



Improved synthesis of (*S*)-7-amino-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one, a building block for γ -secretase inhibitors

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ABSTRACT

An improved synthesis of (*S*)-7-amino-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one (**1**), involving a selective crystallization of epimeric menthylcarbamates for the resolution step followed by simultaneous cleavage of the carbamate and the lactam protecting group is described. Epimerization conditions of the undesired epimer have also been determined.

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1. Introduction

A main pathological hallmark of Alzheimer's disease is the formation of abnormal and characteristic deposits of amyloid- β (A β) peptides in the brain. A β -peptides are 40–42 amino acid peptides generated from the amyloid- β precursor protein by sequential proteolysis by the β -secretase and γ -secretase enzymes. The 'amyloid cascade hypothesis' of Alzheimer's disease postulates a causative role to the accumulation of these A β -peptides in brain tissue.¹ Low molecular weight inhibitors of the γ -secretase enzyme can suppress the production of A β -peptides in vivo and inhibit the deposition of brain amyloid in mouse models. Several γ -secretase inhibitors have been described that contain (*S*)-7-amino-5*H*,7*H*-dibenzo[*b,d*]azepin-6-one **1** as core structure (Fig. 1). The essential properties are then conferred by the side-chain attached to the amino group and the substituent on the nitrogen of the lactam ring.²

The syntheses reported for **1** rely on the separation of the enantiomers via chiral HPLC^{2a} or chromatography of derived epimers.³ Resolution of the *N*-methylated lactam **1** has been reported by crystallization with di-*p*-toluyl-*D*-tartaric acid monohydrate.⁴ We report now an improved synthesis of **1** involving crystallization for the resolution step.

2. Synthesis of racemic amine **7**

Two main approaches have been reported for the preparation of dibenzoazepinone **4**. The first, a two-step route, comprises the cyclization of *N*-biphenyl-2-yl-2-chloro-acetamide **3** via a Friedel–Crafts alkylation.⁵ Alternatively, 2-bromoaniline was coupled to 2-iodophenylacetonitrile and cyclization to the lactam was achieved by saponification⁶ or via a five-step sequence based on an intramolecular Staudinger-aza-Wittig reaction.⁷ We chose to use the first route after improving the cyclization conditions (Scheme 1). Commercially available 2-aminobiphenyl was acylated with chloroacetylchloride in the presence of triethylamine at room temperature, affording 94% crude **3**. Ring closure to dibenzoazepinone **4** was achieved by heating **3** in the presence of 2.2 equiv of AlCl₃ in 1,3-dichlorobenzene at reflux for 9 h. After precipitation by the addition of water, **4** was isolated in 76% yield. Attempts to reduce the amount of AlCl₃ revealed that a minimum of 2.0 equiv was necessary for the reaction to run to completion (after 24 h,

