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Synthesis of (−)-5,8-Dihydroxy-3*R*-methyl-2*R*-(dipropylamino)-1,2,3,4-tetrahydronaphthalene: An Inhibitor of β-Amyloid$_{1–42}$ Aggregation

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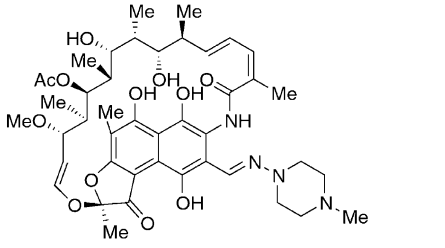
Abstract—A concise synthesis of the β-amyloid$_{1–42}$ aggregation inhibitor (−)-5,8-dihydroxy-3*R*-methyl-2*R*-(dipropylamino)-1,2,3,4-tetrahydronaphthalene [(−)-**2**] has been developed. The key step is a regio- and diastereoselective hydroboration-amination sequence to convert alkene **6** into amine **9**. Enantiomeric resolution was achieved by recrystallization of amine **9** as the dibenzoyl-D-tartaric acid salt. Hydroquinone **2** is a potent inhibitor of the fibrillar aggregation of β-amyloid as determined in two different assay systems.

Introduction

The peptide β-amyloid$_{1–40(42)}$ (Aβ) is keenly involved in the development of Alzheimer's disease.[1] Oligomeric β-amyloid aggregates are neurotoxic in cell culture, and there is a growing consensus that these peptides cause the greatest damage in the transition between monomeric and polymeric forms.[2] Inhibition of Aβ aggregation is an important target for the design of therapeutic agents for the prevention and treatment of Alzheimer's disease.

Several small molecule inhibitors have been reported to inhibit β-amyloid aggregation including the antibiotic rifampicin (Fig. 1).[3] A substructure search of our compound library using rifampicin **1** as a guide, followed by screening for the inhibition of β-amyloid aggregation,[4] led to the identification of racemic 2-aminotetralin **2** as a promising aggregation inhibitor. Compound **2** had been prepared over 10 years ago as part of another research effort, but the sample in the collection was still >50% pure and not oxidized to the corresponding quinone. Subsequently, the (−)-enantiomer was investigated in more detail. Despite structural similarities to 2-aminotetralins that are dopamine or serotonin receptor agonists,[5] such as 8-OH-DPAT (**3**), compound **2** has no appreciable dopaminergic or serotoninergic receptor activity. Because of the rich pharmacological activities reported for aminotetralins, there are many reported methods for their synthesis.[6] We describe here a concise synthesis of an enantiomer of compound **2** which includes the application of an extremely useful hydroboration–amination sequence that introduces the 2-amino group in a diastereoselective manner.



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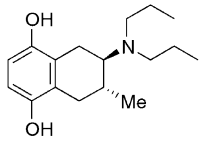

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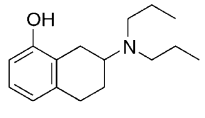

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Figure 1.

