ZPA) was found to be an effective resolving reagent for racemic desmethylzopiclone. It is worth noting

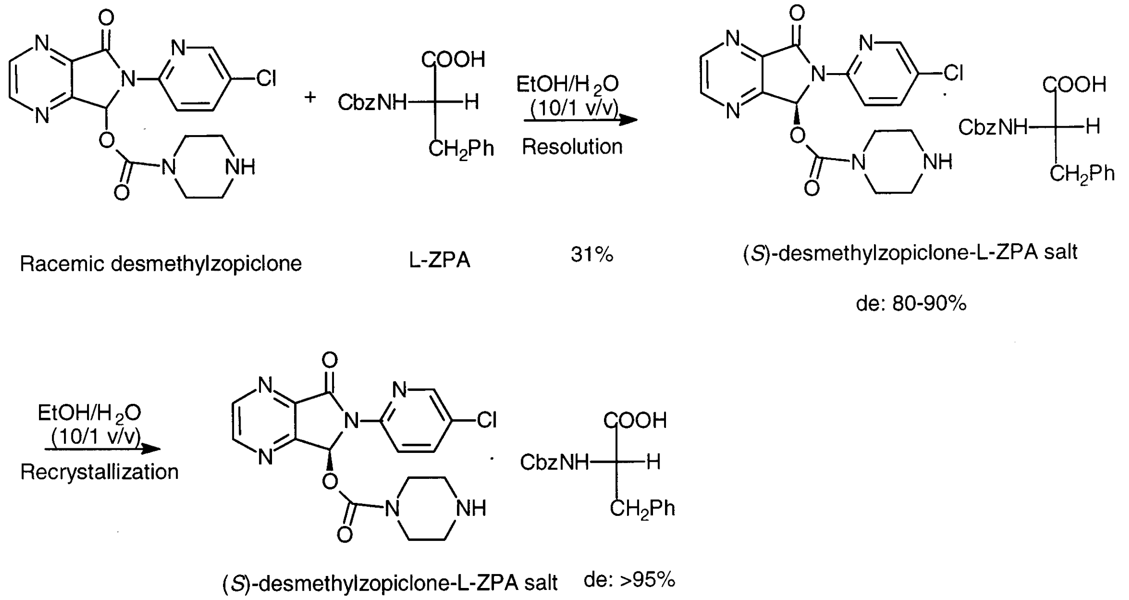


Scheme 1. Synthesis of (*S*)-desmethylzopiclone: Method A

that this L-configured amino acid gave the (*S*)-configured desmethylzopiclone and in the resolution of racemic zopiclone, D-malic acid gave (*S*)-zopiclone.[11] It was also found that other acids suitable for the resolution of zopiclone are ineffective for the resolution of desmethylzopiclone, including di-tolyl D-tartaric acid[12] and D-malic acid.[4] A combination of EtOH and water was identified as a favorable solvent mixture for this resolution. After the resolution, highly enantiomerically enriched (typically >90% de) (*S*)-desmethylzopiclone-L-ZPA salt was isolated in 31% yield (maximum 50%). Further de enrichment to >95% can be achieved by recrystallization from EtOH and water. The free base of (*S*)-desmethylzopiclone can be obtained by the treatment of (*S*)-desmethylzopiclone-L-ZPA salt in EtOAc with K_2CO_3 solution. Scheme 2 describes this resolution process (Method B).

Determination of the absolute configuration of (*S*)-desmethylzopiclone hydrochloride has been achieved by single crystal X-ray diffraction. The presence of a heavy atom (chlorine) allowed for direct assignment of the absolute configuration of this compound. The single-crystal data for (+)-desmethylzopiclone hydrochloride was determined to be the *S*-configuration (Fig. 2).

In summary, two highly efficient and practical methods for the preparation of enantiomerically pure desmethylzopiclone were developed.[13–15] In comparison with alternative methods, the two methods described here possess significant advantages, including higher yields, ease of chemical operation, no chromatographic purification and high purity (*S*)-desmethylzopiclone hydrochloride is produced. The Method A procedure has been demonstrated at >5 kg scale. Further process optimization efforts for both (*S*)-zopiclone and (*S*)-desmethylzopiclone hydrochloride are ongoing.



