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Conformational restriction approach to β-secretase (BACE1) inhibitors III: Effective investigation of the binding mode by combinational use of X-ray analysis, isothermal titration calorimetry and theoretical calculations

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ABSTRACT

For further investigation of BACE1 inhibitors using conformational restriction with sp^3 hybridized carbon, we applied this approach to 6-substituted aminopyrimidone derivatives **3** to improve the inhibitory activity by reducing the entropic energy loss upon binding to BACE1. Among eight stereoisomers synthesized, [*trans*-(1′*R*,2′*R*),6*S*] isomer **6** exhibited the best BACE1 inhibitory activity, which was statistically superior to that of the corresponding ethylene linker compound (***R***)-**3**. Combinational examinations of the binding mode of **6** were performed, which included isothermal titration calorimetry (ITC), X-ray crystallographic structure analysis and theoretical calculations, to clarify the effect of our conformational restriction approach. From the ITC measurement, the binding entropy of **6** was found to be ~0.5 kcal larger than that of (***R***)-**3**, which is considered to be affected by conformational restriction with a cyclopropane ring.

1. Introduction

Alzheimer's disease (AD) is a progressive, neurodegenerative disorder of the brain, characterized by a gradual and progressive loss of memory and cognitive ability, impaired orientation to surroundings, decline of language ability, and inevitably leading to death. AD is currently considered to be the main cause of dementia, and its pathology includes gradual accumulation of amyloid-beta (Aβ) in the brain, the formation of soluble oligomers and senile plaques, and neurofibrillary tangles containing hyperphosphorylated tau protein, which eventually lead to neuronal death.[1] Aβpeptides, including Aβ42, which is thought to be the most pathogenic among the Aβs produced, are generated from amyloid precursor protein (APP) by the action of two key proteases, γ-secretase and β-secretase (BACE1).[2] Thus, BACE1 inhibitors have attracted considerable attentions as an attractive target for treatment of AD.[3] Many BACE1 inhibitors have been reported to date,[4] and recently the reduction of Aβ levels in human CSF has been reported in clinical trials by the inhibition of BACE1.[5]

The AstraZeneca/Astex group reported novel BACE1 inhibitors using a fragment-based drug discovery (FBDD) technique (Fig. 1).[6] Starting from the weak fragment hit **1** which bears an aminopyrimidone ring as a core component, they developed compound **2** bearing a phenyl ring with an ethylene linker. Moreover, introducing a methyl group at the 6-position of the pyrimidone ring was found to be highly effective, leading to a potent compound **3** with an IC_{50} value of 34 μM. Based on the X-ray structure of **3** complexed with BACE1, they incorporated another aromatic ring at the *meta* position of a phenyl ring. This led to compound **4** which has excellent inhibitory activity (IC_{50} 1.6 μM), and through further detailed SAR, to compound **5**, the (*R*)-enantiomer at the 6-position, which was found to exhibit an excellent IC_{50} of 80 nM. Thereafter, the substituted cyclic amidine unit has been utilized as the common motif employed in numerous BACE1 inhibitors.[7]

Our laboratory has been studying the synthesis of optically active cyclopropanes from commercially available chiral epichlorohydrin and their utilization in drug design. We successfully

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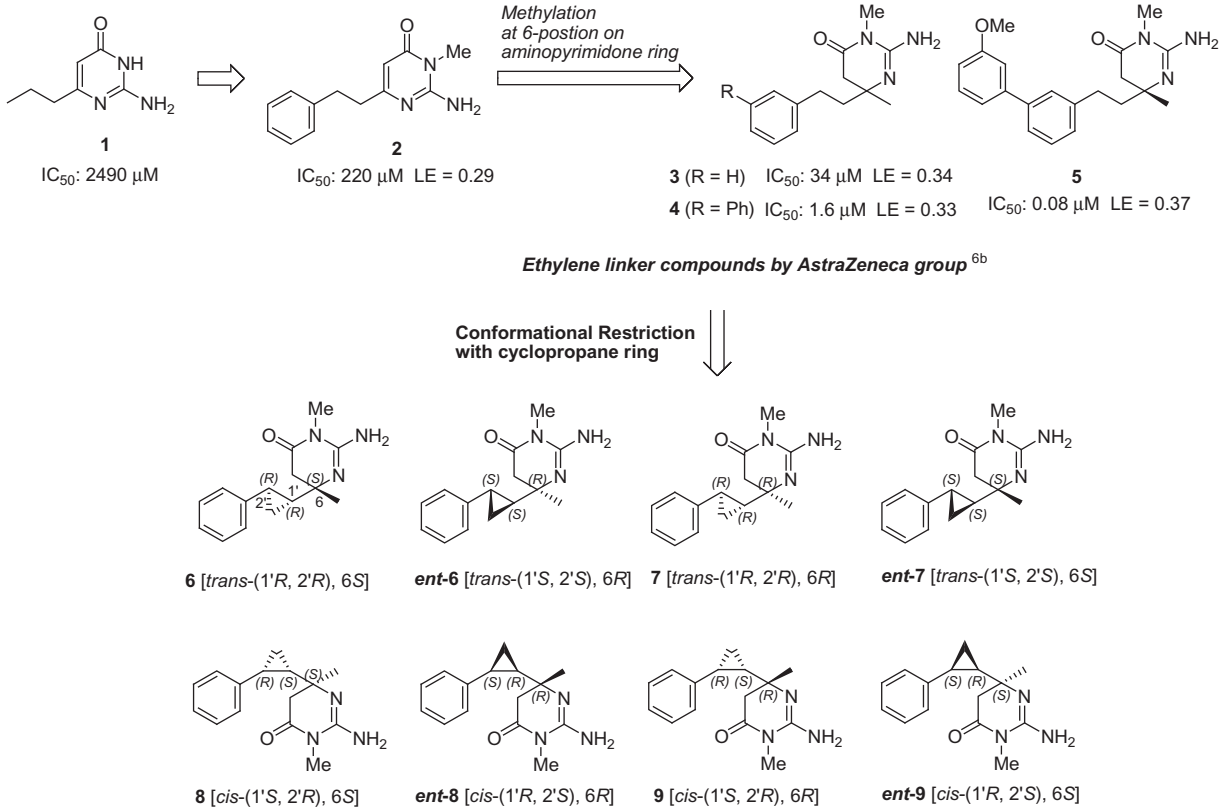


Figure 1. Basic concept of the compound design.

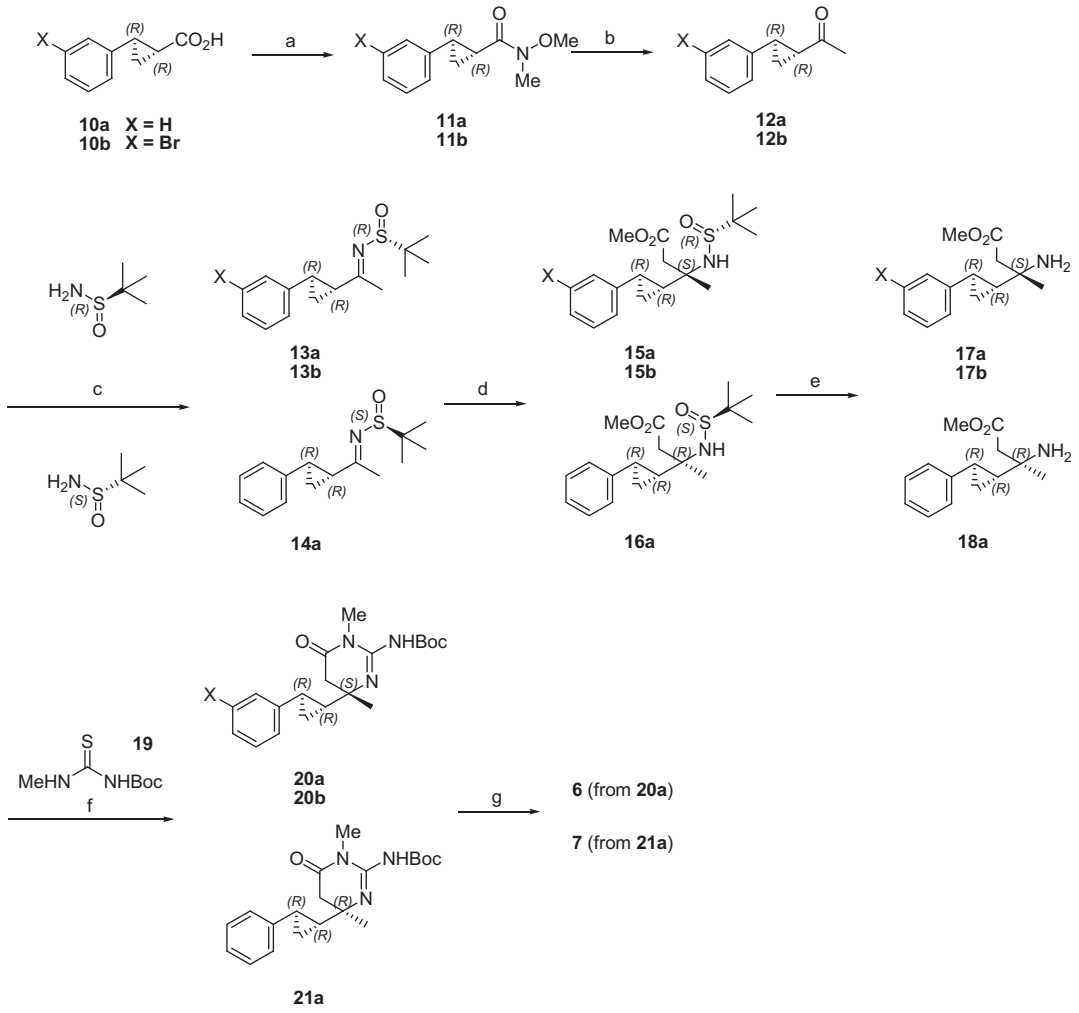
produced novel, selective NMDA antagonists,[8] histamine H_3 agonists,[9,10] and histamine H_3/H_4 antagonists,[10,11] whose conformation is effectively controlled by the characteristic stereochemical features of cyclopropane. In the previous papers, we reported studies on the cyclopropane-based conformational restriction approach using BACE1 inhibitor **2** as a lead.[12] The X-ray crystallographic structure analysis of the complex of BACE1 and the compounds whose ethylene linker was fixed with a cyclopropane ring revealed an unexpected binding mode, induced by a CH–π interaction between the rigid cyclopropane ring and the Tyr71 side chain. As a next step, we investigated the application of this approach to the 6-subsituted aminopyrimidone ring series to improve the inhibitory activity by reducing the entropic energy loss upon binding to BACE1 (Fig. 1). The ethylene linker part of compound **3** was replaced with a cyclopropane ring to design the conformationally restricted analogs **6**–**9** and their enantiomers ***ent*-6**–**9**. Among these synthesized stereoisomers, compound **6** found to be more active than the parent ethylene linker compound **3**. In order to gain further insight into the effect of our conformational restriction approach, we measured thermodynamic parameters upon binding of these conformationally restricted analogs to BACE1 by isothermal titration calorimetry (ITC) and also analyzed the X-ray crystallographic structure of **6** complexed with BACE1. This report presents the details of these studies.

2. Results and discussion

2.1. Syntheses of compounds

Compounds **6** and **7** were prepared in a stereoselective manner starting from chiral *trans*-(1*R*,2*R*)-phenylcyclopropane carboxylic acid **10a** (Scheme 1).[12,13] Compound **10a** was converted to methyl ketone **12a** through a Weinreb amide **11a**. Condensation of **12a** and (*R*)- or (*S*)-methylpropane sulfinamide using $Ti(OEt)_4$ yielded chiral sulfinylimines **13a** and **14a**.[14] Next, we tried to construct the chiral center by addition of a titanium ester enolate, prepared from a lithium enolate of methyl acetate and triisopropoxytitanium (IV) chloride, to the sulfinylimines.[15] Addition of the enolate to (*R*)-sulfinylimine **13a** gave 3-(*S*)-sulfinamide **15a** exclusively, while (*R*)-sulfinamide **16a** was obtained from (*S*)-sulfinylimine **14a**. These results indicate that the stereoselectivity of the reaction is strictly governed by the configuration of the sulfinyl moiety, irrespective of the stereochemistry of the cyclopropane ring. After removal of the chiral auxiliary under acidic conditions, the 6-methyl pyrimidone ring was constructed by condensation between thiourea **19**[7c,f,16] and aminoesters **17a** or **18a** to give the desired pyrimidone compounds **20a** and **21a** in excellent yield, respectively. Finally, removal of the Boc group with TFA yielded targets **6** and **7**, which were readily converted to the corresponding TFA salts. The TFA salt of **6** was contaminated with ~3% of the corresponding 6-methyl epimer, which was readily removed by recrystallization (for details, see Experimental Section). Their enantiomers ***ent*-6**, ***ent*-7**, and 3-bromo derivative **20b** were obtained from the carboxylic acid ***ent*-10a** or **10b**,[17] respectively. *cis* Isomers **8**, ***ent*-8**, **9** and ***ent*-9** were also prepared in the same manner, as shown in Scheme 2, starting from the corresponding chiral *cis*-phenylcyclopropane carboxylic acids **22** or ***ent*-22**.[18] The configuration of the 6-position of the aminopyrimidone ring in **8** and **9** was determined from their NOESY spectra (see Supporting information). All assays and clarifications of the final compounds were done using TFA salts due to the instability of the free amines, and their optical purities were found to be 99–100% e.e. from chiral HPLC analyses.

The *meta*-substituted compounds **33**–**44** were obtained from cross coupling reactions of **20b** and corresponding aryl/alkylboronic acids or trifluoroborates, followed by deprotection with TFA, in good yields (Scheme 3). The stereochemistry of the 6-position of the aminopyrimidone ring in **20b** was determined to be (*S*) by



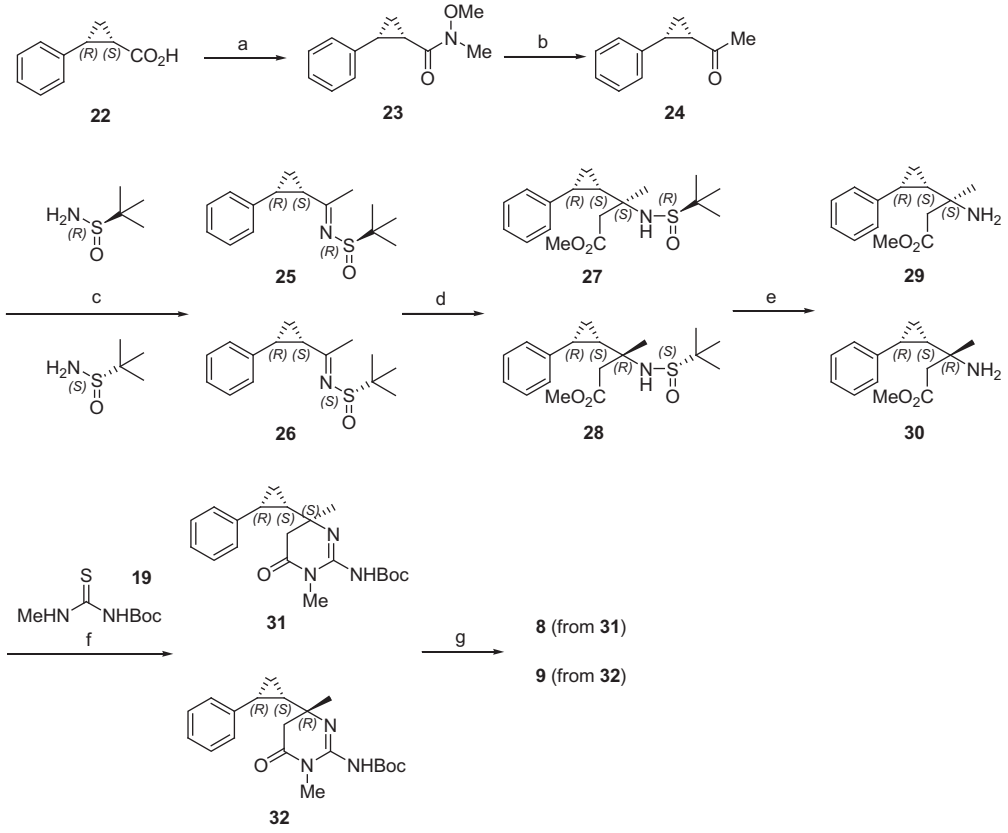
Scheme 1. Synthesis of *trans* isomers **6** and **7**. Reagents and conditions: (a) (i) $(COCl)_2$, cat. DMF, r.t., (ii) HN(OMe)Me HCl, pyridine, CH_2Cl_2, rt, 84% (**11a**), 68% (*trans*:*cis* = 3.4:1)(**11b**); (b) MeMgBr, THF, 0 °C, 95% (**12a**), 75% (**12b**); (c) 2-methylpropane-2-sulfinamide ((*R*)-isomer for **13a**,**b**, (*S*)-isomer for **14a**), $Ti(OEt)_4$, THF, 85 °C, 61% (**13a**), 53% (**13b**), 57% (**14a**); (d) AcOMe, LDA, ClTi(O-*i*-Pr)$_3$, THF, −70 °C, 79% (**15a**), 83% (**15b**), 59% (**16a**); (e) HCl, dioxane, MeOH, rt, 94% (**17a**), 97% (**17b**), 60% (**18a**); (f) **19**, EDC HCl, DIEA, DMF, rt, 98% (**20a**), 99% (**20b**), 97% (**21a**); (g) TFA, CH_2Cl_2, rt, 94% (**6**), 95% (**7**).

comparison of the ^{1}H NMR of the authentic specimen **6** with that derived from **20b** by reducing bromine atom with $(TMS)_3SiH$ (see Supporting information).

