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Synthesis and evaluation of a new class of tertiary alcohol based BACE-1 inhibitors

Francesco Russo, Fredrik Wångsell, Jonas Sävmarker, Micael Jacobsson, Mats Larhed *

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala University, BMC, Box 574, SE-751 23 Uppsala, Sweden

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ABSTRACT

BACE-1 has emerged as one of the best characterized targets for future Alzheimer therapy. In accordance with the successful identification of masked inhibitors of HIV-1 protease, we envisioned that *tert*-alcohol containing transition-state mimicking structures would also be worthwhile evaluating as BACE-1 inhibitors. Twelve novel inhibitors were prepared via synthetic routes using epoxyalcohol derivates as key intermediates. The best synthesized *tert*-hydroxy inhibitor exhibited a BACE-1 IC_{50} value of 0.38 μM.

1. Introduction

Alzheimer's disease (AD) is a dementia-inducing illness, characterized by a decline in cognitive function and progressive memory loss, leading ultimately to death.[1] AD is presently affecting up to 30 million people worldwide.[2] Currently there is no applicable treatment with a significant disease-modifying effect, and the available medications can only partially reduce the symptoms.[3] Two hallmarks for AD are accumulation and aggregation of insoluble extracellular amyloid plaques (Aβ), along with intracellular neurofibrillary tangles in the brain. The human aspartic protease BACE-1, identified and cloned in 1999,[4–8] has long been regarded as a therapeutic target for the reduction of Aβ formation. BACE-1 is the initial protease that process amyloid precursor protein (APP) in the pathway leading to Aβ and inhibition of this protease might be therapeutically useful.[9] The first X-ray crystal structure of BACE-1 and an inhibitor was published by Hong et al. in 2000.[10] Due to its similarity with other pharmaceutically interesting aspartic protease enzymes such as HIV-1 protease, renin, and malarial plasmepsins, the first generation of BACE-1 inhibitors were developed using the same transition-state (TS) mimicking approach.[11–16] By mimicking the natural tetrahedral intermediate with a non-cleavable TS isostere, the protease activity could be strongly reduced.[16] However, these inhibitors were mostly of high molecular weight, furnished low oral bioavailability, poor blood–brain barrier (BBB) penetration, and were susceptible to P-glycoprotein (P-gp) transport.[17] Further work toward improving the pharmacokinetic profile was conducted, and a second generation of improved BACE-1 inhibitors was reported.[14,16,18–22]

Inspired by successful applications in the design of HIV protease and renin inhibitors,[23,24] hydroxyethylamine isostere (HEA, **A**, Fig. 1) derivatives have been extensively evaluated for the preparation of novel BACE-1 inhibitors.[14] The 5-substituted isophthalimide inhibitor **I** reported by Stachel et al. (Fig. 2) served as the lead structure for this investigation.[25] Our previous experience with a *tert*-hydroxy

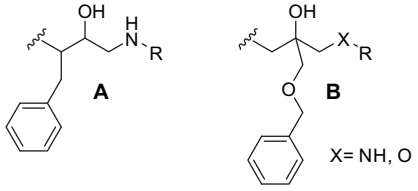

Figure 1. Example of the HEA TS-mimic (**A**) and *tert*-alcohol based TS-mimic (**B**).

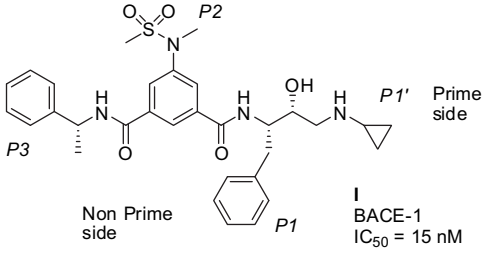

Figure 2. Schematic arrangement of the HEA inhibitor reported by Stachel et al.[25] in the active site of BACE-1.

* Corresponding author. Tel.: +46 18 471 4667; fax: +46 18 471 4474.
E-mail address: mats.larhed@orgfarm.uu.se (M. Larhed).

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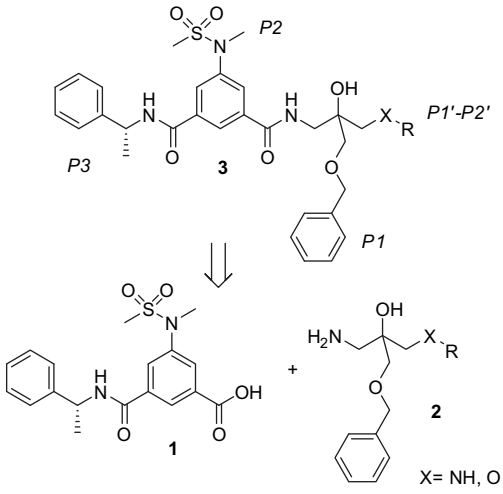
containing TS-mimic for HIV-1 protease inhibitors showed the possibility to retain high antiviral potency, while improving membrane permeability in the Caco-2 cell assay.[26,27] These findings inspired us to further evaluate the masked *tert*-alcohol concept by synthesizing analogues of the generic type **B** (Fig. 1). We herein report the preparation and evaluation of a series of BACE-1 inhibitors comprising a *tert*-alcohol functionality.

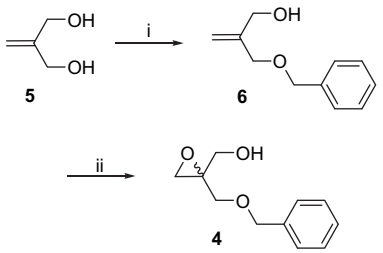
2. Results and discussion

The syntheses of *tert*-alcohol based BACE-1 inhibitors were accomplished by using the 5-substituted isophthalamic acid **1**[25] as the nonprime building block. Amide coupling of **1** to aminoalcohols **2**, containing different functional groups (–X–R), would afford inhibitors **3** encompassing various TS-mimics and prime side (–X–R) chains (Scheme 1).



Scheme 1. Retrosynthetic approach to the synthesis of *tert*-alcohol based BACE-1 inhibitors.

Thus, synthetic protocols for the preparation of a set of β-amino alcohols were developed. The primary amines **2** could be directly obtained from (2-benzyloxymethyloxiranyl)methanol (**4**) by elaboration of the hydroxy group to introduce the P1′–P2′ group[28] and subsequent ring opening with ammonia. The epoxyalcohol **4**, a key intermediate in the synthesis of the *tert*-alcohol inhibitors, was synthesized as depicted in Scheme 2.

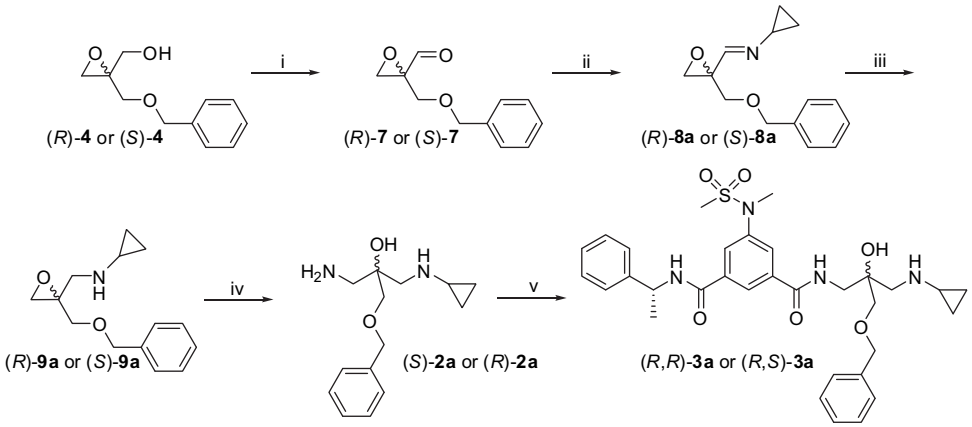


Scheme 2. Reagents and conditions: (i) NaH, THF, 0 °C, BnBr, TBAI, RT, 51%; (ii) (*R*)-**4** (Method A): D-(−)-DET, $Ti(O^iPr)_4$, ^tBuOOH, CH_2Cl_2, −20 °C, 59%, 95% ee; (*S*)-**4** (Method B): L-(+)-DET, $Ti(O^iPr)_4$, ^tBuOOH, CH_2Cl_2, −20 °C, 66%, 95% ee; (*R*,*S*)-**4** (Method C): *m*CPBA, CH_2Cl_2, RT, 91%.

The preparative route involved initial monobenzylation of the commercially available 2-methylene-1,3-propandiol **5** to obtain the benzyloxymethyl allylic alcohol **6**, followed by subsequent epoxidation. The synthesis was planned to allow access to both enantioenriched isomers (*R*)-**4** and (*S*)-**4** by enantioselective epoxidation[29,30] of the allylic alcohol (95% ee as established by chiral GC). After elaboration of the primary alcohol, ring opening with NH_3 followed by amide coupling with **1** gave the final compounds (*R*,*R*)-**3a** and (*R*,*S*)-**3a** with full control of the stereochemistry at the quaternary center (Scheme 3).

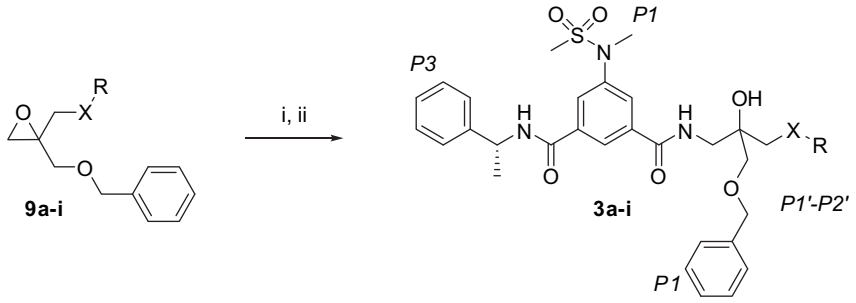
Oxidation of the hydroxyl group of enantioenriched (*R*)-**4** with Dess–Martin periodinane[31] furnished epoxyaldehyde (*R*)-**7**. Next, a stepwise reductive amination[32] was employed to introduce the cyclopropylamine group on the epoxide fragment ((*R*)-**9a**). Standard reductive amination using $NaBH(OAc)_3$[32] in THF was regardless if tried with classical or microwave heating,[33] not effective when cyclopropylamine was used. Epoxide ring opening with NH_3 gave the aminoalcohol (*S*)-**2a**, and a final amide coupling with acid **1** using (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) and *N*,*N*′-diisopropylethylamine (DIPEA) afforded the final *tert*-HEA compound (*R*,*R*)-**3a** as a pure stereoisomer. The corresponding epimer (*R*,*S*)-**3a** was synthesized in more than 95% de employing the identical protocol, starting from the enantioenriched epoxyalcohol (*S*)-**4** (Scheme 3).

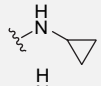
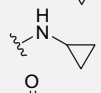
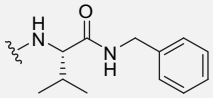
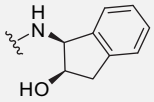
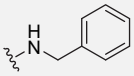
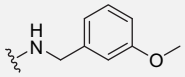
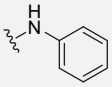
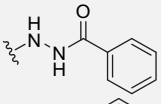
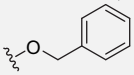
Unfortunately, both compounds (*R*,*R*)-**3a** and (*R*,*S*)-**3a** showed no inhibition in the BACE-1 assay[34] (Table 1, IC_{50}>10 μM). This first result prompted us to screen different P1′–P2′ groups in an attempt to achieve enzymatic inhibition. For this purpose we decided to synthesize and test the final inhibitors as epimeric mixtures, starting from the more easily accessible racemic epoxyalcohol **4** (Method C, Scheme 2). While the aminobenzylated valine epoxy derivative **9b** was generated via the stepwise reductive amination pathway from the epoxyaldehyde **7**, the aminoindanol epoxide



Scheme 3. Reagents and conditions: (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 83%; (ii) cyclopropylamine, THF, RT, quantitative yield; (iii) $NaBH_4$, MeOH, RT, 94%; (iv) aq NH_3, MeOH, RT, 94%; (v) **1**[25], PyBOP, DIPEA, CH_2Cl_2, RT, 23–34%.

Table 1
Synthesis and BACE-1 inhibition data for compounds **3a–i** and **19a–b**



From epoxide	P1′–P2′ group (–X–R)	Compound	Yield[g] (%)	IC_{50} (μM)
(*R*)-**9a**		(*R*)-**3a**[a]	30	>10
(*S*)-**9a**		(*S*)-**3a**[a]	20	>10
9b		**3b**[a,b]	29	>10
9c		**3c**[b,c]	17	>10
9d		**3d**[b,d]	40	7.2
9e		**3e**[b,d]	21	>10
9f		**3f**[b,d]	26	5.4
9g		**3g**[b,d]	18	>10
9h		**3h**[a]	54	6.4
9i		**3i**[b,e]	19	>10
—	—	**I**	—	0.015
—	—	**19a**[f]	—	3.5
—	—	**19b**[f]	—	0.38[h]

Reagents and conditions: (i) NH_3 (aq), MeOH, RT.
[a] (ii) **1**, PyBOP, DIPEA, CH_2Cl_2, RT.
[b] 50/50 epimeric mixture.
[c] (ii) **1**, HATU, DIPEA, CH_2Cl_2, RT.
[d] (ii) **1**, EDC, HOBt, CH_2Cl_2, RT.
[e] (ii) **1**, PyBOP, DIPEA, CH_2Cl_2, RT and subsequent desilylation: TBAF, THF, RT, 31%.
[f] Prepared according to Scheme 7.
[g] Two-step isolated yields.
[h] CatD K_i>5000 nM.