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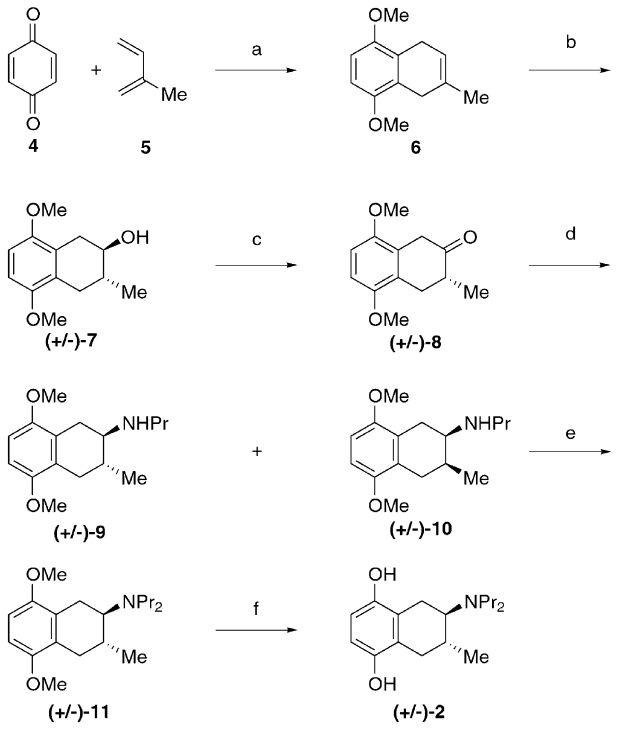
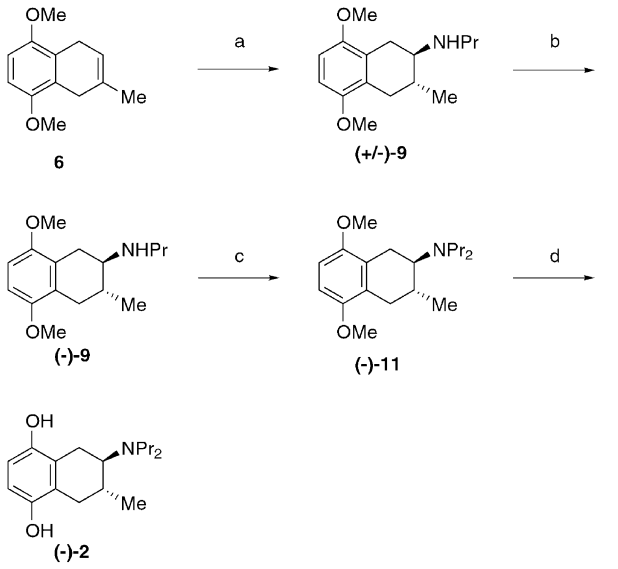


Scheme 1. (a) Toluene, 50 °C, 48 h; then NaOH, H_2O, Me_2SO_4, $BnEt_3NCl$, 80 °C, 4 h, 67%; (b) BH_3–THF, then NaOH, 30% aq H_2O_2, 95%; (c) $(CO)_2Cl_2$, DMSO, Et_3N, CH_2Cl_2, 68%; (d) $PrNH_2$, $NaCNBH_3$, AcOH, CH_3CN, 72%; (e) EtCHO, $NaCNBH_3$, AcOH, CH_3CN (f) 48% HBr, 86%.

Synthetic chemistry

The original synthesis of racemic **2** began with the preparation of alkene **6** by a modification of a literature Diels–Alder reaction (Scheme 1).[7] The adduct of benzoquinone (**4**) and isoprene (**5**) was obtained after heating in toluene for 48 h. The addition of dimethylsulfate, sodium hydroxide, $BnEt_3NCl$ and water to the reaction mixture led to aromatization followed by methylation. This one-pot procedure provided alkene **6** in 67% yield. Hydroboration–oxidation of **6**, followed by Swern oxidation of the resulting *trans* alcohol **7**, provided ketone **8**. Reductive amination of **8** with propylamine gave 2-aminotetralin **9**, which was not separable from minor *cis* isomer **10**. Reductive amination of **9** with propionaldehyde provided dipropylamine **11**, which could be purified at this stage from the corresponding *cis* isomer. Finally, demethylation was accomplished by heating **11** in 48% HBr to provide hydroquinone **2** as its HBr salt in 86% yield. This method of deprotection afforded higher yields than when using BBr_3, which appeared to provide boron adducts or chelates that were difficult to handle.

The poor diastereoselectivity in the reductive amination of ketone **8** and the difficult separation of the resulting mixture of isomers complicated large-scale synthesis of hydroquinone **2**. Therefore, we sought to introduce the 2-amino group in a more stereoselective manner. A hydroboration–amination sequence starting with alkene **6** was an attractive option for accomplishing this task because of the requirement that the 3-methyl be oriented



Scheme 2. (a) $BHCl_2$·DMS, BCl_3, PrN_3, CH_2Cl_2, hexane, 73%; (b) dibenzoyl-D-tartrate, recrystallization 4x from *i*PrOH, 25%, >98% ee; (c) EtCHO, $NaCNBH_3$, AcOH, CH_3CN, 90%; (d) 48% HBr, 86%.