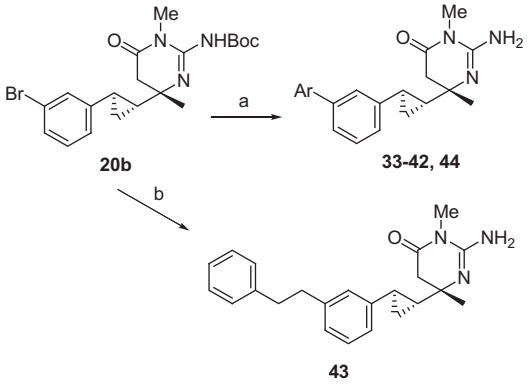
Syntheses of the reference compounds were also investigated. Although the preparation of racemic **3** and **4** had been reported,[6] we decided to synthesize (*R*)-**3**, (*S*)-**3**, (*R*)-**4**, and **5** stereoselectively in the same manner described above to precisely compare their inhibitory activities with those of the cyclopropane compounds strictly (Scheme 4). However, the diastereoselectivity on addition of titanium enolate to sulfinylimine **46a** was lower than those of the conformationally restricted imines; the ratio of the desired stereoisomer **47a** to the nondesired stereoisomer **48a** was 4.9:1 based on ^{1}H NMR analysis of the crude products. This result suggests that the branching of the chain structure at the α-carbon of the ketimine might be closely related to the extent of the diastereoselectivity.[19] Epimers **47a** and **48a** were successfully separated by silica gel chromatography. Thus, through the same synthetic route as that of the cyclopropane derivatives, we obtained (*R*)- and (*S*)-3, whose optical purities were found to be 96.0% and 97.7% e.e. respectively, by chiral HPLC analysis (for details, see Experimental Section). (*R*)-**4** and **5** were readily prepared from **50b** by Suzuki-Miyaura cross coupling in a manner similar to that for the cyclopropane-based derivatives. The stereochemistry of the 6-position of the aminopyrimidone ring in **50b** and its optical purity were determined through a chiral HPLC analysis of (*R*)-**3** derived by reduction of **50b** (see Supporting information).

2.2. BACE1 inhibitory activities of cyclopropane-based compounds 6–9, *ent*-6–9

The results of the HTRF assays for the human BACE1 inhibitory activities of conformationally restricted stereoisomers **6**–**9**, ***ent*-6**–**9**, and reference compounds (*R*)- and (*S*)-**3** are summarized in Table 1. The IC_{50} value of (*R*)-3 was found to be 41.4 μM, almost in accordance with the value reported with racemic **3** (34 μM).[6] Its enantiomer (*S*)-3 was inactive, which is consistent with previously reports that the configuration of this position is important for expression of BACE1 inhibitory activity.[6,7e,20] Among all cyclopropane derivatives evaluated, [*trans*-(1′*R*,2′*R*),6*S*] isomer **6** exhibited an excellent IC_{50} value of 18.0 μM and ligand efficiency (LE) of 0.34. The IC_{50} value of **6** was also superior to that of the ethylene linker compound (*R*)-**3** with a statistically significant difference ($n = 3$, $p < 0.01$). With regard to other *trans* isomers, [*trans*-(1′*S*,2′*S*),6*S*] isomer ***ent*-7** had much weaker activity than **6** (IC_{50} = 132 μM, LE = 0.28). IC_{50} values of 6*R* isomers ***ent*-6** and **7** were over 200 μM, which is similar to the SAR of the ethylene linker compound **3** described above and in previous reports.[6] On the other hand, none of the *cis* cyclopropane-based compounds **8**,



Scheme 2. Synthesis of *cis* isomers **8** and **9**. Reagents and conditions: (a) (i) $(COCl)_2$, cat. DMF, rt, (ii) HN(OMe)Me HCl, pyridine, CH_2Cl_2, rt, 95% (*trans*:*cis* = 1:10); (b) MeMgBr, THF, 0 °C, 85%; (c) 2-methylpropane-2-sulfinamide ((*R*)-isomer for **25**, (*S*)-isomer for **26**), $Ti(OEt)_4$, THF, 85 °C, 48% (**25**, recovered **24** 37%), 47% (**26**, recovered **24** 40%); (d) AcOMe, LDA, ClTi(O-*i*-Pr)$_3$, THF, −70 °C, 84% (**27**), 55% (**28**); (e) HCl, dioxane, MeOH, rt, 88% (**29**), 92% (**30**); (f) **19**, EDC HCl, DIEA, DMF, rt, 89% (**31**), 91% (**32**); (g) TFA, CH_2Cl_2, rt, 94% (**8**), 82% (**9**).

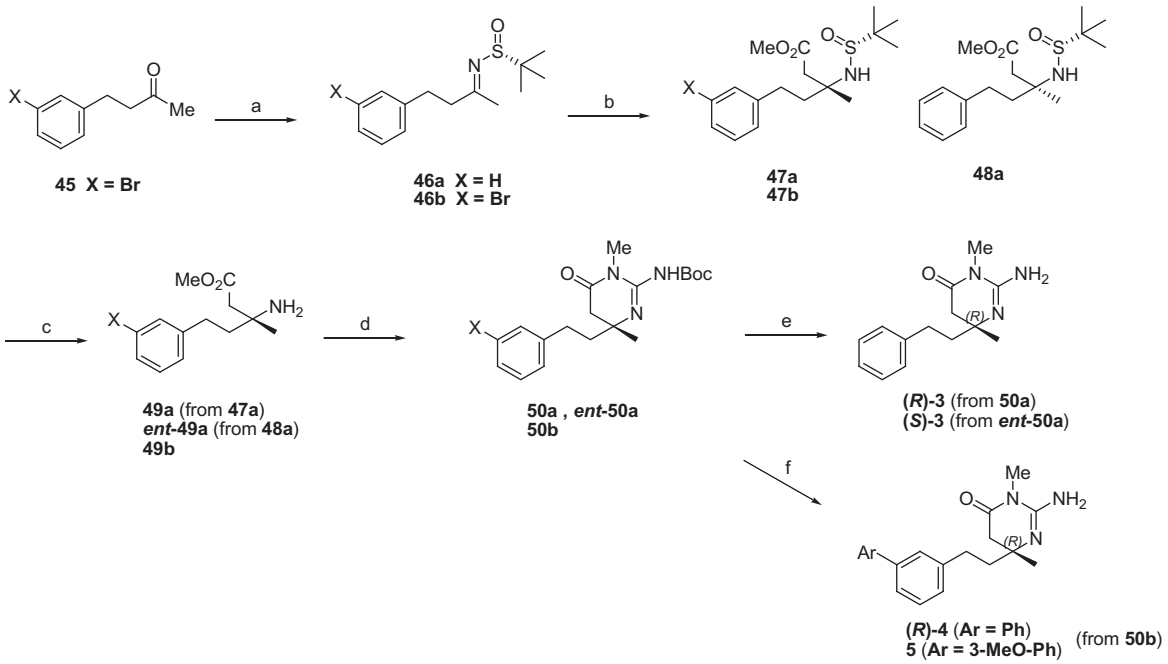


Scheme 3. Synthesis of *meta*-substituted derivatives. Reagents and conditions: (a)(i) Ar-B(OH)$_2$ or Ar-Bpin, K_2CO_3, $PdCl_2(PPh_3)_2$, dioxane, H_2O, 100 °C, (ii) TFA, CH_2Cl_2, rt, 49–94%; (b) (i) $PhCH_2CH_2BF_3K$, $PdCl_2$(dppf), Cs_2CO_3, THF, H_2O, reflux, (ii) TFA, CH_2Cl_2, rt, 86%.

***ent*-8**, **9** and ***ent*-9** showed any significant activity. These results clearly demonstrate that the stereochemistries of both the cyclopropane ring and the 6-position of the aminopyrimidone ring are closely related to the BACE1 inhibitory activity, in which the [*trans*-(1′*R*,2′*R*),6*S*] stereochemistry is likely to be essential for effective binding of the compounds to the target.

2.3. Thermodynamic parameters upon binding to BACE1

Determining the thermodynamic parameters, the enthalpic and entropic energies, in ligand binding to its target, is now widely regarded as an effective approach to investigating the ligand binding mode. In the binding between a ligand and its target biomolecule, while the active enthalpy (ΔH) in the binding is likely to be related to noncovalent polar associations, for instance, Van der Waals interactions, ionic bonds, hydrogen bonds, and dipole interactions, increasing the hydrophobic interactions is generally thought to contribute to the active entropy (ΔS) gain in the binding. Thus, appropriate structural modifications to improve those parameters lead to the higher affinity of the compounds.[21] Excess nonspecific hydrophobic interactions often lead to side-effects of drugs, so that inhibitors with a specific, enthalpically driven binding mode is likely to be more desirable.[22] Conformational restriction of ligands is considered to increase the configurational entropy by limiting movement of ligands into the bioactive conformation before binding to the target protein.[23] Even though some trials have already been performed to evaluate the thermodynamic effect of the conformational constraints, there are few reports that observed a clear gain of the entropic energy.[24] Moreover, compounds used in these previous reports were mostly peptide-based ligands, and therefore, interpretations of the results are rather complicated, because peptides can adopt diverse conformations and make various interactions with the target, due to there being too many hydrogen donors/acceptors and rotatable bonds. We envisioned that our BACE1 inhibitors would be suitable for evaluating the effect of the conformational restriction on the entropy (ΔS) upon their binding to BACE1 because of the simple interaction modes due to their low-molecular weight constrained structures. Thus, in order to investigate the origin of the positive biological result by the conformational restriction (Table 1), we obtained the thermodynamic parameters upon binding of (*R*)-3 and **6** to BACE1



Scheme 4. Synthesis of reference compounds with ethylene linker (**(*R*)-3, (*S*)-3, (*R*)-4, 5**). Reagents and conditions: (a) (*R*)-2-methylpropane-2-sulfinamide, $Ti(OEt)_4$, THF, 85 °C, 76% (**46b**) (b) AcOMe, LDA, $ClTi(O\text{-}i\text{-}Pr)_3$, THF, −70 °C, 51%, 9% (**47a**, **48a**), 33% (**47b**) (c) HCl, dioxane, MeOH, rt, 92% (**49a**), 82% (***ent*-49a**), 96% (**49b**); (d) **19**, EDC HCl, DIEA, DMF, rt; 99% (**50a**), 88% (***ent*-50a**), 95% (**50b**); (e) TFA, CH_2Cl_2, rt; 94% ((**R**)-**3**), 77% ((**S**)-**3**); (f)(i) Ar-$B(OH)_2$, $PdCl_2(PPh_3)_2$, dioxane, H_2O, 100 °C, (ii) TFA, CH_2Cl_2, rt, 83% ((**R**)-**4**), 85% (**5**).

Table 1
BACE1 inhibitory activity of **3** and its conformationally restricted analogs

Compound	BACE1 IC_{50}[a] (μM)	Ligand Efficiency (LE) (kcal/mol per heavy atom)
(*R*)-3	41.4 ± 5.0	0.33
(*S*)-3	>200	—
6	18.0 ± 1.0	0.34
ent-6	>200	—
7	>200	—
ent-7	132	0.28
8	>200	—
ent-8	>200	—
9	>200	—
ent-9	>200	—

[a] Values are means of two experiments, except for **(*R*)-3** and **6** whose values are means of three experiments.

by ITC, which are summarized in Table 2. The K_d value of **6** (26.8 μM), calculated from observed K_a value, was found to be smaller than that of (**R**)-**3** (36.6 μM). This result is consistent with the order of BACE1 inhibitory activity of (*R*)-**3** and **6** shown in Table 1. Both compounds gave similar ΔH values (−6.7 kcal for (**R**)-**3**, −6.4 kcal for **6**). On the other hand, the total binding ΔS of **6** calculated was −0.66 cal/mol/K (−0.2 kcal at 298 K), which is larger than that of (*R*)-3 (−2.2 cal/mol/K, −0.7 kcal at 298 K). In ligand binding to its target biomolecule, the ΔH contributes to the binding energy often more significantly than the ΔS, and the binding of these compounds to BACE1 is also considered to be enthalpy driven, in which the key hydrogen bonds between the amino group of inhibitors and Asp32, Asp228 of BACE1 seems to contribute mainly to the binding. Even though their gap was smaller than we had expected, approximately ~0.5 kcal at 298 K,[25] this result offers evidence to support our concept of the entropic energy loss upon binding BACE1 being reduced by conformational restriction with cyclopropane ring. To the best of our knowledge, this is the first example of the conformational entropic gain being observed using ITC by introducing a conformational constraint with a cyclopropane ring into the nonpeptidic small molecules.

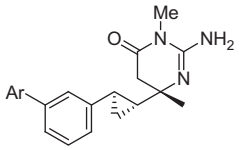
Table 2
Evaluation of energy parameters of **(*R*)-3** and **6** on binding BACE1

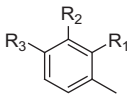
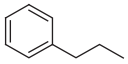
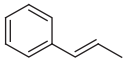
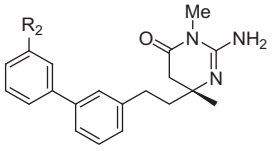
Compound	K_a ($\times 10^4$ M^{-1})	K_d (μM)	ΔH (kcal/mol)[a]	ΔS (cal/mol/K)
(*R*)-3	2.7 ± 0.4	36.6	−6.7 ± 0.4	−2.2
6	3.7 ± 0.7	26.8	−6.4 ± 0.5	−0.66

2.4. Structure–activity relationship of the *meta*-substituted derivatives

Encouraged by the SAR results of the nonsubstituted derivative described above, we applied the conformational restriction approach to the *meta*-substituted derivatives, such as (*R*)-4 and **5**. The *meta*-substituted [*trans*-(1′*R*,2′*R*), 6*S*] derivatives **33**–**44** and the corresponding ethylene linker compounds (*R*)-4, and **5** were prepared using Pd-catalyzed coupling reactions, and their BACE1 inhibitory activities were compared (Table 3). While nonrestricted reference compounds (*R*)-4 or **5** exhibited greatly improved activities (IC_{50} = 1.3–0.16 μM, LE = 0.34–0.36), as described in the previous report,[6] their constrained derivatives **33** or **35** showed only limited IC_{50} values (9.3–3.3 μM) and diminished LE (0.28–0.26). We also modified the structure by changing position of the methoxy group (**34**, **36**), extending the length of the alkyl chain (**37**), introducing hydrophilic substituents (**38**, **39**), replacing the terminal benzene ring with heteroaromatic rings (**40**–**42**), and inserting spacers between the two aromatic rings (**43**, **44**), but the BACE1 inhibitory affinities did not significantly improve. These results show that restriction of the ethylene linker moiety with a cyclopropane ring is not effective in *meta*-substituted derivatives, suggesting that the bioactive conformation of the cyclopropane-based derivatives might be different from that of the unrestricted ethylene linker compounds.