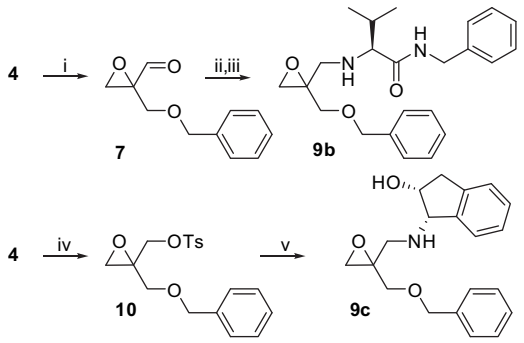
9c was obtained by nucleophilic substitution[35] of the alcohol-derived tosylate **10** with 1-aminoindan-2-ol in DMF using 5% KI (Scheme 4).

The series of the **9d–g** derivatives were directly obtained with the more convenient standard reductive amination protocol[32] utilizing the epoxyaldehyde **7** (Scheme 5).

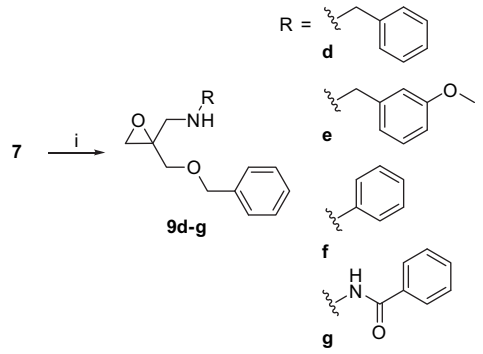
We were also interested in studying the BACE-1 inhibition of compounds lacking the NH group P1′ side. Hence the alternative benzyl ether **9h** and the TBDPS ether-protected epoxyalcohol **9i** were synthesized starting from the 2-methylene-1,3-propandiol **5** (Scheme 6).

The final compounds were prepared using the described protocol to ring open the epoxides **9b–i**, followed by coupling with **1** (Table 1). The amide bond formation was conducted with the described PyBOP protocol (**3b**, **3h**, **3i**) using *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(7-azabenzotriazol-1-yl)-uronium hexafluorophosphate (HATU) and DIPEA for the aminoindanol derivative **3c** or alternatively with the *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and *N*-hydroxybenzotriazole (HOBt) (**3d–g**).

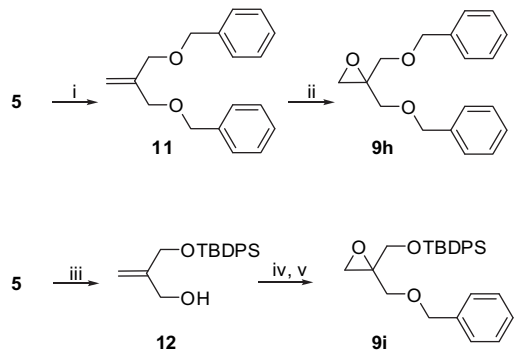
Two-step yields and enzyme inhibition data (BACE-1 IC_{50} values) for the inhibitors **3a–i** are summarized in Table 1. The highly



Scheme 4. Reagents and conditions: (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 83%; (ii) (*S*)-2-amino-*N*-benzyl-3-methylbutyramide,[36] THF, 55 °C, 70%; (iii) $NaBH_4$, MeOH, RT, 19%; (iv) TsCl, TEA, DMAP, CH_2Cl_2, RT, 81%; (v) (1*S*,2*R*)-1-aminoindan-2-ol; KI, DMF, RT, 33%.



Scheme 5. Reagents and conditions: (i) **9d**: $NaBH(OAc)_3$, benzylamine, DCE, RT, 64%; **9e**: $NaBH(OAc)_3$, *m*-methoxybenzyl amine, DCE, RT, 70%; **9f**: $NaBH(OAc)_3$, aniline, DCE, RT, 62%; **9g**: $NaBH(OAc)_3$, benzoic hydrazide, DCE, RT, 26%.



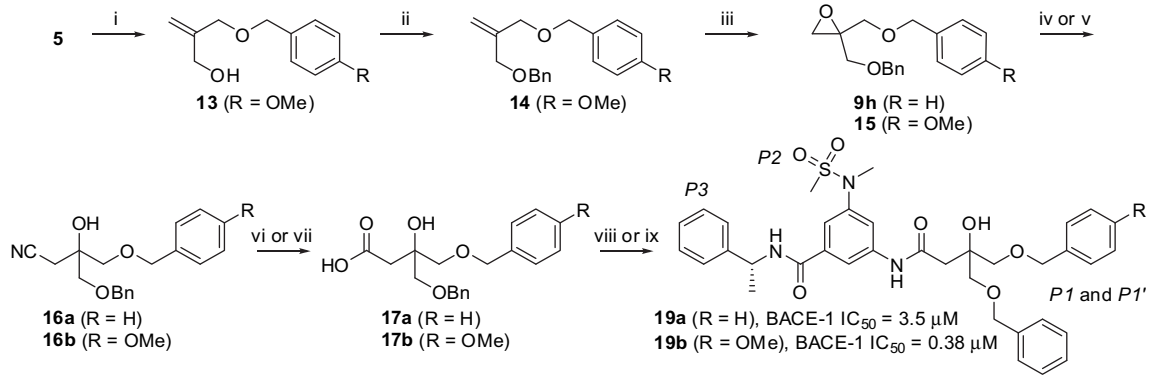
Scheme 6. Reagents and conditions: (i) NaH, THF, 0 °C and then BnBr, TBAI, RT, 20%;[37] (ii) *m*CPBA, CH_2Cl_2, RT, 97%; (iii) NaH, THF, 0 °C and then TBDPSCl, RT, quantitative yield; (iv) *m*CPBA, CH_2Cl_2, RT, 86%; (v) NaH, THF, 0 °C and then BnBr, TBAI, RT, 67%.

potent BACE-1 isophthalimide HEA-type inhibitor **I** is included as a reference compound.[25]

The new *tert*-alcohol compounds **3a**–**i** showed poor or no BACE-1 inhibition, with the most potent compound **3f** displaying an IC_{50} of 5.4 μM. Set against the high activity of **I**, the movement of the P1 group one atom toward the prime side with the retention of the same cyclopropylamine P1′ group in stereopure (*R*,*R*)-**3a** and (*R*,*S*)-**3a** led to complete loss of inhibition (Fig. 2 and Table 1). The presence of the benzyl-valine P1′–P2′ group as in **3b**, or the indanol residue as in **3c**, has been shown to enhance the inhibitors potency of BACE and other aspartic protease inhibitors,[14,38–40] but did not give the same positive result in the case of our *tert*-HEA based compounds. With the benzylamino P1′ in **3d**, it was possible to detect a low activity (IC_{50}=7.2 μM), although the *meta*-methoxy substitution[41,42] of the aromatic ring in **3e** again led to an inactive compound. The best inhibitory properties of the compounds **3a**–**i** were measured with aniline derivative **3f**, where the hydrophobic aromatic ring is positioned closer to the *tert*-alcohol moiety, by chain contraction of one atom. The possibility of additional polar interactions with the catalytic aspartates due to the presence of the hydrazide P1′ group[43–46] in **3g** (IC_{50}>10 μM) led to loss in activity. Changing the nature of the P1′ group to a benzylic ether, as in the stereopure compound **3h**, showed some activity, although still in the micromolar range (IC_{50}=6.4 μM). Whereas total removal of the P1′ side chain and inclusion of an additional primary alcohol,[47] as exemplified with **3i**, gave an inactive epimeric mixture.

To further evaluate the possibility to find active *tert*-alcohol based BACE-1 inhibitors, we decided to synthesize compounds comprising an inverted amide in the nonprime side of the final inhibitor (Scheme 7).

The key epoxy intermediates **9h** (Scheme 6) and **15** (Scheme 7) were synthesized in a similar fashion from the diol **5**. To synthesize **15** the diol **5** was monobenzylated with 4-methoxybenzyl bromide to render **13**, which in the next step was *O*-alkylated with benzyl bromide to furnish **14**. Epoxidation of the alkene **14** with *m*CPBA provided the corresponding epoxide **15** as a racemic mixture. The epoxide in **9h** and **15** was opened with cyanide as nucleophile[48] to give the corresponding hydroxy nitriles **16a** and **16b**. The nitrile groups were hydrolyzed[49] to obtain the acids **17a** and **17b**, and were thereafter coupled to **18** (3-amino-5-(methanesulfonylmethylamino)-*N*-((*R*)-1-phenylethyl)benzamide) by standard peptide chemistry to complete the synthesis of the final inverted amide inhibitors **19a** and **19b**. This relatively small structural change resulted in the slightly better inhibitor **19a**, containing two benzyl groups (IC_{50}=3.5 μM), and a ten-fold more potent inhibitor **19b**, in which the *para*-methoxy group was incorporated as the P1′ substituent (IC_{50}=0.38 μM, CatD[34] K_i> 5000 nM). Efforts were made to synthesize the corresponding *di*-methoxy analog but the synthesis failed in the final amide coupling.



Scheme 7. Reagents and conditions: (i) NaH, THF, 0 °C and then PMBBr, TBAI, RT, 55%; (ii) NaH, THF, 0 °C and then BnBr, TBAI, RT 85%; (iii) *m*CPBA, CH_2Cl_2, RT, 79%; (iv) NaCN, $LiClO_4$, MeOH, 60 °C, 71%; (v) KCN, $LiClO_4$, CH_3CN; 60 °C, 59%; (vi) KOH, H_2O_2 (aq), MeOH, reflux, 96%; (vii) 1 M NaOH (aq), reflux, 44%; (viii) **18**, HATU, DIPEA, DMF, RT, 65%; (ix) **18**, EDC, HOBt, CH_2Cl_2, RT, 20%.

3. Conclusions

The development of novel BACE-1 inhibitors encompassing new TS isosteres that address both high potency, and improved pharmacokinetic and pharmaceutical properties continue to be an ongoing challenge. In this investigation a number of epoxyalcohol derivatives were used as key building blocks in a novel synthetic strategy for the preparation of BACE-1 protease inhibitors containing a shielded *tert*-alcohol in the TS-mimicking scaffold. The synthetic methodology was utilized to introduce different substituents in the prime side of twelve new inhibitors. The inverted amide compound **19b** exhibited the best inhibitory properties for the BACE-1 enzyme in this series with an IC_{50} value of 0.38 μM.

4. Experimental

4.1. General

Analytical reverse-phase electrospray LC–MS was performed on a Gilson HPLC system with a Finnigan AQA quadropole mass spectrometer using a Chromolith Performance RP-18e 4.6×100 mm (Merck KGaA) column, with a gradient of CH_3CN in 0.05% aqueous HCOOH as mobile phase at a flow rate of 4 mL/min. Preparative reverse-phase LC–MS was done under similar conditions but using a Zorbax SB-C8, 5 μm 21.2×150 mm (Agilent technologies) column, at a flow rate of 15 mL/min. Purification by flash column chromatography[50] was performed on Merck silica gel 60 (40–63 μm). Analytical thin layer chromatography was carried out using aluminum sheets precoated with silica gel 60 F_{254}. Optical rotations were obtained on a Perkin–Elmer 241 polarimeter. Specific rotations ($[\alpha]_D^T$) are reported in deg/dm, and the concentration (c) is given as g/100 mL in the specified solvent. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury Plus instruments; ^1H at 399.9 MHz and ^{13}C at 100.6 MHz or ^{13}C at 100.5 MHz. Chemical shifts are reported as δ values (ppm) indirectly referenced to TMS by the solvent residual signal. Coupling patterns are described by abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), b (broad). Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden, or Analytische Laboratorien, Lindlar, Germany. Exact molecular masses were determined on Micromass Q-Tof2 mass spectrometer equipped with an electrospray ion source. Standard GC–MS was performed on an instrument equipped with a CP-Sil 8 CB capillary column (30 m×0.25 mm, 0.25 μm) operating at an ionization energy of 70 eV; the oven temperature was 40–300 °C. Chiral GC–MS was performed on the same instrument but equipped with a HYDRODEX®-β-6TBDMS capillary column (25 m×0.25 mm) conducted at isothermal condition (T=130 °C).

4.2. BACE-1 assay[34]

The BACE-I enzyme assay is based on a homogeneous TRF (time resolved fluorescence) technique (Perkin Elmer). The used substrate is the 'Swedish' mutant sequence (Eu-CEVNLDAEFK-QSY7) coupled to a fluorescent europium chelate, and a quencher QSY 7. β-Secretase (recombinant human BACE-1) was produced by Medivir AB, Huddinge, Sweden. The BACE-1 activity was measured by the increase of the Eu signal.

4.3. Materials

All chemicals were purchased from commercial suppliers and used directly without further purification. Tetrahydrofuran was obtained anhydrous by distillation over sodium wire, after the characteristic blue color of in situ generated sodium diphenylketyl[51] was found to persist. Methylene chloride was dried over calcium hydride.

