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Concise Synthesis of JN403, a Novel Nicotinic Acetylcholine Receptor α7 Selective Agonist

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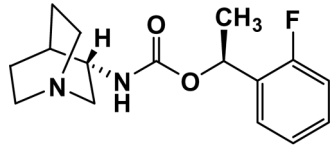
Abstract: A three-step method for the synthesis of (*S*)-(1-aza-bicyclo[2.2.2]oct-3-yl)carbamic acid (*S*)-1-(2-fluorophenyl)ethyl ester HCl salt (**12**) was developed, starting from alcohol **3** and resulting in an overall yield of 50%. A key feature of the present study is the need to use a strong base such as *n*-butyllithium for neutralizing the HCl salt of **5** during the condensation of **4** with **5**.

Keywords: *n*-Butyllithium, condensation, hydrochloride salt, neutralization

INTRODUCTION

Nicotinic acetylcholine receptor (nAChR) α7–related mechanisms have been implicated in sensory gating and cognitive processing and may contribute to the pathophysiology of schizophrenia. Furthermore, α7 nAChR may play a role in pain and epilepsy. JN403 (**1**) was identified[1] as an orally active α7 nChR agonist and was selected for further evaluation in humans as a treatment for schizophrenia.



JN403 (**1**)

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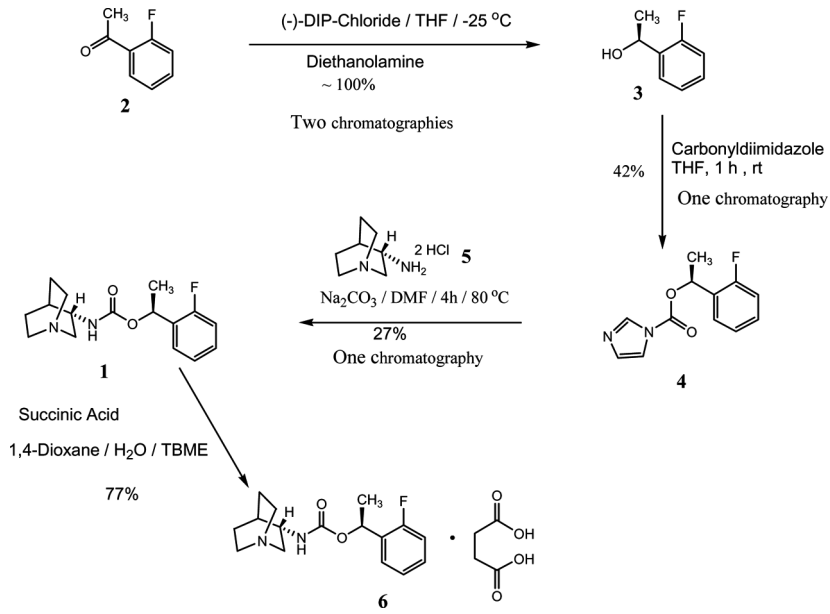
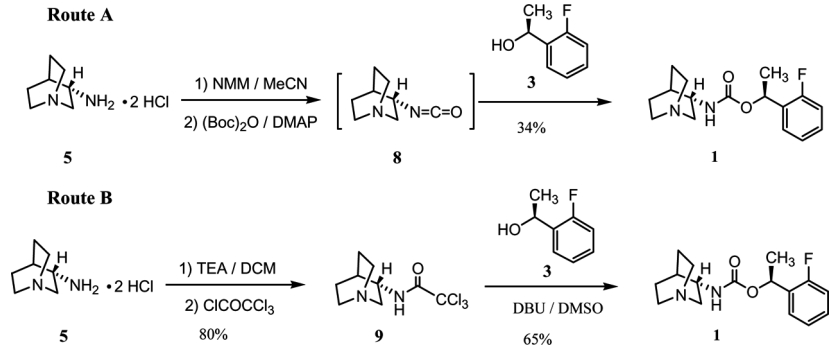


Scheme 1. The research synthesis of **1**.

The research synthesis[2] of **1** (Scheme 1) involved four steps with four chromatographic purifications, yielding the drug substance in an 8% overall yield. The succinate salt was difficult to produce in a 1:1 stoichiometric ratio and was mostly amorphous. In view of these issues, we looked at alternative strategies and at optimizing the current synthesis.

