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PAPER

A practical entry to β-aryl-β-alkyl amino alcohols: application to the synthesis of a potent BACE1 inhibitor†

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The 1,2-addition of alkyl Grignard reagents to readily available *N-tert*-butanesulfinyl ketimines, bearing an α-silyloxy substituent, proceeds in high yields and excellent diastereocontrol. The utility of the present method was demonstrated by the synthesis, in enantiomerically pure form, of one recently disclosed β-secretase (BACE1) inhibitor.

Introduction

The inhibition of β-secretase (BACE1) is believed to represent a potential disease modifying treatment for Alzheimer's disease (AD).[1] AD is characterized by two major central nervous system pathologies: the occurrence of neurofibrillar tangles and amyloid plaques. These insoluble plaques are formed after the aggregation of β-amyloid (Aβ) peptides of 39–43 amino acids which are formed *via* the sequential cleavage of β-amyloid precursor protein (APP) by β- and γ-secretase.[2–5] Many of the on-going efforts in the pharmaceutical industry are based on an anti-amyloid approach, aimed at increasing Aβ-clearance or decreasing Aβ-production and aggregation. The disclosure of a series of thioguanidines[6] and aminopyrimidones[7] as potent BACE1 inhibitors displaying *in vivo* efficacy has paved the way for the identification of drug-like and brain penetrant ligands for this biological target. From our internal medicinal chemistry program, we have recently disclosed a racemic synthesis of aminopiperazinone inhibitors displaying submicromolar activities (Fig. 1).[8] After chiral separation, the (*R*)-configuration at the quaternary stereogenic center was found to be essential for the biological activity, since it distributes the biaryl amide decoration towards S1 and S3 pockets.[9,10]

As an extension of this work, we became interested in the preparation of β-aryl-β-alkyl aminoalcohols (**II**, Scheme 1) that could give rise to densely functionalized amidines (**I**). In order to avoid the complicating factors, which may be present when using racemates in drug discovery programs,[11] having access to enantiomerically pure compounds was deemed essential. It was envisioned that the 1,2-addition of alkyl metal reagents to suitable ketimines (**III**) would allow a quick structure activity relationship (SAR) study at the quaternary stereocenter. Although there are several methods for the preparation of constrained acyclic amino acids,[12,13] our goal was to develop a general methodology for the direct preparation of suitably protected enantiopure aminoalcohols. At the beginning of this project there were some criteria that, for the sake of practicality, were considered highly desirable. These included the possibility of carrying out the chemistry in large scale without rigorous exclusion of air or moisture, the use of commercially available reagents and the avoidance of any tedious separation of enantiomeric and/or diastereomeric mixtures of products. Herein we report an experimentally simple protocol for the synthesis of tertiary carbinamines that proceeds with excellent stereocontrol. We have applied this methodology to the synthesis of 1,4-oxazine-amines that inhibit β-secretase in the submicromolar range, as shown in both the enzymatic and cellular assays.[14,15]

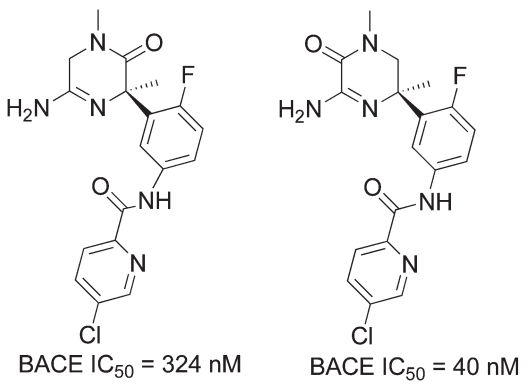

Fig. 1 BACE1 inhibitors containing the tertiary carbinamine motif.

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† Electronic supplementary information (ESI) available: General experimental procedures, BACE1 assays, stereochemical determination of **7** (SFC and VCD analysis) and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/c2ob25845e

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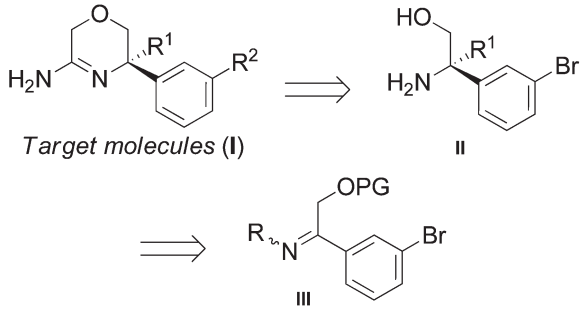

Scheme 1 Retrosynthetic analysis.

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Results and discussion

The 1,2-addition of nucleophiles to *N*-*tert*-butanesulfinyl ketimines is one of the most popular approaches for the asymmetric preparation of α,α-dibranched amines.[16] A clear limitation of this method is that the level of stereoselectivity is affected by the *Z*/*E* geometry of the imine which, in turn, is dependent on the relative size of the substituents. Prompted by the work of Avenoza and Peregrina,[17] 2-hydroxyacetophenone derivatives were selected as precursors of imines that exist predominantly in the (*Z*)-configuration. We also included a *m*-bromoaryl ring in our optimization studies, since it was essential to have an activated site for the late stage Pd-catalyzed derivatization of the products.

As shown in Table 1, 2-hydroxy-1-(3-bromophenyl)-ethanone[18] was initially protected as the corresponding *t*-butyldimethylsilyl (TBS) ether. Condensation of **2a** with (*S*)-(−)-2-methyl-2-propanesulfinamide in refluxing toluene, using titanium(IV) isopropoxide as dehydrating agent, gave *tert*-butylsulfinimine **3a** as a 16 : 1 ratio of *Z*/*E* isomers. It had been previously described that organolithium additions to *N*-sulfinyl ketimines require the preactivation of the electrophilic partner with a Lewis acid ($AlMe_3$) in a non-coordinating solvent (toluene) at low temperature.[19] Under these conditions, the addition of methyllithium to TBS protected ketimine **3a** afforded the tertiary carbinamine **4a** with high stereoselectivity (95 : 5) but in low yield (29%) (Table 1, entry 1). It was reasoned that the well established α-deprotonation of the *N*-sulfinyl ketimine was responsible for the low isolated yield,[19] and that the introduction of a bulkier protecting group could prevent this side reaction. A considerable increase in yield was observed when *tert*-butyldiphenylsilyloxy (OTBDPS) ketimine **3b**, which was obtained as a 13 : 1 *Z*/*E* isomers ratio, was subjected to identical reaction conditions (59% yield, Table 1, entry 2). In order to increase the practicality of the process, our next goal was to omit Lewis acid activation in the process. While this was not possible with organolithium reagents (Table 1, entry 3), treatment of imine **3b** with methylmagnesium bromide at 0 °C in CH_2Cl_2 as solvent[20] gave the desired product **4b** in 92% yield as a single diastereoisomer.[21]