*4.3.1. 1,1-Bisbenzyloxymethylethylene (11)[52] and 2-benzyloxymethyl-prop-2-en-1-ol (**6**)[53].* Under a nitrogen atmosphere, NaH (60% in mineral oil, 0.45 g, 11.3 mmol) was added to a solution of 2-methylene-1,3-propandiol (1.00 g, 11.3 mmol) in anhydrous THF (35 mL) cooled at 0 °C. After 30 min, benzyl bromide (1.34 mL, 11.3 mmol) and tetrabutylammonium iodide (208 mg, 0.56 mmol, 5 mol %) were added, and the mixture stirred for 3 h at RT, then cooled at 0 °C, quenched with ice/water (20 mL) and extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification by flash column chromatography (isohexane/ethyl acetate 10:1, then 1:1) afforded the di-ether **11** (613 mg, 2.3 mmol; yield 20%; colorless oil) and the mono-ether **6** (1.03 g, 5.8 mmol; yield 51%; colorless oil). **11**: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.27 (10H, m); 5.27 (2H, s); 4.52 (4H, s); 4.08 (4H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ:142.6; 138.3; 128.4; 127.7; 127.6; 114.3; 72.2; 70.9. LC–MS m/z (%): 537.3 (8, 2M+H^+), 269.1 (100, M+H^+), HRMS Calcd for m/z $C_{18}H_{20}O_2$+H^+: 269.1536. Found: 269.1542. **6**: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.27 (5H, m); 5.21 (1H, m, A of AB); 5.16 (1H, m, B of AB); 4.53 (2H, s); 4.21 (2H, d, J=5.8 Hz); 4.10 (2H, s); 1.89 (1H, t, J=5.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.0; 137.9; 128.4; 127.7; 127.6; 113.6; 72.3; 71.8; 64.7. LC–MS m/z (%): 357.2 (84, 2M+H^+), 179.1 (100, M+H^+), HRMS Calcd for m/z $C_{11}H_{14}O_2$+H^+: 179.1067. Found: 179.1072.

*4.3.2. (2-Benzyloxymethyloxiranyl)methanol (**4**)[30].* *m*CPBA (70% in water, 2.14 g, 8.7 mmol) was added to a solution of **6** (1.03 g, 5.8 mmol) in 20 mL of CH_2Cl_2. After stirring for 4 h at RT, the mixture was cooled to −20 °C, filtered through Celite® and washed with cold CH_2Cl_2. The filtrate was washed with saturated $Na_2S_2O_3$ (aq) and saturated $NaHCO_3$ (aq) and dried over anhydrous Na_2SO_4. Evaporation gave the epoxyalcohol **4** (1.02 g, yield 91%) as a colorless oil, which was then used for the next reaction without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.28 (5H, m); 4.57 (2H, AB, $\Delta\nu$=17.3 Hz, J=11.9 Hz); 3.84 (2H, AB, $\Delta\nu$=62.3 Hz, J=12.3 Hz); 3.66 (2H, AB, $\Delta\nu$=20.4 Hz, J=11.0 Hz); 2.90 (1H, d, J=4.8 Hz); 2.77 (1H, d, J=4.8 Hz); 1.93 (1H, bs). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.6; 128.4; 127.8; 127.6; 73.4; 70.7; 62.1; 58.5; 48.7. LC–MS m/z (%): 389.2 (100, 2M+H^+); 195.1 (48, M+H^+). GC–MS m/z (%): 163 (0.2); 145 (3); 107 (71); 91 (100, $PhCH_2^+$); 79 (52); 65 (24).

*4.3.3. ((S)-2-Benzyloxymethyloxiranyl)methanol ((S)-**4**)[30].* Under a nitrogen atmosphere, activated powdered molecular sieves 4 Å (20 mg) were slurried in 0.5 mL of CH_2Cl_2. To the cooled (−10 °C) mixture were added (L)-(+)-DET (17 mg, 0.08 mmol) in 2 mL of CH_2Cl_2, $Ti(O^iPr)_4$ (19 μL, 0.06 mmol), and ^{t}BuOOH (0.38 mL of a 5.5 M decane solution, dried over molecular sieves 4 Å 2.09 mmol) under stirring. After 30 min at −10 °C, the mixture was cooled to −45 °C, and allylic alcohol **6** (149 mg, 0.84 mmol) in 2 mL of CH_2Cl_2 was added. The reaction temperature was allowed to reach −20 °C. After 17 h, water (1 mL) was added, and the mixture was stirred 30 min at RT, then cooled again to 0 °C and 30% aqueous NaOH saturated with NaCl (2 mL) was added. After stirring for 10 min the mixture was filtered through a Celite® pad, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4. Evaporation of solvent and purification by flash chromatography (isohexane/ethyl acetate 2:1) gave the epoxy alcohol (*S*)-**4** (108 mg, yield 66%) as a colorless oil. $[\alpha]_D^{25}$ −13.3 (c 1.50 in CH_2Cl_2); ee 95% (by chiral GC–MS), HRMS Calcd for m/z $C_{11}H_{14}O_3$+H^+: 195.1016. Found: 195.1021.

*4.3.4. ((R)-2-Benzyloxymethyloxiranyl)methanol ((R)-**4**)[30].* The same procedure as (*S*)-**4** was utilized, using (D)-(−)-DET as the chiral auxiliary. 91 mg (yield 56%) of (*R*)-**4** was obtained as a colorless oil after purification. $[\alpha]_D^{25}$ +12.9 (c 1.08 in CH_2Cl_2); ee 95% (by chiral GC–MS).

4.3.5. 2-Benzyloxymethyloxirane-2-carbaldehyde (7), (S)-2-benzyloxymethyloxirane-2-carbaldehyde ((S)-7) and (R)-2-benzyloxymethyloxirane-2-carbaldehyde ((R)-7). Dess–Martin periodinane[31] (2.47 g, 5.8 mmol) was added to a cooled (0 °C) solution of epoxyalcohol **4** ((*S*)-**4**, (*R*)-**4**), (1.025 g, 5.3 mmol) in 18 mL of anhydrous CH_2Cl_2. The mixture was stirred at RT for 2 h, then Et_2O (20 mL), saturated $NaHCO_3$ (aq, 10 mL) and saturated $Na_2S_2O_3$ (aq, 10 mL) were added. The organic layer was separated, washed with brine and dried over Na_2SO_4. Removal of the solvent and purification by flash chromatography (isohexane/ethyl acetate 3:1) afforded 850 mg (yield 83%) of the desired aldehyde **7** ((*S*)-**7**, (*R*)-**7**) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, s); 7.38–7.27 (5H, m); 4.58 (2H, AB, $\Delta\nu$=5.7 Hz, J=12.1 Hz); 3.92 (2H, AB, $\Delta\nu$=35.8 Hz, J=11.8 Hz); 3.25 (1H, d, J=5.1 Hz); 3.07 (1H, d, J=5.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.7; 137.5; 128.5; 127.9; 127.8; 73.8; 65.5; 60.6; 47.7. LC–MS *m*/*z* (%): 385.1 (100, 2M+H$^+$); 193.1 (12, M+H$^+$).

*4.3.6. [1-((S)-2-Benzyloxymethyloxiranyl)methylidene]-cyclopropylamine ((S)-8a) and [1-((R)-2-benzyloxymethyloxiranyl)methylidene] cyclopropylamine ((R)-**8a**).* Under a nitrogen atmosphere, cyclopropylamine (346 μL, 5.01 mmol) was added to (*S*)-**7** ((*R*)-**7**) (320 mg, 1.67 mmol) in anhydrous THF (10 mL), and the mixture stirred for 45 min at RT. Removal of the solvent afforded the corresponding imine (*S*)-**8a** ((*R*)-**8a**) (386 mg, quantitative) as a yellow oil, used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (1H, s); 7.36–7.27 (5H, m); 4.58 (2H, AB, $\Delta\nu$=12.6 Hz, J=12.1 Hz); 3.93 (2H, AB, $\Delta\nu$=30.3 Hz, J=11.7 Hz); 3.19 (1H, d, J=5.4 Hz); 2.90 (1H, d, J=5.4 Hz); 2.89–2.85 (1H, m); 0.88–0.82 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.6; 138.1; 128.3; 127.6; 127.5; 73.4; 67.8; 58.0; 49.7; 41.4; 8.6; 8.5. LC–MS *m*/*z* (%): 232.1 (100, M+H$^+$).

*4.3.7. ((S)-2-Benzyloxymethyloxiranylmethyl)-cyclopropylamine (S)-**9a** and ((R)-2-benzyloxymethyloxiranylmethyl)cyclopropylamine ((R)-**9a**).* $NaBH_4$ (94 mg, 2.47 mmol) was added to a stirred solution of imine (*S*)-**8a** ((*R*)-**8a**) (380 mg, 1.64 mmol) in 8.5 mL of MeOH at RT. After 1 h the reaction was quenched by adding 5 mL of 1 M NaOH (aq). The aqueous layer was extracted with Et_2O, and the combined organic phases were washed with brine and dried over Na_2SO_4. Evaporation of the solvent provided the desired epoxy amine (*S*)-**9a** ((*R*)-**9a**) (360 mg, yield 94%) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.27 (5H, m); 4.56 (2H, AB, $\Delta\nu$=12.9 Hz, J=12.0 Hz); 3.62 (2H, AB, $\Delta\nu$=16.8 Hz, J=11.0 Hz); 2.97 (2H, AB, $\Delta\nu$=27.7 Hz, J=13.0 Hz); 2.77 (2H, AB, $\Delta\nu$=22.5 Hz, J=4.9 Hz); 2.13 (1H, tt, J=6.6, 3.4 Hz); 1.70 (1H, bs); 0.44–0.39 (2H, m); 0.32–0.27 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9; 128.4; 127.7; 127.6; 73.3; 71.2; 58.0; 50.5; 49.6; 30.5; 6.6; 6.3. LC–MS *m*/*z* (%): 234.1 (100, M+H$^+$). GC–MS *m*/*z* (%): 234 (8, M$^+$+1); 204 (3); 126 (10); 107 (11); 98 (26); 91 (100, $PhCH_2^+$); 70 (30). (*S*)-**9a**: $[\alpha]_D^{25}$ −10.0 (*c* 1.05 in CH_2Cl_2); ee 95% (by chiral GC–MS). (*R*)-**9a**: $[\alpha]_D^{25}$ +9.8 (*c* 0.98 in CH_2Cl_2); ee 95% (by chiral GC–MS).

*4.3.8. (R)-1-Amino-3-benzyloxy-2-cyclopropylaminomethylpropan-2-ol (R)-**2a** and (S)-1-amino-3-benzyloxy-2-cyclopropylaminomethylpropan-2-ol ((S)-**2a**).* To a solution of (*S*)-**9a** ((*R*)-**9a**) (360 mg, 1.55 mmol) in MeOH (28 mL) was added 25% aqueous NH_3 (28 mL). The mixture was stirred overnight at RT. After removal of the solvent under reduced pressure, the residue was suspended in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave the corresponding aminoalcohol (*R*)-**2a** ((*S*)-**2a**) (343 mg, yield 88%) used for the coupling reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.28 (5H, m); 4.55–4.50 (1H, m); 4.52 (2H, s); 3.36 (2H, AB, $\Delta\nu$=18.3 Hz, J=9.3 Hz); 2.76 (2H, AB, $\Delta\nu$=60.6 Hz, J=12.0 Hz); 2.72 (2H, AB, $\Delta\nu$=47.0 Hz, J=12.9 Hz); 2.14 (1H, tt, J=6.6, 3.5 Hz); 1.60 (3H, bs); 0.45–0.37 (2H, m); 0.33–0.22 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.2; 128.4; 127.7; 127.6; 73.9; 73.5; 72.0; 53.4; 46.4; 30.9; 6.6; 6.5. LC–MS *m*/*z* (%): 251.0 (100, M+H$^+$).

*4.3.9. 5-(Methanesulfonylmethylamino)-N-(R-1-phenyl-ethyl)-isophthalamic acid (**1**)[25].* Synthesis was performed according to the literature procedure, replacing BOP with PyBOP in the amide coupling.

*4.3.10. N-((S)-3-Benzyloxy-2-cyclopropylaminomethyl-2-hydroxy propyl)-5-(methanesulfonylmethylamino)-N′-((R)-1-phenyl-ethyl)isophthalamide ((R,S)-**3a**).* To a solution of (*R*)-**2a** (57 mg, 0.23 mmol) and **1** (85 mg, 0.23 mmol) in CH_2Cl_2 (2.5 mL) were added, under a nitrogen atmosphere, DIPEA (137 μL, 0.78 mmol) and PyBOP (175 mg, 0.33 mmol). The mixture was stirred at RT for 24 h, then the solvent was removed under reduced pressure, and the residue purified by short column flash chromatography (ethyl acetate). Further purification by preparative LC provided the pure compound (*R*,*S*)-**3a** (32 mg, yield 23%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (1H, dd, J=1.5, 1.5 Hz); 7.99 (1H, dd, J=2.0, 1.5 Hz); 7.92 (1H, dd, J=2.0, 1.5 Hz); 7.65 (1H, bt, J=4.5 Hz); 7.41–7.25 (10H, m); 6.92 (1H, bd, J=7.2 Hz); 5.32 (1H, dq, J=7.2, 7.0 Hz); 4.73 (1H, bs); 4.55 (2H, AB, $\Delta\nu$=6.4 Hz, J=12.0 Hz); 3.61–3.51 (2H, m); 3.45 (2H, AB, $\Delta\nu$=13.4 Hz, J=9.4 Hz); 3.34 (3H, s); 2.87 (2H, AB, $\Delta\nu$=30.8 Hz, J=12.4 Hz); 2.84 (3H, s); 2.85–2.83 (1H, bs); 2.17 (1H, tt, J=6.6, 3.6 Hz); 1.61 (3H, d, J=7.0 Hz); 0.50–0.32 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.4; 164.5; 142.8; 142.3; 137.4; 135.9; 135.5; 128.8; 128.6; 128.1; 127.9; 127.8; 127.6; 127.5; 126.3; 123.8; 74.6; 73.8; 71.7; 53.3; 49.7; 45.5; 37.9; 35.5; 31.0; 21.6; 6.2; 6.1. LC–MS *m*/*z* (%): 609.4 (100, M+H$^+$). $[\alpha]_D^{24}$ −17.6 (*c* 0.085 in CH_2Cl_2). Anal. Calcd for $C_{32}H_{40}N_4O_6S\times 2/3H_2O$: C, 61.92; H, 6.71; N, 9.03. Found: C, 61.80; H, 6.82; N, 8.83. BACE-1 (TRF) IC_{50}>10 μM.