Table 3
Structure-activity relationship of meta-substituted derivatives



Compds	Ar	R_1	R_2	R_3	BACE1 IC_{50}[a](μM)	LE[b]
33		H	H	H	9.3	0.26
34		OMe	H	H	7.5	0.26
35		H	OMe	H	3.3	0.28
36		H	H	OMe	23.3	0.24
37		H	O-*n*-Pr	H	8.4	0.24
38		H	CH_2OH	H	20.8	0.24
39		H	NHAc	H	16.6	0.23
40		–	–	–	6.1	0.30
41		–	–	–	7.5	0.29
42		–	–	–	11.8	0.27
43		–	–	–	4.0	0.27
44		–	–	–	2.9	0.28
(***R***)-**4**			H	–	1.3	0.34
5			OMe	–	0.16	0.36

[a] Values are means of at least two experiments.
[b] Ligand efficiency.

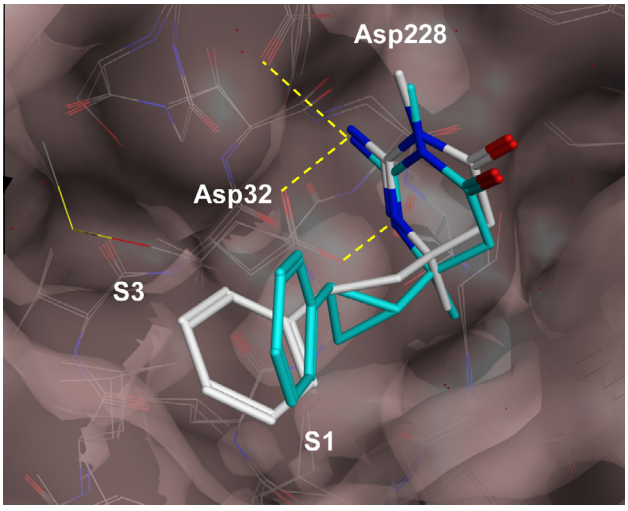


Figure 2. X-ray crystallographic structure of the BACE1 (in cyan) complexed with **6** (in cyan), superimposed with ligand (***R***)-**3** (in white). Key interactions between Asp32, Asp228 and **6** are depicted in dashed yellow line.

2.5. Comparison of the X-ray crystallographic structures of (*R*)-3 and 6 complexed with BACE1

To interpret the results of the ITC measurements and to investigate the origin of the relatively weaker activities of the *meta*-substituted compounds, we prepared the crystalline complexes of (*R*)-3 or **6** and human BACE1, and analyzed the X-ray crystallographic structures (Fig. 2). The cyclopropane ring or ethylene linker adopted the pseudo-axial position with regard to the aminopyrimidone ring, just as observed in previous studies.[6,7] Superposition of these structures revealed that the aminopyrimidone moieties of (*R*)-3 and **6** occupy almost the same position, and two nitrogens of the amidine moiety in both compounds interact with the side chain of Asp32 and Asp228 of BACE1, as expected from the previous X-ray analysis of other cyclic amidine type inhibitors, where no significant difference in their protein structures was observed. On the other hand, the orientation of the benzene rings in each ligand was clearly different; while the benzene ring of (*R*)-3 is accommodated effectively in the hydrophobic S1 pocket, the benzene ring of **6** occupies a shallower space in the pocket near to the solvent region, which might have led to a decrease of hydrophobic interaction between **6** and BACE1 to result in reducing the entropic advantage in the binding.

In the complex of (*R*)-3, a space around the *meta*-position of the benzene ring is observed, which might allow effective accommodation of the *meta*-substituent in the S3 pocket. On the other hand, judging from the obtained X-ray structure, efficient improvement of the binding affinity by the same structural modification in **6** does not seem to occur, because the substituent introduced in the benzene ring of **6** would not be precisely accommodated in the S3 pocket. These considerations agree with the SAR results presented in Table 3.

2.6. Conformational analyses of 6

Conformational analyses by theoretical calculations were performed to obtain the detailed information on conformational stability of **6** in comparison with its conformation in the complex

with BACE1. An initial conformation search was performed using MacroModel, and 12 stable conformers within the 5 kcal/mol range above the minimum energy level were extracted. Each conformer obtained was then minimized by quantum mechanics calculations using Jaguar. From the obtained 12 local-minimum structures, the global-minimum conformation (Fig. 3a) was obtained, in which the cyclopropane ring of **6** was found to occupy the pseudo-equatorial position with regard to the aminopyrimidone ring. On the other hand, the known BACE1 inhibitors of the similar series are known to adopt the pseudo-axial conformation in their X-ray structures complexed with BACE1. Therefore, we obtained the most stable conformation of **6** among the pseudo-axial conformations as shown in Figure 3b, which is 0.8 kcal/mol less stable than the global minimum conformation shown in Figure 3a. In the conformations shown in Figures 3a and 3b, the benzene ring of both was found to take bisected form with regard to the cyclopropane ring, probably due to the hyperconjugation between the π-orbitals of the benzene ring and electron-donating orbitals of the cyclopropane ring. The energy level of the conformation of **6** in the X-ray structure complexed with BACE1 was also calculated under the constraint of the dihedral angles among the aminopyrimidone ring, the cyclopropane ring and the benzene ring (Fig. 3c). The energy difference between the conformation of **6** in the X-ray structure (Fig. 3c) and that of minimum energy (Fig. 3a) was calculated to be 2.18 kcal/mol. This may also explain the small entropic contributions observed for the conformational restriction in **6** (Table 2), in addition to the decreased hydrophobic interactions between **6** and BACE1 suggested from the X-ray structure; due to some steric repulsions between the protein and **6**, the ligand adopts a somewhat less stable conformation on binding to BACE1, which might have caused loss of entropic energy upon binding.

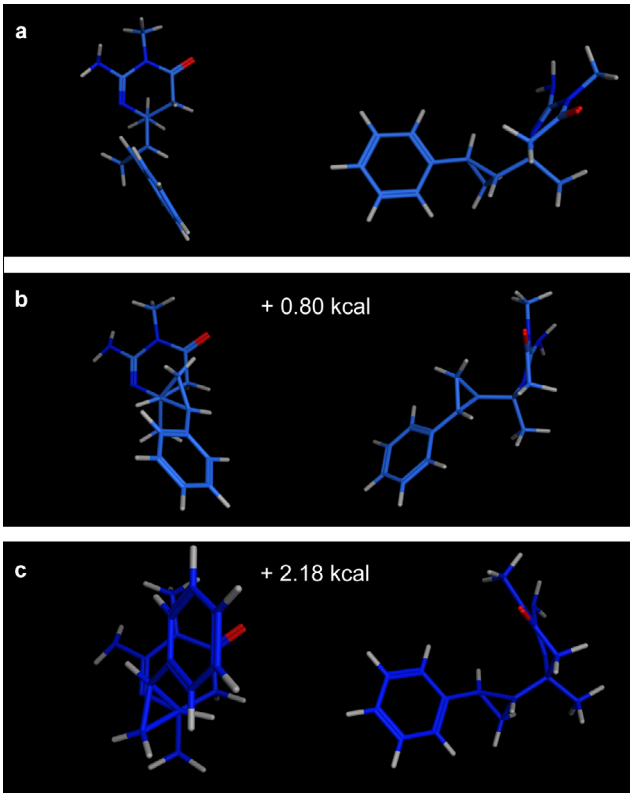


Figure 3. Calculated conformations of **6**; (a) the conformation of global-minimum energy, (b) the most stable pseudo-axial conformation, (c) the conformation in the complex with BACE1. Values in the figures are calculated energy differences between (a) and (b–c). Left: seen from benzene ring side, right: side view.

3. Conclusion

Using the conformational restriction approach, we designed and synthesized the cyclopropane-based 6-substituted aminopyrimidone-type BACE1 inhibitors **6–9** and ***ent*-6–9** with different stereochemistries. Among the stereoisomers synthesized, compound **6**, with [*trans*-(1′*R*,2′*R*),6*S*] configurations, exhibited statistically better inhibitory activities than the corresponding nonrestricted ethylene linker compound (***R***)-**3**. Their ITC measurements on binding to BACE1 revealed that binding entropy of **6** is larger than that of (***R***)-**3**, which would be contributed to by entropic gain probably derived from the conformational constrain due to the cyclopropane ring. Comparison of the results from the conformational analyses of **6** itself with the calculated energy of its binding state in the complex with BACE1 suggests that, on binding to BACE1, **6** adopted a conformation somewhat less stable than the global minimum one, and its benzene ring occupies a shallower space in the pocket, which might decrease the hydrophobic interaction of **6** with BACE1. This might have led to the lower entropic gain of **6** and weaker activities of *meta*-substituted derivatives than we had expected. It should be noted that use of the nonpeptidic, simple BACE1 inhibitors with or without conformational constraint having different binding affinities for the BACE1 and the combinational analysis approach by X-ray crystallography, ITC, and theoretical calculations allowed us to interpret the binding mode and the effect on the affinity of the inhibitors by the conformational restriction. Our findings should offer a good guide for applying conformational restriction to the design of novel inhibitors.

4. Experimental section

4.1. General methods

^{1}H and ^{13}C NMR chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (0.00 ppm). Coupling constants (*J*) were reported in Hz. Silica-gel chromatography was performed on Yamazen Hi-Flash Column (Yamazen Corporation) using automated flash chromatography system W-prep 2XY (Yamazen Corporation). Purity of final products was ⩾95% as determined by LCMS analysis. LC conditions are as follows; Column: intakt Unison U-18 4.6 × 75 mm (3 μm), temperature: 50 °C, eluent: A H_2O (0.1% HCO_2H), B MeCN (0.1% HCO_2H), gradient condition: eluent B 10–95% 6 min, 95% 2 min, flow rate: 2 mL/min. For detailed data of each compound, see Supplementary information.

4.2. Synthetic procedures

4.2.1. (1*R*,2*R*)-*N*-Methoxy-*N*-methyl-2-phenylcyclopropanecarboxamide (11a)

To a solution of **10a** (5.48 g, 33.8 mmol) in dichloromethane (55 mL) were added oxalyl chloride (3.55 mL, 40.5 mmol) and trace amount of DMF. The mixture was stirred for 1 h at room temperature, and the solvent was evaporated. The residue was dissolved in dichloromethane (55 mL). *N*,*O*-Dimethylhydroxylamine hydrochloride (4.94 g, 50.7 mmol) and pyridine (10.9 mL, 135 mmol) were added to the solution, and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was then partitioned between AcOEt and 2 M HCl. The organic layer was washed water, saturated $NaHCO_3$ solution, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography (hexane/AcOEt = 2:1) to obtain **11a** (5.81 g, 28.3 mmol, 84%) as a colorless oil. $[\alpha]_D^{23}$ −238.6° (*c* = 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28–1.33 (1H, m), 1.61–1.66 (1H, m), 2.41 (1H, br s), 2.48–2.53 (1H, m), 3.28 (3H, s), 3.69 (3H, s), 7.12–7.15 (2H, m),

7.17–7.22 (1H, m), 7.26–7.30 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.49, 21.58, 25.92, 32.60, 61.71, 126.25, 126.29, 140.82, 173.15; HRMS (ESI) calcd for $C_{12}H_{15}NO_2Na$: 228.0995 [(M+Na)$^+$], found 228.0993.

4.2.2. (1*S*,2*S*)-*N*-Methoxy-*N*-methyl-2-phenylcyclopropanecarboxamide (*ent*-11a)

Compound ***ent*-11a** (4.22 g, 20.6 mmol, 87%) was obtained as a colorless oil from ***ent*-10a** (3.83 g, 23.6 mmol) by the same procedure used to prepare **11a**. $[\alpha]_D^{23}$ +232.4° (*c* = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{12}H_{15}NO_2Na$: 228.0995 [(M+Na)$^+$], found 228.0994.

4.2.3. (1*R*,2*R*)-2-(3-Bromophenyl)-*N*-methoxy-*N*-methylcyclopropanecarboxamide (mixture with (1*R*,2*S*) *cis* isomer) (11b)

Compound **11b** (1.39 g, 4.88 mmol, 68%) was obtained as a colorless oil from **10b** (1.74 g, 7.22 mmol) by the same procedure used to prepare **11a**. ^{1}H NMR ($CDCl_3$, 500 MHz) *trans* isomer δ 1.23–1.29 (1H, m), 1.58–1.63 (1H, m), 2.37 (1H, br s), 2.41–2.45 (1H, m), 3.21 (3H, s), 3.68 (3H, s), 7.03–7.06 (1H, m), 7.11 (1H, t, *J* = 7.9 Hz), 7.22 (1H, t, *J* = 2.0 Hz), 7.30 (1H, ddd, *J* = 7.9, 2.0, 1.2 Hz).

4.2.4. 1-((1*R*,2*R*)-2-Phenylcyclopropyl)ethanone (12a)

To a solution of **11a** (5.75 g, 28.0 mmol) in THF (86 mL) was added 1.12 M methylmagnesium bromide THF solution (45 mL, 50.4 mmol) at 0 °C under N_2 atmosphere, and the mixture was stirred for 1 h at room temperature. Then to the reaction mixture was added saturated NH_4Cl asolution, and was partitioned between AcOEt and water. The organic layer was washed water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography (hexane/AcOEt = 5:1) to obtain **12a** (4.27 g, 26.7 mmol, 95%) as a colorless oil. $[\alpha]_D^{23}$ −531.4° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.35–1.40 (1H, m), 1.65–1.70 (1H, m), 2.19–2.24 (1H, m), 2.30 (3H, s), 2.50–2.55 (1H, m), 7.08–7.11 (2H, m), 7.18–7.23 (1H, m), 7.26–7.31 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.13, 29.03, 30.85, 32.89, 126.03, 126.53, 128.50, 140.33, 206.85; HRMS (ESI) calcd for $C_{11}H_{12}ONa$: 183.0780 [(M+Na)$^+$], found 183.0781.

4.2.5. 1-((1*S*,2*S*)-2-Phenylcyclopropyl)ethanone (*ent*-12a)

Compound ***ent*-12a** (1.50 g, 9.34 mmol, 90%) was obtained as a colorless oil from ***ent*-11a** (2.13 g, 10.4 mmol) by the same procedure used to prepare **12a**. $[\alpha]_D^{23}$ +501.0° (*c* = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{11}H_{13}O$: 161.0961 [(M+Na)$^+$], found 161.0963.

4.2.6. 1-((1*R*,2*R*)-2-(3-Bromophenyl)cyclopropyl)ethanone (12b)

Compound **12b** (809 mg, 3.38 mmol, 75%) was obtained as a colorless oil from **11b** (1.28 g, 4.51 mmol) by the same procedure used to prepare **12a**. $[\alpha]_D^{23}$ −370.4° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34–1.37 (1H, m), 1.64–1.67 (1H, m), 2.18–2.23 (1H, m), 2.31 (3H, s), 2.46–2.51 (1H, m), 7.03–7.06 (1H, m), 7.11 (1H, t, *J* = 7.9 Hz), 7.22 (1H, t, *J* = 2.0 Hz), 7.30 (1H, ddd, *J* = 7.9, 2.0, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ19.08, 28.25, 30.92, 32.68, 122.65, 124.96, 129.01, 129.61, 130.00, 142.76, 206.39; HRMS (ESI) calcd for $C_{11}H_{11}BrONa$: 260.9886 [(M+Na)$^+$], found 260.9889.

4.2.7. (*R*,*E*)-2-Methyl-*N*-(1-((1*R*,2*R*)-2-phenylcyclopropyl)ethylidene)propane-2-sulfinamide (13a)

To a solution of titanium (IV) ethoxide (2.14 g, 9.36 mmol) in THF (5 mL) were added **12a** (1.00 g, 6.24 mmol) in THF (2 mL) and (*R*)-2-methylpropane-2-sulfinamide (832 mg, 9.36 mmol). The reaction mixture was stirred at 85 °C under N_2 atmosphere for 5 h. Then the mixture was cooled to room temperature, and AcOEt (20 mL) and saturated NaCl solution added (2 mL). The suspension was stirred for 30 min, and the insoluble precipitate was filtered off. The filtrate was partitioned between AcOEt and water, and was extracted with AcOEt. The organic layer was washed with water, brine and dried with Na_2SO_4. The solvent was evaporated, and the residue was purified by silicagel chromatography (Hexane/AcOEt = 2:1) to obtain **13a** (1.00 g, 3.80 mmol, 61%) as colorless solid. Starting material **12a** (269 mg, 1.68 mmol, 27%) was recovered. $[\alpha]_D^{23}$ −535.8° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (9H, s), 1.39–1.43 (1H, m), 1.70–1.74 (1H, m), 1.90–1.95 (1H, m), 2.46 (3H, s), 2.51–2.57 (1H, m), 7.09–7.12 (2H, m), 7.18–7.23 (1H, m), 7.26–7.31 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.15, 22.16, 24.11, 30.01, 33.17, 56.27, 126.08, 126.45, 128.51, 140.65, 185.85; HRMS (ESI) calcd for $C_{15}H_{21}NOSNa$: 286.1236 [(M+Na)$^+$], found 286.1235.