trans to the 2-amino group (Scheme 2). Hydroboration of alkene **6** with borane, followed by treatment with either sodium azide/HCl, hydroxylamine-*O*-sulfonic acid,[8] or chloramine[9] resulted in either decomposition or production of alkene isomer **12**. Alternatively, hydroboration of alkene **6** with dichloroborane[10] proceeded smoothly to generate alkyldichloroborane **13**. Treatment of **13** with hydroxylamine-*O*-sulfonic acid led to decomposition. However, when this dichloroborane was treated with propylazide,[11] secondary amine **9** was obtained in good yield. In a modification of a published method, we found that separation of intermediate **13** from the precipitated BCl_3·Me_2S was not necessary. The product could be obtained in high purity by recrystallization of the HCl salt, avoiding the need for chromatography. There was no evidence of the formation of either regio- or stereoisomers, although aryl chloride **14** (mixture of regioisomers) was observed in about 1–5% yield (Fig. 2).

Several attempts to extend this procedure to generate amine (−)-**9** in an enantioselective fashion were unsuccessful. However, resolution of racemic (±)-**9** was readily achieved by crystallization of the dibenzoyl-D-tartaric acid addition salt. Enantiomeric excess of greater than 98% could be obtained after four crystallizations.[12] The X-ray crystal structure of the dibenzoyl-D-tartaric acid salt of secondary amine (−)-**9** indicated this enantiomer has the (2*R*,3*R*) absolute stereochemistry.

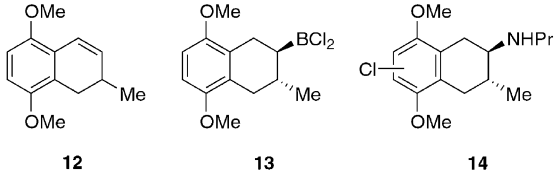


Figure 2.

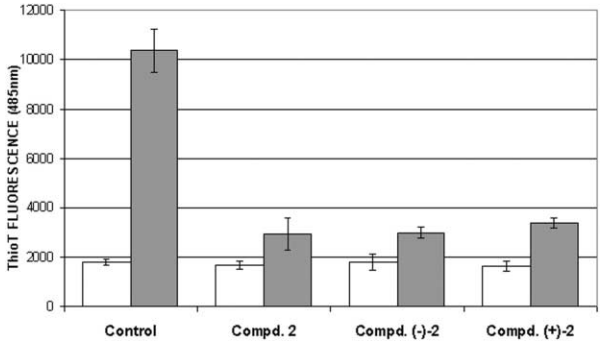


Figure 3. Thio T fluorescence timecourse of $A\beta_{1-42}$ fibrillization. $A\beta_{1-42}$ (100 μM) was incubated with 100 μM compound **2**, (−)-**2**, (+)-**2**, or vehicle control at 37 °C 10 mM HEPES, pH 7.4 for 3 days. Relative to the control incubation, compounds **2**, (−)-**2**, and (+)-**2** inhibited $A\beta_{1-42}$ fibril formation by ca. 85%. Day 0 (white bar), day 3 (black bar). Similar results were observed for compound **2** when the assay was performed in PBS, pH 7.4 (data not shown).

Antiaggregation testing

Compound **2** was tested for its ability to inhibit the aggregation of β-amyloid. Originally, compound **2** was tested in a synthaloid microplate assay for peptide deposition[4] and its IC_{50} was determined to be 1 μM. This assay measures the ability of test compounds to inhibit the deposition of fluorescently-labeled β-amyloid$_{1-42}$ onto preformed amyloid fibrils formed on the walls of the plastic microplate. Among the large number of compounds we have evaluated using this assay (>500), compound **2** reproducibly is among the most active.