RESULTS AND DISCUSSION

At the outset, we tried two alternative approaches for preparing **1** as shown in Scheme 2. Route A is very attractive because it is a one-pot operation. Isocyanate **8** was made in situ by treating **5** with $(t\text{-Boc})_2O$/ dimethylaminopyridine (DMAP) in the presence of N-methylmorpholine in acetonitrile. Addition of **3** resulted in the isolation of **1** in 34% yield after chromatography. In the second approach, trichloroacetamide **9** was used as a key intermediate, and the product was isolated in 65% yield. Although these approaches appeared interesting because route A was shorter than the research synthesis, the isolation of the drug substance appeared problematic. In route B, a reasonable overall yield



Scheme 2. Alternative approaches for preparing **1**.

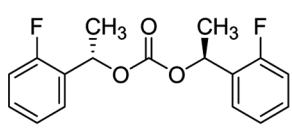
was obtained, but a highly toxic and corrosive reagent, trichloroacetyl chloride, was used. Because the parallel approach of optimizing the research synthesis proved to be more fruitful and because of time constraints, we did not pursue these alternative strategies further.

Optimizations of the Synthesis of 3

In the research synthesis, **3** was produced in 91% ee by asymmetric reduction of **2** using commercial (–)-DIPCl. Alcohol **3** that was produced under these conditions was of low optical purity and contaminated with pinene. By replacing (–)-B-chlorodiisopinocamheylborane [(–)-DIPCl] with (*R*)-MeCBS and BH_3-N,N-diethylaniline (DEAN), we were able to obtain **3** in 95.5% yield with 98.1% ee.[3] At this stage, the decision was made to outsource this material.

Formation of Imidazolyl Carbamate (4)

In the research procedure, compound **3** and carbonyldiimidazole were combined and heated at 50°C in tetrahydrofuran (THF)/Et_2O, and compound **4** was obtained in 40% yield after chromatography. Symmetrical carbonate **10**, formed by the reaction of **3** with the intermediate **4**, was the major by-product produced under these conditions. By changing the addition order (i.e., a slow addition of a THF solution of **3** to a solution of carbonyldiimidazole in THF at 50°C) and increasing the ratio of carbonyldiimidazole to 1.5 equiv, carbamate **4** was produced in almost quantitative yield with acceptable purity, thus avoiding further purification (Scheme 3).



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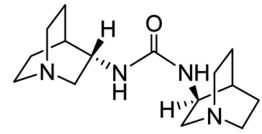

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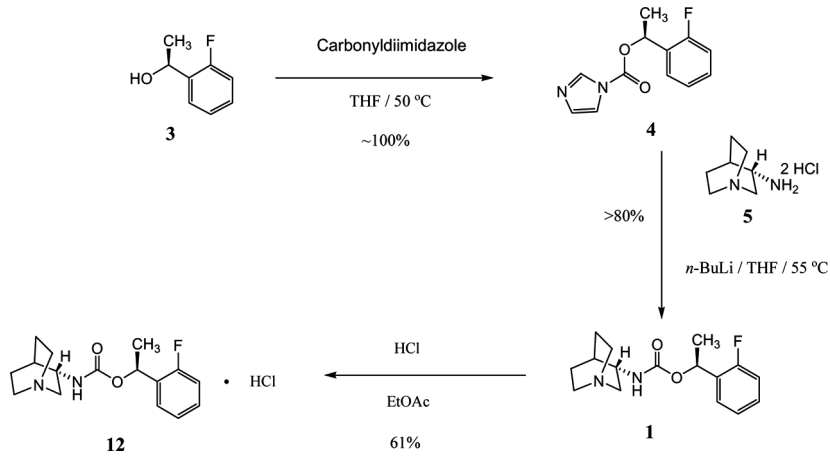
Coupling of Carbamate 4 with Amine 5