*4.3.11. N-((R)-3-Benzyloxy-2-cyclopropylaminomethyl-2-hydroxy propyl)-5-(methanesulfonylmethylamino)-N′-((R)-1-phenyl-ethyl)-isophthalamide ((R,R)-**3a**).* Under nitrogen atmosphere, DIPEA (186 μL, 1.1 mmol) and PyBOP (238 mg, 0.46 mmol) were added to a solution of (*S*)-**2a** (76 mg, 0.30 mmol) and **1** (115 mg, 0.30 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at RT for 18 h then the solvent was removed under reduced pressure, and the residue purified by short column flash chromatography (ethyl acetate). Further purification by preparative LC provided the pure compound (*R*,*R*)-**3a** (63 mg, yield 34%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, bs); 8.46 (1H, m); 8.05 (1H, dd, J=2.0, 1.4 Hz); 8.02 (1H, dd, J=2.0, 1.4 Hz); 7.58 (1H, bd, J=7.2 Hz); 7.46–7.20 (10H, m); 5.28 (1H, dq, J=7.2, 7.0 Hz); 4.56 (2H, s); 3.66–3.55 (3H, m); 3.58 (2H, s); 3.33 (3H, s); 3.14–3.10 (1H, m); 3.12 (2H, s); 2.85 (3H, s); 2.37 (1H, tt, J=6.8, 3.8 Hz); 1.63 (3H, d, J=7.0 Hz); 0.81–0.63 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0; 164.5; 143.5; 142.4; 136.7; 135.8; 134.3; 128.8; 128.7; 128.5; 128.4; 128.3; 128.1; 127.2; 126.4; 124.0; 75.6; 74.1; 71.8; 53.8; 50.0; 45.1; 37.9; 35.8; 31.7; 22.0; 4.8; 4.6. LC–MS *m*/*z* (%): 609.1 (100, M+H$^+$). $[\alpha]_D^{24}$ −39.0 (*c* 0.1 in CH_2Cl_2). Anal. Calcd for $C_{32}H_{40}N_4O_6S\times 2H_2O\times HCOOH$: C, 57.38; H, 6.71; N, 8.11. Found: C, 56.96; H, 6.62; N, 8.01. BACE-1 (TRF) IC_{50}>10 μM.

*4.3.12. (S)-2-Amino-N-benzyl-3-methylbutyramide; hydrochloride (**S1**).* ((*S*)-1-Benzylcarbamoyl-2-methyl-propyl)carbamic acid *tert*-butyl ester[54] (50 mg, 0.16 mmol) was slowly added to a 4 M HCl/dioxane solution[55] (1 mL) under a nitrogen atmosphere. After stirring for 1 h at RT, the solvent was removed under reduced pressure to afford 39 mg (quantitative yield) of **S1** as a white solid, which was used in the next reaction without further purification. ^{1}H NMR (400 MHz, D_2O) δ: 7.46–7.34 (5H, m); 4.44 (2H, AB, $\Delta\nu$=54.6 Hz, J=15.0 Hz); 3.82 (1H, d, J=6.0 Hz); 2.22 (1H, septd, J=6.9, 6.0 Hz); 1.01 (3H, d, J=6.9); 1.00 (3H, d, J=6.9).

*4.3.13. (S)-2-Amino-N-benzyl-3-methylbutyramide (**S2**)*[36]. To a suspension of **S1** (30 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (1 mL), zinc powder[56] (12 mg, 0.18 mmol) was added under a nitrogen atmosphere. The mixture was stirred for 10 min at RT, filtered, and the solvent evaporated, to give 22 mg (yield 88%) of valine derivative **S2** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (1H, bm); 7.25–7.16 (5H, m); 4.31 (2H, AB of ABX, $\Delta\nu$=100.5 Hz, J=14.6, 6.3, 4.3 Hz); 4.18 (1H, bm); 2.28 (1H, septd, J=6.5, 6.2 Hz); 2.00 (2H, bs); 1.00 (3H, d, J=6.5); 0.96 (3H, d, J=6.5). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.6; 137.6; 128.6; 127.8; 127.4; 58.9; 43.6; 30.3; 18.4; 18.3. LC–MS m/z (%): 207.1 (100, M+H$^+$). $[\alpha]_D^{26}$ −27.6 (c 1.03 in CH_2Cl_2).

*4.3.14. S)-N-Benzyl-2-{[1-((S,R)-2-benzyloxymethyloxiranyl)methylidene]amino}-3-methylbutyramide (**8b**).* Under a nitrogen atmosphere, (*S*)-2-Amino-*N*-benzyl-3-methylbutyramide **S2** (54 mg, 0.26 mmol) was added to **7** (50 mg, 0.26 mmol) in anhydrous THF (3 mL), and the mixture stirred over night at 55 °C. Then H_2O (3 mL) and Et_2O (3 mL) were added, and the organic phase was washed with brine, dried over Na_2SO_4, and the solvent removed under reduced pressure to give the corresponding imine **8b** (yellow oil) as a 50/50 epimeric mixture (69 mg, yield 70%), used for the next step without further purification. LC–MS m/z (%) (one peak): 381.1 (100, M+H$^+$).

*4.3.15. (S)-N-Benzyl-2-[((S,R)-2-benzyloxymethyloxiranyl-methyl)-amino]-3-methylbutyramide (**9b**).* $NaBH_4$ (10 mg, 0.27 mmol) was added to a stirred solution of the 50/50 epimeric mixture **8b** (69 mg, 0.18 mmol) in 2 mL of MeOH. After 3 h the reaction was quenched by the addition of 2 mL of 1 M NaOH (aq). The aqueous layer was extracted with Et_2O, and the combined organic phases were washed with brine and dried over Na_2SO_4. Evaporation of the solvent and flash column purification (isohexane/ethyl acetate 1:1) provided **9b** (colorless oil) as a 50/50 epimeric mixture (13 mg, yield 19%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 and 7.47 (1H, bs and bs); 7.35–7.21 (10H, m); 4.60–4.32 (4H); 3.56 and 3.55 (2H, AB, $\Delta\nu$=95.3 Hz, J=11.0 Hz and AB, $\Delta\nu$=94.6 Hz, J=10.9 Hz); 2.97–2.63 (5H, m); 2.12 (1H, bm); 1.64 (1H, bs); 0.98 and 0.89 (3H, d, J=7.3 Hz and d, J=6.9 Hz); 0.96 and 0.86 (3H, d, J=7.1 Hz and d, J=6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.3 and 173.1; 138.7 and 138.6; 137.6 and 137.5; 128.6; 128.5 and 128.4; 127.9 and 127.8; 127.7; 127.6; 127.3; 73.4 and 73.3; 72.0 and 71.0; 68.5 and 68.4; 57.7 and 57.6; 50.8 and 50.1; 49.9 and 49.4; 43.0 and 42.9; 31.4; 19.6 and 17.8; 19.5 and 17.7. LC–MS m/z (%) (one peak): 383.0 (100, M+H$^+$). GC–MS m/z (%): Rt 6.67 min: 325 (1); 191 (1); 129 (1); 107 (100, BnO$^+$); 105 (21, BnN$^+$); 91 (94, Bn$^+$); 79 (78); 77 (52); 65 (33). Rt 7.09 min: 267 (1); 191 (4); 107 (32, BnO$^+$); 105 (26, BnN$^+$); 91 (100, Bn$^+$), 79 (38); 77 (24); 65 (25). HRMS Calcd for m/z $C_{23}H_{30}N_2O_3$+H$^+$: 383.2329. Found: 383.2335.

*4.3.16. (S)-2-((R,S)-3-Amino-2-benzyloxymethyl-2-hydroxypropylamino)-N-benzyl-3-methylbutyramide (**2b**).* To the 50/50 epimeric mixture **9b** (11 mg, 0.03 mmol) in MeOH (0.6 mL) was added 25% aqueous NH_3 (0.6 mL). The mixture was stirred for 18 h at RT. After removal of the solvent under reduced pressure, the residue was solubilized in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave 10 mg (yield 83%) of the corresponding amino-alcohol **2b** as 50/50 epimeric mixture confirmed by LC–MS and used for the coupling reaction without further purification. LC–MS m/z (%) (one peak): 400.1 (44, M+H$^+$); 241.7 (49); 221.2 (100).

*4.3.17. N-{(S,R)-2-[((S)-1-Benzylcarbamoyl-2-methyl-propylamino)-methyl]-3-benzyloxy-2-hydroxypropyl}-5-(methanesulfonylmethyl-amino)-N′-((R)-1-phenylethyl)-isophthalamide (**3b**).* Under a nitrogen atmosphere, DIPEA (18 μL, 0.105 mmol) and PyBOP (19 mg, 0.036 mmol) were added to a solution of 50/50 epimeric mixture **2b** (12 mg, 0.03 mmol) and **1** (13 mg, 0.033 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at RT, and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 18 h, the solvent was removed under reduced pressure, and the residue purified by flash column chromatography (ethyl acetate). Subsequent preparative LC purification afforded a 50/50 epimeric mixture of **3b** (8.0 mg, yield 35%) as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 9.00 (1H, d, J=7.4); 8.45 (1H, bm); 8.39 (1H, bm); 8.27 and 8.26 (1H, dd, J=1.5, 1.4 Hz and t, J=1.5 Hz); 8.02–7.97 (2H, m) 7.42–7.16 (15H, m); 5.19 (1H, dq, J=7.4, 7.0 Hz); 4.86 (1H, bs); 4.49 and 4.48 (2H, s and s); 4.33–4.24 (2H, m); 3.53–3.39 (4H, m); 3.29 and 3.28 (3H, s and s); 3.01 and 3.00 (3H, s and s); 2.73 and 2.71 (1H, d, J=6.0 Hz and d, J=6.0 Hz); 2.61 (2H, AB, $\Delta\nu$=7.2 Hz, J=12.0 Hz); 2.04–1.97 (1H, m); 1.80 (1H, bs); 1.50 (3H, d, J=7.0 Hz); 0.86 and 0.84 (3H, d, J=6.8 Hz and d, J=6.9 Hz); 0.83 and 0.82 (3H, d, J=6.8 Hz and d, J=6.7 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 173.38 and 173.29; 165.6; 164.0; 146.2; 144.5; 141.4; 139.3; 138.2; 138.0; 128.0;127.9; 127.8; 127.2; 127.0; 126.9; 126.8; 126.5; 125.8; 127.5; 127.3; 124.7; 73.2; 72.4 and 72.3; 68.3; 52.6 and 52.2; 48.3; 44.2; 41.7; 37.4; 35.8; 35.3; 30.9; 21.8; 19.3; 18.4. LC–MS m/z (%) (one peak): 758.4 (100, M+H$^+$). HRMS Calcd for $C_{41}H_{51}N_5O_7S$+H$^+$: 758.3587. Found: 758.3588. BACE-1 (TRF) IC_{50}>10 μM.

*4.3.18. (1S,2R)-1-{[1-((S,R)-2-Benzyloxymethyloxiranyl)-methylidene]amino}indan-2-ol (**8c**).* Under a nitrogen atmosphere, (1*S*,2*R*)-1-amino-indan-2-ol (48 mg, 0.32 mmol) was added to **7** (58 mg, 0.30 mmol) in anhydrous THF (2 mL), and the mixture stirred 45 min at RT. Removal of the solvent and flash chromatography purification (isohexane/ethyl acetate 2:1) afforded the corresponding imine **8c** (yellow oil) as a 50/50 epimeric mixture (95 mg, yield 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.39 (1H, m); 7.35–7.10 (9H, m); 4.94 and 4.78 (1H, d, J=5.4 Hz and d, J=5.3 Hz); 4.69 and 4.62 (1H, td, J=5.4, 1.6 Hz and td, J=5.3, 1.9 Hz); 4.55 and 4.52 (2H, AB, $\Delta\nu$=6.7 Hz, J=11.9 Hz and AB, $\Delta\nu$=17.8 Hz, J=12.0 Hz); 4.32 and 4.21 (1H, bs and bs); 3.78 and 3.68 (2H, AB, $\Delta\nu$=16.4 Hz, J=11.2 Hz and AB, $\Delta\nu$=54.7 Hz, J=11.2 Hz); 3.21–3.05 (2H, m); 2.92 and 2.84 (2H, AB, $\Delta\nu$=61.0 Hz, J=5.4 Hz and AB, $\Delta\nu$=4.6 Hz, J=5.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.1; 142.42 and 142.36; 138.0 and 137.9; 136.45 and 136.38; 128.45 and 128.41; 128.36 and 128.34; 127.82 and 127.74; 127.72 and 127.69; 127.17 and 127.15; 125.85 and 125.79; 124.85 and 124.79; 73.8 and 73.7; 70.4 and 70.1; 69.5; 68.5 and 68.3; 57.7; 50.0 and 49.3; 39.3. LC–MS m/z (%): t_R 1.54 min: 324.1 (100, M+H$^+$). t_R=1.73 min: 324.1 (100, M+H$^+$). GC–MS m/z (%) (one peak): 324 (3); 294 (2); 187 (3); 160 (100); 115 (87); 103 (11); 91 (44); 77 (20); 65 (18).