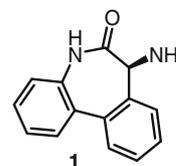
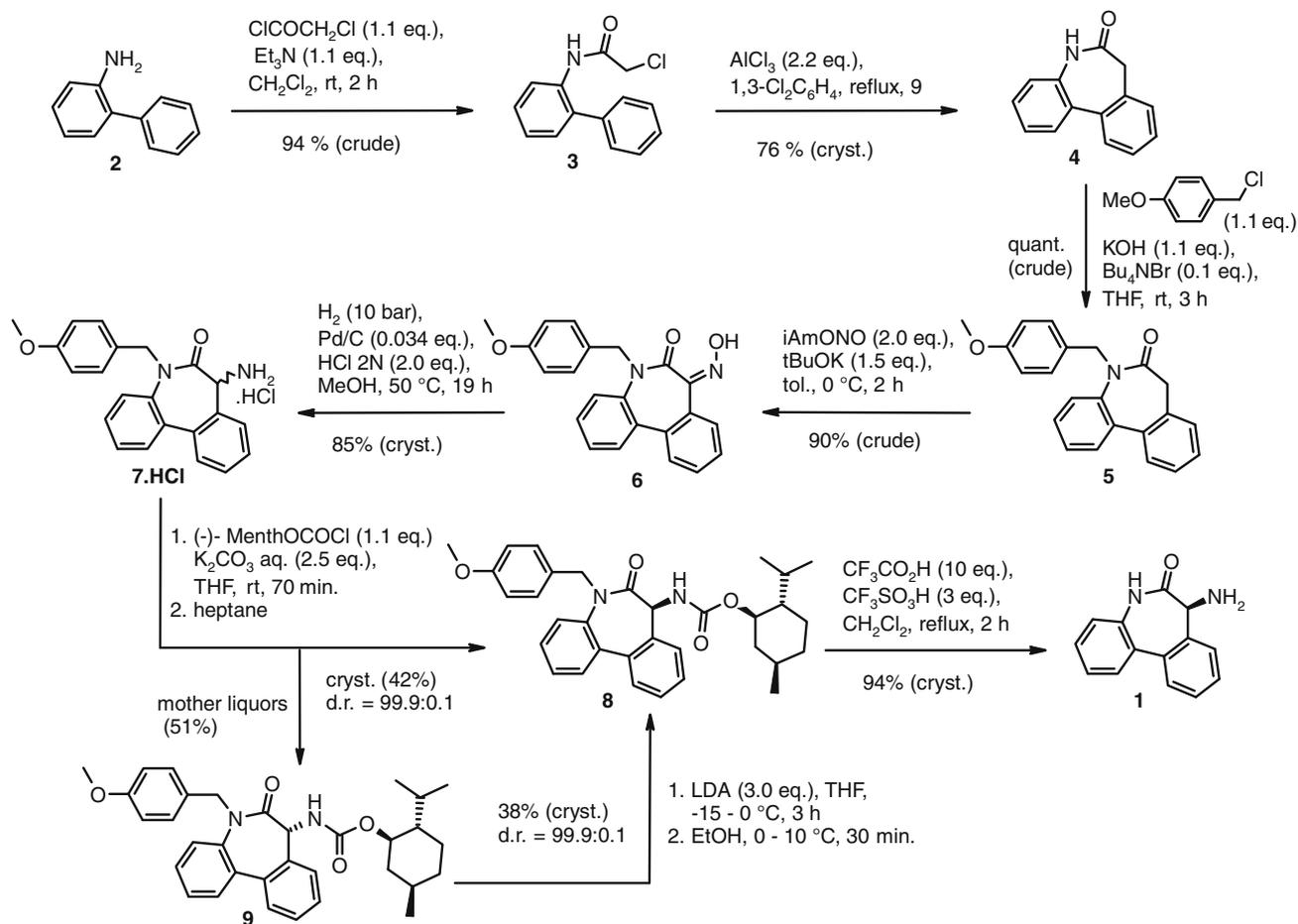


Figure 1.

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Scheme 1. Synthesis of **1** with resolution via crystallization.

only 0.3% starting material **3** remaining vs 28% with 1.5 equiv AlCl_3). Two approaches have been described for the N-alkylation of the lactam and the introduction of the amino group in the alpha position of the carbonyl group.⁴ One route applied a sequence of iodination, substitution by azide, reduction, then lactam alkylation whereas the other commenced with alkylation of the lactam followed by nitrosation at C(7), and reduction. We applied the latter, safer option and optimized the reaction conditions. The use of aqueous KOH and a catalytic amount of Bu_4NBr in THF was preferred to NaH in DMF for the protection of the lactam function of **4**, because of easier handling of the base and lower toxicity of the solvent. Crude *p*-methoxybenzyl lactam **5** was obtained quantitatively. On a kg-scale, **5** was filtered through a pad of silica gel with the aid of CH_2Cl_2 then crystallized from CH_2Cl_2 /TBME affording 70% of pure **5**. The usually reported base, KHMDS employed with isoamyl nitrite for the nitrosylation of **5** was replaced by cheaper and easier to handle *t*BuOK providing 90% crude oxime **6**. Crystallization of the crude product from EtOAc/*n*-hexane afforded 63% of **6**. However, this purification was not mandatory and the crude oxime was smoothly hydrogenated at 10 bar H_2 in the presence of 2 N HCl/MeOH and Pd/C at 50 °C. Racemic amine **7** was crystallized as the HCl salt to be isolated in 85% yield from MeCN or in 73% yield from EtOAc. Despite the lower yield, the latter solvent was preferred for larger scale work for economical, ecological, and toxicity reasons.

3. Resolution of racemic amine **7**

Attempts to crystallize the free amine of **7** selectively with chiral acids failed to afford any useful enantiomeric enrichment.⁸ In

contrast, the corresponding epimeric menthylcarbamates **8** and **9** displayed differing crystallization behavior. Thus, the crude mixture of **8** and **9** obtained after the treatment of **7** with (–)-menthylchloroformate and pyridine in CH_2Cl_2 afforded **8** in 44% yield and with a dr = 97.5:2.5 after crystallization from *n*-heptane. Furthermore, when the menthylcarbamates were generated in the presence of aqueous K_2CO_3 in THF, **8** precipitated directly from the reaction mixture upon addition of *n*-heptane and was isolated in 42% yield with a dr = 99.9:0.1.^{9,10} Concentration of the mother liquors furnished 51% **9** with a dr = 4.4:95.6. When the reaction was performed with hydrochloride salt of **7**, 2.5 equiv of aqueous K_2CO_3 was required, whereas 2.0 equiv was sufficient when the free amine of **7** was used. The menthylcarbamate and *p*-methoxybenzyl group were cleaved simultaneously by stirring **8** in CH_2Cl_2 in the presence of an excess of $\text{CF}_3\text{CO}_2\text{H}$ and $\text{CF}_3\text{SO}_3\text{H}$ in CH_2Cl_2 at reflux for 2 h. After crystallization from TBME/*n*-heptane, **1** was isolated in 94% yield.¹¹ Thus, **1** could be synthesized in a seven-step sequence, involving four crystallizations as purification operations, and with 22% overall yield on a laboratory scale. In a 3 kg campaign, an overall yield of 13% was attained.

