Pergamon

SCIENCE DIRECT®

Bioorganic & Medicinal Chemistry 11 (2003) 1723–1743

BIOORGANIC & MEDICINAL CHEMISTRY

Design and Synthesis of Orally Bioavailable Inhibitors of Inducible Nitric Oxide Synthase. Identification of 2-Azabicyclo[4.1.0]heptan-3-imines

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Received 18 December 2002; accepted 24 December 2002

Abstract—Further chemical modification of 2-iminopiperidines fused to cyclopropane rings was performed. Optically active isomers **2** and **13** were synthesized and their biological activity was evaluated. Compound **2** exhibited greater potency and more isoform selectivity than enantiomer **13** in the iNOS inhibition assay. One of the *gem*-chlorines on the fused cyclopropane moiety of **2** was eliminated to produce **3**, which showed reduced potency for iNOS inhibition, as well as **4** with an increased potency. The isoform selectivity of **4** was also much higher than that of **3**. This was also true for the corresponding methyl derivatives **6**–**9**. The structure–activity relationship (SAR) study and computer aided docking study of the most optimized structure **4** with human iNOS will also be reported.

Introduction

Nitric oxide (NO) is an endogenous chemical mediator that has a role in various physiological processes, such as endothelium-dependent vasodilatation, cell-to-cell communication, and the cytotoxicity of phagocytes.[1] NO is produced by at least three isoforms of nitric oxide synthase (NOS), which include two constitutive isoforms (neuronal NOS (nNOS) and endothelial NOS (eNOS)) and an inducible isoform (iNOS).[2–4] These three isoforms of NOS catalyze NO production via the oxidation of L-arginine to L-citrulline. The constitutive isoforms (cNOS) are regulated by calmodulin and by the Ca^{2+} concentration. In contrast, the iNOS binds strongly to calmodulin, rendering its activity independent of the Ca^{2+} concentration.[5]

Administration of the nonselective NOS inhibitor N^G-methyl-L-arginine (L-NMA)[6,7] has been shown to cause a marked and sustained increase of blood pressure, indicating the importance of NO synthesis by the vascular endothelium in vasoregulation.[8] Due to the importance of cNOS in normal physiology, selective inhibition of iNOS would be a favorable characteristic for a drug targeting diseases mediated by overproduction of NO.

Initial reports about NOS inhibitors focused on structural analogues of the natural substrate L-arginine. In recent years, a variety of structures including non-amino acid inhibitors such as aminoguanidines,[9] isothioureas,[10] 2-iminopiperidines[11] and 2-aminopyridines[12] have been reported to be selective inhibitors of iNOS. We have also reported that dihydropyridin-2-imines are selective inhibitors of iNOS.[13] In an effort to identify non-amino acid iNOS selective inhibitors starting from the chemical modification of 2-iminopiperidines,[11] we discovered 5-methyl-2-azabicyclo [4.1.0]heptane-3-imine **1** (Chart 1) as a structurally new chemical lead. In the process of further optimization of **1**, introduction of a *gem*-dichloro group into the cyclopropane ring was found to be effective for maintaining

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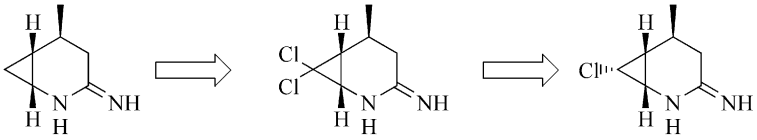
doi:10.1016/S0968-0896(03)00034-8



	1 (racemic)	**2** (optically active)	**4** (optically active)
Inhibition of iNOS IC_{50} (μM)	0.087	0.020	0.011
Selectivity heNOS/hiNOS	2.1	8.0	10.9

Chart 1. Molecular design of 2-iminopiperidine fused to a substituted cyclopropane.

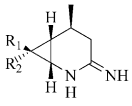
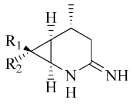
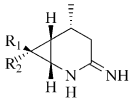
potent iNOS inhibition while improving isoform selectivity, as illustrated in Chart 1. Further chemical modification of the cyclopropane moiety in the bicyclic system was carried out with the hope of identifying a new selective iNOS inhibitor. Here we report on the discovery process for a selective inhibitor of iNOS, compound **4**.

Chemistry

Synthesis of all the test compounds presented in Tables 1 and 2 are outlined in Schemes 1–9. Preparation of enantiomeric isomers **26** and **27** is described in Scheme 1. The optically active starting material **19**, which was obtained by chemicoenzymatic hydrolysis of the corresponding symmetrical diester,[14a] was converted to **20**[14b] and δ-lactone **21**[14c] by reduction with diborane (94% yield) or reduction with lithium borohydride followed by acid treatment (90% yield), respectively. Aminolysis of **20** and **21** with *p*-methoxybenzylamine gave **22** and **23** at a good yield (**22**: 97% yield, **23**: 96% yield). Oxidation of **22** and **23** produced the cyclic hemiacetals **24** and **25** at a yield of 57 and 43%, respectively. Acidic dehydration of **24** and **25** produced **26** and **27** at a yield of 60 and 65%, respectively.

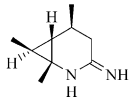
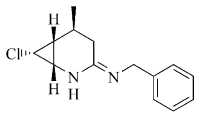
As described in Scheme 2, cyclopropanation of **26** with $CHCl_3$ under alkaline conditions resulted in **28a-*anti*** (the newly introduced cyclopropane moiety and the methyl moiety showed *anti*-stereochemistry: 62% yield) and **28a-*syn*** (the newly introduced cyclopropane moiety and the methyl moiety showed *syn*-stereochemistry: 12% yield), which were separated by column chromatography on silica gel. