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Crystallization-induced Dynamic Resolution towards the Synthesis of (S)-7-Amino-5H,7H-dibenzo[b,d] -azepin-6-one: An Important Scaffold for γ-Secretase Inhibitors

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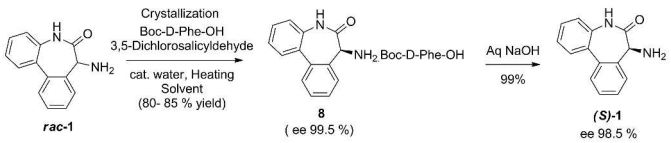
Graphic for TOC Only



ABSTRACT

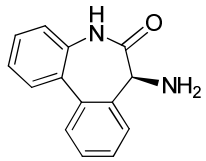
An enantioselective synthesis of (*S*)-7-amino-5H,7H-dibenzo[b,d]azepin-6-one (***S*-1**) is described. Key step in the sequence involved crystallization-induced dynamic resolution (CIDR) of compound **7** using Boc-D-phenylalanine as a chiral resolving agent and 3,5-dichlorosalicylaldehyde as a racemization catalyst to afford ***S*-1** in 81% overall yield with 98.5% enantiomeric excess.

KEYWORDS

Alzheimer's disease, Notch inhibitors, DKR, CIDR, 3,5-dichloro salicylaldehyde, Boc-D-Phenylalanine, Dibenzoazepenone

INTRODUCTION

Alzheimer's disease (AD) [1, 2] is characterized by the formation of abnormal and characteristic deposits of amyloid-β (Aβ) peptides in the brain. It has been established that β- and γ–secretase enzymes cause sequential proteolysis of the amyloid-precursor protein (APP) to generate amyloid-β-peptides. The amyloid cascade hypothesis of Alzheimer's disease postulates a causative role to the accumulation of these amyloid-β-peptides in brain tissue.[3] In mouse models, small molecule inhibitors of the γ-secretase enzyme have been shown to suppress the production of amyloid-β-peptides *in-vivo* and inhibit deposition of amyloid peptides in the brain. γ-Secretase inhibitors are also being developed as anticancer agents owing to their ability to modulate the Notch signaling pathway.[4] Several γ-secretase inhibitors have been described based on (*S*)-7-amino-5H,7H dibenzo[*b*,*d*]azepin-6-one (***S*-1**) as the core structure.[5] The essential level of potency and drug-like properties are then conferred by attaching a side-chain to the amino group and an optional substituent on the nitrogen of the central lactam ring.[6]



***S*-1**

Figure 1: (*S*)-7-amino-5H,7H dibenzo[b,d]azepin-6-one (***S*-1**)

The reported syntheses of ***S*-1** and its analogs rely on enantiomer separation via chiral HPLC[6a] or chromatography of derived diastereoisomers.[7] Resolution of the *N*-methylated lactam of **1** has been reported by crystallization with di-*p*-toluyl-D-tartaric acid monohydrate.[8] Hoffman-Emery *et al* reported an improved synthesis of ***S*-1** based on a selective crystallization of epimeric menthyl carbamates followed by simultaneous cleavage of the carbamate and the lactam

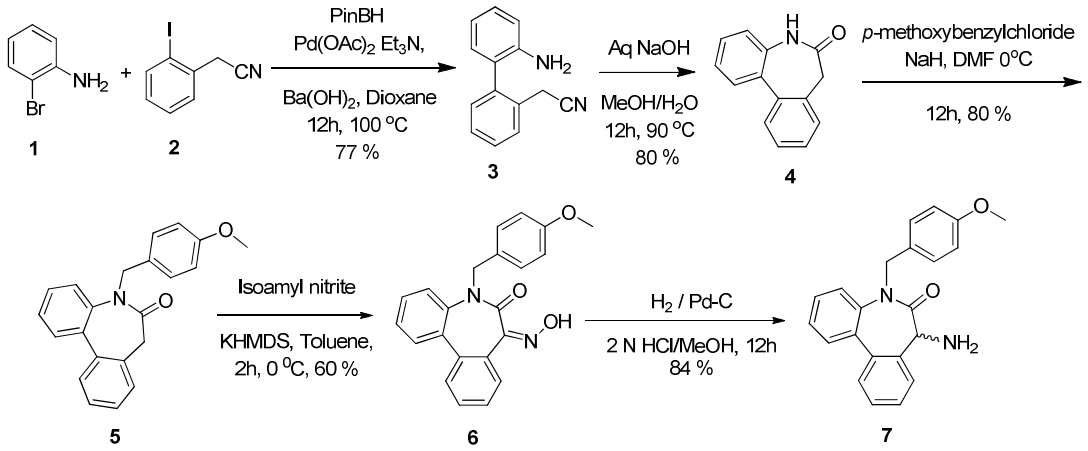
protecting groups.[9] The undesired menthyl carbamate was epimerized by treatment with LDA to improve the overall yield of ***S*-1**. Although this methodology is attractive in terms of the overall yield, it is not preferred since it employs the expensive menthyl chloroformate and requires additional synthetic steps for protection and removal of the chiral auxiliary group. As part of our γ–secretase inhibitor program, we required compound ***S*-1** in large quantity to synthesize a developmental candidate for toxicology studies. We sought an efficient, scalable and cost effective synthesis of enantiopure ***S*-1** by applying crystallization-induced dynamic resolution (CIDR).[10] CIDR is a process that has the potential to afford a quantitative yield of the chiral product from a racemic starting material through *in-situ* epimerization, resolution and crystallization with a chiral resolving agent.

RESULTS AND DISCUSSION

Several approaches have been reported for the preparation of dibenzoazepinone core **4**.[11-13] We decided to follow the palladium-catalyzed coupling of 2-bromoaniline (**1**) with 2-iodophenylacetonitrile (**2**) as shown in Scheme 1 due to the availability and inexpensive nature of both starting materials.

One-pot palladium acetate catalyzed borylation-Suzuki coupling (BSC) reaction between 2-bromoaniline (**1**) and 2-iodophenylacetonitrile (**2**) provided 2,2'-disubstituted biphenyl **3**.[11] Cyclization of **3** to the lactam **4** was promoted by aqueous potassium hydroxide at 60 °C to provide dibenzoazepinone core **4** in 62% yield over two steps. Two methods have been reported for the *N*-alkylation of the lactam and the introduction of the amino group in the alpha position of the carbonyl group,[8] one route applied a sequence of iodination, substitution by azide, reduction, and then lactam alkylation, the other route commenced with alkylation of the lactam followed by nitrosation at C(7), and reduction. We followed the latter as it seemed a safer

alternative. Accordingly, compound **4** was subjected to sodium hydride and *p*-methoxy benzyl chloride in DMF[a] to afford **5** in 80 % yields. Compound **5** was treated with *iso*-amyl nitrite and KHMDS in anhydrous THF followed by hydrogenation of the resulting *N*-hydroxyl imine-derivative **6** to furnish racemic 2-amino dibenzoazepinone **7** in 50 % yield over two steps (Scheme 1).

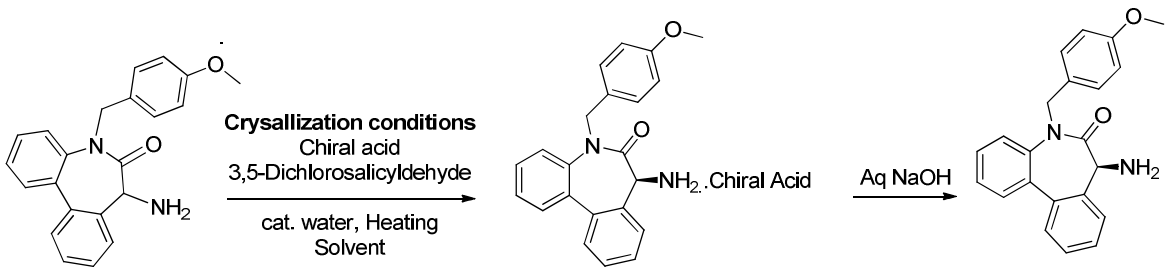


Scheme 1: Synthesis of racemic N-PMB protected amino dibenzoazepinone

With a scalable method to prepare the racemic intermediate **7** in hand, we were intrigued by the possibility of simultaneously racemizing the undesired enantiomer of **7** during the resolution process (a dynamic resolution), thus converting all of the racemate to the desired enantiomer. Initially, we attempted classical crystallization with various chiral acids in different solvent system combinations as the first step towards **7** establishing the proposed CIDR but we did not have any success (See **Table 1).** Our results were largely in accordance with reported results by

[a]The combination of DMF and NaH is not advisable for larger scale operations but due to lack of other suitable scalable method the reagent was used without any safety issue for the scales we handled following the guidance provided in the literature.[15]

Table 1: Screening of rac-7[b]

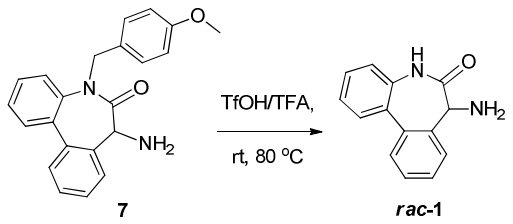


S1 = Acetonitrile; S2 = Ethyl acetate , S3 = 1,2-Dichloroethane; S4= Methanol, S5 = THF ; S6 = n-BuOH; S7 = Toluene.

Vial	Chiral Acids	S1	S2	S3	S4	S5	S6	S7	S8
1	D-(−)-Tartaric acid	-	-	-	-	-	T	-	-
2	(+)-*O,O′*-Di-*p*-toluoyl-D-tartaric acid	-	-	-	-	-	-	-	T
3	Boc-D-Phe-OH	-	-	LS	-	-	LS	T	
4	(1*R*)-(−)-10-Camphorsulfonic acid	-	-	-	-	-	-	-	T
5	Boc-D-Phg-OH	-	-	O	-	T	-	O	-
6	(*S*)-(−)-2-Pyrrolidone-5-carboxylic acid	-	-	-	-	-	-	-	-
7	*(R)*-(-)-Mandelic acid	-	-	-	-	-	-	-	-

[b]Following solvents were selected for ***rac*-7** **S**1 = Acetonitrile; S2 = Ethyl acetate , S3 = 1,2-Dichloroethane; S4= Methanol, S5 = THF ; S6 = n-BuOH; S7 = Toluene S8 = MTBE. The classical resolution screening of amine ***rac*-7** was performed in parallel manner in vials utilizing commercially available chiral acid and solvent (S1 – S8). Each vial solvent concentration was maintained 30- 40 mg /ml with equamolar ratio of resolving acid and racemate. The vials were heated until clear solution obtained and left overnight under closed system. T = Vial solution was found Turbid, O = vial contained an oil, LS = Vial contained little amount solid. Blank Cells = vials found either clear solution or only chiral acid separated out as solid.

Hoffman-Emery *et al*.[9] Further, it was decided to remove the PMB group attached to the amide nitrogen before attempting a classical resolution or CIDR. Accordingly, compound **7** was heated at 80 °C with a mixture of trifluoromethanesulfonic acid and trifluroacetic acid to afford solid compound ***rac*-1**.

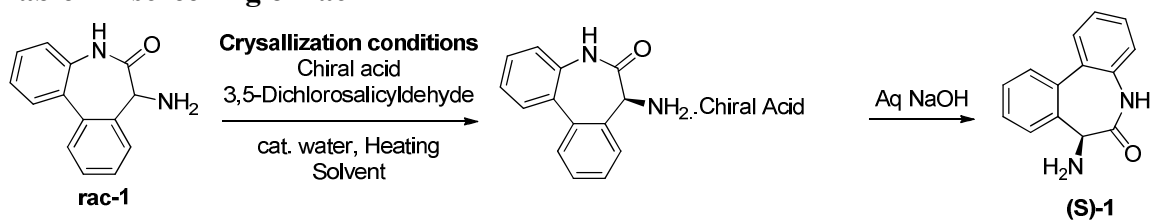


7 ***rac*-1**

Scheme 2: Deprotection of *p*-methoxybenzyl group

After examining numerous chiral acids and solvent combinations for resolution of ***rac*-1**, (see **Table – 2**) we were delighted to find that Boc-D-Phe-OH proved to be optimal to provide pure crystals as a single enantiomer in solvents such as dichloroethane, toluene, ethyl acetate and acetonitrile. Initially, the resolution was performed in acetonitrile with addition of Boc-D-Phe-OH at room temperature to afford desired crystalline salt **8** in 43% yields and 99.5% ee (by chiral HPLC) and the undesired *R*-isomer remained in the solution. Subsequently, based on previous reported work with similar structural motifs, [14] few aromatic aldehydes (salicylaldehyde, benzaldehyde, 2-chlorobenzaldehyde and 3,5-dichlorosalicylaldehyde were screen as racemization catalysts under refluxing condition with different solvent (dichloroethane, toluene, ethyl acetate, acetonitrile or chloroform) and traces of water. We were delighted to find that 3,5-dichlorosalicylaldehyde was optimal catalyst for the racemization of the undesired enantiomer. Solvents like toluene, dichloroethane, chloroform or acetonitrile were found to be effective at their respective reflux temperatures and suitable to achieve DKR process. Based on literature precedence, [10(d)] traces of water were found to be critical for racemization. In the

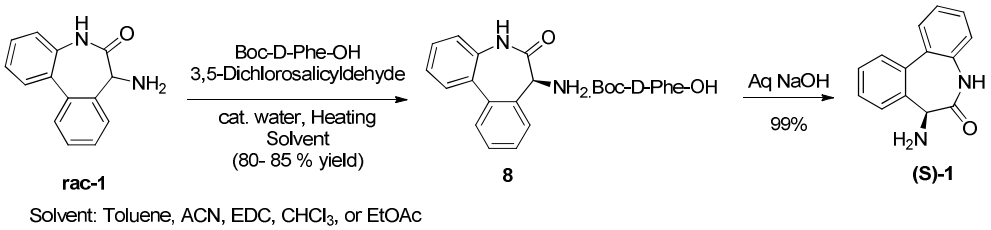
Table – 2 screening of rac-1[c]



S1 = Acetonitrile; S2 = Ethyl acetate , S3 = 1,2-Dichloroethane; S4= Methanol, S5 = THF ; S6 = n-BuOH; S7 = Toluene.

Vial	Acids	S1	S2	S3	S4	S5	S6	S7
1	D-(−)-Tartaric acid	-	T	-	-	-	-	-
2	(+)-*Di-p-toluoyl-D-tartaric Acid*	-	-	-	-	-	-	-
3	**Boc-D-Phe-OH**	**S**	**S**	**S**	**O**	**O**	**T**	S
4	(1*R*)-(−)-10-Camphorsulfonic acid	-	-	-	-	-	-	
5	Boc-D-Phg-OH	LS	T	-	O	O	T	LS
6	(*S*)-(−)-2-Pyrrolidone-5-carboxylic acid	LS	T	T	O	O	T	LS
7	*(R)*-(-)-Mandelic acid	-	T	-	-	-	-	-

[c]These solvents were selected for *rac*-**1** **S**1 = Acetonitrile; S2 = Ethyl acetate , S3 = 1,2-Dichloroethane; S4= Methanol, S5 = THF ; S6 = n-BuOH; S7 = Toluene. The classical resolution screening of amine ***rac*-1** was performed in parallel manner in vials utilizing commercially available chiral acid and solvent (S1 – S7). Each vial solvent concentration was maintained 30- 40 mg /ml with equimolar ratio of resolving acid and racemate. The vials were heated until clear solution obtained and left overnight under closed system. T = Vial solution was found Turbid, S = Vial contained large amount of solid materials that was free flowing, O = vial contained an oil, LS = Vial contained little amount solid. Blank Cells = vials found either clear solution or only chiral acid separated out as solid.