Compound **2** and its enantiomers (−)-**2** and (+)-**2** were evaluated in a more robust assay involving incubation with nonfibrillar $A\beta_{1-42}$ for 3 days to evaluate effects on the formation of fibrillar Aβ.[13] In this assay, fibrillar $A\beta_{1-42}$ is detected with the dye thioflavin T (Thio T) which fluoresces upon binding to amyloid deposits in which the peptide strands are arranged in β-sheet aggregates. Unbound Thio T fluoresces weakly at 438 nm when it is excited at 350 nm. In the presence of amyloid fibrils, a strong Thio T fluorescence emission is observed at 490 nm upon excitation at 450 nm. At a 1:1 ratio of compound to peptide, **2** inhibited $A\beta_{1-42}$ fibril formation by 85% and enantiomers (−)-**2** and (+)-**2** had similar activity (Fig. 3). This is comparable to the activity seen with other small molecule inhibitors of Aβ aggregation such as rifampicin and benzofuran derivatives. Rifampicin (10 μM) was reported to inhibit the fibrillization of 20 μM $A\beta_{1-40}$ by ca. 65% (1:2 compound/$A\beta_{1-40}$ ratio) in a thioflavin T binding assay while derivatives of benzofuran were active at ca. 1:1 compound:$A\beta_{1-40}$ ratio (11 μM compound to 11.6 μM $A\beta_{1-40}$) in a fibrillization immunoassay.[3a,14]

Summary

Based on a substructure search of our corporate compound collection using rifampicin as a template, we identified hydroquinone **2** as a robust inhibitor of the aggregation of β-amyloid$_{1-42}$. A regio- and diastereoselective synthesis of the (−)-enantiomer involving a key hydroboration–amination reaction was developed, which was suitable for the preparation of multigram quantities. Testing of (−)-**2** in both the synthaloid and thioflavin T assays revealed that it is a potent inhibitor of Aβ fibrillar aggregation, and more extensive biological evaluation is underway and the results will be reported separately.

Experimental

General methods

All chemicals were reagent grade and were used as purchased without further purification; solvents were HPLC grade. Reactions were performed under an inert argon or nitrogen atmosphere. ^{1}H NMR spectra were obtained at 300 or 400 MHz in $CDCl_3$ (unless otherwise noted) with Me_4Si as an internal reference (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broadened). In general, electrospray (ES) or fast-atom bombardment (FAB) mass spectra were obtained to characterize intermediates, while accurate mass measurements (HRMS) were obtained, in FAB mode, to characterize key compounds.

5,8-Dimethoxy-2-methyl-1,4-dihydronaphthalene (6). To a solution of benzoquinone (100 g, 0.92 mol) in toluene (1 L) in a 3-L three-neck flask equipped with a condenser, isoprene (97 mL, 0.96 mol) was added. The solution was stirred by mechanical stirring at 50 °C for 48 h. After the reaction mixture was cooled to room temperature, sodium hydroxide (76 g in 600 mL water) and benzyltriethylammonium chloride (10.5 g, 3 mol%) were added slowly and the temperature rose briefly to 55 °C. The resulting mixture was stirred at room temperature for 1 h before dimethylsulfate (180 mL, 1.88 mol) was added slowly over a 25-min period. The reaction mixture was heated to 80 °C for 4 h before being cooled back to room temperature. The toluene layer was separated, washed with brine, and dried with Na_2SO_4. The solution was concentrated and redissolved in 1.5 L hexane. This dark mixture was filtered through silica gel twice to obtain a light yellow solution. The solution was concentrated and the residue was crystallized from hexane to give alkene **6** (127 g, 67% yield) as light-yellow solid. Mp 48–49 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (s, 3H), 3.10–3.17 (m, 2H), 3.25 (br s, 2H), 3.75 (s, 3H), 3.76 (s, 3H), 5.53 (br s, 1H), 6.56 (s, 2H).