The scope and generality of Grignard additions to **3b** in dichloromethane was then examined. While increasing the size of the nucleophile resulted in slightly lower yields, the levels of diastereocontrol were excellent in all cases, as determined by ^{1}H NMR and LC-MS (Table 1, entries 5–7). When PhMgBr was used (Table 1, entry 8) a complex reaction mixture was obtained from which no product could be isolated. The presence of an electron donating group in the phenyl ring does not have a noticeable effect on the reactivity of the corresponding imine, as 1,2-addition product **4h** can be obtained in good yield (Table 1, entry 10).[22] The stereochemical outcome was in agreement with previously observed additions to *N*-sulfinyl ketimines, in which the incoming nucleophile coordinates the sulfinyl imine oxygen in a six-membered transition state (Fig. 2).

The 1,2-addition product **4b** proved to be an orthogonally protected building block. Whereas treatment with hydrochloric acid in methanol gave free amine **6** in good yield (73%), alcohol **5** could be smoothly revealed upon treatment with TBAF in THF. Both protecting groups could be also simultaneously removed upon treatment with 37% aqueous hydrochloric acid in dioxane at reflux temperature. The enantiomeric purity of (*R*)-aminoalcohol **7** (97% ee) was determined by chiral supercritical fluid chromatography (SFC),[23] and the absolute configuration was confirmed by vibrational circular dichroism analysis (VCD). To expand the versatility of the process, the transformation into the corresponding Boc-protected amino acid derivative **9** was also demonstrated (Scheme 2). This procedure constitutes then a new approach for the synthesis of acyclic quaternary α-amino acids.[12,13]

The usefulness of this methodology was demonstrated by the synthesis of a nanomolar BACE1 inhibitor (**15**) from our recently reported BACE1 chemical series.[14] Previously, the preparation of these analogues series relied on a racemic synthesis with later chiral SFC for the isolation of enantiomerically pure intermediates and final products. As shown in Scheme 3, (*R*)-aminoalcohol **7** was treated with 2-chloroacetyl chloride at −78 °C to give the corresponding chloroamide intermediate which after addition of KO*t*Bu and warming to −10 °C, gave morpholinone **10** in 87% yield. The amide functionality was smoothly transformed into amidine **12** *via* the corresponding thioamide **11**. A Buchwald-type coupling using benzophenone imine as ammonia synthetic equivalent yielded protected amidine **13** in 82% yield. Finally, hydrolysis of the imine to give **14**, and subsequent coupling with 5-chloropyridine-2-carboxylic acid provided the enantiomerically pure target compound (*R*)-**15** with moderate yield (70%). Interestingly, the protection of the sensitive amidine functionality could be avoided by using *N*,*N*-dimethylaniline as base in the final amide coupling.[24] Compound **15** showed 130 and 6.9 nM activity in the enzymatic and cellular hAβTOT assays respectively.[25] This result demonstrates that the presence of a carbonyl in the amidine containing ring is not required for *in vitro* potency.[26] Moreover, there are no difficulties with cell permeation as this and other compounds of the 1,4-oxazineamines series[14] show good cellular activity.

Conclusions

We have described an expeditious synthesis of enantiomerically pure β,β-dibranched aminoalcohols making use of Ellman's sulfinyl chemistry. The efficiency of the process, both in terms of yield and stereocontrol is combined with a high degree of experimental simplicity. Noteworthy is the fact that the nucleophiles are simple commercially available Grignard reagents and that the chemistry is amenable to being carried out on a multigram scale.

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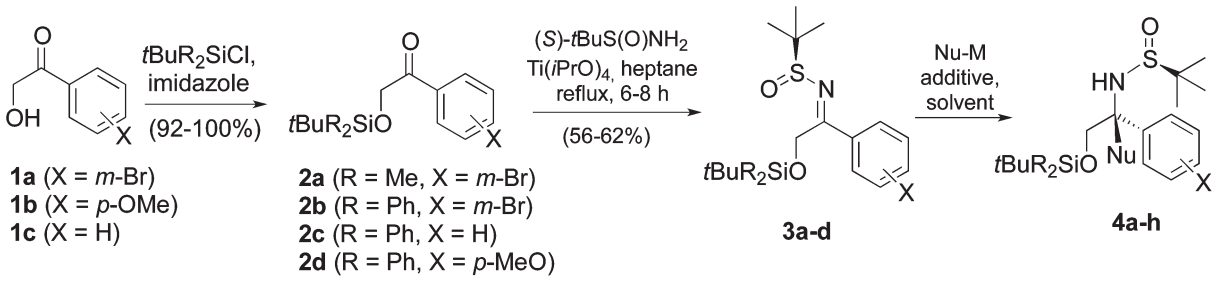
Table 1 Optimization and substrate scope of the 1,2-addition to sulfinyl imines **3**



1a (X = *m*-Br)
1b (X = *p*-OMe)
1c (X = H)

2a (R = Me, X = *m*-Br)
2b (R = Ph, X = *m*-Br)
2c (R = Ph, X = H)
2d (R = Ph, X = *p*-MeO)