Scheme 3: Resolution of amino dibenzoazepinone

absence of water, no racemization was seen to take place. The best results were found with toluene as the solvent, which gave the shortest reaction time and highest ee (> 99 % ee). Thus, one-pot resolution-racemization of ***rac*-1** was achieved using 3,5-dichlorosalicylaldehyde (2 mol %), water (1.5-2.0 mole %), and Boc-D-Phe-OH in toluene under heating for 12 h to provide the resolved salt **8** in 82 % yield and 99.4% ee. The salt **8** was characterized by NMR analysis and confirmed to have an optical purity of 99.4% ee *via* chiral HPLC analysis. The conversion of the salt **8** to free base (*S*)-**1** was accomplished by addition of aqueous solution of sodium hydroxide to the salt, followed by extraction with methylene chloride and vacuum concentration. Compound **(*S*)-1** was characterized by NMR, LCMS and chemical purity and optical purity were found to be 97 % and 99 % (ee) respectively. The overall yield of the free amine **(*S*)-1** from ***rac*-1** was 80 %.

CONCLUSION

In conclusion, we have developed a novel, scalable and economically viable synthesis of optically pure **(*S*)-1** through dynamic kinetic resolution using Boc-D-Phe-OH as a chiral resolving agent and 3, 5-dichlorosalicylaldehyde as a racemization agent. Efforts to develop DKR with other amino dibenzo[*b*,*d*] azepin-6-one cores are ongoing.

EXPERIMENTAL SECTION

(7*S*)-6-Oxo-6,7-dihydro-*5H*-dibenzo[*b*,*d*]azepin-7-aminium (*R*)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate (8). To a dry RB flask was charged racemic 7-amino-*5H*-dibenzo[*b*,*d*]azepin-6(*7H*)-one (6.0 g, 26.8 mmol) **(*rac*-1)**, 3,5-dichlorosalicylaldehyde (0.256 g, 1.338 mmol), toluene (120 mL), Boc-D-phenylalanine (7.10 g, 26.8 mmol), followed by water (0.222 g, 12.31 mmol) and heated to 100 ºC overnight. The progress of the reaction was monitored by chiral HPLC (Initially, two peaks was observed at 4.87 min and 8.43 min corresponding to *R* and *S* isomer of **1** respectively and on completion of DKR the peak corresponding to *R*-isomer disappeared and only peak at 8.43 found along with peak of Boc-D-Phe-OH). The obtained thick slurry was filtered, washed with toluene and dried under vacuum to obtain the salt **8** (10.7 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (s, 9H), 2.83 (dd, *J*=14.06, 10.54 Hz, 1H), 3.02 (dd, *J*=14.05, 4.52 Hz, 1H), 4.00-4.09 (m, 1H), 4.12 (s, 1H), 7.00 (br. s., 1H), 7.15-7.33 (m, 7H), 7.37-7.56 (m, 4H), 7.61-7.73 (m, 2H), 10.22 (s, 1H); LCMS(EI) for $C_{28}H_{31}N_3O_5$, $(M+H)^+$ calcd.489.2; found, 490.2.

(*S*)-7-Amino-*5H*—dibenzo[b,d]azepin-6(*7H*)-one (*S*-1). The above salt **8** (10.7 g) was basified with using 50% aqueous NaOH solution (100 mL) and extracted with DCM (2 × 200 mL). The combined organic layers were washed with water (75 mL), brine solution (75 mL), dried over Na_2SO_4, and concentrated in vacuum to obtain compound (***S*-1**) (4.8 g, 80 % yield) as white foam, chiral purity: > 99.0 % ee.

Absolute configuration was assigned by comparing chiral HPLC (SFC method) retention time of the sample prepared by DKR method and literature[9] known sample under above conditions (Co-injection). $[\alpha]^{25}_D$ -203 (C = 1.0 MeOH) ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (s, 2H), 4.10 (s, 1H), 7.12 (s, 1H), 7.21 (dd, *J* = 8.03, 1.00 Hz, 1H), 7.26-7.34 (m, 1H), 7.43 (ddd, *J* = 5.65,

4.14, 1.76 Hz, 2H), 7.45-7.56 (m, 2H), 7.65 (dd, *J* = 7.78, 1.25 Hz, 1H), 7.70 (d, *J* = 8.03 Hz, 1H); LCMS(EI) for $C_{14}H_{12}N_2O$, $(M+H)^+$ calcd.224.1; found, 225.2.

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SUPPORTING INFORMATION

Supporting Information contains experimental and analytical data for the intermediates **3**, **4**, **5**, **6** and **7** and the analytical data for the compounds **8** and ***S-1***

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