4. Epimerization of **9**

In order to improve the overall yield of **8**, we examined the racemization at C-7 of the epimer **9**. Treatment of **9** with 3 equiv LDA at –75 °C for 2.5 h followed by quenching with MeOH did not lead to any epimerization. However, treatment of **9** (dr 10.1:89.9) with 3 equiv LDA at –15 to 0 °C for 3 h followed by quenching with EtOH at 0–10 °C, afforded **8** in 38% yield with a dr = >99.9:0.1 after

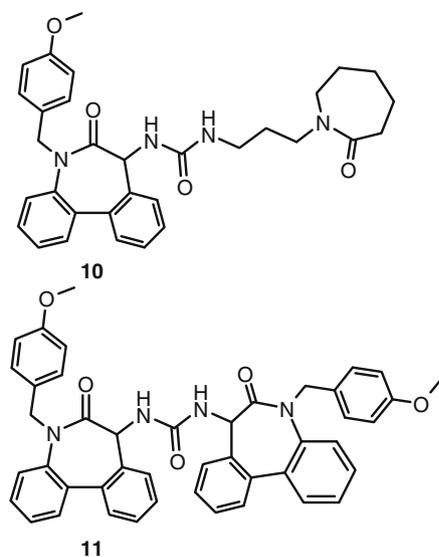


Figure 2.

work-up and crystallization from THF/*n*-heptane.¹² Including this epimerization loop, the overall yield of **1** from **2** was improved to 30%.

Other epimerization attempts failed. Stirring **9** in neat DBU at room temperature, in toluene in the presence of *t*BuOK, in *o*-xylene with DABCO or phosphazene-base P1-*t*-Bu at reflux did not lead to changes in the diastereoisomeric ratio of the reaction mixture. Finally, heating **9** at 135 °C in neat DBU for 24 h afforded 23% urea **10** resulting from reaction with *N*-(3-aminopropyl)- ϵ -caprolactam, the precursor of DBU and 28% of urea **11** (Fig. 2).

In conclusion, we have described an improved synthesis of **1**, using only crystallizations for purification or separation of enantiomers. **1** was obtained in 7 steps and 22% overall yield. Including epimerization of the undesired isomer the overall yield was further increased to 30%.

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10. **Representative procedure to 8:** 14.4 kg of **7**.HCl (37.8 mol) were suspended in 54 L THF at room temperature and a solution of 13.1 kg (93.7 mol, 2.5 equiv) K₂CO₃ in 72 L water was added over 15 min. After stirring for 20 min, 9.36 kg (–)-menthylchloroformate (41.9 mol, 1.1 equiv) were added over 15 min so that the temperature did not exceed 40 °C. The feeding vessel was rinsed with 5 L THF. The reaction mixture was stirred for 70 min at room temperature, warmed to 65 °C and 200 L *n*-heptane were added over 2 h. After the addition of 60 L *n*-heptane, crystallization commenced. The suspension was cooled to room temperature over 6 h and stirred for a further 12 h. The precipitate was filtered, washed with 18 L water followed by 70 L *n*-heptane, then dried at 45 °C under 20 m bar yielding 8.43 kg (42.4%) **8** as white crystals of dr = 99.9:0.1. Mp = 203–209 °C; [α]_D²⁰ –158.4 (*c* = 1.45, CHCl₃); IR (Nujol) ν 3402, 2923, 2854, 1709, 1655, 1499, 1452, 1396, 1377, 1244, 1193, 1049, 756 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.53–7.27 (m, 8H), 6.71 (d, 2H), 6.60 (d, 2H), 6.41 (d, 1H), 5.25–5.17 (m, 2H), 4.76 (d, 1H), 4.51 (m, 1H), 3.70 (s, 3H), 2.07–1.97 (m, 2H), 1.66 (d, 2H), 1.50–1.37 (m, 2H), 1.08–1.02 (m, 2H), 0.90 (d, 6H), 0.75 (d, 3H); ISP-MS (*m/z*) 549 (M+Na⁺, 9), 527 (M+H⁺, 100).