3a-d

4a-h

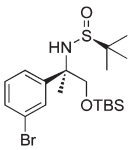
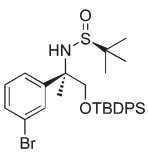
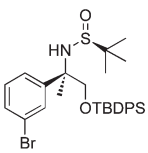
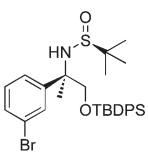
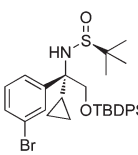
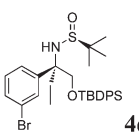
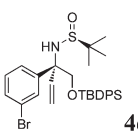
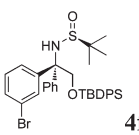
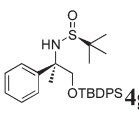
Entry	Imine	Product	Nu-M/additive	Solvent	Yield[a] (%)	d.r.[b]
1	**3a** (R = Me, X = *m*-Br)	 **4a**	$MeLi/AlMe_3$	Toluene	29	95 : 5
2	**3b** (R = Ph, X = *m*-Br)	 **4b**	$MeLi/AlMe_3$	Toluene	59	>97 : 3
3	**3b** (R = Ph, X = *m*-Br)	 **4b**	MeLi	Toluene	0	—
4	**3b** (R = Ph, X = *m*-Br)	 **4b**	MeMgBr	CH_2Cl_2	92	>97 : 3
5	**3b** (R = Ph, X = *m*-Br)	 **4c**	*c*-PrMgBr	CH_2Cl_2	69	>97 : 3
6	**3b** (R = Ph, X = *m*-Br)	 **4d**	EtMgBr	CH_2Cl_2	75	>97 : 3
7	**3b** (R = Ph, X = *m*-Br)	 **4e**	$H_2C{=}CHMgBr$	CH_2Cl_2	75	>97 : 3
8	**3b** (R = Ph, X = *m*-Br)	 **4f**	PhMgBr	CH_2Cl_2	0	—
9	**3c** (R = Ph, X = H)	 **4g**	MeMgBr	CH_2Cl_2	78	>97 : 3

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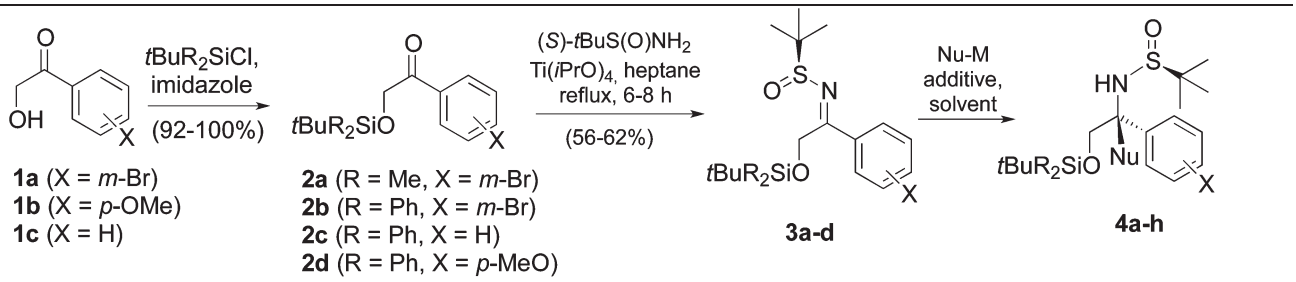
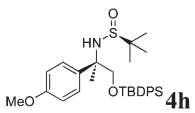
Table 1 *(Contd.)*



Entry	Imine	Product	Nu-M/additive	Solvent	Yield[a] (%)	d.r.[b]
10	**3d** (R = Ph, X = *p*-MeO)	 **4h**	MeMgBr	CH_2Cl_2	62	>97 : 3

[a] Isolated yields. [b] Determined by ^{1}H NMR.

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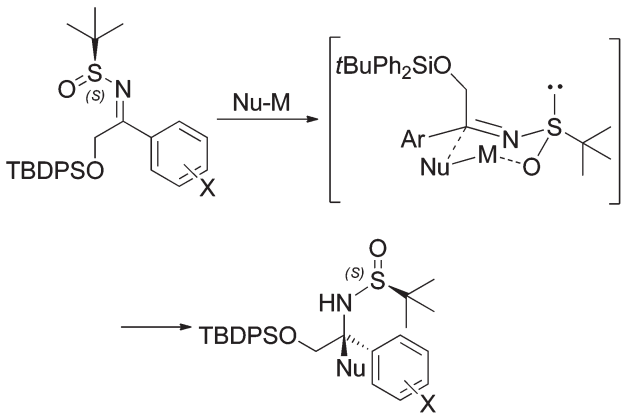

Fig. 2 Proposed transition state for the 1,2-addition of Grignard reagents to sulfinyl imines **3**.

Efforts directed towards the preparation of additional analogues of protease inhibitors bearing this moiety are currently under way in our laboratories and will be reported in due course.

Experimental section

1-(3-Bromophenyl)-2-(*tert*-butyldiphenylsilyloxy)ethanone (2b)

tert-Butyl(chloro) diphenylsilane (1.42 ml, 5.50 mmol) was added dropwise to a stirred solution of 2-hydroxy-1-(3-bromophenyl)ethanone[18] (1.08 g, 5.02 mmol) and imidazole (0.37 g, 5.50 mmol) in CH_2Cl_2 (50 ml) at room temperature under nitrogen. Then DMAP (40 mg, 0.32 mmol) was added and the resulting mixture was stirred at room temperature for 90 minutes. The mixture was treated with water and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4) and the solvents evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel; EtOAc in Hexane 0/100 to 20/80) to yield ketone **2b** as a colorless oil (2.4 g, 100%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9H), 4.78 (s, 2H), 7.23 (t, J = 7.9 Hz, 1H), 7.30–7.39 (m, 6H), 7.58–7.71 (m, 6H), 7.93 (t, J = 1.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 19.3, 26.7, 67.7, 122.8, 126.4, 127.8, 129.9, 130.1, 131.1, 132.7, 135.6, 136.0, 136.7, 195.7. HRMS (FAB) calcd for $C_{24}H_{25}O_2BrSiNa$ [M + Na^+]: 475.0699, found: 475.0689.

General procedure for the synthesis of ketimines 3

(*S*)-(−)-2-Methyl-2-propanesulfinamide (1.4 eq.) was added to a stirred solution of ketone **2** (1.0 eq.) and titanium tetraisopropoxide (2.5 eq.) in heptane (6 ml $mmol^{-1}$) at room temperature under nitrogen. The mixture was heated at 90 °C for 2.5 hours and then allowed to reach room temperature. The mixture was poured into an equal volume of brine while rapidly stirring. The resulting suspension was filtered through a plug of Celite, and the filter cake was washed with EtOAc. The layers were separated and the organic phase was washed with brine, dried, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel; EtOAc in hexane gradient) to yield imine **3**.

(*S*,*Z*)-*N*-(1-(3-Bromophenyl)-2-(*tert*-butyldiphenylsilyloxy)-ethylidene)-2-methylpropane-2-sulfinamide (3b). The title compound was obtained according to the general procedure described above starting from ketone **2b** (1.20 g, 2.64 mmol). Purification by flash chromatography (silica gel; EtOAc in hexane gradient from 0/100 to 10/90) gave imine **3b** (0.87 g, 60%) as a bright yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.00 (s, 9H), 1.24 (s, 9H), 5.03 (br d, J = 12.7 Hz, 1H), 5.32 (br d, J = 12.7 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.36–7.49 (m, 6H), 7.53–7.66 (m, 6H), 7.87 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 19.1, 22.6, 26.6, 58.0, 61.3, 122.1, 127.0, 127.5, 127.8 (2C), 129.5, 129.9, 131.5, 132.4, 133.6, 134.7, 135.5 (2C), 138.8, 176.1. HRMS (FAB) calcd for $C_{28}H_{35}NO_2SSiBr$ [M + H^+]: 556.1336, found: 556.1348.

(*S*,*Z*)-*N*-(2-(*tert*-Butyldiphenylsilyloxy)-1-(4-methoxyphenyl)-ethylidene)-2-methylpropane-2-sulfinamide (3d). The title compound was obtained according to the general procedure

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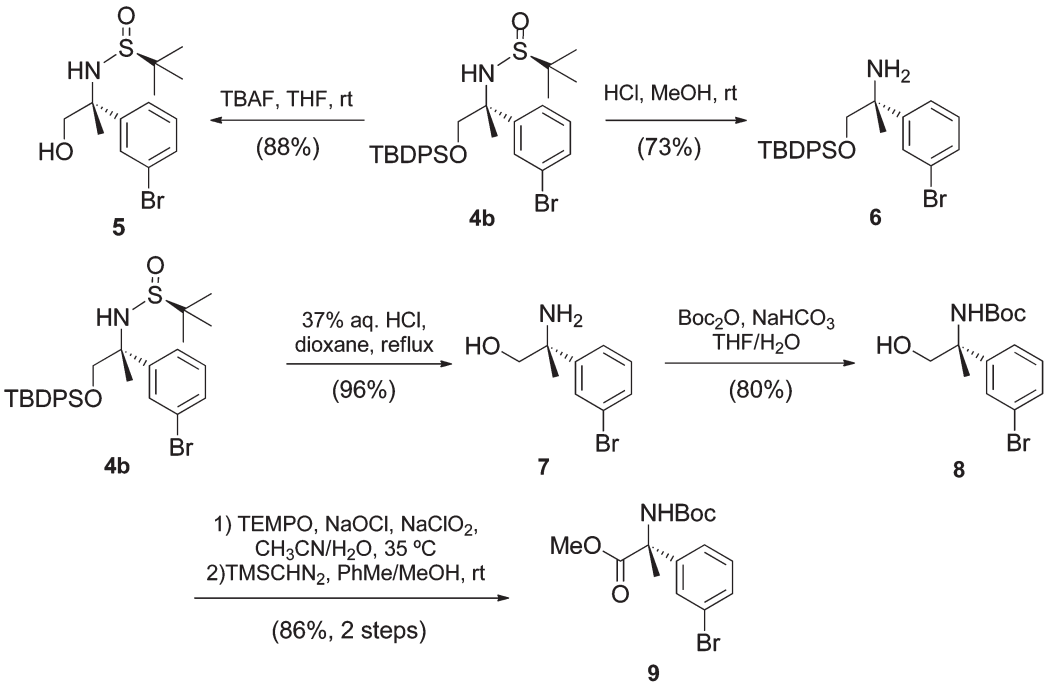
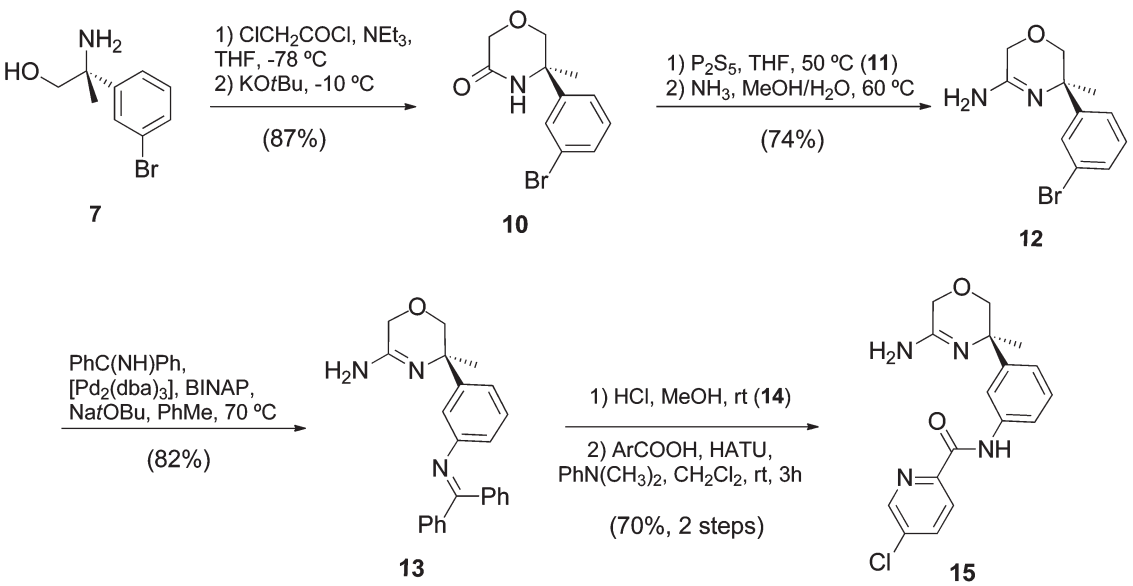


Scheme 2 Synthesis of aminoester **9**.



Scheme 3 Synthesis of BACE1 inhibitor **15**.

described above starting from ketone **2d**[27] (136 mg, 0.26 mmol). Purification by flash chromatography (silica gel; EtOAc in hexane gradient from 0/100 to 10/90) gave imine **3d** (81 mg, 62%) as a bright yellow oil. $[\alpha]_D^{25}$ = +7.8 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.00 (s, 9H), 1.24 (s, 9H), 3.85 (s, 3H), 4.97 (br s, 1H), 5.24 (br s, 1H), 6.85–6.90 (m, 2H), 7.34–7.46 (m, 6H), 7.62–7.82 (m, 6H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 19.2, 22.5, 26.7, 55.3, 57.2, 61.3, 113.4, 127.7, 127.8, 129.4, 129.9 (2C), 130.5 (2C), 132.7 (2C), 135.6 (2C), 162.1. HRMS (FAB) calcd for $C_{29}H_{38}NO_3SSi$ [M + H^+]: 508.2336, found: 508.2336.