*4.3.19. Toluene-4-sulfonic acid 2-benzyloxymethyloxiranylmethyl ester (**10**).* Triethylamine (107 μL, 0.77 mmol), DMAP (5.0 mg, 0.04 mmol), and *p*-toluenesulfonyl chloride (147 mg, 0.77 mmol) were added to a solution of **4** (150 mg, 0.77 mmol) in anhydrous CH_2Cl_2 (4 mL). The mixture was stirred for 5 h at RT under nitrogen atmosphere and then quenched by the addition of water (4 mL) and Et_2O (4 mL). The organic layer was washed with satd NH_4Cl (aq), brine and dried over Na_2SO_4. Evaporation of the solvent and purification by flash chromatography (isohexane/ethyl acetate 5:1, then 2:1) afforded 216 mg (yield 81%) of the desired tosyl epoxyalcohol **10** (colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (2H, d, J=8.4); 7.36–7.24 (7H, m); 4.48 (2H, AB, $\Delta\nu$=13.4 Hz, J=11.9 Hz); 4.18 (2H, AB, $\Delta\nu$=28.9 Hz, J=10.9 Hz); 3.58 (2H, AB, $\Delta\nu$=33.5 Hz, J=11.0 Hz); 2.76 (2H, s); 2.43 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.0; 137.5; 132.6; 129.9; 128.4; 128.0; 127.8; 127.6; 69.5; 69.4; 56.1; 49.1; 21.6. LC–MS m/z (%): 349.0 (100, M+H$^+$). HRMS Calcd for m/z $C_{18}H_{20}O_5S$+H$^+$: 349.1104. Found: 349.1110.

*4.3.20. (1S,2R)-1-[((S,R)-2-Benzyloxymethyloxiranyl-methyl)-amino]indan-2-ol (**9c**).* Under a nitrogen atmosphere, (1*S*,2*R*)-1-amino-indan-2-ol (44 mg, 0.29 mmol) was added to a solution of

10 (68 mg, 0.19 mmol) and KI (2 mg, 5% mol) in anhydrous DMF (2 mL), and the mixture was stirred for six days at RT. The reaction was quenched by the addition of 20 mL of saturated $NaHCO_3$ (aq), then extracted with Et_2O, and the organic phase washed with H_2O (5×), brine and dried over Na_2SO_4. Evaporation of the solvent and flash chromatography purification (isohexane/ethyl acetate 1:1) afforded **9c** (colorless oil) as a 50/50 epimeric mixture (21 mg, yield 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.18 (9H, m); 4.59 and 4.58 (2H, AB, $\Delta\nu$=16.0 Hz, J=12.0 Hz and AB, $\Delta\nu$=15.9 Hz, J=11.9 Hz); 4.44 and 4.43 (1H, M of ABMX, td, J=5.2, 2.6 Hz and M of ABMX, td, J=5.2, 2.6 Hz); 4.09 and 4.08 (1H, X of ABMX, d, J=5.2 Hz and X of ABMX, d, J=5.2 Hz); 3.72–3.63 (1H, m); 3.70 and 3.65 (2H, AB, $\Delta\nu$=71.7 Hz, J=10.8 Hz and AB, $\Delta\nu$=57.0 Hz, J=10.8 Hz); 3.16 and 3.13 (2H, AB, $\Delta\nu$=70.9 Hz, J=13.0 Hz and AB, $\Delta\nu$=5.7 Hz, J=13.0 Hz); 3.00 (2H, AB of ABMX, $\Delta\nu$=31.1 Hz, J=16.4; 5.2, 2.6 Hz); 2.85 and 2.82 (2H, AB, $\Delta\nu$=81.7 Hz, J=4.8 Hz and AB, $\Delta\nu$=14.3 Hz, J=4.8 Hz); 1.71 (1H, bs). LC–MS m/z (%) (one peak): 326.1 (100, M+H$^+$). GC–MS m/z (%) (one peak): 326 (2); 305 (2); 269 (3); 197 (7); 160 (100); 115 (81); 91 (72).

*4.3.21. (1S,2R)-1-((R,S)-3-Amino-2-benzyloxymethyl-2-hydroxypropylamino)indan-2-ol (**2c**).* To the 50/50 mixture **9c** (30 mg, 0.09 mmol) in MeOH (2 mL) was added 25% aqueous NH_3 (2 mL). The mixture was stirred for four days at RT. After removal of the solvent under reduced pressure, the residue was solubilized in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave 30 mg (yield 97%) of the corresponding aminoalcohol **2c** as a 50/50 epimeric mixture confirmed by LC–MS and used for the coupling reaction without further purification. LC–MS m/z (%) (one peak): 343.2 (40, M+H$^+$); 213.2 (100).

*4.3.22. N-{(S,R)-3-Benzyloxy-2-hydroxy-2-[((1S,2R)-2-hydroxyindan-1-ylamino)methyl]propyl}-5-(methanesulfonylmethylamino)-N′-((R)-1-phenylethyl)isophthalamide (**3c**).* Under a nitrogen atmosphere, DIPEA (54 μL, 0.31 mmol) and HATU (41 mg, 0.11 mmol) were added to a solution of **2c** (50/50 epimeric mixture, 30 mg, 0.09 mmol) and **1** (34 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (2 mL). The mixture was stirred at RT, and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 5 h, the reaction was quenched with 2 mL of satd NH_4Cl (aq), then washed with satd $NaHCO_3$ (aq), brine and dried over anhydrous Na_2SO_4. Flash column chromatography (ethyl acetate, then ethyl acetate/MeOH 1:1) and subsequent preparative LC purification afforded a 50/50 epimeric mixture of **3c** (11 mg, yield 18%) as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 9.05–9.01 (1H, m); 8.66–8.61 and 8.57–8.50 (1H, m and m); 8.29 and 8.27 (1H, dd, J=1.5, 1.4 Hz and dd, J=1.5, 1.4 Hz); 8.02–7.96 (2H, m) 7.42–7.07 (14H, m); 5.19 (1H, dq, J=7.2, 7.0 Hz); 4.94 (1H, bs); 4.75–4.70 (1H, bm); 4.51 and 4.49 (2H, s and AB, $\Delta\nu$=9.5 Hz, J=12.0 Hz); 4.40–4.34 (1H, m); 3.91–3.87 (1H, m); 3.58–3.42 (4H, m); 3.28 (3H, s); 3.01 and 3.00 (3H, s and s); 2.94–2.84 (2H, m); 2.81–2.72 (2H, m); 2.03–1.96 (1H, bm); 1.51 and 1.50 (3H, d, J=7.0 and d, J=7.0). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 167.7; 164.1; 144.6; 143.9; 143.4; 142.1; 141.8; 138.3; 136.2; 128.27 and 128.25; 128.20 and 128.14; 127.6; 127.4; 127.3; 127.0; 126.7; 126.1; 126.0; 125.9; 124.8; 124.4; 114.5; 75.2; 73.8; 72.7; 70.8; 66.7; 55.2; 48.7; 43.2; 37.69 and 37.66; 35.56 and 35.53; 37.4 and 37.3; 22.1. LC–MS m/z (%) (one peak): 701.3 (100, M+H$^+$). HRMS Calcd for $C_{38}H_{44}N_4O_7S$+H$^+$: 701.3009. Found: 701.3008. BACE-1 (TRF) IC_{50}>10 μM.

*4.3.23. Benzyl(2-benzyloxymethyloxiranylmethyl)amine (**9d**).* Sodium triacetoxyborohydride (59 mg, 0.28 mmol) was added to a solution of the epoxyaldehyde **7** (48 mg, 0.25 mmol) and benzylamine (31 μL, 0.28 mmol) in DCE (2.5 mL). The mixture was stirred for 45 min at RT, then satd $NaHCO_3$ (aq) (2 mL) and ethyl acetate (2 mL) were added. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and flash column chromatography (isohexane/ethyl acetate 1:1+2.5% TEA) gave 45 mg (yield 63%) of pure **9d** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.22 (10H, m); 4.55 (2H, AB, $\Delta\nu$=10.6 Hz, J=12.0 Hz); 3.79 (2H, s); 3.66 (2H, AB, $\Delta\nu$=5.9 Hz, J=11.0 Hz); 2.92 (2H, AB, $\Delta\nu$=18.9 Hz, J=12.9 Hz); 2.79 (2H, AB, $\Delta\nu$=35.4 Hz, J=5.0 Hz); 1.58 (1H, bs). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.2; 137.9; 128.4; 128.3; 128.0; 127.7; 127.6; 126.9; 73.4; 71.3; 58.2; 53.8; 50.0; 49.5. LC–MS m/z (%): 284.0 (100, M+H$^+$). GC–MS m/z (%): 284 (96, M$^+$+1); 210 (24); 176 (11, M$^+$-BnO); 120 (48); 106 (77, BnNH$^+$); 91 (100, Bn$^+$); 65 (24). HRMS Calcd for m/z $C_{18}H_{21}NO_2$+H$^+$: 284.1645. Found: 284.1651.

*4.3.24. 1-Amino-2-(benzylaminomethyl)-3-benzyloxy-propan-2-ol (**2d**).* To the oxirane **9d** (41 mg, 0.14 mmol) in MeOH (3 mL) was added 25% aqueous NH_3 (3 mL). The mixture was stirred for 18 h at rt. After removal of the solvent under reduced pressure, the residue was solubilized in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave 42 mg (quantitative yield) of the desired aminoalcohol **2d** confirmed by LC–MS and used for the coupling reaction without further purification. LC–MS m/z (%): 301.0 (55, M+H$^+$); 212.7 (19); 192.1 (100).

*4.3.25. N-[(S,R)-2-(Benzylaminomethyl)-3-benzyloxy-2-hydroxypropyl]-5-(methanesulfonylmethylamino)-N′-((R)-1-phenylethyl)isophthalamide (**3d**).* Under a nitrogen atmosphere, EDC×HCl (30 mg, 0.15 mmol) and HOBt (21 mg, 0.15 mmol) were added to a solution of **2d** (42 mg, 0.14 mmol) and **1** (53 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL). The mixture was stirred at RT, and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 2 h H_2O (2 mL) and ethyl acetate (3 mL) were added. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. Preparative LC purification gave a 50/50 epimeric mixture of **3d** (36 mg, yield 40%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (1H, bs); 8.19 (1H, m); 8.01 (1H, m); 7.94 (1H, m); 7.75 (1H, bs); 7.42–7.19 (15H, m); 6.96 (1H, bt, J=6.6 Hz); 5.33 (1H, dq, J=7.2, 6.9 Hz); 4.52 (2H, s); 3.81 (2H, s); 3.64–3.52 (3H, m); 3.45 and 3.44 (2H, AB, $\Delta\nu$=9.3 Hz, J=9.5 Hz and AB, $\Delta\nu$=5.9 Hz, J=9.4 Hz); 3.34 (3H, s); 2.84 and 2.83 (3H, s and s); 2.79 (2H, AB, $\Delta\nu$=29.3 Hz, J=12.3 Hz); 1.63 and 1.62 (3H, d, J=6.9 Hz and d, J=6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.7; 164.5; 142.90 and 142.85; 142.3 and 142.2; 137.2; 136.7; 135.9; 135.3; 128.74; 128.71 and 128.70; 128.6; 127.41 and 127.40; 128.1; 128.04; 128.02; 127.9; 127.80 and 127.78; 127.5; 126.3; 123.9; 74.9; 73.8; 72.1; 53.6; 52.3; 49.7; 45.4; 37.9; 35.5; 21.73 and 21.68. LC–MS m/z (%) (one peak): 659.2 (100, M+H$^+$). Anal. Calcd for $C_{36}H_{42}N_4O_6S\times1.5H_2O$: C, 63.05; H, 6.61; N, 8.17. Found: C, 63.33; H, 6.46; N, 7.91. BACE-1 (TRF) IC_{50}=7.2 μM.

*4.3.26. (2-Benzyloxymethyloxiranylmethyl)(3-methoxybenzyl)amine (**9e**).* Sodium triacetoxyborohydride (83 mg, 0.39 mmol) was added to a solution of the epoxyaldehyde **7** (47 mg, 0.24 mmol) and *m*-methoxy benzylamine (36 μL, 0.28 mmol) in DCE (5 mL). The mixture was stirred for 1 h at RT, then satd $NaHCO_3$ (aq) (5 mL) and ethyl acetate (5 mL) were added. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification by flash column chromatography (isohexane/ethyl acetate 1:1+2.5% TEA) afforded 54 mg (yield 70%) of pure **9e** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.20 (6H, m); 6.94–6.77 (3H, m); 4.55 (2H, AB, $\Delta\nu$=10.4 Hz, J=11.9 Hz); 3.79 (3H, s); 3.79–3.77 (2H, m); 3.66 (2H, s); 2.93 (2H, AB, $\Delta\nu$=23.0 Hz, J=12.9 Hz); 2.80 (2H, AB, $\Delta\nu$=36.8 Hz, J=5.0 Hz); 2.21 (1H, bs). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7; 141.7; 137.9; 129.3; 128.4; 127.7; 127.6; 120.3; 113.5; 112.4; 73.4; 71.3; 58.1; 55.2; 53.7; 49.9; 49.5. LC–MS m/z (%): 627.1 (20, 2M+H$^+$); 314.0 (100, M+H$^+$). GC–MS m/z

(%): 300 (2); 241 (3); 180 (21); 164 (29); 136 (3); 121 (100, $MeOPhCH_2^+$, $PhCH_2OCH_2^+$); 91 (15); 77 (12); 58 (22).

*4.3.27. 1-Amino-3-benzyloxy-2-[(3-methoxybenzyl-amino)methyl]-propan-2-ol (**2e**).* To the oxirane **9e** (62 mg, 0.20 mmol) in MeOH (3 mL) was added 25% aqueous NH_3 (3 mL). The mixture was stirred for 18 h at RT. After removal of the solvent under reduced pressure, the residue was solubilized in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave 64 mg (yield 98%) of the desired aminoalcohol **2e** confirmed by LC–MS and used for the coupling reaction without further purification. LC–MS *m*/*z* (%): 311.0 (40, $M+H^+$); 207.1 (100).