A sample of the mother-liquor was purified by flash chromatography (eluent: CH₂Cl₂/EtOAc 98:2) to afford a pure sample of **9** as a white foam of dr = >99.9:0.1. [α]_D²⁰ +74.66 (*c* = 0.999, CHCl₃); IR (Nujol) ν 3413, 3326, 2921, 2855, 1720, 1666, 1513, 1486, 1456, 1377, 1246, 1177, 1049 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.51–7.35 (m, 8H), 6.72 (d, 2H), 6.60 (d, 2H), 6.40 (d, 1H), 5.25–5.16 (m, 2H), 4.67 (d, 1H), 4.53 (m, 1H), 3.70 (s, 3H), 2.11–1.94 (m, 2H), 1.70–1.63 (m, 2H), 1.46–1.37 (m, 2H), 1.07–0.97 (m, 2H), 0.96 (d, 3H), 0.88 (d, 3H), 0.81 (d, 3H); ISP-MS (*m/z*) 549 (M+Na⁺, 20), 527 (M+H⁺, 100), 389 (34), 345 (49).

11. **Representative procedure to 1:** 8.43 kg of **8** (16.0 mol) were dissolved in 134 L CH₂Cl₂ and cooled to 0 °C. 18.6 kg trifluoroacetic acid (160 mol) were added, the feeding vessel rinsed with 10 L CH₂Cl₂, 7.4 kg trifluoromethanesulfonic acid (48.3 mol) were added slowly, so that the temperature never exceeded 5 °C (caution: exothermic) and the feeding vessel was rinsed with 10 L CH₂Cl₂. The reaction mixture was stirred for 10 min at 0 °C and 2 h at reflux. After cooling to room temperature, 140 L water and 22 L acetic acid were added. The biphasic mixture was stirred for 15 min at room temperature and the phases were separated. The organic phase was diluted with 6.7 L acetic acid and extracted with 45 L water then further diluted with 3.4 L acetic acid and extracted with 45 L water. Eighty-four litres of CH₂Cl₂ were added to the combined aqueous phases which were adjusted to ca. pH 11 by the addition over 1 h of 80 L 28% aqueous NaOH with stirring. After separation of the phases, the aqueous layer was further extracted with two portions of 45 L CH₂Cl₂. The combined organic layers were concentrated under reduced pressure at 50 °C to a volume of 17 L and the solvent was exchanged at constant volume with 70 L *tert*-butyl-methyl-ether, inducing crystallization. The suspension was cooled to 0 °C and 42 L *n*-heptane were added within 20 min. After 1 h at 0 °C, the suspension was filtered, the crystallization vessel rinsed with 10 L *n*-heptane precooled to 0 °C and the precipitate washed with 20 L *n*-heptane precooled to 0 °C affording, after drying at 45 °C under 1 mbar, 3.4 kg (94%) **1** as white crystals of dr = 99.85:0.15. Mp = 164.5–168 °C; [α]_D²⁰ –216.6 (*c* = 0.991, CH₃OH); IR (Nujol) ν 3368, 3206, 2926, 2855, 1674, 1584, 1466, 756, 730 cm^{–1}; ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s_{br}, 1H), 7.70–7.63 (m, 2H), 7.52–7.31 (m, 5H), 7.14 (dd, 1H), 4.38 (s, 1H), 2.03 (s_{br}, 2H); ISP-MS (*m/z*) 449 (2M+H⁺, 11), 225 (M+H⁺, 100).

12. **Representative procedure of the racemization of 9 and isolation of 8:** A solution of 32.3 g mother liquor concentrate (61 mmol, dr = 10.1:89.9) in 130 mL THF was cooled to –15 °C and 92 mL LDA (2 M solution in THF/heptane/methylbenzene, 184 mmol, 3 equiv) were added over 30 min so that the temperature did not exceed –10 °C. The dropping funnel was rinsed with 7 mL THF and the reaction mixture was stirred at 0 °C for 3 h. Fourteen millilitres of EtOH were added dropwise at 0–10 °C and stirring was continued for 30 min. 44 mL EtOAc were added to the clear solution and after cooling to –15 °C, 50 mL aq 25% HCl (385 mmol, 6.3 equiv) were added bringing the aqueous phase to pH 1–2. After separating the phases, the organic layer was washed with 44 mL aq 3 N HCl and twice with 105 mL water. The organic phase was concentrated under reduced pressure and the residue was taken up in 65 mL THF. To this orange suspension, 224 mL *n*-heptane were added dropwise at 30–40 °C and the suspension was further stirred at room temperature for 1 h. The precipitate was filtered, washed with three portions of 44 mL *n*-heptane, and dried under reduced pressure at 50 °C affording 12.2 g (38%) **8** as yellow-white crystals of dr = >99.9:0.1.