General procedure for the synthesis of sulfinamides 4

A solution of imine **3** (1.0 eq.) in CH_2Cl_2 (6 ml $mmol^{-1}$) was added dropwise to a stirred solution of the corresponding Grignard reagent (3 M in Et_2O or 1 M in THF, 5.0 eq.) in CH_2Cl_2 (6 ml $mmol^{-1}$) at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 20 minutes and then quenched by the addition of 0.5 N HCl. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash

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chromatography (silica gel; EtOAc in hexane gradient) to afford compound **4**.

(*S*)-*N*-((*R*)-2-(3-Bromophenyl)-1-(*tert*-butyldiphenylsilyloxy)-propan-2-yl)-2-methylpropane-2-sulfinamide (4b). The title compound was obtained according to the general procedure described above starting from imine **3b** (0.45 g, 0.81 mmol) and methylmagnesium bromide (3 M in Et_2O, 1.47 ml, 4.42 mmol). Flash chromatography (silica gel; EtOAc in hexane gradient from 5/95 to 35/65) gave **4b** (0.425 g, 92%) as a white solid. Mp 131.2 °C. $[\alpha]_D^{25}$ = +3.8 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.98 (s, 9H), 1.26 (s, 9H), 1.60 (s, 3H), 3.76 (d, *J* = 9.7 Hz, 1H), 3.81 (d, *J* = 9.7 Hz, 1H), 4.33 (s, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.29–7.44 (m, 9H), 7.51–7.59 (m, 3H), 7.62 (t, *J* = 1.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 19.1, 22.6, 24.9, 26.6, 56.1, 61.7, 72.3, 122.3, 126.0, 127.7 (2C), 129.6, 129.8 (2C), 130.1, 130.2, 132.3, 132.7, 135.3 (2C), 146.7. HRMS (FAB) calcd for $C_{25}H_{31}NOSiBr$ [M − (*t*-BuSO) + H^+]: 468.1353, found: 468.1345.

(*S*)-*N*-((*R*)-1-(3-Bromophenyl)-2-(*tert*-butyldiphenylsilyloxy)-1-cyclopropylethyl)-2-methylpropane-2-sulfinamide (4c). Bromocyclopropane (0.63 ml, 7.90 mmol) was added to a suspension of magnesium turnings (208 mg, 7.90 mmol) in Et_2O (4 ml) at room temperature. The resulting mixture was refluxed for 30 minutes and allowed to reach room temperature. A solution of imine **3b** (0.88 g, 1.58 mmol) in CH_2Cl_2 (10 ml) was added dropwise to the freshly prepared solution of cyclopropylmagnesium bromide at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 10 minutes and then quenched by the addition of 0.5 N HCl (5 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel; EtOAc in hexane gradient from 5/95 to 40/60) to yield **4c** (0.65 g, 69%) as a colorless oil. $[\alpha]_D^{25}$ = −2.4 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.15–0.23 (m, 1H), 0.32–0.40 (m, 1H), 0.42–0.51 (m, 1H), 0.53–0.64 (m, 1H), 0.94 (s, 9H), 1.10–1.21 (m, 1H), 1.25 (s, 9H), 3.77 (d, *J* = 9.8 Hz, 1H), 3.99 (d, *J* = 9.8 Hz, 1H), 4.31 (s, 1H), 7.20 (t, *J* = 8.3 Hz, 1H), 7.32–7.59 (m, 9H), 7.58–7.64 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 1.6, 2.2, 17.8, 19.0, 22.7, 26.6, 56.0, 64.9, 70.3, 121.8, 127.6, 127.7 (2C), 129.3, 129.8 (2C), 130.1, 131.7, 132.2, 132.7, 135.4, 135.6, 143.5. HRMS (FAB) calcd for $C_{31}H_{41}NO_2BrSSi$ [M + H^+]: 598.1805, found: 598.1802.

(*S*)-*N*-((*R*)-2-(3-Bromophenyl)-1-(*tert*-butyldiphenylsilyloxy)-butan-2-yl)-2-methylpropane-2-sulfinamide (4d). The title compound was obtained according to the general procedure described above starting from imine **3b** (100 mg, 0.18 mmol) and ethylmagnesium bromide (1 M in THF, 0.89 ml, 0.89 mmol). Purification by flash chromatography (silica gel; EtOAc in hexane gradient from 5/95 to 50/50) gave **4d** (65 mg, 65%) as a colorless oil. $[\alpha]_D^{25}$ = +22.9 (*c* 0.87, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.63 (t, *J* = 7.3 Hz, 3H), 0.94 (s, 9H), 1.21 (s, 9H), 1.88 (dq, *J* = 14.7, 7.3 Hz, 1H), 2.00 (dq, *J* = 14.6, 7.3 Hz, 1H), 3.90 (AB q, *J* = 9.8 Hz, 2H), 4.10 (s, 1H), 7.12 (t, *J* = 7.9 Hz, 1H), 7.28–7.40 (m, 8H), 7.43–7.54 (m, 5H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 7.8, 19.2, 22.8, 26.8, 30.2, 56.4, 64.8, 68.5, 122.4, 126.1, 127.7 (2C), 129.6, 129.8 (2C), 130.2, 130.6, 132.5, 132.9, 135.6, 135.7, 144.4. HRMS (FAB) calcd for $C_{30}H_{41}NO_2BrSSi$ [M + H^+]: 586.1805, found: 586.1808.

(*S*)-*N*-((*R*)-2-(3-Bromophenyl)-1-(*tert*-butyldiphenylsilyloxy)-but-3-en-2-yl)-2-methylpropane-2-sulfinamide (4e). The title compound was obtained according to the general procedure described above starting from imine **3b** (100 mg, 0.18 mmol) and vinylmagnesium bromide (1 M in THF, 0.54 ml, 0.54 mmol). Purification by flash chromatography (silica gel; EtOAc in hexane gradient from 5/95 to 50/50) gave **4e** (78 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ = +23.3 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.98 (s, 9H), 1.26 (s, 9H), 3.95 (d, *J* = 9.6 Hz, 1H), 4.13 (d, *J* = 9.6 Hz, 1H), 4.42 (s, 1H), 5.24 (dd, *J* = 17.4, 0.6 Hz, 1H), 5.36 (dd, *J* = 10.8, 0.6 Hz, 1H), 5.94 (dd, *J* = 17.4, 10.8 Hz, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.33–7.51 (m, 10H), 7.57–7.61 (m, 3H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 19.5, 23.1, 27.0, 56.7, 66.5, 70.2, 117.8, 122.6, 127.5, 128.1 (2C), 129.9, 130.2 (2C), 131.0, 131.9, 132.7, 133.1, 135.9, 136.0, 140.2, 143.1. HRMS (FAB) calcd for $C_{30}H_{38}NO_2BrSSi$ [M + H^+]: 584.1649, found: 584.1639.