*4.3.28. N-{(S,R)-3-Benzyloxy-2-hydroxy-2-[(3-methoxy-benzylamino)methyl]propyl}-5-(methanesulfonylmethylamino)-N′-((R)-1-phenylethyl)isophthalamide (**3e**).* Under a nitrogen atmosphere, EDC×HCl (40 mg, 0.21 mmol) and HOBt (28 mg, 0.21 mmol) were added to a solution of **2e** (64 mg, 0.19 mmol) and **1** (71 mg, 0.19 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at RT, and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 1.5 h, H_2O (2 mL) and ethyl acetate (3 mL) were added. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. Preparative LC purification gave a 50/50 epimeric mixture of **3e** (27 mg, yield 21%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30–8.27 (1H, m); 8.09 (1H, bs); 8.04–8.01 (1H, m); 7.98–7.96 (1H, m); 7.42–7.16 (12H, m); 6.83–6.75 (3H, m); 5.32 (1H, dq, J=7.2, 7.0 Hz); 4.51 and 4.50 (2H, s and s); 4.05 (1H, bs); 3.82 (2H, s); 3.80–3.75 (1H, m); 3.74 and 3.73 (3H, s and s); 3.58 and 3.57 (2H, AB, $\Delta\nu$=36.6 Hz, J=14.0 Hz and AB, $\Delta\nu$=35.1 Hz, J=14.1 Hz); 3.47 and 3.46 (2H, s); 3.32 (3H, s); 2.85 (2H, AB, $\Delta\nu$=12.3 Hz, J=12.0 Hz); 2.84 and 2.83 (3H, s and s); 1.62 and 1.61 (3H, d, J=7.0 Hz and d, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.3; 164.8; 160.1; 143.3 and 143.2; 142.52 and 142.51; 137.31 and 137.29; 136.10 and 136.09; 135.35 and 135.33; 130.12 and 130.10; 128.9; 128.8; 128.51; 128.49; 128.4; 128.1; 127.94 and 127.92; 127.67 and 127.66; 126.57 and 126.56; 124.1; 120.95 and 120.94; 114.51 and 114.50; 113.76 and 113.72; 75.38 and 75.34; 74.1; 72.4; 55.4; 53.46 and 53.41; 53.35 and 53.32; 49.9; 45.5; 38.2; 35.80 and 35.78; 22.0 and 21.9. LC–MS *m*/*z* (%) (one peak): 689.1 (100, $M+H^+$). Anal. Calcd for $C_{37}H_{44}N_4O_7S\times 2H_2O$: C, 61.31; H, 6.67; N, 7.73. Found: C, 61.48; H, 6.34; N, 7.60. BACE-1 (TRF) IC_{50}>10 μM.

*4.3.29. (2-Benzyloxymethyloxiranylmethyl)phenylamine (**9f**).* Sodium triacetoxyborohydride (40 mg, 0.19 mmol) was added to a solution of the epoxyaldehyde **7** (34 mg, 0.18 mmol) and aniline (17 μL, 0.19 mmol) in DCE (2 mL). The mixture was stirred for 3 h at RT, then satd $NaHCO_3$ (aq) (2 mL) and ethyl acetate (3 mL) were added. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification by flash column chromatography (isohexane/ethyl acetate 5:1) afforded 29 mg (yield 62%) of pure **9f** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40–7.29 (5H, m); 7.17 (2H, dd, J=8.6, 7.3 Hz); 6.72 (1H, tt, J=7.3, 1.0 Hz); 6.62 (2H, dd, J=8.6, 1.0 Hz); 4.58 (2H, AB, $\Delta\nu$=16.8 Hz, J=11.9 Hz); 3.88 (1H, bs); 3.64 (2H, AB, $\Delta\nu$=14.5 Hz, J=10.7 Hz); 3.56–3.45 (2H, bs); 2.81 (2H, AB, $\Delta\nu$=38.1 Hz, J=4.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.0; 137.7; 129.3; 128.5; 127.84; 127.75; 117.7; 112.9; 73.5; 71.5; 57.7; 49.7; 44.5. LC–MS *m*/*z* (%): 270.0 (100, $M+H^+$).

*4.3.30. 1-Amino-3-benzyloxy-2-phenylaminomethylpropan-2-ol (**2f**).* To the oxirane **9f** (29 mg, 0.11 mmol) in MeOH (2 mL) was added 25% aqueous NH_3 (2 mL). The mixture was stirred for 18 h at RT. After removal of the solvent under reduced pressure, the residue was solubilized in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave 28 mg (yield 90%) of the desired aminoalcohol **2f** confirmed by LC–MS and used for the coupling reaction without further purification. LC–MS *m*/*z* (%): 287.0 (100, $M+H^+$).

*4.3.31. N-((S,R)-3-Benzyloxy-2-hydroxy-2-phenylamino-methylpropyl)-5-(methanesulfonylmethylamino)-N′-((R)-1-phenylethyl)isophthalamide (**3f**).* Under a nitrogen atmosphere, EDC×HCl (21 mg, 0.11 mmol) and HOBt (15 mg, 0.11 mmol) were added to a solution of **2f** (28 mg, 0.10 mmol) and **1** (37 mg, 0.10 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at RT, and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 4 h, H_2O (2 mL) and ethyl acetate (3 mL) were added. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. Preparative LC purification gave a 50/50 epimeric mixture of the pure compounds **3f** (18 mg, yield 29%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (1H, m); 7.95 (1H, m); 7.86 (1H, m); 7.39–7.24 (10H, m); 7.14 (2H, t, J=7.4 Hz); 7.00 (1H, bt, J=5.8 Hz); 6.74–6.69 (1H, bm); 6.70 (1H, t, J=7.4 Hz); 6.64 (2H, d, J=7.9 Hz); 5.30 (1H, dq, J=7.2, 7.0 Hz); 4.53 (2H, s); 3.77 and 3.74 (1H, A of ABX, J=14.1, 6.2 Hz and A of ABX, J=14.1, 6.2 Hz); 3.74 (1H, bs); 3.55 (1H, B of ABX, J=14.1, 5.6 Hz); 3.50 (2H, AB, $\Delta\nu$=21.3 Hz, J=9.2 Hz); 3.30 (3H, s); 3.24 and 3.23 (2H, s and s); 2.81 (3H, s); 1.93 (1H, bs); 1.60 (3H, d, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2; 164.7; 148.6; 142.9; 142.5; 137.7; 136.20 and 136.19; 135.5; 129.5; 129.0; 128.8; 128.3; 128.2; 127.86; 127.76; 127.75; 126.5; 124.2; 118.08 and 118.07; 113.5; 74.2; 73.9; 73.03 and 73.02; 50.0; 48.4; 45.5; 38.1; 35.7; 21.9. LC–MS *m*/*z* (%) (one peak): 645.2 (100, $M+H^+$). Anal. Calcd for $C_{35}H_{40}N_4O_6S\times 1H_2O$: C, 63.43; H, 6.39; N, 8.45. Found: C, 63.54; H, 6.56; N, 8.32. BACE-1 (TRF) IC_{50}=5.4 μM.

*4.3.32. Benzoic acid N′-(2-benzyloxymethyloxiranyl-methyl)hydrazide (**9g**).* Sodium triacetoxyborohydride (55 mg, 0.26 mmol) was added to a solution of the epoxyaldehyde **7** (34 mg, 0.18 mmol) and benzoic hydrazide (26 mg, 0.19 mmol) in DCE (2 mL). The mixture was stirred for 18 h at RT, then satd $NaHCO_3$ (aq) (2 mL) and ethyl acetate (3 mL) were added. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification by flash column chromatography (isohexane/ethyl acetate 1:1, then 1:2) afforded 14 mg (yield 26%) of pure **9g** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (1H, bs); 7.61–7.67 (2H, m); 7.52–7.27 (8H, m); 4.58 (2H, AB, $\Delta\nu$=14.5 Hz, J=11.7 Hz); 3.68 (2H, s); 3.26 (2H, bAB, $\Delta\nu$=32.5 Hz, J=12.1 Hz); 2.92 (1H, d, J=4.9 Hz); 2.77 (1H, d, J=4.9 Hz); 1.71 (1H, bs). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3; 137.6; 131.7; 128.6; 128.5; 128.4; 127.9; 127.8; 126.8; 73.6; 71.5; 57.7; 52.9; 49.2. LC–MS *m*/*z* (%): 313.0 (100, $M+H^+$).

*4.3.33. Benzoic acid N′-(3-amino-2-benzyloxymethyl-2-hydroxypropyl)hydrazide (**2g**).* To the oxirane **9g** (14 mg, 0.045 mmol) in MeOH (1 mL) was added 25% aqueous NH_3 (1 mL). The mixture was stirred for 18 h at RT. After removal of the solvent under reduced pressure, the residue was solubilized in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave 14 mg (yield 93%) of the desired aminoalcohol **2g** confirmed by LC–MS and used for the coupling reaction without further purification. LC–MS *m*/*z* (%): 330.0 (100, $M+H^+$).

*4.3.34. N-[(R,S)-2-(N′-Benzoylhydrazinomethyl)-3-benzyloxy-2-hydroxypropyl]-5-(methanesulfonylmethyl-amino)-N′-((R)-1-phenylethyl)isophthalamide (**3g**).* Under a nitrogen atmosphere, EDC×HCl (9.0 mg, 0.047 mmol) and HOBt (7.0 mg, 0.047 mmol) were added to a solution of **2g** (14 mg, 0.43 mmol) and **1** (16 mg, 0.043 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at RT and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 3 h, H_2O (1 mL) and ethyl acetate (3 mL) were added. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. Preparative LC

purification gave a 50/50 epimeric mixture of **3g** (6.0 mg, yield 20%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (1H, bs); 8.06 (1H, bs); 8.00 (2H, bs); 7.89–7.82 (1H, m); 7.66–7.29 (15H, m); 7.02–6.98 (1H, m); 5.28 (1H, dq, J=7.2, 7.0 Hz); 4.57 (2H, s); 3.81–3.65 (2H, m); 3.50 (2H, s); 3.33 (3H, s); 3.23 (1H, bm); 3.15–3.05 (2H, m); 2.82 (3H, s); 1.63 (1H, bs); 1.54 and 1.51 (3H, d, J=7.0 and d, J=7.0). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.7; 166.9; 164.7; 151.03 and 150.9; 142.8; 142.3; 137.4; 131.9; 131.15 and 130.99; 128.70; 128.68; 128.63; 128.59; 128.05; 127.96; 127.89; 127.7; 127.5; 126.93 and 126.92; 126.3; 123.9; 73.8; 73.6; 67.6; 56.7; 49.7; 45.6; 37.9; 35.6; 21.6. LC–MS m/z (%) (one peak): 688.2 (100, M+H$^+$). HRMS Calcd for $C_{36}H_{41}N_5O_7S$+H$^+$: 688.2805. Found: 688.2823. BACE-1 (TRF) IC_{50}>10 μM.

*4.3.35. 2,2-Bisbenzyloxymethyloxirane (**9h**).* A solution of **11** (0.61 g, 2.27 mmol) in 8 mL of CH_2Cl_2 was added to a mixture of *m*CPBA (70% in water, 1.265 g, 5.14 mmol) in 10 mL of CH_2Cl_2. After stirring overnight at RT, the mixture was cooled to −20 °C, filtered through Celite®, washed with cold CH_2Cl_2. The filtrate was washed with saturated $Na_2S_2O_3$ (aq) and saturated $NaHCO_3$ (aq) and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the oxirane **9h** (0.63 g, yield 97%) as a colorless oil, which was then used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.27 (10H, m); 4.56 (4H, AB, $\Delta\nu$=11.3 Hz, J=12.0 Hz); 3.69 (4H, AB, $\Delta\nu$=5.0 Hz, J=11.0 Hz); 2.80 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9; 128.4; 127.7; 127.6; 73.4; 70.1; 57.7; 48.7. LC–MS m/z (%): 285.0 (100, M+H$^+$). HRMS Calcd for m/z $C_{18}H_{20}O_3$+H$^+$: 285.1485. Found: 285.1491.

*4.3.36. 1-Amino-3-benzyloxy-2-benzyloxymethylpropan-2-ol (**2h**).* To a solution of **9h** (314 mg, 1.10 mmol) in MeOH (20 mL) was added 25% aqueous NH_3 (20 mL). The mixture was stirred overnight at RT. After removal of the solvent under reduced pressure, the residue was solubilized in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave the aminoalcohol **2h** (306 mg, yield 92%) used for the coupling reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.27 (10H, m); 4.53 (4H, s); 3.47 (4H, AB, $\Delta\nu$=6.3 Hz, J=9.4 Hz); 2.82 (2H, s); 2.01 (3H, bs). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.1; 128.4; 127.7; 127.6; 73.5; 73.1; 72.3; 49.1. LC–MS m/z (%): 603.2 (10, 2M+H$^+$); 302.1 (100, M+H$^+$). HRMS Calcd for m/z $C_{18}H_{23}NO_3$+H$^+$: 302.1751. Found: 302.1756.