4.2.8. (*S*,*E*)-2-Methyl-*N*-(1-((1*S*,2*S*)-2-phenylcyclopropyl)ethylidene)propane-2-sulfinamide (*ent*-13a)

Compound ***ent*-13a** (507 mg, 1.93 mmol, 67%) was obtained as a colorless solid from ***ent*-12a** (460 mg, 2.87 mmol) and (*S*)-2-methylpropane-2-sulfinamide (383 mg, 3.16 mmol) by the same procedure used to prepare **13a**. $[\alpha]_D^{20}$ +552.6° (*c* = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{21}NOSNa$: 286.1236 [(M+Na)$^+$], found 286.1236.

4.2.9. (*R*,*E*)-*N*-(1-((1*R*,2*R*)-2-(3-Bromophenyl)cyclopropyl)ethylidene)-2-methylpropane-2-sulfinamide (13b)

Compound **13b** (552 mg, 1.61 mmol, 53%) was obtained as a colorless oil from **12b** (730 mg, 3.05 mmol) and (*R*)-2-methylpropane-2-sulfinamide (407 mg, 3.36 mmol) by the same procedure used to prepare **13a**. Starting material **12b** (265 mg, 1.11 mmol, 36%) was recovered. $[\alpha]_D^{20}$ −460.4° (*c* = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20 (9H, s), 1.34–1.37 (1H, m), 1.66–1.70 (1H, m), 1.87–1.91 (1H, m), 2.44 (3H, s), 2.45–2.50 (1H, m), 7.01–7.03 (1H, m), 7.12 (1H, t, *J* = 7.8 Hz), 7.17–7.20 (1H, m), 7.30 (1H, ddd, *J* = 8.1, 2.0, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ19.22, 22.16, 24.17, 29.24, 33.03, 56.32, 122.65, 125.08, 128.92, 129.53, 130.01, 143.08, 185.37; HRMS (ESI) calcd for $C_{15}H_{20}BrNOSNa$: 364.0341 [(M+Na)$^+$], found 364.0341.

4.2.10. (*S*,*E*)-2-Methyl-*N*-(1-((1*R*,2*R*)-2-phenylcyclopropyl)ethylidene)propane-2-sulfinamide (14a)

Compound **14a** (212 mg, 0.803 mmol, 57%) was obtained as a colorless oil from **12a** (227 mg, 1.42 mmol) and (*S*)-2-methylpropane-2-sulfinamide (189 mg, 1.56 mmol) by the same procedure used to prepare **13a**. $[\alpha]_D^{20}$ −371.2° (*c* = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (9H, s), 1.40–1.45 (1H, m), 1.71–1.76 (1H, m), 1.91–1.96 (1H, m), 2.46 (3H, s), 2.46–2.50 (1H, m), 7.09–7.12 (2H, m), 7.18–7.23 (1H, m), 7.27–7.31 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.68, 22.19, 29.56, 33.23, 56.34, 126.05, 126.45, 128.52, 140.68, 185.58; HRMS (ESI) calcd for $C_{15}H_{21}NOSNa$: 286.1236 [(M+Na)$^+$], found 286.1236.

4.2.11. (*R*,*E*)-2-Methyl-*N*-(1-((1*S*,2*S*)-2-phenylcyclopropyl)ethylidene)propane-2-sulfinamide (*ent*-14a)

Compound ***ent*-14a** (383 mg, 1.46 mmol, 54%) was obtained as a colorless oil from ***ent*-12a** (434 mg, 2.71 mmol) and (*R*)-2-methylpropane-2-sulfinamide (361 mg, 2.98 mmol) by the same procedure used to prepare **13a**. $[\alpha]_D^{20}$ +385.5° (*c* = 0.51, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{21}NOSNa$: 286.1236 [(M+Na)$^+$], found 286.1236.

4.2.12. (*S*)-Methyl 3-((*R*)-1,1-dimethylethylsulfinamido)-3-((1*R*,2*R*)-2-phenylcyclopropyl)butanoate (15a)

Diisopropylamine (1.72 mL, 12.2 mmol) was dissolved in THF (6 mL), and cooled to −70 °C. *n*-Butyllithium 1.63 M hexane solution was added for 15 min maintaining the temperature below −60 °C. After the addition was complete, the reaction temperature was raised to 0 °C, and then cooled to −70 °C again. Methyl acetate (0.886 mL, 11.1 mmol) in THF (2 mL) was added for 5 min maintaining the temperature below −60 °C. The mixture was stir-

red for 15 min at −70 °C, then triisopropoxytitanium (IV) chloride (3.72 mL, 15.6 mmol) in THF (6 mL) was added for 10 min maintaining the temperature below −60 °C. After the mixture was stirred for 20 min at −70 °C, **13a** (977 mg, 3.71 mmol) in THF (4 mL) was added for 5 min maintaining the temperature below −60 °C. The reaction mixture was stirred for 1 h, and the reaction temperature was poured into NH_4Cl (1.19 g) solution in water (4 mL) at 0 °C. AcOEt (10 mL) and celite (2 g) were added, and the suspension was stirred for 10 min at room temperature. The insoluble precipitate was filtered off through the celite pad, and the filtrate was extracted with AcOEt. The organic layer was washed with water, brine and dried with Na_2SO_4. The solvent was evaporated, and the residue was purified by silicagel chromatography (Hexane/AcOEt = 1:2) to obtain **15a** (990 mg, 2.93 mmol, 79%) as colorless oil. $[\alpha]_D^{23}$ −121.0° (*c* = 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.84–0.92 (2H, m), 1.13–1.18 (1H, m), 1.20 (9H, s), 1.44 (3H, s), 1.98–2.03 (1H, m), 2.56, 2.82 (2H, ABq, *J* = 14.9 Hz), 3.53 (3H, s), 5.05 (1H, s), 7.04–7.07 (2H, m), 7.12–7.16 (1H, m), 7.22–7.26 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.15, 22.16, 30.01, 33.17, 56.17, 126.08, 126.45, 128.51, 140.65, 185.85; HRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$: 360.1604 [(M+Na)$^+$], found 360.1601.

4.2.13. (*R*)-Methyl 3-((*S*)-1,1-dimethylethylsulfinamido)-3-((1*S*,2*S*)-2-phenylcyclopropyl)butanoate (*ent*-15a)

Compound ***ent*-15a** (508 mg, 1.51 mmol, 84%) was obtained as a colorless oil from ***ent*-13a** (475 mg, 1.80 mmol) by the same procedure used to prepare **15a**. $[\alpha]_D^{23}$ +125.4° (*c* = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$: 360.1604 [(M+Na)$^+$], found 360.1599.

4.2.14. (*S*)-Methyl 3-((1*R*,2*R*)-2-(3-bromophenyl)cyclopropyl)-3-((*R*)-1,1-dimethylethylsulfinamido)butanoate (15b)

Compound **15b** (792 mg, 1.90 mmol, 83%) was obtained as a colorless oil from **13b** (781 mg, 2.28 mmol) by the same procedure used to prepare **15a**. $[\alpha]_D^{23}$ −104.2° (*c* = 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86–0.94 (2H, m), 1.08–1.15 (1H, m), 1.21 (9H, s), 1.44 (3H, s), 1.96–2.01 (1H, m), 2.56, 2.83 (2H, ABq, *J* = 15.3 Hz), 3.57 (3H, s), 5.10 (1H, s), 6.98–7.02 (1H, m), 7.10 (1H, t, *J* = 7.8 Hz), 7.20 (1H, t, *J* = 1.7 Hz), 7.27 (1H, ddd, *J* = 7.8, 1.7, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.97, 19.69, 22.86, 24.44, 33.66, 46.82, 51.75, 54.97, 55.85, 122.41, 124.69, 128.78, 129.04, 129.76, 144.65, 172.54; HRMS (ESI) calcd for $C_{18}H_{26}BrNO_3SNa$: 438.0709 [(M+Na)$^+$], found 438.0714.

4.2.15. (*R*)-Methyl 3-((*S*)-1,1-dimethylethylsulfinamido)-3-((1*R*,2*R*)-2-phenylcyclopropyl)butanoate (16a)

Compound **16a** (150 mg, 0.444 mmol, 59%) was obtained as a colorless solid from **14a** (197 mg, 0.748 mmol) by the same procedure used to prepare **15a**. $[\alpha]_D^{23}$ +1.7° (*c* = 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.93–0.99 (1H, m), 1.11–1.17 (1H, m), 1.20–1.25 (1H, m), 1.25 (9H, s), 1.45 (3H, s), 1.78–1.83 (1H, m), 2.59, 2.83 (2H, ABq, *J* = 15.2 Hz), 3.66 (3H, s), 4.93 (1H, s), 7.06–7.09 (2H, m), 7.13–7.18 (1H, m), 7.22–7.26 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.20, 18.42, 22.88, 24.44, 32.63, 46.97, 51.67, 55.00, 55.86, 125.76, 126.13, 128.35, 142.22, 172.39; HRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$: 360.1604 [(M+Na)$^+$], found 360.1599.

4.2.16. (*S*)-Methyl 3-((*R*)-1,1-dimethylethylsulfinamido)-3-((1*S*,2*S*)-2-phenylcyclopropyl)butanoate (*ent*-16a)

Compound ***ent*-16a** (327 mg, 0.969 mmol, 72%) was obtained as a colorless solid from ***ent*-14a** (354 mg, 1.34 mmol) by the same procedure used to prepare **15a**. $[\alpha]_D^{23}$ −5.0° (*c* = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$: 360.1604 [(M+Na)$^+$], found 360.1602.

4.2.17. (*S*)-Methyl 3-amino-3-((1*R*,2*R*)-2-phenylcyclopropyl)-butanoate (17a)

To a solution of **15a** (954 mg, 2.83 mmol) in MeOH (9.5 mL) was added 4 M HCl in dioxane (2.12 mL), and the mixture was stirred for 2 h at room temperature. The reaction mixture was partitioned between AcOEt and saturated $NaHCO_3$, and was extracted with AcOEt. The organic layer was washed with water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography ($CHCl_3$/MeOH = 10:1) to give **17a** (620 mg, 2.66 mmol, 94%) as a colorless oil. $[\alpha]_D^{23}$ −77.7° (*c* = 0.53, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.78–0.82 (1H, m), 0.95–1.00 (1H, m), 1.20 (3H, s), 1.21–1.26 (1H, m), 1.89–1.93 (1H, m), 2.47, 2.52 (2H, ABq, *J* = 14.2 Hz), 3.52 (3H, s), 7.05–7.07 (2H, m), 7.11–7.15 (1H, m), 7.22–7.26 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.27, 19.06, 28.23, 33.40, 47.69, 50.27, 51.35, 125.45, 125.88, 128.23, 143.03, 172.32; HRMS (ESI) calcd for $C_{14}H_{20}NO_2$: 234.1489 [(M+H)$^+$], found 234.1486.

4.2.18. (*R*)-Methyl 3-amino-3-((1*S*,2*S*)-2-phenylcyclopropyl)butanoate (*ent*-17a)

Compound ***ent*-17a** (308 mg, 1.32 mmol, 96%) was obtained as a colorless oil from ***ent*-15a** (465 mg, 1.38 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{23}$ +76.2° (*c* = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{20}NO_2$: 234.1489 [(M+H)$^+$], found 234.1486.

4.2.18. (*R*)-Methyl 3-amino-3-((1*S*,2*S*)-2-phenylcyclopropyl)butanoate (*ent*-17a)

Compound **17b** (551 mg, 1.76 mmol, 97%) was obtained as a colorless oil from **15b** (759 mg, 1.82 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{23}$ −63.7° (*c* = 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.77–0.82 (1H, m), 0.99–1.03 (1H, m), 1.17–1.22 (1H, m), 1.20 (3H, s), 1.86–1.91 (1H, m), 2.47, 2.52 (2H, ABq, *J* = 14.2 Hz), 3.54 (3H, s), 6.97–7.01 (1H, m), 7.10 (1H, t, *J* = 7.8 Hz), 7.19 (1H, t, *J* = 2.0 Hz), 7.26 (1H, ddd, *J* = 7.8, 2.0, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ11.31, 18.84, 28.41, 33.62, 47.69, 50.15, 51.43, 122.41, 124.69, 128.51, 128.91, 129.73, 145.64, 172.25; HRMS (ESI) calcd for $C_{14}H_{19}BrNO_2$: 312.0594 [(M+H)$^+$], found 312.0598.

4.2.20. (*R*)-Methyl 3-amino-3-((1*R*,2*R*)-2-phenylcyclopropyl)-butanoate (18a)

Compound **18a** (54.2 mg, 0.232 mmol, 60%) was obtained as a colorless oil from **16a** (130 mg, 0.384 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{23}$ −56.1° (*c* = 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.81–0.86 (1H, m), 0.98–1.03 (1H, m), 1.20 (3H, s), 1.20–1.25 (1H, m), 1.86–1.91 (1H, m), 2.48, 2.52 (2H, ABq, *J* = 14.1 Hz), 3.69 (3H, s), 7.06–7.10 (2H, m), 7.12–7.16 (1H, m), 7.22–7.27 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.38, 18.69, 27.72, 33.43, 47.96, 50.24, 51.39, 125.48, 126.02, 128.27, 143.04, 172.28; HRMS (ESI) calcd for $C_{14}H_{20}NO_2$: 234.1489 [(M+H)$^+$], found 234.1486.

4.2.21. (*S*)-Methyl 3-amino-3-((1*S*,2*S*)-2-phenylcyclopropyl)butanoate (*ent*-18a)

Compound ***ent*-18a** (183 mg, 0.786 mmol, 93%) was obtained as a colorless oil from ***ent*-16a** (286 mg, 0.848 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{23}$ +53.7° (*c* = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{20}NO_2$: 234.1489 [(M+H)$^+$], found 234.1487.

4.2.22. *tert*-Butyl(*S*)-1,4-dimethyl-6-oxo-4-((1*R*,2*R*)-2-phenylcyclopropyl)-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (20a)

Compound **17a** (306 mg, 1.31 mmol) and compound **19** (308 mg, 1.31 mmol) were dissolved in DMF (3.1 mL) under N_2 atmosphere, and to the solution were added DIEA (0.916 mL, 5.24 mmol) and EDC HCl (352 mg, 1.84 mmol). The reaction

mixture was stirred at room temperature for 17 h, and was partitioned between AcOEt and water. The mixture was extracted with AcOEt, and the organic layer was washed with water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography (hexane/AcOEt = 2:1) to give **20a** (460 mg, 1.29 mmol, 98%) as a colorless oil. $[\alpha]_D^{23}$ −181.8° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96–1.05 (2H, m), 1.15–1.18 (1H, m), 1.39 (3H, s), 1.53 (9H, s), 1.81–1.86 (1H, m), 2.70, 2.76 (2H, ABq, J = 15.8 Hz), 3.32 (3H, s), 7.02–7.04 (2H, m), 7.14–7.18 (1H, m), 7.23–7.27 (2H, m), 9.84 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.90, 19.59, 26.74, 28.25, 28.46, 31.52, 43.19, 51.09, 79.82, 126.17, 126.32, 128.50, 140.81, 157.76, 163.99, 168.07; HRMS (ESI) calcd for $C_{20}H_{28}N_3O_3$: 358.2125 [(M+H)$^+$], found 358.2124.

4.2.23. *tert*-Butyl (*R*)-1,4-dimethyl-6-oxo-4-((1*S*,2*S*)-2-phenylcyclopropyl)-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (*ent*-20a)

Compound ***ent*-20a** (308 mg, 1.32 mmol, 96%) was obtained as a colorless oil from ***ent*-17a** (465 mg, 1.38 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{23}$ +176.2° (c = 0.50, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{28}N_3O_3$: 358.2125 [(M+H)$^+$], found 358.2125.