***trans*-5,8-Dimethoxy-2-hydroxy-3-methyl-1,2,3,4-tetrahydronaphthalene (7).** A solution of alkene **6** (5.00 g, 24.5 mmol) in tetrahydrofuran (100 mL) was cooled to 0 °C and treated with borane–tetrahydrofuran complex (1 M in THF, 24.5 mL, 24.5 mmol) and the resulting solution was stirred at room temperature for 4 h. Then aqueous NaOH (3 N, 12 mL) solution was added slowly to the stirring reaction solution followed by the addition of aqueous hydrogen peroxide (30%, 6 mL). After stirring for 30 min, the resultant mixture was diluted with

ethyl acetate (500 mL) and washed by brine (2×100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated, and the residue was purified on silica gel (30% ethyl acetate in hexane) to give alcohol **7** as a white solid (5.17g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, 3H, J = 6.51 Hz), 1.60 (d, 1H), 1.75–1.90 (m, 1H), 2.26 (dd, 1H, J = 10.0 Hz, 17.57 Hz), 2.48 (dd, 1H, J = 8.93 Hz, 17.10 Hz), 2.96 (dd, 1H, J = 5.31, 17.7 Hz), 3.16 (dd, 1H, J = 5.33, 5.35 Hz), 3.63–3.69 (m, 1H), 3.78 (s, 6H), 6.62 (s, 2H).

5,8-Dimethoxy-3-methyl-2-tetralone (8). A solution of alcohol 7 (10 g, 45 mmol) and dichloromethane (200 mL) at −30 °C was treated dropwise with oxalyl chloride (4.92 g, 24 mL, 0.275 mol). The reaction was stirred at −30 °C for 30 min, cooled to −60 °C, and DMSO (6.4 mL) was added slowly over 15 min. The reaction was stirred for 1 h, cooled to −78 °C for 30 min, and then treated dropwise with triethylamine (40 mL). The reaction was warmed to room temperature and stirred for 1 h, followed by the addition of water and dichloromethane with thorough mixing. The organic layer was separated, dried with $MgSO_4$, filtered and the solvent was evaporated to an oil. Purification of this material using flash chromatography (flash silica, 30% ethyl acetate in hexane) afforded tetralone **8** as a white crystalline solid (6.80g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.7 (m, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.5 (dd, 2H), 3.3 (m, 1H), 2.55 (m, 2H), 1.2 (d, 3H).

5,8-Dimethoxy-3-methyl-2-propylamino-1,2,3,4-tetrahydronaphthalene [(±)-9]. To a solution of tetralone **8** (0.15 g, 0.68 mmol) in acetonitrile (10 mL) was added sodium cyanoborohydride (0.085 g, 1.30 mmol), acetic acid (0.05 mL) and *n*-propylamine (0.08 mL, 1.3 mmol). The resulting solution was stirred at room temperature overnight and poured into 10 mL of 1 N NaOH solution. The mixture was extracted with ethyl acetate, dried over sodium sulfate, concentrated, and the residue purified by chromatography (30% ethyl acetate in hexane) to give amine **9** as a colorless oil, containing 40% of *cis* isomer **10** (0.13g, 72%). ^{1}H NMR (300 MHz, CD_3OD) δ 0.85 (d, 3H, J = 7.07 Hz), 0.93–0.97 (m, 3H), 1.09 (t, 2H), 1.49–1.61 (m, 2H), 2.12–2.42 (m, 2H), 2.51–2.76 (m, 4H), 2.82–3.08 (m, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 6.65 (s, 2H).