(*S*)-*N*-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-phenylpropan-2-yl)-2-methylpropane-2-sulfinamide (4g). The title compound was obtained according to the general procedure described above starting from imine **3c**[17] (96 mg, 0.21 mmol) and methylmagnesium bromide (3 M in Et_2O, 0.36 ml, 1.08 mmol). Purification by flash chromatography (silica gel; EtOAc in hexane gradient from 5/95 to 40/60) gave **4g** (81 mg, 78%) as a colorless oil. $[\alpha]_D^{25}$ = +0.3 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 9H), 1.25 (s, 9H), 1.67 (3H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.86 (d, *J* = 9.6 Hz, 1H), 4.31 (s, 3H), 7.26–7.40 (m, 11H), 7.48–7.56 (m, 4H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 19.2, 22.7, 25.0, 26.7, 56.0, 61.9, 72.5, 127.0, 127.2, 127.6, 127.7, 128.1, 129.7 (2C), 132.6, 133.0, 135.6 (2C), 143.8. HRMS (FAB) calcd for $C_{29}H_{40}NO_2SSi$ [M + H^+]: 494.2544, found: 494.2547.

(*S*)-*N*-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)-2-(4-methoxyphenyl)-propan-2-yl)-2-methylpropane-2-sulfinamide (4h). The title compound was obtained according to the general procedure described above starting from imine **3d** (40 mg, 0.078 mmol) and methylmagnesium bromide (3 M in Et_2O, 0.131 ml, 0.39 mmol). Purification by flash chromatography (silica gel; EtOAc in hexane gradient from 5/95 to 40/60) gave **4h** (31 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ = +8.1 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 9H), 1.24 (s, 9H), 1.62 (s, 3H), 3.76 (d, *J* = 9.6 Hz, 1H), 3.81 (s, 3H), 3.86 (d, *J* = 9.6 Hz, 1H), 4.27 (s, 1H), 6.86 (d, *J* = 8.9 Hz, 2H), 7.31–7.44 (m, 10H), 7.53–7.58 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 18.9, 22.5, 25.0, 26.5, 55.0, 55.7, 61.1, 72.2, 113.1, 127.4, 127.5, 128.0, 129.5 (2C), 132.5, 132.8, 135.3, 135.4, 135.5, 158.5. HRMS (FAB) calcd for $C_{30}H_{42}NO_3SSi$ [M + H^+]: 524.2649, found: 524.2672.

(*S*)-*N*-((*R*)-2-(3-Bromophenyl)-1-hydroxypropan-2-yl)-2-methylpropane-2-sulfinamide (5). TBAF (1 M in THF, 0.73 ml, 0.73 mmol) was added dropwise to a stirred solution of sulfinyl amine **4b** (320 mg, 0.56 mmol) in THF (5 ml) at room temperature. The mixture was stirred for 3 hours at room temperature. The mixture was treated with water and extracted with EtOAc.

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The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel; MeOH in CH_2Cl_2 0/100 to 10/90). The desired fractions were collected and concentrated *in vacuo* to yield alcohol **5** (164 mg, 88%) as a white solid. Mp 151.1 °C. $[\alpha]_D^{25}$ = +45.1 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 9H), 1.49 (s, 3H), 3.72–3.94 (m, 3H), 4.21 (d, *J* = 10.1 Hz, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 7.32–7.36 (m, 1H), 7.42 (ddd, *J* = 7.9, 1.9, 1.1 Hz, 1H), 7.59 (t, *J* = 1.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 22.6, 29.3, 56.5, 61.8, 68.1, 122.6, 124.9, 129.9, 130.0, 130.4, 145.8. HRMS (FAB) calcd for $C_{13}H_{21}NO_2SBr$ [M + H^+]: 334.0471, found: 334.0484.

(*R*)-2-(3-Bromophenyl)-1-(*tert*-butyldiphenylsilyloxy)propan-2-amine (6). HCl (2 M in Et_2O, 1.0 ml, 2.0 mmol) was added dropwise to a stirred solution of sulfinyl amine **4b** (160 mg, 0.28 mmol) in MeOH (2 ml) at room temperature. The mixture was stirred for 2 hours at room temperature. The mixture was treated with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel; MeOH in CH_2Cl_2 0/100 to 5/95). The desired fractions were collected and concentrated *in vacuo* to yield amine **6** (95 mg, 73%) as a colorless oil. $[\alpha]_D^{25}$ = +6.6 (*c* 1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.02 (s, 9H), 1.45 (s, 3H), 1.79 (s, 2H), 3.60–3.68 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.31–7.52 (m, 10H), 7.56–7.62 (m, 2H), 7.66 (t, *J* = 1.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 19.2, 26.8, 27.0, 56.4, 73.3, 122.4, 124.5, 127.7, 129.3, 129.5, 129.7, 133.0, 133.1, 135.5, 149.2. HRMS (FAB) calcd for $C_{25}H_{31}NOSiBr$ [M + H^+]: 468.1358, found: 468.1374.

(*R*)-2-Amino-2-(3-bromophenyl)propan-1-ol (7). HCl (37% in H_2O, 10 ml) was added dropwise to a stirred solution of sulfinyl amine **4b** (0.96 g, 1.67 mmol) in 1,4-dioxane (10 ml) at room temperature. The mixture was refluxed for 3 hours and then allowed to reach room temperature. The mixture was basified with sat. aq. Na_2CO_3 and extracted with EtOAc. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel; 7 N NH_3/MeOH in CH_2Cl_2 0/100 to 10/90). The desired fractions were collected and concentrated *in vacuo* to yield amino alcohol **7** (340 mg, 88%) as a glassy solid. $[\alpha]_D^{25}$ = −9.7 (*c* 0.64, MeOH). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3H), 2.47 (s, 3H), 3.55 (AB q, *J* = 10.8 Hz, 2H), 7.20 (t, *J* = 7.9 Hz, 1H), 7.31–7.40 (m, 2H), 7.59 (t, *J* = 1.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 26.9, 56.4, 71.3, 122.7, 124.1, 128.8, 129.8, 129.9, 148.6. HRMS (FAB) calcd for $C_9H_{13}NOBr$ [M + H^+]: 230.0175, found: 230.0169.