4.2.24. *tert*-Butyl (*S*)-4-((1*R*,2*R*)-2-(3-bromophenyl)cyclopropyl)-1,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (20b)

Compound **20b** (718 mg, 1.65 mmol, 99%) was obtained as a colorless oil from **17b** (520 mg, 1.66 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{23}$ −138.4° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00–1.04 (2H, m), 1.15–1.20 (1H, m), 1.38 (3H, s), 1.53 (9H, s), 1.78–1.83 (1H, m), 2.70, 2.75 (2H, ABq, J = 16.1 Hz), 3.32 (3H, s), 6.95-6.98(1H, m), 7.11 (1H, t, J = 7.9 Hz), 7.15 (1H, t, J = 2.0 Hz), 7.30 (1H, ddd, J = 7.9, 2.0, 1.0 Hz), 9.86 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.24, 19.26, 26.59, 28.24, 28.46, 31.82, 43.20, 51.01, 79.92, 122.66, 125.23, 129.11, 129.31, 130.03, 143.29, 157.72, 164.01, 167.93; HRMS (ESI) calcd for $C_{20}H_{26}BrN_3O_3Na$: 458.1050 [(M+Na)$^+$], found 458.1055

4.2.25. *tert*-Butyl (*R*)-1,4-dimethyl-6-oxo-4-((1*R*,2*R*)-2-phenylcyclopropyl)-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (21a)

Compound **21a** (61.6 mg, 0.172 mmol, 97%) was obtained as a colorless oil from 18a (41.6 mg, 0.178 mmol) by the same procedure used to prepare 20a. $[\alpha]_D^{23}$ −3.0° (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87-0.93 (1H, m), 0.98-1.03 (1H, m), 1.19-1.23 (1H, m), 1.39 (3H, s), 1.53 (9H, s), 1.87-1.91 (1H, m), 2.71, 2.77 (2H, ABq, J = 16.0 Hz), 3.30 (3H, s), 7.05-7.08 (2H, m), 7.16-7.20 (1H, m), 7.24-7.29 (2H, m), 9.83 (1H, s); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 11.27, 18.65, 26.49, 28.26, 28.44, 31.40, 43.48, 51.05, 79.82, 126.14, 126.18, 128.50, 141.16, 157.74, 163.99, 168.10; HRMS (ESI) calcd for $C_{20}H_{27}N_3O_3Na$: 380.1945 [(M+Na)$^+$], found 380.1941.

4.2.26. *tert*-Butyl (*S*)-1,4-dimethyl-6-oxo-4-((1*S*,2*S*)-2-phenylcyclopropyl)-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (*ent*-21a)

Compound ***ent*-21a** (226 mg, 0.631 mmol, 96%) was obtained as a colorless oil from ***ent*-18a** (154 mg, 0.660 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{23}$ 0° (c = 0.31, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{28}N_3O_3$: 358.2125 [(M+H)$^+$], found 358.2125.

4.2.27. (*S*)-2-amino-3,6-dimethyl-6-((1*R*,2*R*)-2-phenylcyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (6) TFA salt

To a solution of **20a** (520 mg, 1.46 mmol) in dichloromethane (5.2 mL) was added TFA (5.2 mL). The reaction mixture was stirred for 1.5 h, and then evaporated. The residue was partitioned between AcOEt and 5% K_2CO_3 solution. The mixture was extracted with AcOEt, and the organic layer was washed with water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography (NH silica gel, $CHCl_3$/MeOH = 50:1) to give 6 (352 mg, 1.37 mmol, 94%) as a colorless solid. ^{1}H NMR analysis revealed that this contained ~3% diastereomer as an impurity. **6** (164 mg) was subjected to the recrystallization from hexane (2 mL) and AcOEt (1.4 mL) to obtain pure 6, which was then dissolved in dichloromethane (0.2 mL) and TFA (0.2 mL) and evaporated. The residue was rinsed with hexane–AcOEt (10:1) to obtain **6** TFA salt (105.2 mg) as a colorless solid. mp 207–209 °C; $[\alpha]_D^{20}$ −64.4° (c = 0.50, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.00–1.04 (2H, m), 1.30–1.35 (1H, m), 1.41 (3H, s), 1.86–1.90 (1H, m), 2.92 (2H, s), 3.31 (3H, s), 7.05–7.08 (2H, m), 7.12-7.16 (1H, m), 7.21–7.25 (2H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.94, 20.63, 25.29, 28.80, 32.00, 42.90, 53.60, 127.18, 129.51, 142.40, 156.83, 168.03; HRMS (ESI) calcd for $C_{15}H_{20}N_3O$: 258.1601 [(M+H)$^+$], found 258.1600; Anal. calcd for $C_{15}H_{19}N_3O{\cdot}CF_3CO_2H$: C, 54.98; H, 5.43; N, 11.32; F, 15.35. found: C, 54.81; H, 5.39; N, 11.25; F, 15.32. Optical purity: 100% e.e. (Column: Daicel CHIRALPAK IC 4.6 × 250 mm, eluent: n-hexane/IPA/EtOH/diethylamine/TFA = 75:25:3:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 7.9 min).

4.2.28. (*R*)-2-Amino-3,6-dimethyl-6-((1*S*,2*S*)-2-phenylcyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (*ent*-6) TFA salt

Compound ***ent*-6** (227 mg, 0.883 mmol, 89%) was obtained as a colorless solid from ***ent*-20a** (465 mg, 1.38 mmol), and ***ent*-6** TFA salt (63.9 mg) from ***ent*-6** (202 mg) by the same procedure used to prepare **6** TFA salt. $[\alpha]_D^{20}$ +62.6° (c = 0.50, MeOH); HRMS (ESI) calcd for $C_{15}H_{20}N_3O$: 258.1601 [(M+H)$^+$], found 258.1600; Anal. calcd for $C_{15}H_{19}N_3O{\cdot}CF_3CO_2H$: C, 54.98; H, 5.43; N, 11.32; F, 15.35. found: C, 54.81; H, 5.35; N, 11.41; F, 15.16. Optical purity: 100% e.e. (Column: Daicel CHIRALPAK IC 4.6 × 250 mm, eluent: n-hexane/IPA/EtOH/diethylamine/TFA = 75:25:3:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 6.9 min).

4.2.29. (*R*)-2-Amino-3,6-dimethyl-6-((1*R*,2*R*)-2-phenylcyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (7) TFA salt

To a solution of **21a** (48.8 mg, 0.137 mmol) in dichloromethane (0.5 mL) was added TFA (0.5 mL). The reaction mixture was stirred for 2 h, and then evaporated. The residue was partitioned between AcOEt and 5% K_2CO_3 solution. The mixture was extracted with AcOEt, and the organic layer was washed with water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography (NH silica gel, AcOEt/MeOH = 94:6) to give **7** (33.6 mg, 0.130 mmol, 95%) as a colorless solid. The entire solid was dissolved in dichloromethane (0.3 mL) and TFA (0.3 mL) and evaporated. The residue was rinsed with hexane–AcOEt (5:1) to obtain **7** TFA salt (43.3 mg) as a colorless solid. mp 196–198 °C; $[\alpha]_D^{20}$ −64.4° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.93–0.98 (1H, m), 1.01–1.04 (1H, m), 1.33–1.38 (1H, m), 1.41 (3H, s), 1.94–1.99 (1H, m), 2.90, 2.94 (2H, ABq, J = 16.5 Hz), 3.29 (3H, s), 7.08–7.17 (3H, m), 7.22–7.26 (2H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 11.90, 19.69, 25.27, 28.75, 31.85, 42.90, 53.58, 127.13, 129.53, 142.67, 156.79, 168.02; HRMS (ESI) calcd for $C_{15}H_{20}N_3O$: 258.1601 [(M+H)$^+$], found 258.1601; Anal. calcd for $C_{15}H_{19}N_3O{\cdot}CF_3CO_2H$: C, 54.98; H, 5.43; N, 11.32; F, 15.35. found: C, 54.92; H, 5.45; N, 11.33; F, 15.36. Optical purity: 100% e.e. (Column: Daicel CHIRALPAK AY-H 4.6 × 250 mm, eluent: n-hexane/IPA/EtOH/diethylamine/TFA = 95:5:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 11.0 min).

4.2.30. (*S*)-2-Amino-3,6-dimethyl-6-((1*S*,2*S*)-2-phenylcyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (*ent*-7) TFA salt

Compound ***ent*-7** (132 mg, 0.515 mmol, 94%) was obtained as a colorless solid from ***ent*-21a** (195 mg, 0.547 mmol), and ***ent*-7** TFA salt (141 mg) from ***ent*-7** (105 mg) by the same procedure used to prepare **7** TFA salt. $[\alpha]_D^{20}$ +66.0° (c = 0.50, MeOH); HRMS (ESI) calcd for $C_{15}H_{20}N_3O$: 258.1601 [(M+H)$^+$], found 258.1600; Anal. calcd for $C_{15}H_{19}N_3O{\cdot}CF_3CO_2H$: C, 54.98; H, 5.43; N, 11.32; F, 15.35. found: C,

54.96; H, 5.44; N, 11.35; F, 15.30. Optical purity: 100% e.e. (Column: Daicel CHIRALPAK AY-H 4.6 × 250 mm, eluent: *n*-hexane/IPA/diethylamine/TFA = 95:5:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 12.0 min).

4.2.31. (1*S*,2*R*)-*N*-Methoxy-*N*-methyl-2-phenylcyclopropanecarboxamide (mixture with (1*R*,2*R*) *trans* isomer) (23)

Compound **23** (422 mg, 2.12 mmol, 95%) was obtained as a colorless oil from **22** (362 mg, 2.23 mmol) by the same procedure used to prepare **11a**. *cis* isomer: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.27–1.32 (1H, m), 1.79–1.83 (1H, m), 2.50–2.58 (2H, m), 3.02 (3H, s), 3.67 (3H, s), 7.12–7.18 (1H, m), 7.19–7.27 (4H, m).

4.2.32. (1*R*,2*S*)-*N*-Methoxy-*N*-methyl-2-phenylcyclopropanecarboxamide (mixture with (1*S*,2*S*) *trans* isomer) (*ent*-23)

Compound ***ent*-23** (542 mg, 2.64 mmol, 96%) was obtained as a colorless oil from ***ent*-22** (445 mg, 2.75 mmol) by the same procedure used to prepare **11a**.

4.2.33. 1-((1*S*,2*R*)-2-Phenylcyclopropyl)ethanone (24)

Compound **24** (273 mg, 1.71 mmol, 85%) was obtained as a colorless oil from **23** (411 mg, 2.00 mmol) by the same procedure used to prepare **12a**. $[\alpha]_D^{23}$ +38.3° (*c* = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28–1.33 (1H, m), 1.81–1.86 (1H, m), 2.01 (3H, s), 2.40–2.45 (1H, m), 2.66–2.72 (1H, m), 7.16–7.22 (3H, m), 7.24–7.28 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.66, 28.25, 30.21, 31.22, 126.72, 128.01, 129.10, 136.00, 204.24; HRMS (ESI) calcd for $C_{11}H_{12}ONa$: 183.0780 [$(M+H)^+$], found 183.0782.

4.2.34. 1-((1*R*,2*S*)-2-Phenylcyclopropyl)ethanone (*ent*-24)

Compound ***ent*-24** (356 mg, 2.23 mmol, 87%) was obtained as a colorless oil from ***ent*-23** (527 mg, 2.57 mmol) by the same procedure used to prepare **12a**. $[\alpha]_D^{23}$ −34.7° (*c* = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{11}H_{12}ONa$: 183.0780 [$(M+H)^+$], found 183.0783.

4.2.35. (*R*,*E*)-2-Methyl-*N*-(1-((1*S*,2*R*)-2-phenylcyclopropyl)ethylidene)propane-2-sulfinamide (25)

Compound **25** (105 mg, 0.397 mmol, 48%) was obtained as a colorless oil from **24** (133 mg, 0.830 mmol) and (*R*)-2-methylpropane-2-sulfinamide (131 mg, 2.98 mmol) by the same procedure used to prepare **13a**. Starting material **12c** (49.5 mg, 0.309 mmol, 37%) was recovered. $[\alpha]_D^{20}$ +104.1° (*c* = 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.95 (9H, s), 1.25–1.30 (1H, m), 1.88–1.92 (1H, m), 2.17–2.24 (1H, m), 2.24 (3H, s), 2.70–2.76 (1H, m), 7.14–7.19 (3H, m), 7.19–7.24 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.86, 21.80, 24.94, 28.33, 30.27, 55.64, 126.67, 128.09, 129.55, 136.42, 182.48; HRMS (ESI) calcd for $C_{15}H_{21}NOSNa$: 286.1236 [$(M+Na)^+$], found 286.1236.

4.2.36. (*S*,*E*)-2-Methyl-*N*-(1-((1*R*,2*S*)-2-phenylcyclopropyl)ethylidene)propane-2-sulfinamide (*ent*-25)

Compound ***ent*-25** (140 mg, 0.533 mmol, 38%) was obtained as a colorless oil from ***ent*-24** (227 mg, 1.42 mmol) and (*S*)-2-methylpropane-2-sulfinamide (224 mg, 1.84 mmol) by the same procedure used to prepare **13a**. Starting material ***ent*-24** (115 mg, 0.720 mmol, 51%) was recovered. $[\alpha]_D^{20}$ −104.5° (*c* = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{21}NOSNa$: 286.1236 [$(M+Na)^+$], found 286.1235.

4.2.37. (*S*,*E*)-2-Methyl-*N*-(1-((1*S*,2*R*)-2-phenylcyclopropyl)ethylidene)propane-2-sulfinamide (26)

Compound **26** (125 mg, 0.475 mmol, 47%) was obtained as a colorless oil from **24** (162 mg, 1.01 mmol) and (*S*)-2-methylpropane-2-sulfinamide (159 mg, 1.31 mmol) by the same procedure used to prepare **13a**. Starting material **24** (65.3 mg, 0.408 mmol, 40%) was recovered. $[\alpha]_D^{20}$ +134.1° (*c* = 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (9H, s), 1.23–1.33 (1H, m), 1.71–1.78 (1H, m), 2.15–2.21 (1H, m), 2.17 (3H, s), 2.66–2.73 (1H, m), 7.17–7.28 (5H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.83, 22.06, 24.03, 27.42, 30.12, 56.19, 126.88, 128.36, 129.62, 136.45, 181.98; HRMS (ESI) calcd for $C_{15}H_{21}NOSNa$: 286.1236 [$(M+Na)^+$], found 286.1236.

4.2.38. (*R*,*E*)-2-Methyl-*N*-(1-((1*R*,2*S*)-2-phenylcyclopropyl)ethylidene)propane-2-sulfinamide (*ent*-26)

Compound ***ent*-26** (84.8 mg, 0.322 mmol, 47%) was obtained as a colorless oil from ***ent*-24** (110 mg, 0.688 mmol) and (*R*)-2-methylpropane-2-sulfinamide (108 mg, 0.895 mmol) by the same procedure used to prepare **13a**. Starting material ***ent*-24** (84.8 mg, 0.322 mmol, 38%) was recovered. $[\alpha]_D^{20}$ −131.1° (*c* = 0.10, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{21}NOSNa$: 286.1236 [$(M+Na)^+$], found 286.1235.

4.2.39. (*S*)-Methyl 3-((*R*)-1,1-dimethylethylsulfinamido)-3-((1*S*,2*R*)-2-phenylcyclopropyl)butanoate (27)

Compound **27** (99.6 mg, 0.295 mmol, 84%) was obtained as a colorless oil from **25** (93.1 mg, 0.353 mmol) by the same procedure used to prepare 15a. $[\alpha]_D^{23}$ −12.3° (*c* = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (3H, s), 1.06–1.12 (1H, m), 1.14 (9H, s), 1.34–1.45 (2H, m), 2.22–2.29 (1H, m), 2.50, 2.60 (2H, ABq, *J* = 15.2 Hz), 3.68 (3H, s), 4.60 (1H, s), 7.16-7.21 (1H, m), 7.25-7.33 (4H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.07, 21.01, 22.69, 24.57, 28.69, 46.04, 51.58, 55.46, 56.87, 126.32, 128.27, 130.07, 137.55, 172.20; HRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$: 360.1604 [$(M+Na)^+$], found 360.1602.

4.2.40. (*R*)-Methyl 3-((*S*)-1,1-dimethylethylsulfinamido)-3-((1*R*,2*S*)-2-phenylcyclopropyl)butanoate (*ent*-27)

Compound ***ent*-27** (65.3 mg, 0.193 mmol, 87%) was obtained as a colorless oil from ***ent*-25** (58.7 mg, 0.223 mmol) by the same procedure used to prepare **15a**. $[\alpha]_D^{23}$ +7.3° (*c* = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$: 360.1604 [$(M+Na)^+$], found 360.1607.