(2*R*,3*R*)-5,8-Dimethoxy-3-methyl-2-propylamino-1,2,3,4-tetrahydronaphthalene [(−)-9]. 1-Propylbromide (24.6 g, 0.20 mol) and sodium azide (13.0 g, 0.20 mol) were combined in DMF (50 mL) and stirred at room temperature overnight. The reaction mixture was allowed to settle and was decanted into a separatory funnel and diluted with water. The residual solid was washed 2–3 times with hexane and these washes were added to the separatory funnel. After mixing, the DMF layer was drained and the hexane layer was washed 2–3 times with brine and then dried over $MgSO_4$. The solution was filtered and the propyl azide solution was used as is. In a separate flask, boron trichloride (1.0 M in heptane, 100 mL, 0.1 mol) was added to 100 mL of dry dichloromethane. To this solution was added dichloroborane–methyl sulfide complex (12.1 mL, 0.105 mol) and the reaction mixture was stirred for 1 h at room temperature, and then cooled in an ice bath. To this was added alkene **6** (19.4 g, 0.095 mol) in 100 mL of 1:1 dichloromethane/hexane. The reaction mixture was stirred 4 h at 0 °C, and then the azide solution from above was added slowly dropwise. The reaction mixture was allowed to stir and slowly warm to room temperature overnight. The reaction was quenched with water, made basic with 6 N sodium hydroxide, and transferred to a separatory funnel. The aqueous layer was extracted with diethyl ether (2×). The combined organic layers were washed with brine, dried with K_2CO_3 and concentrated. The residue was dissolved in isopropanol and treated with HCl (1.0 M in diethyl ether, 100 mL). The solvent was evaporated and the residue was triturated with acetone. The resulting white solid was collected and recrystallized from isopropanol to give amine **9** (20.8 g, 73% yield) as the HCl salt. The racemic HCl salt of **9** (10.00 g, 33.35 mmol) was added to 1 N NaOH and extracted with dichloromethane. The organic solution was dried, concentrated, and redissolved in isopropanol. Dibenzoyl-D-tartaric acid (11.95 g, 33.35 mmol) was dissolved in a minimal amount of methanol and this solution was added to the amine. The solution was heated to boiling until the boiling point reached 82 °C. The solution was then allowed to cool to room temperature and left to stand overnight. The white solid precipitate enriched in the desired enantiomer was collected by filtration. A small sample was converted to the free base and analyzed by HPLC to determine enantiomeric ratio (Chiralcel OD, 98:2:0.1 hexane/isopropanol/diethyl amine, 1.0 mL/min, UV @ 238 nm). After at least four crystallizations, the undesired enantiomer was no longer detectable (ee > 98%). ^{1}H NMR of the free base (300 MHz, CD_3OD) δ 1.04 (t, 3H, J = 7.4 Hz), 1.16 (d, 3H, J = 6.7 Hz), 1.65–1.80 (m, 2H), 2.14–2.23 (m, 1H), 2.48 (dd, 1H, J = 17.9, 7.6 Hz), 2.76 (dd, 1H, J = 17.6, 7.3 Hz), 2.90 (dd, 1H, J = 17.9, 5.4 Hz), 2.98–3.12 (m, 3H), 3.29–3.33 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 6.76 (s, 2H).

5,8-Dimethoxy-3*R*-methyl-2*R*-dipropylamino-1,2,3,4-tetrahydronaphthalene [(−)-11]. Amine **9** (0.26 g, 0.99 mmol), propionaldehyde (.114 g, 0.142 mL, 1.97 mmol) and acetic acid (0.059 g, 0.057 mL, 0.99 mmol) were dissolved in acetonitrile (25 mL) and the mixture was stirred for 1 h at room temperature. Sodium cyanoborohydride (0.186 g, 2.96 mmol) was then added all at once. The suspension was stirred overnight at room temperature. The reaction was quenched with 2 N sodium hydroxide (∼20 mL) and extracted with ethyl acetate (2×25 mL). The combined extracts were dried ($MgSO_4$) and concentrated to an orange oil which was chromatographed over silica gel (10% ethyl acetate in hexane) to provide dipropyl amine (−)-**11** (0.271 g, 0.90 mmol, 90% yield) as a colorless oil. $[\alpha]_D = -121.7°$ (*c* 1.59, MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 0.88 (t, 6H, J = 7.4 Hz), 1.08 (d, 3H, J = 6.7 Hz), 1.40–1.53 (m, 4H), 1.72–1.85 (m, 1H), 2.11 (dd, 1H, J = 17.9, 7.6 Hz), 2.29–2.54 (m, 6H), 2.84–3.01 (m, 2H), 3.71 (s, 3H), 3.73 (s, 3H), 6.60 (s, 2H).

5,8-Dihydroxy-3*R*-methyl-2*R*-dipropylamino-1,2,3,4-tetrahydronaphthalene (−)-2. Dipropyl amine (−)-**11** was dissolved in 48% HBr (∼25 mL per gram of amine).