(*R*)-*tert*-Butyl 2-(3-bromophenyl)-1-hydroxypropan-2-yl carbamate (8). Di-*tert*-butyl dicarbonate (137 mg, 0.63 mmol) was added portion wise to a stirred mixture of **7** (48 mg, 0.21 mmol) in THF (4 ml) and sat. aq. $NaHCO_3$ (4 ml) at 0 °C. The mixture was stirred at room temperature for 16 hours. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel; EtOAc in hexane 0/100 to 20/80) to afford alcohol **8** (53 mg, 80%) as a colorless oil. $[\alpha]_D^{25}$ = −6.1 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.40 (br s, 9H), 1.58 (s, 3H), 3.53–3.77 (m, 3H), 5.30 (br s, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.38 (ddd, *J* = 7.8, 1.8, 1.2 Hz, 1H), 7.55 (t, *J* = 1.8 Hz, 1H), 7. ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 24.5, 28.2, 59.6, 70.8, 80.2, 122.7, 124.3, 128.9, 130.0, 130.1, 146.0, 155.8. HRMS (FAB) calcd for $C_{14}H_{20}NO_3BrNa$ [M + Na^+]: 352.0519, found: 352.0509.

(*R*)-Methyl 2-(3-bromophenyl)-2-(*tert*-butoxycarbonylamino)-propanoate (9). A solution of $NaClO_2$ (80% purity, 27 mg, 0.24 mmol) in sodium phosphate buffer (pH = 6.7) was added dropwise to a stirred mixture of alcohol **8** (40 mg, 0.121 mmol) and TEMPO (1.9 mg, 0.012 mmol) in acetonitrile (1 ml) at room temperature. The reaction temperature was risen to 35 °C and then a solution of NaOCl (14% active Cl, 5 μL) in water (1 ml) was added dropwise over a period of 1 hour. The reaction mixture was stirred at 35 °C for 18 hours. After cooling the reaction mixture to 25 °C, water was added and the pH was adjusted to 8.0 by addition of 2 N NaOH. The reaction mixture was then poured into ice-cold sodium sulfite solution. After stirring for 30 minutes at room temperature Et_2O was added and the organic layer was separated and discarded. More Et_2O was added and the mixture was acidified with 2 N HCl to pH 3–4. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine and then concentrated *in vacuo* to yield the crude carboxylic acid as a white solid. This material was dissolved in a mixture of toluene (2 ml) and MeOH (0.2 ml) at room temperature. Then TMS–diazomethane (2 M in hexane, 0.104 ml, 0.21 mmol) was added and the mixture was stirred at room temperature for 30 minutes. The excess diazomethane was quenched by the addition of few droplets of AcOH and the solvents were evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel; EtOAc in hexane 10/90 to 40/60). The desired fractions were collected and concentrated *in vacuo* to yield methyl ester **9** (32 mg, 86%) as a colorless oil. $[\alpha]_D^{25}$ = −42.9 (*c* 1.07, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.36 (br s, 3H), 1.97 (s, 3H), 3.70 (s, 3H), 5.90 (br s, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.36–7.43 (m, 2H), 7.58 (t, *J* = 1.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 23.1, 28.2, 53.2, 61.4, 80.1, 122.6, 124.6, 129.2, 130.0, 130.8, 143.3, 153.9, 173.1. HRMS (FAB) calcd for $C_{15}H_{20}NO_4BrNa$ [M + Na^+]: 380.0468, found: 380.0477.

(*R*)-5-(3-Bromophenyl)-5-methylmorpholin-3-one (10). 2-Chloroacetylchloride (0.658 ml, 8.26 mmol) was added dropwise to a stirred solution of amino alcohol **7** (1.90 g, 8.26 mmol) and DIPEA (1.71 ml, 9.90 mmol) in THF (70 ml) at −78 °C. The mixture was stirred for 20 minutes at −78 °C. Then potassium *tert*-butoxide (2.32 g, 20.6 mmol) was added and the mixture was allowed to reach −10 °C over 60 minutes. The mixture was diluted with saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel; MeOH in CH_2Cl_2 0/100 to 3/97). The desired fractions were collected and the solvents evaporated *in vacuo* to yield lactam **10** (1.93 g, 87%) as a white solid. Mp 127.8 °C. $[\alpha]_D^{25}$ = −66.5 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 3H), 3.73 (d, *J* = 11.7 Hz, 1H), 3.85 (d, *J* = 11.7 Hz, 1H), 4.24 (s, 2H), 6.85 (br s, 1H),

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7.26–7.37 (m, 2H), 7.47 (dt, J = 7.7, 1.5 Hz, 1H), 7.56 (t, J = 1.9 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 25.8, 57.7, 67.4, 74.3, 123.0, 124.1, 128.7, 130.3, 130.8, 145.3, 169.2. HRMS (FAB) calcd for $C_{11}H_{12}NO_2Br$ [M + H^+]: 270.0124, found: 270.0116.

(*R*)-5-(3-Bromophenyl)-5-methylmorpholine-3-thione (11). Phosphorus pentasulfide (3.29 g, 14.8 mmol) was added to a solution of amide **10** (5.00 g, 18.5 mmol) in THF (192 ml) at room temperature. The mixture was stirred at 50 °C for 60 minutes and then allowed to reach room temperature. The mixture was filtered over cotton and evaporated *in vacuo*. The crude product was purified by flash column chromatography (silica gel; CH_2Cl_2). The desired fractions were collected and evaporated *in vacuo* to yield thioamide **11** (4.70 g, 89%) as a sticky foam. $[\alpha]_D^{25}$ = −137.6 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.70 (s, 3H), 3.75 (d, J = 11.8 Hz, 1H), 3.87 (d, J = 11.8 Hz, 1H), 4.57 (s, 2H), 7.26–7.30 (m, 2H), 7.45–7.50 (m, 2H), 8.80 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 24.7, 59.2, 73.0, 73.6, 123.2, 124.3, 128.8, 130.5, 131.4, 143.7, 198.8. HRMS (FAB) calcd for $C_{11}H_{13}NOSBr$ [M + H^+]: 285.9896, found: 285.9903.