4.2.41. (*R*)-methyl 3-((*S*)-1,1-dimethylethylsulfinamido)-3-((1*S*,2*R*)-2-phenylcyclopropyl)butanoate (28)

Compound **28** (77.2 mg, 0.229 mmol, 55%) was obtained as a colorless solid from **26** (109 mg, 0.413 mmol) by the same procedure used to prepare **15a**. Starting material **26** (27.5 mg, 0.104 mmol, 25%) was recovered. $[\alpha]_D^{23}$ +52.7° (*c* = 0.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96–1.02 (1H, m), 1.00 (9H, s), 1.06–1.12 (1H, m), 1.24 (3H, s), 1.52–1.58 (1H, m), 2.26–2.33 (1H, m), 2.67, 2.71 (2H, ABq, *J* = 14.7 Hz), 3.70 (3H, s), 7.18–7.22 (1H, m), 7.27–7.32 (2H, m), 7.40–7.44 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.34, 21.85, 22.55, 25.00, 28.47, 47.57, 51.54, 55.52, 57.34, 126.71, 128.59, 130.38, 138.21, 171.61; HRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$: 360.1604 [$(M+Na)^+$], found 360.1602.

4.2.42. (*S*)-Methyl 3-((*R*)-1,1-dimethylethylsulfinamido)-3-((1*R*,2*S*)-2-phenylcyclopropyl)butanoate (*ent*-28)

Compound ***ent*-28** (83.7 mg, 0.248 mmol, 69%) was obtained as a colorless solid from ***ent*-26** (95.3 mg, 0.362 mmol) by the same procedure used to prepare **15a**. Starting material ***ent*-26** (18.7 mg, 0.0710 mmol, 20%) was recovered. $[\alpha]_D^{23}$ −58.0° (*c* = 0.15, $CHCl_3$); HRMS (ESI) calcd for $C_{18}H_{27}NO_3SNa$: 360.1604 [$(M+Na)^+$], found 360.1605.

4.2.43. (*S*)-methyl 3-amino-3-((1*S*,2*R*)-2-phenylcyclopropyl)butanoate (29)

Compound **29** (51.3 mg, 0.220 mmol, 88%) was obtained as a colorless oil from **27** (84.1 mg, 0.249 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{23}$ +76.1° (*c* = 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90–0.96 (1H, m), 1.03 (3H, s), 1.15-1.20 (1H, m),

1.25–1.31 (1H, m), 2.17–2.24 (1H, m), 2.33, 2.41 (2H, ABq, J = 14.2 Hz), 3.68 (3H, s), 7.16–7.20 (1H, m), 7.25–7.30 (2H, m), 7.32–7.36 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.38, 20.85, 28.62, 29.26, 47.99, 51.37, 51.61, 126.22, 128.28, 129.98, 138.16, 172.32; $C_{14}H_{20}NO_2$: 234.1489 [(M+H)$^+$], found 234.1490.

4.2.44. (*R*)-Methyl 3-amino-3-((1*R*,2*S*)-2-phenylcyclopropyl)-butanoate (*ent*-29)

Compound ***ent*-29** (59.6 mg, 0.255 mmol, 93%) was obtained as a colorless oil from ***ent*-27** (92.8 mg, 0.275 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{23}$ −64.7° (c = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{20}NO_2$: 234.1489 [(M+H)$^+$], found 234.1491.

4.2.45. (*R*)-Methyl 3-amino-3-((1*S*,2*R*)-2-phenylcyclopropyl)butanoate (30)

Compound **30** (41.8 mg, 0.179 mmol, 92%) was obtained as a colorless oil from **28** (65.7 mg, 0.159 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{23}$ +35.3° (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91–0.97 (1H, m), 1.04 (3H, s), 1.21–1.32 (2H, m), 2.20–2.26 (1H, m), 2.36, 2.42 (2H, ABq, J = 14.0 Hz), 3.80 (3H, s), 7.17–7.21 (1H, m), 7.26–7.31 (2H, m), 7.36–7.39 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.49, 21.42, 28.30, 29.52, 48.13, 51.33, 51.98, 126.27, 128.39, 129.99, 138.30, 172.20; HRMS (ESI) calcd for $C_{14}H_{20}NO_2$: 234.1489 [(M+H)$^+$], found 234.1492.

4.2.46. (*S*)-Methyl 3-amino-3-((1*R*,2*S*)-2-phenylcyclopropyl)butanoate (*ent*-30)

Compound ***ent*-30** (58.2 mg, 0.249 mmol, 95%) was obtained as a colorless oil from ***ent*-28** (89.0 mg, 0.264 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{23}$ −35.7° (c = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{20}NO_2$: 234.1489 [(M+H)$^+$], found 234.1491.

4.2.47. *tert*-Butyl (*S*)-1,4-dimethyl-6-oxo-4-((1*S*,2*R*)-2-phenylcyclopropyl)-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (31)

Compound **31** (53.6 mg, 0.150 mmol, 89%) was obtained as a colorless oil from **29** (39.6 mg, 0.168 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{23}$ +27.0° (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98–1.02 (1H, m), 1.06-1.12 (1H, m), 1.12 (3H, s), 1.23–1.29 (1H, m), 1.50 (9H, s), 2.23–2.29 (1H, m), 2.48, 2.61 (2H, ABq, J = 15.6 Hz), 3.27 (3H, s), 7.18–7.23 (1H, m), 7.23–7.30 (4H, m), 9.21 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.40, 20.31, 26.17, 27.36, 28.30, 28.44, 44.32, 51.70, 79.43, 126.73, 128.64, 129.56, 136.25, 156.99, 163.28, 168.38; HRMS (ESI) calcd for $C_{20}H_{27}N_3O_3$Na: 380.1945 [(M+Na)$^+$], found 380.1943.

4.2.48. *tert*-Butyl(*R*)-1,4-dimethyl-6-oxo-4-((1*R*,2*S*)-2-phenylcyclopropyl)-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (*ent*-31)

Compound ***ent*-31** (61.5 mg, 0.172 mmol, 91%) was obtained as a colorless oil from ***ent*-29** (44.1 mg, 0.189 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{23}$ −29.0° (c = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{27}N_3O_3$Na: 380.1945 [(M+Na)$^+$], found 380.1948.

4.2.49. *tert*-Butyl(*R*)-1,4-dimethyl-6-oxo-4-((1*S*,2*R*)-2-phenylcyclopropyl)-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (32)

Compound **32** (61.7 mg, 0.173 mmol, 94%) was obtained as a colorless oil from **30** (42.7 mg, 0.183 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{23}$ +23.3° (c = 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.01 (3H, s), 1.08–1.14 (1H, m), 1.06–1.12 (1H, m), 1.33–1.39 (1H, m), 1.55 (9H, s), 2.29–2.35 (1H, m), 2.35, 2.57 (2H, ABq, J = 16.1 Hz), 3.12 (3H, s), 7.18–7.22 (1H, m), 7.25–7.32 (4H, m), 9.84 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.29, 21.31, 26.24, 28.10, 28.28, 28.36, 43.27, 51.97, 79.52, 126.72, 128.50, 129.79, 136.28, 156.84, 163.86, 168.29; HRMS (ESI) calcd for $C_{20}H_{27}N_3O_3$Na: 380.1945 [(M+Na)$^+$], found 380.1945.

4.2.50. *tert*-Butyl(*S*)-1,4-dimethyl-6-oxo-4-((1*R*,2*S*)-2-phenylcyclopropyl)-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (*ent*-32)

Compound ***ent*-32** (43.1 mg, 0.121 mmol, 91%) was obtained as a colorless oil from ***ent*-30** (31.1 mg, 0.133 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{23}$ −25.3° (c = 0.30, $CHCl_3$); HRMS (ESI) calcd for $C_{20}H_{27}N_3O_3$Na: 380.1945 [(M+Na)$^+$], found 380.1946.

4.2.51. (*S*)-2-Amino-3,6-dimethyl-6-((1*S*,2*R*)-2-phenylcyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (8) TFA salt

Compound **38** (27.3 mg, 0.106 mmol, 94%) was obtained as a colorless oil from **31** (40.3 mg, 0.113 mmol), and **8** TFA salt (20.9 mg) from **8** (16.3 mg) by the same procedure used to prepare **7** TFA salt. mp 221–223 °C; $[\alpha]_D^{20}$ +53.7° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.09 (3H, s), 1.08–1.14 (2H, m), 1.38–1.44 (1H, m), 2.31–2.37 (1H, m), 2.67, 2.75 (2H, ABq, J = 16.3 Hz), 3.26 (3H, s), 7.22–7.26 (1H, m), 7.32–7.35 (4H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 5.88, 21.39, 25.36, 27.91, 28.75, 43.85, 54.20, 127.90, 129.78, 130.76, 137.95, 156.00, 167.92; HRMS (ESI) calcd for $C_{15}H_{20}N_3O$: 258.1601 [(M+H)$^+$], found 258.1602. Optical purity: 100% *ee* (Column: Daicel CHIRALPAK IC 4.6 × 250 mm, eluent: *n*-hexane/IPA/EtOH/diethylamine/TFA = 75:25:3:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 28.6 min).

4.2.52. (*R*)-2-Amino-3,6-dimethyl-6-((1*R*,2*S*)-2-phenylcyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (*ent*-8) TFA salt

Compound ***ent*-8** (32.0 mg, 0.124 mmol, 98%) was obtained as a colorless oil from ***ent*-31** (45.3 mg, 0.127 mmol), and ***ent*-8** TFA salt (41.1 mg) as a colorless solid from ***ent*-8** (32.0 mg) by the same procedure used to prepare **7** TFA salt. $[\alpha]_D^{20}$ −58.0° (c = 0.30, MeOH); HRMS (ESI) calcd for $C_{15}H_{20}N_3O$: 258.1601 [(M+H)$^+$], found 258.1600; Anal. calcd for $C_{15}H_{19}N_3O{\cdot}CF_3CO_2H$: C, 54.98; H, 5.43; N, 11.32; F, 15.35. found: C, 54.85; H, 5.41; N, 11.35; F, 15.32. Optical purity: 100% *ee* (Column: Daicel CHIRALPAK IC 4.6 × 250 mm, eluent: *n*-hexane/IPA/EtOH/diethylamine/TFA = 75:25:3:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 23.1 min).

4.2.53. (*R*)-2-Amino-3,6-dimethyl-6-((1*S*,2*R*)-2-phenylcyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (9) TFA salt

Compound **9** (18.9 mg, 0.0734 mmol, 82%) was obtained as a colorless solid from **32** (31.9 mg, 0.0892 mmol), and **9** TFA salt (16.5 mg) from **9** (18.9 mg) as a colorless solid by the same procedure used to prepare **7** TFA salt. mp 145–146 °C; $[\alpha]_D^{20}$ +32.7° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.08–1.14 (1H, m), 1.19–1.24 (1H, m), 1.37 (3H, s), 1.39–1.45 (1H, m), 2.31–2.37 (1H, m), 2.54, 2.74 (2H, ABq, J = 16.5 Hz), 2.84 (3H, s), 7.19–7.23 (1H, m), 7.24–7.27 (2H, m), 7.29–7.33 (2H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 5.10, 22.98, 28.65, 28.72, 30.44, 42.55, 53.86, 127.67, 129.78, 130.63, 138.08, 155.65, 167.79; HRMS (ESI) calcd for $C_{15}H_{20}N_3O$: 258.1601 [(M+H)$^+$], found 258.1600. Optical purity: 100% *ee* (Column: Daicel CHIRALPAK IC 4.6 × 250 mm, eluent: *n*-hexane/IPA/EtOH/diethylamine/TFA = 75:25:3:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 8.9 min).

4.2.54. (*S*)-2-Amino-3,6-dimethyl-6-((1*R*,2*S*)-2-phenylcyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (*ent*-9) TFA salt

Compound ***ent*-9** (24.0 mg, 0.09334 mmol, 72%) was obtained as a colorless solid from ***ent*-32** (46.1 mg, 0.0129 mmol), and ***ent*-9** TFA salt (32.3 mg) from ***ent*-9** (24.0 mg) as a colorless solid by the same procedure used to prepare **7** TFA salt. $[\alpha]_D^{20}$ −35.3° (c = 0.30, MeOH); HRMS (ESI) calcd for $C_{15}H_{20}N_3O$: 258.1601 [(M+H)$^+$], found 258.1601; Anal. calcd for $C_{15}H_{19}N_3O{\cdot}CF_3CO_2H$: C, 54.98; H, 5.43; N, 11.32; F, 15.35. Found: C, 54.76; H, 5.40; N, 11.28; F, 15.37. Optical purity: 100% *ee* (Column: Daicel CHIRALPAK IC 4.6 × 250 mm, eluent: *n*-hexane/IPA/EtOH/

diethylamine/TFA = 75:25:3:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 13.0 min).

4.2.55. Suzuki–Miyaura coupling: typical procedures. (*S*)-2-amino-6-((1*R*,2*R*)-2-(3′-methoxybiphenyl-3-yl)cyclopropyl)-3,6-dimethyl-5,6-dihydropyrimidin-4(3*H*)-one (35) TFA salt

To a solution of 20b (51.5 mg, 0.118 mmol) in dioxane (1.0 mL) and water (0.5 mL) was added 3-methoxyphenylboronic acid (26.9 mg, 0.127 mmol), potassium carbonate (48.9 mg, 0.354 mmol), dichlorobis(triphenylphosphine)palladium (4.1 mg, 0.0059 mmol), and the mixture was heated at 100 °C for 2 h. The reaction mixture was partitioned between AcOEt and water. The organic layer was washed water, brine, dried with Na_2SO_4, and evaporated. The residue was dissolved in dichloromethane (0.6 mL) and TFA (0.6 mL) was added. The mixture was stirred for 1 h, and evaporated. The residue was partitioned between AcOEt and 5% potassium carbonate. The organic layer was washed water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography (NH silica gel, AcOEt/MeOH = 10:1) to obtain free form of **35**. This was dissolved in dichloromethane (0.6 mL) and TFA (0.6 mL), and evaporated. The residue was triturated from AcOEt/Et_2O to give **35** TFA salt (47.8 mg, 0.100 mmol, 85%) as a colorless powder. $[\alpha]_D^{20}$ −51.0° (*c* = 0.10, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.02–1.07 (1H, m), 1.09–1.14 (1H, m), 1.35–1.40 (1H, m), 1.43 (3H, s), 1.93-2.01 (1H, m), 2.93, 2.97 (2H, ABq, *J* = 16.1 Hz), 3.33 (3H, s), 3.85 (3H, s), 6.91 (1H, dd, *J* = 8.3, 2.5 Hz), 7.04 (1H, d, *J* = 7.8 Hz), 7.10-7.12 (1H, m), 7.15 (1H, d, *J* = 7.6 Hz), 7.29–7.35 (3H, m), 7.40 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.75, 20.76, 25.33, 28.84, 32.07, 42.99, 53.63, 55.79, 113.80, 120.50, 126.02, 126.07, 126.30, 130.04, 130.89, 142.68, 142.94, 143.88, 156.85, 161.62, 168.11; HRMS (ESI) calcd for $C_{22}H_{26}N_3O_2$: 364.2020 [(M+H)$^+$], found 364.2022; Anal. calcd for $C_{22}H_{25}N_3O{\cdot}CF_3CO_2H{\cdot}0.6H_2O$: C, 59.03; H, 5.61; N, 8.61. Found: C, 59.12; H, 5.51; N, 8.53.

4.2.56. (*S*)-2-Amino-6-((1*R*,2*R*)-2-(biphenyl-3-yl)cyclopropyl)-3,6-dimethyl-5,6-dihydropyrimidin-4(3*H*)-one (33) TFA salt

Compound **33** TFA salt (36.0 mg, 0.0805 mmol, 73%) was obtained as a colorless solid from **20b** (48.4 mg, 0.111 mmol) and phenylboronic acid (20.4 mg, 0.167 mmol) by the same procedure used to prepare 35. mp 157–159 °C; $[\alpha]_D^{20}$ −58.0° (*c* = 0.10, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.04–1.09 (1H, m), 1.09–1.14 (1H, m), 1.37–1.40 (1H, m), 1.43 (3H, s), 1.94–1.99 (1H, m), 2.92, 2.96 (2H, ABq, *J* = 16.4 Hz), 3.32 (3H, s), 7.05 (1H, d, *J* = 7.6 Hz), 7.30–7.35 (3H, m), 7.39–7.44 (3H, m), 7.56–7.59 (2H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.86, 20.74, 25.29, 28.83, 32.09, 42.98, 53.62, 125.96, 126.00, 126.15, 128.07, 128.44, 129.87, 130.06, 142.43, 142.80, 143.02, 156.83, 168.13; HRMS (ESI) calcd for $C_{21}H_{24}N_3O$: 334.1914 [(M+H)$^+$], found 334.1914; Anal. calcd for $C_{21}H_{23}N_3O{\cdot}CF_3$-$CO_2H{\cdot}0.4H_2O$: C, 60.76; H, 5.50; N, 9.24; F, 12.54. found: C, 60.77; H, 5.35; N, 9.35; F, 12.44.