Scheme 2. Preparation of (*S*)-desmethylzopiclone: Method B

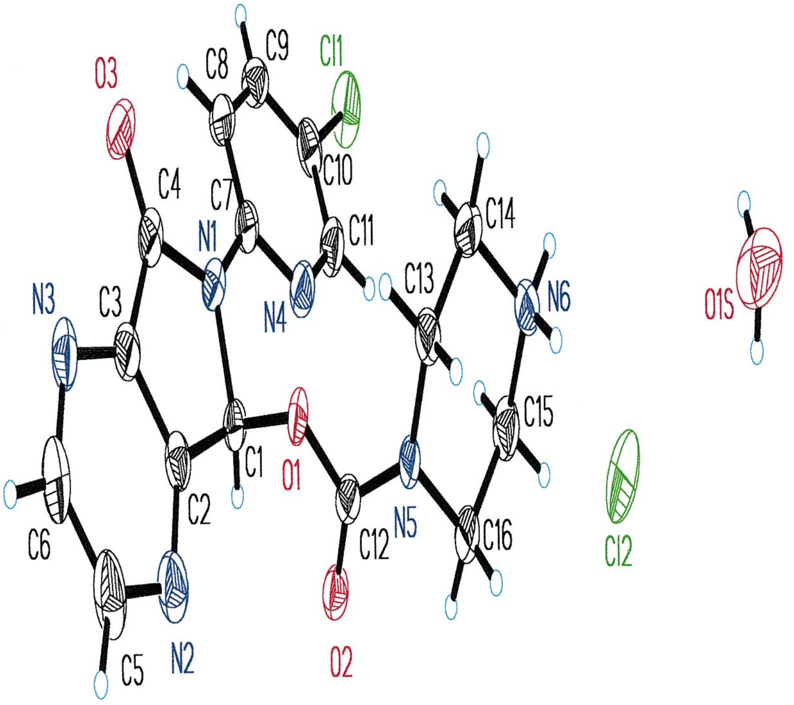


Figure 2. X-Ray structures of (*S*)-(+)-desmethylzopiclone hydrochloride hydrate

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11. A chiral HPLC method was developed to determine the ee of desmethylzopiclone. Column: Chiralcel OD-R, 10 mm, 4.6×25 cm; mobile phase: 100% MeOH/0.1% diethyl amine; wavelength: 305 μm; (*R*)-enantiomer 9.35 min; (*S*)-enantiomer 11.65 min.
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13. **Method A. Demethylation**: To a 12 L reaction flask under argon were charged (*S*)-zopiclone (778 g, 2.0 mmol), acetonitrile (4 L) and 1-chloroethyl chloroformate (328.9 g, 2.3 mol). The reaction mixture was heated at 80–83°C for 3–4 h with stirring. MeOH (1.0 L) was added and the mixture was heated under reflux for 3–4 h. The reaction mixture was cooled to 5–10°C for 2 h. The solid product was isolated via filtration, followed by washing with acetonitrile (400 mL×2). The wet cake product was dried in an oven for 12 h (28 mmHg) at 40–45°C. The isolated product was 610 g (74%). **Recrystallization**: To a 12 L reaction flask equipped with overhead stirrer under argon were charged crude (*S*)-desmethylzopiclone hydrochloride salt (450 g), EtOH (4.8 L) and water (1.5 L). The reaction mixture was heated under reflux for 0.5 h, and then cooled to 20°C over 1 h. The resulting slurry was further cooled to 0–5°C and stirred at that temperature for 1 h. The white solid product was isolated by filtration followed by washing with EtOH (500 mL). The final product was dried in an oven for 12 h (28 inHg) at 40–45°C. The isolated product was 377 g (84%). ^{1}H NMR (300 MHz, DMSO-d_6), δ (ppm): 9.60 (br s, 2H, H_2N^+), 9.02, 8.98 (2 distorted d, 2H, $J=9.8$ Hz), 8.59 (dd, 1H, $J=$ 1.83, 0.73 Hz), 8.44 (dd, 1H, $J=9.03$, 0.73 Hz), 8.13 (dd, 1H, $J=9.03$, 1.83 Hz), 7.79 (s, 1H), 3.38–3.80 (br m, 4H), 2.62–3.20 (br m, 4H). ^{13}C NMR (75.4 MHz, DMSO-d_6), δ (ppm): 163.9, 155.9, 153.6, 149.4, 148.8, 148.6, 147.2, 144.0, 139.3, 127.9, 116.5, 80.18, 42.9. MS 374 (M^+).
14. **Method B**. Desmethylzopiclone (8.0 g, 21.3 mmol) and 6.4 g L-ZPA (21.3, 1 equiv.) were dissolved in 40 mL water and 400 mL EtOH. The mixture was heated to 75–78°C to form a clear solution. The mixture was cooled to 20°C overnight. The solid was collected by filtration and washed with 150 mL EtOH. The wet cake was transferred into a 500 mL flask with 150 mL EtOH. The slurry was refluxed for 2 h. The slurry was cooled to 0–5°C for 1 h. The solid product was isolated via filtration and was washed with EtOH (25 mL). The final product was dried in an oven for 12 h (28 inHg) at 45–50°C to give (*S*)-desmethylzopiclone-L-ZPA salt (4.5 g, 31.4%, 90% de). Recrystallization with EtOH and water enriches the de to >95%.
15. (*S*)-Zopiclone: ee >99%, $[\alpha]_D^{20}=+138.0$ (*c* 0.5, acetone); (*S*)-desmethylzopiclone free base: ee >99% $[\alpha]_D^{20}=+160.2$ (*c* 1.0, $CHCl_3$); (*S*)-desmethylzopiclone hydrochloride: ee >99%, $[\alpha]_D^{20}=+98.2$ (*c* 1.0, H_2O); (*S*)-desmethylzopiclone-L-ZPA salt: de >99%, $[\alpha]_D^{20}=+62.1$ (*c* 0.1, $CHCl_3$).