Based on the research procedure, condensation of **4** with **5** in the presence of sodium carbonate in DMF at 80°C for 4 h afforded **1** in 27% yield after chromatography. Based on our preliminary experimentation, this low yield was attributed to the formation of significant amounts of by-products **10** and **11** under these experimental conditions. The immediate area of concern in this step was the insolubility of **5** under these conditions, and we needed to find a facile method for neutralization of the hydrochloride salt. To regenerate free amine, **5** was dissolved in water and neutralized with aqueous sodium hydroxide. Extraction with organic solvents [EtOAc or tert-butyl methyl ether (TBME)] gave a low yield of the free amine, because the free amine is highly soluble in water. A few alternatives were screened with the objectives of in situ regeneration of the free amine. The first attempt was to conduct the reaction in toluene with 50% aqueous sodium hydroxide as a base at 20°C. About 10% of **1** was formed. Increasing the reaction temperature resulted in minor



Scheme 3. The optimized synthesis of **1**.

change only. The poor yield of **1** was attributed to the hydrolysis of **4** and **1** under these basic aqueous conditions. However, when *n*-BuLi, a strong base was used, **1** was formed in a good yield within 1 h at 55°C, and these conditions were selected for scaleup.

Preparation of HCl Salt 12

The succinate salt of **1** was originally chosen as the salt form. This salt was prepared by dissolving **1** (46.9 mmol) and succinic acid (49 mmol) in 1,4-dioxane and water at 50°C. Cooling the solution in an ice bath and addition of TBME resulted in the precipitation of the salt. Because the precipitated salt was sticky, isolation became problematic. In addition, as the 1:1 ratio was not reproducible, we looked for other crystalline salts forms and found that the hydrochloride salt of **1** could be formed by treatment of crude **1** in ethyl acetate with hydrogen chloride. Not only did this salt turn out to be crystalline and easy to filter, most impurities from previous steps were also removed in the mother liquor. With this salt-formation procedure, **12** was prepared in good yield and with good purity.

CONCLUSIONS

In conclusion, an optimized method for the preparation of **1** in good yield and of good quality has been presented. The highlights of the present work are the formation of imidazolecarbamate in quantitative yield by slow addition of **3** in THF to a solution of carbonyldiimidazole and the need to use a strong base such as *n*-butyllithium for neutralization of the di-HCl salt **5**.

EXPERIMENTAL

Melting points were measured on a Mel-Temp 3.0 melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 400 or Bruker Avance 500 instruments. Chemical shifts are given on a δ (ppm) scale. Enantiomeric purity of compounds was determined by chiral high-performance liquid chromatography (HPLC). For compound **1**, a Chiralpak AS-H 4.6-mm $\times$ 250-mm column was used. The mobile phase was hexane/2-propanol/diethylamine 83:17:0.1. The chiral method conditions were isocratic run for 30 min, column temperature 20 ± 5°C, flow rate 0.7 mL/min, and wavelength 230 nm.

Imidazole-1-carboxylic Acid (*S*)-1-(2-Fluorophenyl)ethyl Ester (4)

1,1′-Carbonyldiimidazole (86.8 g, 0.54 mol) and tetrahydrofuran (500 mL, 444.5 g) were added to a 1-L, three-necked flask, and the resulting suspension was stirred and heated to $52 \pm 3°C$. A solution of **3** (50 g, 0.36 mol in 20 mL of THF) was added slowly to the resulting solution, and the mixture was stirred at this temperature for 1 h. The mixture was quenched with *tert*-butyl methyl ether (500 mL, 374 g) and water (100 mL, 100 g). The two layers were separated, and the oraganic layer was washed with 5% sodium bicarbonate solution (100 mL). The organic layer was separated, washed successively with water (100 mL) and saturated sodium chloride solution (100 mL), dried with magnesium sulfate (7.0 g), filtered, and evaporated to dryness under reduced vacuum to give **4** as an oil (82.0 g, 98% yield). ^{1}H NMR ($CDCl_3$) δ 1.75 (d, $J = 6.6$ Hz, 3H), 6.35 (q, $J = 6.6$ Hz, 1H), 7.06–7.21 (m, 3H), 7.32–7.45 (m, 3H), 8.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.94, 71.74, 115.8, 116.1, 117.1, 124.3, 124.6, 126.8, 127.1, 127.3, 130.4, 135.1, 137.1, 147.8, 158.2, 161.5.