4.2.57. (*S*)-2-Amino-6-((1*R*,2*R*)-2-(2′-methoxybiphenyl-3-yl) cyclopropyl)-3,6-dimethyl-5,6-dihydropyrimidin-4(3*H*)-one (34) TFA salt

Compound **34** TFA salt (38.5 mg, 0.0806 mmol, 85%) was obtained as a colorless amorphous from **20b** (41.2 mg, 0.0944 mmol) and 2-methoxyphenylboronic acid (21.5 mg, 0.142 mmol) by the same procedure used to prepare **35**. $[\alpha]_D^{20}$ −52.5° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.00–1.10 (2H, m), 1.32–1.38 (1H, m), 1.42 (3H, s), 1.88–1.94 (1H, m), 2.93 (2H, s), 3.31 (3H, s), 3.78 (3H, s), 6.97–7.02 (2H, m), 7.05 (1H, d, *J* = 8.1 Hz), 7.17 (1H, s), 7.21–7.33 (4H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.82, 20.73, 25.36, 28.83, 32.04, 42.96, 53.61, 56.09, 112.70, 121.96, 125.45, 128.52, 128.62, 129.10, 129.87, 131.69, 131.99, 140.36, 141.89, 156.84, 157.95, 168.05; HRMS (ESI) calcd for $C_{22}H_{26}N_3O_2$: 364.2020 [(M+H)$^+$], found 364.2016.

4.2.58. (*S*)-2-Amino-6-((1*R*,2*R*)-2-(4′-methoxybiphenyl-3-yl)cyclopropyl)-3,6-dimethyl-5,6-dihydropyrimidin-4(3*H*)-one (36) TFA salt

Compound **36** TFA salt (45.7 mg, 0.0957 mmol, 84%) was obtained as a colorless solid from **20b** (49.9 mg, 0.114 mmol) and 4-methoxyphenylboronic acid (26.1 mg, 0.172 mmol) by the same procedure used to prepare **35**. mp 191–192 °C; $[\alpha]_D^{20}$ −55.6° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.02–1.07 (1H, m), 1.07–1.13 (1H, m), 1.35–1.40 (1H, m), 1.42 (3H, s), 1.92–2.01 (1H, m), 2.93-2.95 (2H, m), 3.32 (3H, s), 3.82 (3H, s), 6.96–7.01 (3H, m), 7.26 (1H, s), 7.29 (1H, t, *J* = 7.9 Hz), 7.36 (1H, d, *J* = 7.9 Hz), 7.52 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.81, 20.77, 25.28, 28.84, 32.04, 42.98, 53.64, 55.80, 115.29, 125.35, 125.53, 125.70, 129.07, 129.99, 134.81, 142.42, 142.88, 156.85, 160.86, 168.10; HRMS (ESI) calcd for $C_{22}H_{26}N_3O_2$: 364.2020 [(M+H)$^+$], found 364.2017.

4.2.59. (*S*)-2-Amino-3,6-dimethyl-6-((1*R*,2*R*)-2-(3′-propoxybiphenyl-3-yl)cyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (37) TFA salt

Compound **37** TFA salt (30.7 mg, 0.0607 mmol, 94%) was obtained as a colorless solid from **20b** (28.2 mg, 0.0646 mmol) and 3-propoxyphenylboronic acid (17.5 mg, 0.0972 mmol) by the same procedure used to prepare **35**. mp 154–156 °C; $[\alpha]_D^{20}$ −51.4° (*c* = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.02–1.08 (1H, m), 1.07 (3H, t, *J* = 7.5 Hz), 1.09–1.14 (1H, m), 1.36–1.41 (1H, m), 1.43 (3H, s), 1.78–1.86 (2H, m), 1.94–1.99 (1H, m), 2.93, 2.97 (2H, ABq, *J* = 16.4 Hz), 3.33 (3H, s), 4.00 (2H, t, *J* = 6.5 Hz), 6.89 (1H, ddd, *J* = 8.3, 2.5, 1.0 Hz), 7.04 (1H, d, *J* = 7.8 Hz), 7.09–7.11 (1H, m), 7.14 (1H, ddd, *J* = 7.8, 1.7, 1.0 Hz), 7.29–7.34 (3H, m), 7.40 (1H, ddd, *J* = 7.6, 1.7, 1.2 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.78, 10.92, 20.75, 23.78, 25.31, 28.84, 32.08, 42.97, 53.64, 70.66, 114.40, 114.41, 120.39, 126.01, 126.04, 126.26, 130.03, 130.87, 142.73, 142.93, 143.85, 156.85, 161.08, 168.11; HRMS (ESI) calcd for $C_{24}H_{30}N_3O_2$: 392.2333 [(M+H)$^+$], found 392.2330.

4.2.60. (*S*)-2-Amino-6-((1*R*,2*R*)-2-(3′-(hydroxymethyl)biphenyl-3-yl)cyclopropyl)-3,6-dimethyl-5,6-dihydropyrimidin-4(3*H*)-one (38) TFA salt

Compound **38** TFA salt (21.5 mg, 0.0450 mmol, 71%) was obtained as a colorless powder from **20b** (14.4 mg, 0.0949 mmol) and 3-(hydroxymethyl)phenylboronic acid (17.5 mg, 0.0972 mmol) by the same procedure used to prepare **35**. $[\alpha]_D^{20}$ −49.2° (*c* = 0.10, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.03–1.09 (1H, m), 1.09–1.14 (1H, m), 1.37–1.42 (1H, m), 1.43 (3H, s), 1.94–1.99 (1H, m), 2.95 (2H, s), 3.33 (3H, s), 4.67 (2H, s), 7.05 (1H, d, *J* = 7.8 Hz), 7.30–7.35 (3H, m), 7.38–7.44 (2H, m), 7.49 (1H, d, *J* = 7.8 Hz), 7.59 (1H, s); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.91, 20.76, 25.24, 28.85, 32.10, 42.96, 53.65, 65.23, 125.97, 126.05, 126.11, 126.64, 126.99, 127.06, 129.92, 130.07, 142.50, 142.75, 143.02, 143.37, 156.85, 168.08; HRMS (ESI) calcd for $C_{22}H_{26}N_3O_2$: 364.2020 [(M+H)$^+$], found 364.2017.

4.2.61. *N*-(3′-((1*R*,2*R*)-2-((*S*)-2-Amino-1,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrimidin-4-yl)cyclopropyl)biphenyl-3-yl)acetamide (39) TFA salt

Compound **39** TFA salt (22.1 mg, 0.0438 mmol, 67%) was obtained as a colorless powder from **20b** (28.2 mg, 0.0646 mmol) and 3-acetoamidophenylboronic acid (17.4 mg, 0.0969 mmol) by the same procedure used to prepare **24**. $[\alpha]_D^{20}$ −34.2° (*c* = 0.10, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.03–1.09 (1H, m), 1.09–1.14 (1H, m), 1.37–1.42 (1H, m), 1.42 (3H, s), 1.94–2.00 (1H, m), 2.15 (3H, s), 2.94 (2H, s), 3.33 (3H, s), 7.06 (1H, d, *J* = 7.8 Hz),

7.30–7.35 (3H, m), 7.37 (1H, t, J = 7.8 Hz), 7.39–7.43 (2H, m), 7.90 (1H, s); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.99, 20.74, 23.93, 25.11, 28.88, 32.10, 42.97, 66.94, 119.89, 120.10, 123.85, 125.97, 126.13, 126.19, 130.08, 130.31, 140.42, 142.49, 143.06, 143.09, 156.84, 168.05, 171.83; HRMS (ESI) calcd for $C_{23}H_{27}N_4O_2$: 391.2129 [$(M+H)^+$], found 391.2124.

4.2.62. (*S*)-2-Amino-3,6-dimethyl-6-((1*R*,2*R*)-2-(3-(thiophen-2-yl)phenyl)cyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (40) TFA salt

Compound **40** TFA salt (44.0 mg, 0.0970 mmol, 75%) was obtained as a colorless solid from **20b** (56.2 mg, 0.129 mmol) and thiophen-2-ylboronic acid (24.7 mg, 0.193 mmol) by the same procedure used to prepare **35**. mp 151-154 °C; $[\alpha]_D^{20}$ −50.2° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.03–1.12 (2H, m), 1.35–1.42 (1H, m), 1.42 (3H, s), 1.91–1.97 (1H, m), 2.93, 2.96 (2H, ABq, J = 16.3 Hz), 3.32 (3H, s), 6.99 (1H, d, J = 7.7 Hz), 7.08 (1H, dd, J = 5.1, 3.0 Hz), 7.27 (1H, t, J = 7.7 Hz), 7.34 (1H, s), 7.36 (1H, d, J = 5.1 Hz), 7.37 (1H, d, J = 3.0 Hz), 7.43 (1H, d, J = 7.7 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.85, 20.63, 25.21, 28.85, 32.04, 48.53, 53.62, 124.40, 124.73, 124.89, 125.94, 126.15, 129.14, 130.24, 136.03, 143.28, 145.33, 156.85, 168.07; HRMS (ESI) calcd for $C_{19}H_{22}N_3OS$: 340.1478 [$(M+H)^+$], found 340.1475; Anal. calcd for $C_{19}H_{21}N_3OS{\cdot}CF_3CO_2H{\cdot}0.3H_2O$: C, 54.96; H, 4.96; N, 9.16; F, 12.42; S, 6.99. found: C, 55.09; H, 4.84; N, 9.25; F, 12.41; S, 6.61.

4.2.63. (*S*)-2-AMINO-3,6-dimethyl-6-((1*R*,2*R*)-2-(3-(thiophen-3-yl)phenyl)cyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (41) TFA salt

Compound **41** TFA salt (42.1 mg, 0.0928 mmol, 78%) was obtained as a colorless solid from **20b** (52.1 mg, 0.119 mmol) and thiophen-3-ylboronic acid (22.9 mg, 0.179 mmol) by the same procedure used to prepare **35**. mp 156–158 °C; $[\alpha]_D^{20}$ −49.8° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.02–1.07 (1H, m), 1.08–1.13 (1H, m), 1.35–1.40 (1H, m), 1.43 (3H, s), 1.92–1.97 (1H, m), 2.93, 2.96 (2H, ABq, J = 17.0 Hz), 3.33 (3H, s), 6.99 (1H, d, J = 7.7 Hz), 7.28 (1H, t, J = 7.7 Hz), 7.36 (1H, s), 7.42-7.48 (3H, m), 7.59 (1H, dd, J = 2.7, 1.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.77, 20.72, 25.28, 28.84, 31.97, 42.98, 53.62, 121.40, 125.27, 125.44, 125.83, 127.20, 127.31, 130.07, 137.45, 143.00, 143.46, 156.85, 168.12; HRMS (ESI) calcd for $C_{19}H_{22}N_3OS$: HRMS (ESI) calcd for $C_{19}H_{22}N_3OS$: 340.1478 [$(M+H)^+$], found 340.1475.

4.2.64. (*S*)-2-Amino-3,6-dimethyl-6-((1*R*,2*R*)-2-(3-(pyridin-3-yl)phenyl)cyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (42) bis TFA salt

Compound **42** TFA salt (49.0 mg, 0.0871 mmol, 89%) was obtained as a colorless powder from **20b** (42.5 mg, 0.0974 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (30.0 mg, 0.146 mmol) by the same procedure used to prepare **35**. $[\alpha]_D^{20}$ −44.5° (c = 0.31, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.07–1.14 (1H, m), 1.14–1.20 (1H, m), 1.43–1.47 (1H, m), 1.44 (3H, s), 1.99–2.04 (1H, m), 2.95 (2H, s), 3.33 (3H, s), 7.22–7.26 (1H, m), 7.42–7.48 (2H, m), 7.53–7.58 (1H, m), 7.80–7.96 (1H, m), 8.45–8.62 (1H, m), 8.65–8.73 (1H, m), 8.95–9.03 (1H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 11.19, 20.60, 24.71, 28.82, 32.34, 42.93, 53.62, 126.20, 126.32, 127.89, 128.69, 130.84, 136.17, 141.17, 143.11, 144.34, 156.86, 168.16; HRMS (ESI) calcd for $C_{20}H_{23}N_4O$: 335.1866 [$(M+H)^+$], found 335.1865.

4.2.65. (*S*)-2-Amino-3,6-dimethyl-6-((1*R*,2*R*)-2-(3-phenethylphenyl)cyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (43) TFA salt

Compound **20b** (54.9 mg, 0.105 mmol), potassium trifluoro(phenethyl)borate (41.6 mg, 0.196 mmol) were dissolved in THF (0.9 mL) and water (0.09 mL), and cesium carbonate (96 mg, 0.294 mmol), dichloro(diphenylphosphinoferrocene)palladium CH_2Cl_2 complex (12.0 mg, 0.0147 mmol) were added. The mixture was stirred under reflux for 4 h. The reaction mixture was partitioned between AcOEt and water. The organic layer was washed with water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography (Hexane/AcOEt = 3:1) and concentrated to give the residue containing the coupling product. To a solution of the residue in CH_2Cl_2 (0.6 mL) was added trifluoroacetic acid (0.6 mL), and the mixture was stirred for 1 h. The solvent was evaporated, and the residue was partitioned between AcOEt and 5% K_2CO_3 solution. The organic layer was washed with water, brine, dried with Na_2SO_4, and evaporated. The residue was purified by silicagel chromatography (NH-silicagel, EtOAc/MeOH = 20:1) to obtain free **43**. This was dissolved in dichloromethane (0.3 mL) and TFA (0.3 mL), and evaporated. The residual crystalline was washed with hexane–AcOEt to give **43** TFA salt (28.6 mg, 0.0602 mmol, 86%) as a colorless solid. mp 174–177 °C; $[\alpha]_D^{20}$ −54.5° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 0.93–1.00 (2H, m), 1.20–1.25 (1H, m), 1.40 (3H, s), 1.79–1.84 (1H, m), 2.85–2.87 (4H, m), 2.90 (2H, s), 3.30 (3H, s), 6.78 (1H, s), 6.87 (1H, d, J = 7.7 Hz), 6.98 (1H, d, J = 7.7 Hz), 7.10–7.16 (4H, m), 7.20–7.25 (2H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.83, 20.62, 25.33, 28.83, 31.91, 39.01, 39.07, 42.93, 53.59, 124.87, 126.91, 127.42, 127.48, 129.30, 129.46, 129.66, 142.20, 143.02, 143.25, 156.83, 168.01; HRMS (ESI) calcd for $C_{23}H_{28}N_3O$: 362.2227 [$(M+H)^+$], found 362.2225; Anal. calcd for $C_{23}H_{27}N_3O{\cdot}CF_3CO_2H{\cdot}0.2H_2O$: C, 62.67; H, 5.97; N, 8.77; F, 11.90. found: C, 62.51; H, 5.89; N, 8.89; F, 12.11.

4.2.66. (*S*)-2-Amino-3,6-dimethyl-6-((1*R*,2*R*)-2-(3-styrylphenyl)cyclopropyl)-5,6-dihydropyrimidin-4(3*H*)-one (44) TFA salt

Compound **44** TFA salt (26.8 mg, 0.0566 mmol, 49%) was obtained as a colorless solid from **20b** (50.2 mg, 0.115 mmol) and (*E*)-styrylboronic acid (25.5 mg, 0.123 mmol) by the same procedure used to prepare **35**. mp 198–201 °C; $[\alpha]_D^{20}$ −59.3° (c = 0.30, MeOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 1.03–1.11 (2H, m), 1.36–1.41 (1H, m), 1.42 (3H, s), 1.90–1.95 (1H, m), 2.92, 2.96 (2H, ABq, J = 16.4 Hz), 3.33 (3H, s), 6.97 (1H, d, J = 7.6 Hz), 7.13–7.17 (2H, m), 7.22–7.26 (3H, m), 7.32–7.38 (3H, m), 7.53–7.55 (2H, d, J = 7.4 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 10.94, 20.63, 25.21, 28.84, 31.97, 42.95, 53.63, 125.45, 126.08, 126.52, 127.58, 128.70, 129.53, 129.76, 129.89, 129.96, 138.82, 139.07, 142.89, 156.82, 168.12; HRMS (ESI) calcd for $C_{23}H_{26}N_3O$: 360.2070 [$(M+H)^+$], found 360.2072.