*4.3.37. N-(3-Benzyloxy-2-benzyloxymethyl-2-hydroxypropyl)-5-(methanesulfonylmethylamino)-N′-((R)-1-phenylethyl)isophthalamide (**3h**).* Under a nitrogen atmosphere, DIPEA (49 μL, 0.28 mmol) and PyBOP (50 mg, 0.10 mmol) were added to a solution of **2h** (26 mg, 0.09 mmol) and **1** (30 mg, 0.08 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at RT, and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 24 h, the solvent was removed under reduced pressure, and the residue taken up in ethyl acetate filtered through a pad of silica. Flash column chromatography (isohexane/ethyl acetate 1:3) and subsequent preparative LC purification afforded the pure compound **3h** (32 mg, yield 59%) as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 9.01 (1H, d, J=7.4 Hz); 8.39 (1H, t, J=6.0 Hz); 8.27 (1H, dd, J=1.5, 1.5 Hz); 8.00 (1H, dd, J=2.0, 1.5 Hz); 7.98 (1H, dd, J=2.0, 1.5 Hz); 7.42–7.21 (15H, m); 5.20 (1H, dq, J=7.4, 7.0 Hz); 4.98 (1H, s); 4.50 (4H, s); 3.50 (2H, d, J=6.0 Hz); 3.44 (4H, AB, $\Delta\nu$=7.0 Hz, J=9.5 Hz); 3.29 (3H, s); 3.02 (3H, s); 1.51 (3H, d, J=7.0 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 165.9; 164.4; 144.6; 141.7; 138.5; 135.6; 135.5; 128.3; 128.1; 127.8; 127.4; 127.3; 127.2; 126.7; 126.1; 124.9; 73.7; 72.6; 72.2; 48.6; 44.1; 37.7; 35.6; 22.1. LC–MS m/z (%): 660.2 (100, M+H$^+$). $[\alpha]_D^{24}$ −11.1 (c 0.325 in CH_2Cl_2). Anal. Calcd for $C_{36}H_{41}N_3O_7S\times 1/2H_2O$: C, 64.61; H, 6.34; N, 6.45. Found: C, 64.90; H, 6.65; N, 6.17. BACE-1 (TRF) IC_{50}=6.4 μM.

*4.3.38. 2-(tert-Butyldiphenylsilanyloxymethyl)prop-2-en-1-ol (**12**).* Under a nitrogen atmosphere, NaH (60% in mineral oil, 0.45 g, 11.3 mmol) was added to a cooled (0 °C) solution of 2-methylene-1,3-propandiol (1.0 g, 11.3 mmol) in anhydrous THF (28 mL). After 1 h, TBDPSCl (3.11 g, 11.3 mmol) was added, and the mixture was stirred for 18 h at RT. The solution was then cooled to 0 °C, quenched with ice/water (20 mL) and extracted with Et_2O. The combined organic layers were washed with satd K_2CO_3 (aq), brine and dried over anhydrous Na_2SO_4. Evaporation of solvent afforded **12** (3.70 g, quantitative yield) as colorless oil, which was used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70–7.66 (4H, m); 7.46–7.36 (6H, m); 5.15 (1H, m); 5.12 (1H, m); 4.26 (2H, s); 4.18 (2H, s); 1.77 (1H, bs); 1.07 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.1; 135.5; 133.2; 129.8; 127.7; 111.1; 65.6; 64.5; 26.8; 19.2. LC–MS m/z (%): 653.2 (100, 2M+H$^+$), 327.1 (95, M+H$^+$).

*4.3.39. [2-(tert-Butyldiphenylsilanyloxymethyl)-oxiranyl]methanol (**S3**).* *m*CPBA (70% in water, 2.09 g, 8.48 mmol) was added to a solution of **12** (1.88 g, 5.6 mmol) in 20 mL of CH_2Cl_2. After stirring for 24 h at RT, the mixture was cooled to −20 °C, filtered through Celite® and washed with cold CH_2Cl_2. The filtrate was washed with saturated $Na_2S_2O_3$ (aq) and saturated $NaHCO_3$ (aq) and dried over anhydrous Na_2SO_4. Evaporation gave the epoxyalcohol **S3** (1.67 g, yield 86%) as a colorless oil, which was then used for the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69–7.65 (4H, m); 7.46–7.37 (6H, m); 3.87 (2H, AB of ABX, $\Delta\nu$=60.1 Hz, J=12.2, 8.3, 4.3 Hz); 3.81 (2H, AB, $\Delta\nu$=21.8 Hz, J=11.4 Hz); 2.86 (1H, d, J=4.8 Hz); 2.66 (1H, d, J=4.8 Hz); 1.76 (1H, bs); 1.06 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.57; 135.56; 132.9; 132.8; 129.90; 129.88; 127.8; 127.8; 64.9; 61.9; 59.5; 48.9; 26.8; 19.2. LC–MS m/z (%): 343.1 (100, M+H$^+$).

*4.3.40. (2-Benzyloxymethyloxiranylmethoxy)tert-butyl-diphenylsilane (**9i**).* Under a nitrogen atmosphere, **S3** (130 mg, 0.38 mmol) in anhydrous THF (1 mL) was added to a cooled (0 °C) suspension of NaH (60% in mineral oil, 164 mg, 0.41 mmol) in THF (1 mL). After 30 min, benzyl bromide (49 μL, 0.41 mmol) and tetrabutylammonium iodide (7.0 mg, 0.02 mmol) were added, and the mixture stirred for 18 h at RT. The mixture was then cooled to 0 °C, quenched with ice/water (2 mL) and extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by flash column chromatography (isohexane/ethyl acetate 15:1) afforded **9i** (110 mg, yield 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.69–7.65 (4H, m); 7.45–7.27 (11H, m); 4.55 (2H, AB, $\Delta\nu$=7.7 Hz, J=11.9 Hz); 3.84 (2H, AB, $\Delta\nu$=30.2 Hz, J=11.3 Hz); 3.71 (2H, AB, $\Delta\nu$=6.5 Hz, J=10.9 Hz); 2.73 (2H, AB, $\Delta\nu$=12.0 Hz, J=5.0 Hz); 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9; 135.62; 135.57; 134.8; 133.17; 133.14; 129.73; 129.71; 128.4; 127.70; 127.69; 127.67; 73.4; 70.0; 63.9; 58.8; 48.8; 26.7; 19.3. LC–MS m/z (%): 865.2 (52, 2M+H$^+$); 474.0 (100, M+CH_3CN+H$^+$); 433.0 (78, M+H$^+$).

*4.3.41. 1-Amino-3-benzyloxy-2-(tert-butyldiphenylsilanyloxymethyl)propan-2-ol (**2i**).* To the oxirane **9i** (110 mg, 0.26 mmol) in MeOH (5 mL) was added 25% aqueous NH_3 (5 mL). The mixture was stirred for 18 h at RT. After removal of the solvent under reduced pressure, the residue was solubilized in ethyl acetate and dried over Na_2SO_4. Evaporation of the solvent gave 89 mg (yield 77%) of the desired aminoalcohol **2i** confirmed by LC–MS and used for the coupling reaction without further purification. LC–MS m/z (%): 450.0 (100, M+H$^+$).

*4.3.42. N-[(S,R)-3-Benzyloxy-2-(tert-butyldiphenylsilanyloxymethyl)-2-hydroxypropyl]-5-(methanesulfonylmethylamino)-N′-((R)-1-phenylethyl)isophthalamide (**S4**).* Under a nitrogen atmosphere, DIPEA (122 μL, 0.70 mmol) and PyBOP (156 mg, 0.30 mmol) were

added to a solution of **2i** (89 mg, 0.20 mmol) and **1** (76 mg, 0.20 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at RT, and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 20 h, the solvent was removed under reduced pressure, the residue filtered though a pad of silica and washed with ethyl acetate. Further purification by flash column chromatography (isohexane/ethyl acetate 1:1, then 1:2) afforded a 50/50 epimeric mixture **S4** (40 mg, yield 25%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05–8.04 (1H, m); 7.97 (1H, dd, J=1.9, 1.7 Hz); 7.85 (1H, dd, J=1.9, 1.7 Hz); 7.64–7.60 (4H, m); 7.41–7.25 (16H, m); 6.76 (1H, bt, J=5.4 Hz); 6.56 (1H, bd, J=7.2 Hz); 5.32 (1H, dq, J=7.2, 6.9 Hz); 4.53 (2H, s); 3.75–3.61 (2H, m); 3.65 (2H, s); 3.54 (2H, AB, $\Delta\nu$=33.0 Hz, J=9.3 Hz); 3.35 (3H, s); 2.83 (3H, s); 2.75 (1H, bs); 1.63 (3H, d, J=6.9 Hz); 1.05 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.1; 164.5; 142.6; 142.2; 137.6; 135.9; 135.7; 135.56; 135.54; 132.71; 132.67; 131.47; 129.88 and 129.87; 128.83; 128.4; 127.81; 127.79; 127.76; 127.65; 127.4; 127.3 126.3; 125.3; 123.81 and 123.80; 74.0; 73.6; 71.6; 65.46 and 65.45; 49.7; 43.79 and 43.78; 37.9; 35.3; 26.8; 21.7; 19.2. LC–MS m/z (%) (one peak): 808.2 (100, $M+H^+$).

*4.3.43. N-((S,R)-3-Benzyloxy-2-hydroxy-2-hydroxy-methylpropyl)-5-(methanesulfonylmethylamino)-N′-((R)-1-phenylethyl)isophthalamide (**3i**).* TBAF×3H_2O (65 mg, 0.25 mmol) was added to a 50/50 epimeric mixture **S4** (40 mg, 0.05 mmol) in distilled THF (1 mL). Two drops of H_2O were added, and the mixture stirred at RT. After 18 h, H_2O (2 mL) and ethyl acetate (2 mL) were added, the organic layer was separated and washed with brine and then dried over anhydrous Na_2SO_4. Evaporation of the solvent, purification by flash column chromatography (ethyl acetate), and further preparative LC purification gave a 50/50 epimeric mixture of **3i** (9.0 mg, yield 31%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09–8.07 (1H, m); 7.98 (1H, dd, J=1.7, 1.5 Hz); 7.90 (1H, dd, J=1.8, 1.7 Hz); 7.40–7.27 (10H, m); 6.99 (1H, bt, J=6.0 Hz); 6.64 (1H, bd, J=7.2 Hz); 5.31 (1H, dq, J=7.2, 7.0 Hz); 4.56 (2H, AB, $\Delta\nu$=11.7 Hz, J=11.9 Hz); 3.74 (1H, A of ABX, J=14.2, 6.9 Hz); 3.56–3.44 (3H, m); 3.53 (2H, AB, $\Delta\nu$=32.9 Hz, J=9.4 Hz); 3.36 (1H, bs); 3.35 (3H, s); 3.31 (1H, bs); 2.85 (3H, s); 1.62 (3H, d, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.4; 164.4; 142.6; 142.3; 137.4; 136.0; 134.9; 128.9; 128.7; 128.2; 128.0; 127.93 and 127.91; 127.89; 127.81; 126.52 and 126.51; 124.28 and 124.27; 74.3; 73.8; 72.64 and 72.63; 64.3; 49.81 and 49.80; 43.87 and 43.86; 37.9; 35.5; 21.6. LC–MS m/z (%) (one peak): 1139.4 (27, $2M+H^+$); 570.2 (100, $M+H^+$). Anal. Calcd for $C_{29}H_{35}N_3O_7S\times1H_2O$: C, 59.27; H, 6.35; N, 7.15. Found: C, 59.23; H, 6.09; N, 6.85. BACE-1 (TRF) IC_{50}>10 μM.

*4.3.44. 2-(4-Methoxybenzyloxymethyl)-prop-2-en-1-ol (**13**).* 2-Metylene-1,3-propandiol (1.02 g, 11.6 mmol) was dissolved in anhydrous THF (58 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil) (487 mg, 12.18 mmol) was added to the solution, and after 30 min at 0 °C tetrabutylammonium iodide (214 mg, 0.58 mmol) and 4-methoxybenzyl bromide (1.80 mL, 12.18 mmol) were added. The reaction mixture was allowed to attain room temperature, and after 3 h methanol (10 mL) was added to quench the reaction. The mixture was acidified to pH 1 with 1 M HCl and extracted with DCM (3×15 mL) and brine (20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (isohexane/ethyl acetate, 1:1) afforded the desired mono protected **13** (1.24 g, 52%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, J=8.5 Hz, 2H), 6.86 (d, J=8.5 Hz, 2H), 5.18 (s, 1H), 5.12 (s, 1H), 4.43 (s, 2H), 4.18 (s, 2H), 4.05 (s, 2H), 3.79 (s, 3H), 2.12 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 145.1, 130.0, 129.4, 113.8, 113.5, 71.9, 71.5, 64.5, 55.2. MS m/z 417.2 [$(2M+H)^+$ calcd for $C_{12}H_{16}O_3^+$ 209.12].

*4.3.45. 1-(2-Benzyloxymethylallyloxymethyl)-4-methoxybenzene (**14**).* Compound **13** (1.20 g, 5.77 mmol) was dissolved in anhydrous THF (29 mL) and cooled to 0 °C. NaH (60% dispersion in mineral oil) (254 mg, 6.35 mmol) was added to the solution, and after 30 min at 0 °C tetrabutylammonium iodide (117 mg, 0.32 mmol) and benzyl bromide (0.745 mL, 6.35 mmol) were added. The reaction mixture was allowed to attain ambient temperature and was stirred over night. The mixture was acidified to pH 1 with 1 M HCl and extracted with DCM (3×10 mL) and brine (20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (isohexane/ethyl acetate, 9:1) afforded the desired **14** (1.46 g, 85%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.38 (m, 4H), 7.36–7.30 (m, 3H), 6.93 (d, J=8.6 Hz, 2H), 5.32 (s, 2H), 4.57 (s, 2H), 4.50 (s, 2H), 4.13 (s, 2H), 4.10 (s, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 142.7, 138.2, 130.2, 129.2, 128.2, 127.5, 127.4, 114.0, 113.6, 72.0, 71.7, 70.8, 70.4, 55.0.