(*S*)-(1-Aza-bicyclo)2.2.2]oct-3-yl)carbamic Acid (*S*)-1-(2-Fluorophenyl)ethyl Ester (1)

A 1-L, three-necked flask was charged with **5** (65.7 g, 0.33 mol) and THF (450 mL). The suspension was stirred and cooled to $0 \pm 5°C$, followed by the slow addition of *n*-butyllithium (257.4 mL, 2.5 M in hexane, 0.64 mol) while maintaining the temperature at $0 \pm 5°C$. The reaction mixture was allowed to warm to room temperature over 1 h and cooled back to 0–5°C. A solution of **4** (70.26 g, 0.30 mol dissolved in 20 mL of THF) was slowly added. The reaction mixture was warmed and heated at $55 \pm 3°C$ for 2 h. The mixture was evaporated to dryness, and *tert*-butyl methyl ether (650 mL) and water (200 mL) were added. The two layers were separated, and the oraganic layer was washed twice with water (200 mL). The organic layer was separated, washed with brine, and evaporated to dryness under vacuum to give **1** (74.09 g, 84.5% yield); mp 84°C; MS (M + 1) m/z 293.2; ^{1}H NMR ($CDCl_3$) δ 1.32–1.50 (m, 1H), 1.55 (d, $J = 6.6$ Hz, 3H), 1.53–1.65 (m, 3H), 1.85 (s, 1H), 2.47 (dd, $J = 15$ Hz, 6 Hz, 1H), 2.75–2.85 (m, 4H), 3.32 (t, $J = 6$ Hz, 1H), 3.68 (s, 1H), 5.06 (s, 1H), 6.04 (m, 1H), 7.01–7.02 (m, 1H), 7.06–7.12 (m, 1H), 7.18–7.20 (m, 1H), 7.21–7.23 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.95, 21.49, 25.58, 25.84, 46.41, 47.41, 48.10, 56.21, 67.34, 115.46, 115.74, 124.17, 127.15, 129.15, 129.25, 129.47, 155.3, 158.1, 161.3.

(*S*)-(1-Aza-bicyclo)[2.2.2]oct-3-yl)carbamic Acid (*S*)-1-(2-Fluorophenyl)ethyl Ester HCl Salt (12)

A 1-L, three-necked flask was charged with **1** (74.1 g, 0.254 mol) and ethyl acetate (300 mL). The resulting solution was stirred and cooled to $0 \pm 3°C$. Hydrogen chloride (81 mL in ethyl acetate, 0.1375 g/mL, 0.30 mol) was slowly added at a rate to maintain the temperature at $0 \pm 3°C$ (30 min). After the addition, the pH of the suspension was checked with pH paper; the pH should be less than 4. The reaction mixture was stirred at this temperature for 1 h. The suspension was filtered and washed twice with ethyl acetate (75 mL), and the solid was dried at 65°C for 14 h under vacuum to give 60.3 g of **12** (61% yield); mp 203°C; MS (M + 1) *m/z* 293.2. Anal. calcd. for $C_{16}H_{22}FClN_2O_2$: C, 58.44; H, 6.74; Cl, 10.78; N, 8.52. Found: C, 58.24; H, 6.71; Cl, 10.80; N, 8.61. ^{1}H NMR ($CDCl_3$) δ 1.49 (d, $J = 6.6$ Hz, 3H), 1.59–1.68 (m, 1H), 1.72–1.88 (m, 2H), 1.92–1.98 (m, 2H), 2.19–2.22 (m, 1H), 3.05–3.18 (m, 4H), 3.31 (brs, 1H), 3.50–3.55 (m, 1H), 3.86 (brs, 1H), 7.17–7.25 (m, 2H), 7.32–7.38 (m, 1H), 7.42–7.48 (m, 1H), 7.85 (d, $J = 6.6$ Hz, 1H), 10.5 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.70, 21.13, 21.20, 24.44, 44.60, 45.20, 51.01, 66.01, 115.23, 115.52, 124.54, 124.59, 126.94, 126.99, 129.03, 129.20, 129.49, 129.60, 154.86, 157.35, 160.60.

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