4.2.67. Synthesis of reference compounds (Scheme 4)(*R*,*E*)-*N*-(4-(3-bromophenyl)butan-2-ylidene)-2-methylpropane-2-sulfinamide (46b)

Compound **46b** (1.35 g, 4.10 mmol, 76%) was obtained as a colorless oil from 45 (1.22 g, 5.36 mmol) and (*R*)-2-methylpropane-2-sulfinamide (779 mg, 6.43 mmol) by the same procedure used to prepare **13a**. $[\alpha]_D^{20}$ −83.2° (c = 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20 (9H, s), 2.34 (3H, s), 2.67–2.80 (2H, m), 2.84–2.94 (2H, m), 7.11 (1H, d, J = 7.7 Hz), 7.15 (1H, t, J = 7.7 Hz), 7.33 (1H, d, J = 7.7 Hz), 7.34 (1H, s); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 22.21, 23.21, 30.95, 44.16, 56.39, 122.54, 126.93, 129.27, 130.06, 131.39, 143.22, 183.63; HRMS (ESI) calcd for $C_{14}H_{20}BrNOSNa$: 352.0341 [$(M+Na)^+$], found 352.0341

4.2.68. (*R*)-Methyl 3-((*R*)-1,1-dimethylethylsulfinamido)-3-methyl-5-phenylpentanoate (47a) and (*S*)-methyl 3-((*R*)-1,1-dimethylethylsulfinamido)-3-methyl-5-phenylpentanoate (48a)

Compound **47a** (309 mg, 0.949 mmol, 51%) and **48a** (54.2 mg, 0.167 mmol, 9%) were obtained as a colorless oil from **46a**[26]

(468 mg, 1.86 mmol) by the same procedure used to prepare **15a**. NMR analysis of the crude reaction mixture revealed that the ratio of **47a**:**48a** was 4.9:1. They were separated by silica gel chromatography (hexane/EtOAc = 1:1). **47a**: $[\alpha]_D^{20}$ −75.6° (*c* = 0.30, $CDCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25 (9H, s), 1.47 (3H, s), 1.88–2.00 (2H, m), 2.58, 2.78 (2H, ABq, *J* = 15.9 Hz), 2.59–2.70 (2H, m), 3.68 (3H, s), 4.71 (1H, s), 7.15–7.21 (3H, m), 7.26–7.30 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.80, 25.69, 30.12, 43.02, 45.23, 51.65, 55.78, 56.18, 125.98, 128.33, 128.50, 141.78, 172.41; HRMS (ESI) calcd for $C_{17}H_{27}NO_3Na$: 348.1604 [(M+Na)$^+$], found 348.1603. 48a: $[\alpha]_D^{20}$ −69.4° (*c* = 0.10, $CDCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (9H, s), 1.41 (3H, s), 1.93–2.00 (1H, m), 2.09–2.17 (1H, m), 2.49, 2.79 (2H, ABq, *J* = 15.6 Hz), 2.64–2.74 (2H, m), 3.69 (3H, s), 4.49 (1H, s), 7.16–7.22 (3H, m), 7.25–7.30 (2H, m); HRMS (ESI) calcd for $C_{17}H_{27}NO_3Na$: 348.1604 [(M+Na)$^+$], found 348.1602.

4.2.69. (*R*)-Methyl 5-(3-bromophenyl)-3-((*R*)-1,1-dimethylethylsulfinamido)-3-methylpentanoate (48b)

Compound **48b** (516 mg, 1.28 mmol, 33%) was obtained as a colorless oil from **46b** (1.30 g, 3.93 mmol) by the same procedure used to prepare **15a**. $[\alpha]_D^{20}$ −67.9° (*c* = 0.30, $CDCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.25 (9H, s), 1.46 (3H, s), 1.85–1.98 (2H, m), 2.56, 2.79 (2H, ABq, *J* = 15.9 Hz), 2.56–2.68 (2H, m), 3.69 (3H, s), 4.74 (1H, s), 7.08–7.12 (1H, m), 7.15 (1H, t, *J* = 7.9 Hz), 7.30–7.34 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.80, 25.60, 29.82, 42.73, 45.23, 51.70, 55.83, 56.10, 122.50, 127.03, 129.13, 130.07, 131.40, 144.12, 172.33; HRMS (ESI) calcd for $C_{17}H_{26}BrNO_3Na$: 426.0709 [(M+Na)$^+$], found 426.0706.

4.2.70. (*R*)-methyl 3-amino-3-methyl-5-phenylpentanoate (49a)

Compound **49a** (173 mg, 0.782 mmol, 92%) was obtained as a colorless oil from **47a** (275 mg, 0.846 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{20}$ −3.9° (*c* = 0.30, $CDCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.24 (3H, s), 1.71–1.82 (2H, m), 2.44, 2.48 (2H, ABq, *J* = 14.5 Hz), 2.62–2.72 (2H, m), 3.69 (3H, s), 7.16–7.21 (3H, m), 7.26–7.30 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.06, 30.64, 45.15, 46.62, 51.29, 51.42, 125.83, 128.32, 128.44, 142.24, 172.38; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$: 222.1489 [(M+H)$^+$], found 222.1490.

4.2.71. (*S*)-Methyl 3-amino-3-methyl-5-phenylpentanoate (*ent*-49a)

Compound ***ent*-49a** (26.2 mg, 0.118 mmol, 82%) was obtained as a colorless oil from **48a** (47.2 mg, 0.145 mmol) by the same procedure used to prepare **17a**. HRMS (ESI) calcd for $C_{13}H_{20}NO_2$: 222.1489 [(M+H)$^+$], found 222.1489.

4.2.72. (*R*)-Methyl 3-amino-5-(3-bromophenyl)-3-methylpentanoate (49b)

Compound **49b** (246 mg, 0.819 mmol, 96%) was obtained as a colorless oil from **47b** (344 mg, 0.850 mmol) by the same procedure used to prepare **17a**. $[\alpha]_D^{20}$ −5.6° (*c* = 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (3H, s), 1.70–1.77 (2H, m), 2.43, 2.47 (2H, ABq, *J* = 14.8 Hz), 2.59–2.70 (2H, m), 3.70 (3H, s), 7.11 (1H, dt, *J* = 7.6, 1.5 Hz),7.14 (1H, t, *J* = 7.6 Hz), 7.30–7.33 (1H, m), 7.33–7.35 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.06, 30.34, 44.78, 46.62, 51.24, 51.48, 122.46, 127.02, 128.96, 130.00, 131.40, 144.64, 172.27; HRMS (ESI) calcd for $C_{13}H_{19}BrNO_2$: 300.0594 [(M+H)$^+$], found 300.0595.

4.2.73. (*R*)-*tert*-Butyl 1,4-dimethyl-6-oxo-4-phenethyl-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (50a)

Compound **50a** (233 mg, 0.676 mmol, 99%) was obtained as a colorless oil from **49a** (151 mg, 0.684 mmol) by the same procedure used to prepare **20a**. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (3H, s), 1.52 (9H, s), 1.83–1.97 (2H, m), 2.63, 2.72 (2H, ABq, *J* = 16.0 Hz), 2.60–2.72 (2H, m), 3.30 (3H, s), 7.14–7.18 (2H, m), 7.18–7.23 (1H, m), 7.27–7.32 (2H, m), 9.98 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.08, 28.26, 28.50, 30.10, 42.39, 42.93, 51.56, 79.73, 126.35, 128.20, 128.65, 140.42, 157.49, 164.01, 168.31; HRMS (ESI) calcd for $C_{13}H_{20}NO_2$: 222.1945 [(M+H)$^+$], found 222.1944.

4.2.74. (*S*)-*tert*-Butyl 1,4-dimethyl-6-oxo-4-phenethyl-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (*ent*-50a)

Compound ***ent*-50a** (27.8 mg, 0.0805 mmol, 88%) was obtained as a colorless oil from ***ent*-49a** (20.2 mg, 0.0913 mmol) by the same procedure used to prepare **20a**. HRMS (ESI) calcd for $C_{19}H_{27}N_3O_3$: 222.1945 [(M+H)$^+$], found 222.1944.

4.2.75. (*R*)-*tert*-Butyl 4-(3-bromophenethyl)-1,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrimidin-2-ylcarbamate (50b)

Compound **50b** (300 mg, 0.708 mmol, 95%) was obtained as a colorless oil from **49b** (223 mg, 0.743 mmol) by the same procedure used to prepare **20a**. $[\alpha]_D^{20}$ −59.6° (*c* = 0.30, $CDCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.39 (3H, s), 1.52 (9H, s), 1.81–1.95 (2H, m), 2.63, 2.71 (2H, ABq, *J* = 16.1 Hz), 2.58–2.69 (2H, m), 3.31 (3H, s), 7.07–7.10 (1H, m), 7.16 (1H, t, *J* = 7.7 Hz), 7.31–7.33 (1H, m), 7.33–7.36 (1H, m), 9.99 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.12, 28.26, 28.53, 29.78, 42.10, 42.92, 51.46, 79.82, 122.67, 126.91, 129.53, 130.21, 131.28, 142.70, 157.46, 164.03, 168.16; HRMS (ESI) calcd for $C_{19}H_{26}BrN_3O_3Na$: 446.1050 [(M+H)$^+$], found 446.1046.

4.2.76. (*R*)-2-Amino-3,6-dimethyl-6-phenethyl-5,6-dihydropyrimidin-4(3*H*)-one ((*R*)-3) TFA salt

Compound (***R***)-**3** (136 mg, 0.553 mmol, 94%) was obtained as a colorless solid from **50a** (203 mg, 0.588 mmol), and (***R***)-**3** TFA salt (100 mg) as a colorless solid from (***R***)-**3** (69.8 mg) by the same procedure used to prepare **7** TFA salt. mp 210–213 °C; $[\alpha]_D^{20}$ +11.2° (*c* = 0.50, MeOH); ^1H NMR (CD_3OD, 500 MHz) δ 1.42 (3H, s), 1.88–1.99 (2H, m), 2.62–2.74 (2H, m), 2.82, 2.94 (2H, ABq, *J* = 16.5 Hz), 3.27 (3H, s), 7.15-7.23 (3H, m), 7.25–7.30 (2H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 25.47, 28.79, 28.80, 30.93, 42.50, 53.96, 127.29, 129.36, 129.68, 142.20, 156.53, 168.22; HRMS (ESI) calcd for $C_{14}H_{20}N_3O$: 246.1601 [(M+H)$^+$], found 246.1599; Anal. calcd for $C_{14}H_{19}N_3O{\cdot}CF_3CO_2H$: C, 53.48; H, 5.61; N, 11.69; F, 15.86. found: C, 53.30; H, 5.60; N, 11.60; F, 15.82. Optical purity: 96.0% *ee* (Column: Daicel CHIRALPAK IC 4.6 × 250 mm, eluent: *n*-hexane/IPA/EtOH/diethylamine/TFA = 75:25:3:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 9.5 min).

4.2.77. (*S*)-2-Amino-3,6-dimethyl-6-phenethyl-5,6-dihydropyrimidin-4(3*H*)-one ((*S*)-3) TFA salt

Compound (***S***)-**3** (11.3 mg, 0.0461 mmol, 77%) was obtained as a colorless solid from ***ent*-50a** (20.7 mg, 0.0599 mmol), and (***S***)-**3** TFA salt (15.4 mg) as a colorless solid from (***S***)-**3** (11.3 mg) by the same procedure used to prepare **7** TFA salt. $[\alpha]_D^{20}$ −10.0° (*c* = 0.10, MeOH); HRMS (ESI) calcd for $C_{14}H_{20}N_3O$: 246.1601 [(M+H)$^+$], found 246.1601; Optical purity: 97.7% *ee* (Column: Daicel CHIRALPAK IC 4.6 × 250 mm, eluent: *n*-hexane/IPA/EtOH/diethylamine/TFA = 75:25:3:0.1:0.1, 1.0 mL/min, 40 °C, 200 nm; retention time: 10.4 min).

4.2.78. (*R*)-2-Amino-6-(2-(biphenyl-3-yl)ethyl)-3,6-dimethyl-5,6-dihydropyrimidin-4(3*H*)-one ((*R*)-4) TFA salt

Compound (***R***)-**4** TFA salt (38.5 mg, 0.0884 mmol, 83%) was obtained as a colorless solid from **50b** (45.0 mg, 0.106 mmol) and phenylboronic acid (19.4 mg, 0.159 mmol) by the same procedure used to prepare 24. NMR Spectrum data was found to be identical to that in the literature.[6] mp 191–192 °C; $[\alpha]_D^{20}$ +12.0° (*c* = 0.30,

MeOH); HRMS (ESI) calcd for $C_{20}H_{24}N_3O$: 322.1914 [$(M+H)^+$], found 322.1916.

4.2.79. (*R*)-2-Amino-6-(2-(3′-methoxybiphenyl-3-yl)ethyl)-3,6-dimethyl-5,6-dihydropyrimidin-4(3*H*)-one (5) TFA salt

Compound **5** TFA salt (46.1 mg, 0.0990 mmol, 85%) was obtained as a colorless solid from **50b** (49.2 mg, 0.116 mmol) and 3-methoxyphenylboronic acid (26.4 mg, 0.174 mmol) by the same procedure used to prepare **24**. NMR Spectrum data was found to be identical to that in the literature.[6] mp 178–180 °C; $[\alpha]_D^{20}$ +11.0° (c = 0.30, MeOH); HRMS (ESI) calcd for $C_{21}H_{26}N_3O_2$: 352.2020 [$(M+H)^+$], found 352.2022.

4.3. Protein expression, purification and HTRF assay

Protein expression, purification, and biological evaluation based on HTRF assay were performed according to the previous report.[12a]

4.4. Crystallography

Crystallization of BACE1, preparation of the complexes of (***R***)-**3** or **6** with BACE1, and their X-ray analyses were done according to the previous report.[12a] The structure factors and coordinates of (***R***)-**3**, **6** are available in the accession number 3WB4 and 3WB5, respectively.

4.6. Isothermal titration calorimetry (ITC)

Isothermal titration calorimetry measurements were performed with an ITC200 calorimeter (Microcal, GE Healthcare) using a time spacing of 180 s between injections, a stirrer speed of 1000 rpm, a filter period of 5 s, and a reference power of 20.9 μcal/sec. Experiments were carried out at 25 °C in an acetate buffer (50 mM, pH 5.0, 200 mM NaCl, and 0.005% Tween20). Prior to ITC experiments protein solution was dialyzed against buffer at 4 °C overnight. Inhibitor was prepared as a 100 mM stock solution in DMSO, and diluted into buffer to a concentration of 1.5 mM.

Titration experiments consisted of titrating of an inhibitor solution into a sample cell containing 0.2 mL of a protein solution with a total of 14 injections (0.4 μl for the first injection and 3 μl for the remaining injections).

To account for the heat of the dilution, the buffer without the protein was also titrated with the inhibitor solution, and the generated data were subtracted from the results of the protein titration. The experimental data fitted to a theoretical titration curve brought up the association constant K_a, the enthalpy of binding ΔH and their standard deviations by nonlinear regression using ORIGIN 7 Software (Microcal, GE Healthcare). The stoichiometry parameter was fixed at 1. The other thermodynamic parameters such as free energy ΔG and entropy ΔS were calculated from the equation: $\Delta G = \Delta H - T\Delta S = -RT\ln K_a$

4.6. Molecular modeling

Figure 3a and b: A conformational search was carried out by MacroModel using mixed torsional/low-mode sampling method and OPLS 2005 force-field with implicit water solvent model, and obtained 12 conformers within 5 kcal/mol above the lowest energy one were then optimized using Jaguar at DFT/B3LYP 6-31G** level with the PBF solvation model for water. Calculations were performed on HP Z600 workstation.

Figure 3c: The energy level of the conformation of **6** in the X-ray structure complexed with BACE1 was also calculated using Jaguar at DFT/B3LYP 6-31G** level with the PBF solvation model for water under the constraint of the dihedral angles among the aminopyrimidone ring, the cyclopropane ring and the benzene ring.

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Supplementary data

Supplementary data (synthesis, determination of the stereochemistry and optical purity of (1*R*,2*R*)-*tert*-butyl 2-(3-bromophenyl)cyclopropanecarboxylate (a raw material for **10b**), determination of the stereochemistry of 6-position in the aminopyrimidone ring of **8**, **9**, **20b**, **50b**, LCMS (ESI-LRMS) data of final products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.08.036.

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