*4.3.46. 2-Benzyloxymethyl-2-(4-methoxybenzyloxy-methyl)-oxirane (**15**).* Compound **14** (1.46 g, 4.90 mmol) was dissolved in dry DCM (24.5 mL). *m*CPBA (2.42 g, 9.80 mmol) was added, and the mixture was stirred at reflux temperature overnight. The mixture was extracted with DCM (3×25 mL) and water (30 mL), the combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (isohexane/ethyl acetate, 6:1) gave the epoxide **15** (1.22 g, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38–7.29 (m, 5H), 7.26 (d, J=8.6 Hz, 2H), 6.88 (d, J=8.6 Hz, 2H), 4.60 (d, J=12.1 Hz, 1H), 4.55 (d, J=12.1 Hz, 1H), 4.53 (d, J=11.5 Hz, 1H), 4.49 (d, J=11.5 Hz, 1H), 3.80 (s, 3H), 3.72 (d, J=11.1 Hz, 1H), 3.68 (d, J=11.1 Hz, 1H), 3.67 (s, 2H), 2.81 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.2, 137.8, 133.6, 129.9, 129.3, 128.3, 127.6, 113.7, 73.3, 73.0, 70.0, 69.6, 57.4, 55.2, 48.7. MS m/z 315.2 [$(M+H)^+$ calcd for $C_{19}H_{23}O_4^+$ 315.16].

*4.3.47. 4-Benzyloxy-3-benzyloxymethyl-3-hydroxy-butyronitrile (**16a**).* Potassium cyanide (87 mg, 1.34 mmol) and lithium perchlorate (143 mg, 1.34 mmol) were added to a solution of **9h** (253 mg, 0.89 mmol) in 5 mL of CH_3CN. After stirring for 20 h at 60 °C, water was added to quench the reaction. The mixture was extracted with Et_2O and the organic phase dried over Na_2SO_4. Evaporation of the solvent and purification by flash chromatography (isohexane/ethyl acetate 3:1) gave the desired compound **16a** (163 mg, yield 59%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.28 (10H, m); 4.56 (4H, s); 3.53 (4H, s); 2.90 (1H, bs); 2.69 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.3; 128.5; 128.0; 127.7; 117.0; 73.7; 72.1; 72.0; 24.5. LC–MS m/z (%): 623.5 (100, $2M+H^+$); 312.2 (53, $M+H^+$). HRMS Calcd for m/z $C_{19}H_{21}NO_3+H^+$: 312.1594. Found: 312.1600.

*4.3.48. 3-Benzyloxymethyl-3-hydroxy-4-(4-methoxy-benzyloxy)-butyronitrile (**16b**).* Compound **15** (910 mg, 2.89 mmol) was dissolved in methanol (15 mL) and lithium perchlorate (393 mg, 4.34 mmol) was added. Sodium cyanide (213 mg, 4.34 mmol) was added to the solution, and the mixture was stirred at 60 °C overnight. The mixture was extracted with DCM (3×20 mL) and water (30 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (isohexane/ethyl acetate, 3:1) gave **16b** (696 mg, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39–7.27 (m, 5H); 7.23 (d, J=8.6 Hz, 2H); 6.89 (d, J=8.6 Hz, 2H); 4.55 (s, 2H); 4.49 (s, 2H); 3.81 (s, 3H); 3.52 (s, 2H); 3.50 (s, 2H); 2.97 (s, 1H); 2.67 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.4; 137.3; 129.4; 129.3; 128.4; 127.9; 127.7; 117.0; 113.8; 73.6; 73.2; 72.1; 72.0; 71.7; 55.2; 24.4. MS m/z 342.2 [$(M+H)^+$ calcd for $C_{20}H_{24}NO_4^+$ 342.17].

*4.3.49. 4-Benzyloxy-3-benzyloxymethyl-3-hydroxy-butyric acid (**17a**).* To a 1 M NaOH solution (10 mL), **16a** (163 mg, 0.52 mmol) was added, and the mixture was refluxed for 18 h. The reaction was

cooled to RT, and conc HCl added to reach pH <4. The mixture was then extracted with ethyl acetate, and the combined organic layers dried over Na_2SO_4. Evaporation of the solvent under reduced pressure and purification by flash column chromatography (isohexane/ethyl acetate 3:1+1% TFA) provided 76 mg (yield 44%) of the desired acid **17a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.54 (1H, s); 7.37–7.26 (10H, m); 5.65 (1H, bs); 4.56 (4H, s); 3.54 (4H, s); 2.68 (2H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.5; 137.5; 128.3; 127.7; 127.6; 73.4; 73.0; 72.6; 38.6. LC–MS *m*/*z* (%): 661.6 (84, 2M+H$^+$); 331.3 (100, M+H$^+$). GC–MS *m*/*z* (%): 197 (4); 155 (2); 108 (43); 91 (100, $PhCH_2^+$); 79 (17); 77 (10, Ph^+). HRMS Calcd for *m*/*z* $C_{19}H_{22}O_5$+H$^+$: 331.1540. Found: 331.1545.

*4.3.50. 3-Benzyloxymethyl-3-hydroxy-4-(4-methoxy-benzyloxy)-butyric acid (**17b**)*[49]. Compound **16b** (59 mg, 0.172 mmol) was dissolved in methanol (1.7 mL), and potassium hydroxide (192 mg, 3.42 mmol) was added. The mixture was stirred for 15 min at 100 °C, and H_2O_2 (1 mL, 30% aq) was added to the solution. The mixture was stirred over night at 100 °C. The residue was acidified to pH 1 with 1 M HCl and concentrated. The mixture was extracted with DCM (3×10 mL) and water (15 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to give the acid **17b** (59.4 mg, 96%) as a white solid, which was used in the next step without further purification. ^{1}H NMR (CD_3OD, 400 MHz) δ: 7.32–7.28 (m, 5H); 7.22 (d, *J*=8.6 Hz, 2H); 6.85 (d, *J*=8.6 Hz, 2H); 4.50 (s, 2H); 4.44 (s, 2H); 3.75 (s, 3H); 3.58–3.44 (m, 4H); 2.55 (s, 2H). ^{13}C NMR (CD_3OD, 100 MHz) δ: 175.3; 160.7; 139.7; 131.6; 130.4; 129.3; 128.7; 128.6; 114.7; 74.5; 74.2; 74.1; 74.0; 73.8; 55.6; 39.9. MS *m*/*z* 361.2 [(M+H)$^+$ calcd for $C_{20}H_{25}O_6^+$ 361.16].

*4.3.51. 3-Amino-5-methanesulfonylamino-N-((R)-1-phenylethyl)benzamide (**S5**).* DIPEA (10.19 g, 78.8 mmol) and PyBOP (12.31 g, 23.7 mmol) were added to a solution of 3,5-diaminobenzoic acid (3.00 g, 19.7 mmol) and *R*-(+)-1-phenylethylamine (9.55 g, 78.8 mmol) in CH_2Cl_2 (70 mL). The mixture was stirred at RT overnight, and then the solvent was removed under reduced pressure. Purification by flash column chromatography (isohexane/ethyl acetate 1:4) gave crude compound 3,5-diamino-*N*-((*R*)-1-phenylethyl)benzamide (4.01 g, crude yield 79%) as a white solid, which was used without further purification in the next step, where 100 mL anhydrous 3:1 CH_2Cl_2:pyridine was added to the product. The slurry was cooled to 0 °C, and methanesulfonyl chloride (1.22 mL, 15.7 mmol) was added with a syringe needle. After 4 h the solvent was removed in vacuo, and the residue purified by flash column chromatography (isohexane/ethyl acetate 1:4) providing 2.88 g (yield 55%) of **S5** as white crystals. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.41–7.19 (5H, m); 6.89 (1H, dd, *J*=1.9, 1.6 Hz); 6.86 (1H, dd, *J*=2.0, 1.6 Hz); 6.77 (1H, dd, *J*=2.0, 2.0 Hz); 5.19 (1H, q, *J*=7.0 Hz); 2.97 (3H, s); 1.53 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 169.9; 150.6; 145.3; 140.5; 138.2; 129.5; 128.1; 127.2; 111.0; 110.2; 109.3; 50.7; 39.2; 22.3. LC–MS *m*/*z* (%): 334.4 (100, M+H$^+$).

*4.3.52. 3-Amino-5-methanesulfonylmethylamino-N-((R)-1-phenylethyl)benzamide (**18**).* Compound **S5** (1.15 g, 3.46 mmol) was dissolved in DMF and cooled to 0 °C, and NaH (138.4 mg, 3.46 mmol) was added dropwise, approx. 10 min after completed addition. MeI (982 mg, 6.92 mmol) was added. The mixture was stirred at 0 °C for 90 min and then stopped by the addition of 15 mL H_2O. Extraction with 50 mL ethyl acetate gave crude product, which was purified by flash column chromatography (isohexane/ethyl acetate 1:3, then ethyl acetate) providing pure **18** (652 mg, yield 54%) as a white powder. ^{1}H NMR (400 MHz, CD_3OD) δ: 7.40–7.20 (5H, m); 7.08 (1H, dd, *J*=2.0, 1.5 Hz); 7.04 (1H, dd, *J*=2.1, 1.5 Hz); 6.88 (1H, dd, *J*=2.1, 2.0 Hz); 5.20 (1H, q, *J*=7.0 Hz); 3.26 (3H, s); 2.90 (3H, s); 1.54 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ: 169.4; 150.6; 145.3; 144.1; 137.8; 129.6; 128.1; 127.2; 116.9; 114.6; 113.7; 50.7; 38.6; 35.5; 22.3. LC–MS *m*/*z* (%): 348.2 (100, M+H$^+$). HRMS Calcd for $C_{17}H_{22}N_3O_3S$+H$^+$: 348.1382. Found: 348.1390.

*4.3.53. 3-(4-Benzyloxy-3-benzyloxymethyl-3-hydroxy-butyrylamino)-5-(methanesulfonylmethylamino)-N-((R)-1-phenylethyl)benzamide (**19a**).* Under a nitrogen atmosphere, EDC×HCl (18 mg, 0.09 mmol) and HOBt (13 mg, 0.09 mmol) were added to a solution of **17a** (25 mg, 0.08 mmol) and **18** (32 mg, 0.09 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at RT, and the outcome of the reaction was monitored by LC–MS analysis until its completion. After 48 h, the solvent was removed under reduced pressure, and the residue taken up in ethyl acetate. The organic phase was then washed with H_2O, brine and dried over anhydrous Na_2SO_4. Flash column chromatography (isohexane/ethyl acetate 1:2), and subsequent preparative LC purification gave the pure compound **19a** (10 mg, yield 20%) as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 10.15 (1H, s); 8.85 (1H, d, *J*=7.4); 7.95 (1H, dd, *J*=1.8, 1.6 Hz); 7.83 (1H, dd, *J*=1.9, 1.8 Hz); 7.56 (1H, dd, *J*=1.9, 1.6 Hz); 7.41–7.20 (15H, m); 5.17 (1H, dq, *J*=7.4, 7.0 Hz); 5.04 (1H, s); 4.51 (4H, s); 3.51 (4H, AB, $\Delta\nu$=13.4 Hz, *J*=9.3 Hz); 3.24 (3H, s); 2.99 (3H, s); 2.56 (2H, s); 1.48 (3H, d, *J*=7.0 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 169.7; 165.0; 144.7; 141.8; 139.6; 138.5; 136.0; 128.2; 128.1; 127.3; 127.2; 126.6; 126.1; 119.7; 117.2; 73.4; 73.0; 72.6; 48.5; 41.6; 37.9; 35.4; 22.1. LC–MS *m*/*z* (%): 660.3 (100, M+H$^+$). $[\alpha]_D^{24}$ −21.8 (*c* 0.055 in CH_2Cl_2). Anal. Calcd for $C_{36}H_{41}N_3O_7S$: C, 65.53; H, 6.26; N, 6.37. Found: C, 65.85; H, 6.52; N, 6.20. BACE-1 (TRF) IC_{50}=3.5 μM.

*4.3.54. 3-[3-Benzyloxymethyl-3-hydroxy-4-(4-methoxy-benzyloxy)-butyrylamino]-5-(methanesulfonylmethyl-amino)-N-((R)-1-phenylethyl)-benzamide (**19b**).* Compound **17b** (600 mg, 1.67 mmol), and **18** (578 mg, 1.67 mmol) was dissolved in DMF (8.3 mL). DIPEA (0.580 mL, 3.33 mmol) and HATU (348 mg, 0.915 mmol) were added to the solution and stirred at room temperature. The reaction mixture was stirred for 30 min, and HATU (348 mg, 0.915 mmol) was added. After 2 h, the mixture was concentrated and purified by flash column chromatography (isohexane/ethyl acetate, 1:3) and further purified by preparative LC/MS (60 min gradient from 40% to 100% CH_3CN in 0.05% aqueous HCOOH, 10 mL/min) to give compound **19b** 747 mg, 65% as white crystals after lyophilization. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.88 (m, 1H); 7.78 (m, 1H); 7.58 (m, 1H); 7.41–7.38 (m, 2H); 7.34–7.15 (m, 10H); 6.79–6.76 (m, 2H); 5.23 (m, 1H); 4.50 (s, 2H); 4.43 (s, 2H); 3.69 (s, 3H); 3.58–3.48 (m, 4H); 3.28 (s, 3H); 2.89 (s, 3H); 2.64 (s, 2H); 1.56 (d, *J*=7.0 Hz, 3H). ^{13}C NMR (CD_3OD, 100 MHz) δ: 172.5; 168.3; 160.7; 145.2; 143.7; 140.6; 139.5; 137.5; 131.4; 130.5; 129.9; 129.6; 129.3; 129.2; 128.8; 128.6; 128.1; 127.2; 122.0; 121.5; 118.8; 114.7; 74.8; 74.7; 74.6; 74.2; 74.1; 55.6; 50.8; 42.4; 38.4; 35.7; 22.2. HRMS Calcd for *m*/*z* $C_{37}H_{44}N_3O_8S$+H$^+$: 690.2844. Found: 690.2849 BACE-1 (TRF) IC_{50}=0.38 μM.

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