(*R*)-5-(3-Bromophenyl)-5-methyl-5,6-dihydro-2*H*-1,4-oxazin-3-amine (12). A suspension of thioamide **11** (1.86 g, 6.50 mmol) in ammonia (32% aqueous, 30 ml) was stirred at 60 °C for 3 hours in a sealed tube. The mixture was cooled to 0 °C and a 7 N solution of ammonia in MeOH (10 ml, 70 mmol) was added. The resulting mixture was stirred at 60 °C for 3 hours. The mixture was cooled to room temperature, diluted with water and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash chromatography (silica gel; MeOH in CH_2Cl_2 0/100 to 5/95; then (7 N ammonia in MeOH) in CH_2Cl_2 5/95). The desired fractions were collected and concentrated *in vacuo* to yield amidine **12** (1.45 g, 83%) as a glassy solid. $[\alpha]_D^{25}$ = −125.8 (*c* 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 3H), 3.54 (d, J = 11.3 Hz, 1H), 3.65 (d, J = 11.3 Hz, 1H), 3.97–4.14 (m, 4H), 7.18 (t, J = 7.8 Hz, 1H), 7.28–7.38 (m, 2H), 7.57 (t, J = 1.8 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 26.8, 56.0, 62.6, 73.3, 122.5, 124.4, 129.3, 129.6, 129.7, 148.7, 156.2. HRMS (FAB) calcd for $C_{11}H_{14}BrN_2O$ [M + H^+]: 269.0284, found: 269.0293.

(*R*)-5-[3-(Benzhydrylideneamino)phenyl]-5-methyl-2,6-dihydro-2*H*-1,4-oxazin-3-amine (13). The mixture of amidine **12** (130 mg, 0.48 mmol), $Pd_2(dba)_3$ (44 mg, 0.048 mmol), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (90 mg, 0.145 mmol) and sodium *tert*-butoxide (69 mg, 0.72 mmol) in toluene (4 ml) was purged with nitrogen for five minutes before the addition of benzophenone imine (0.105 ml, 0.628 mmol). The resulting mixture was stirred in a sealed tube at 70 °C for 18 hours. After cooling, the solvents were removed *in vacuo*. The crude product was purified by flash chromatography (silica gel; 7 N NH_3 in MeOH in CH_2Cl_2 0/100 to 6/94). The desired fractions were collected and concentrated *in vacuo* to yield **13** (146 mg, 82%) as a yellow oil. $[\alpha]_D^{25}$ = −16.1 (*c* 0.51, DMF). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 3.27 (d, J = 11.3 Hz, 1H), 3.49 (d, J = 11.3 Hz, 1H), 3.94 (d, J = 15.3 Hz, 1H), 4.06 (d, J = 15.5 Hz, 1H), 6.64–6.71 (m, 2H), 6.96–7.02 (m, 1H), 7.08–7.15 (m, 3H), 7.21–7.27 (m, 3H), 7.38–7.49 (m, 3H), 7.72–7.77 (m, 2H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 26.4, 56.0, 62.7, 73.5, 118.9, 119.7, 120.8, 127.9, 128.2, 128.3, 128.4, 129.3, 129.6, 130.6, 136.3, 139.7, 146.3, 150.9, 155.9, 168.3. HRMS (FAB) calcd for $C_{24}H_{24}N_3O$ [M + H^+]: 370.1919, found: 370.1910.

(*R*)-5-(3-Aminophenyl)-5-methyl-5,6-dihydro-2*H*-1,4-oxazin-3-amine (14). The mixture of amidine **12** (1.00 g, 3.71 mmol), $Pd_2(dba)_3$ (340 mg, 0.17 mmol), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (694 mg, 1.11 mmol) and sodium *tert*-butoxide (535 mg, 5.57 mmol) in toluene (30 ml) was purged with nitrogen for five minutes before the addition of benzophenone imine (0.810 ml, 4.83 mmol). The resulting mixture was stirred in a sealed tube at 70 °C for 18 hours. After cooling, 1 N HCl (20 ml) was added and the mixture stirred at room temperature for 1 hour. The mixture was diluted with water and washed with EtOAc. The aqueous layer was basified with sat. aq. Na_2CO_3 and extracted with CH_2Cl_2/EtOH (9/1, 10 times). The combined organic layers were dried (Na_2SO_4), filtered and the solvents concentrated *in vacuo*. The crude product was purified by flash column chromatography (silica gel; 7 N NH_3 in MeOH in CH_2Cl_2 0/100 to 10/90). The desired fractions were collected and concentrated *in vacuo* to yield **14** (410 mg, 54%) as a glassy solid. This material was used in the following reaction without further purification.

(*R*)-*N*-(3-(5-Amino-3-methyl-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-phenyl)-5-chloropicolinamide (15). 5-Chloropyridine-2-carboxylic acid (28 mg, 0.146 mmol) was added to a solution of amidine **14** (20 mg, 0.097 mmol) in CH_2Cl_2 (1.5 ml) at room temperature. Then *N*,*N*-dimethylaniline (18.5 µl, 0.146 mmol) was added and after stirring for 5 minutes at room temperature, HATU (42 mg, 0.112 mmol) was added. The mixture was stirred at room temperature for 2.5 hours. The mixture was diluted with water and sat. Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), filtered and the solvents evaporated *in vacuo*. The crude product was purified by flash chromatography (silica; (7 N ammonia in MeOH) in CH_2Cl_2 0/100 to 4/96). The desired fractions were collected and concentrated *in vacuo*. The product was then purified again by flash chromatography (silica; MeOH in CH_2Cl_2 0/100 to 4/96). The desired fractions were collected and concentrated *in vacuo* yielding **15** (26 mg, 70%) as a sticky white product. $[\alpha]_D^{25}$ = −88.8 (*c* 0.68, DMF). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3H), 3.63 (d, J = 11.3 Hz, 1H), 3.74 (d, J = 11.6 Hz, 1H), 4.08–4.18 (m, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.70–7.80 (m, 2H), 7.89 (dd, J = 8.4, 2.3 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.55 (d, J = 2.0 Hz, 1H), 9.85 (br s, 1H). ^{13}C-NMR ($CDCl_3$, 100.6 MHz) δ 26.9, 56.2, 62.9, 73.5, 117.4, 118.1, 122.0, 123.4, 129.1, 135.3, 137.4, 137.5, 147.0, 147.2, 148.0, 156.5, 161.1. HRMS (FAB) calcd for $C_{17}H_{18}N_4O_2Cl$ [M + H^+]: 345.1118, found: 345.1114.

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