The solution was heated to reflux for 3 h. The reaction was concentrated under vacuum and the solid residue was crystallized from methanol/isopropanol or from acetonitrile to provide the hydroquinone (−)-**2** as the HBr salt (86% yield) as a slightly off-white powder. Mp 127–130 °C. $[\alpha]_D = -74.4°$ (*c* 1.00, MeOH). ^{1}H NMR (300 MHz, CD_3OD) δ 1.03 (t, 6H, $J = 7.3$ Hz), 1.21 (d, 3H, $J = 6.4$ Hz), 1.65–1.92 (m, 4H), 2.21–2.30 (m, 1H), 2.39 (dd, 1H, $J = 16.7$, 9.8 Hz), 2.85 (dd, 1H, $J = 16.8$, 9.9 Hz), 3.01–3.11 (m, 3H), 3.17–3.30 (m, 3H), 3.46–3.55 (m, 1H), 6.50 (s, 2H). Anal. calcd for $C_{17}H_{27}NO_2 \cdot HBr \cdot 0.8CH_3CN \cdot 0.2H_2O$: C, 56.59, H 7.86, Br 20.24, N 6.39. Found: C 56.96, H 7.60, Br 19.98, N 6.71.

Thioflavin T assay. A 2 mM solution of $A\beta_{1-42}$ (Palomar) in DMSO was prepared and filtered through a 0.2 μm nylon filter to remove fibrillar $A\beta_{1-42}$.[13] The $A\beta_{1-42}$ solution was then diluted to 114 μM in 10 mM HEPES, pH 7.4/0.02% NaN_3. Compounds were first diluted to 10 mM in DMSO and then diluted to 800 μM in 10 mM HEPES (pH 7.4) with 0.02% NaN_3. To each well of a 96-well microplate was added 70 μL of 114 μM $A\beta_{1-42}$ and 10 μL of 800 μM compound for a final concentration of 100 μM $A\beta_{1-42}$ and 100 μM compound. The plate was sealed and incubated at 37 °C. At various timepoints, 2 μL aliquots of the $A\beta_{1-42}$ incubations were then tested in the Thioflavin T assay. A 10 μM solution of Thioflavin T (Thio T, Sigma) in 100 mM glycine–NaOH, pH 8.6 was prepared and filtered through a 0.2 μm polyether sulfone filter. To each well of a 96-well microplate was added 18 μL H_2O, 2 μL $A\beta_{1-42}$ and 20 μL 10 μM Thio T solution. The plate was equilibrated for 3–5 min. Fluorescence at 485 nm was measured with an LJL Analyst (excitation at 450 nm, emission at 485 nm).

Crystal structure determination for (−)-9. A crystal of the salt [(−)-**9**][dibenzoyl-D-tartaric acid], obtained from EtOH, was mounted on a glass fibre and used for a room temperature X-ray structure determination. All measurements were made on a *Rigaku AFC5R* diffractometer using graphite-monochromated Mo K_α radiation ($\lambda = 0.71069$ Å) and a 12 kW rotating anode generator. The unit cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of 25 carefully centered reflections in the range $25° < 2\theta < 37°$. The $\omega/2\theta$ scan mode was employed for data collection, where the ω scan width was $(1.21 + 0.35 \tan\theta)°$ the ω scan speed was 16° min^{-1}. The weaker reflections [$I < 10\sigma(I)$] were rescanned up to a maximum of four scans and the counts were accumulated. Stationary background counts were recorded on each side of the reflection with a peak/background counting time ratio of 2:1. The structure was solved by direct methods using *SHELXS97*, which revealed the positions of all non-hydrogen atoms. ($C_{16}H_{26}NO_2^+$) ($C_{18}H_{13}O_8^-$), colourless, prism, monoclinic, space group *C*2, $T = 295$ K, $Z = 4$. Unit cell parameters: $a = 24.677$ (2) Å, $b = 8.428$ (3) Å, $c = 15.775$ (2) Å, $\alpha = 90°$, $\beta = 100.355$ (8) °, $\lambda = 90°$, $V = 3227$ (1) Å.[3]

References and Notes

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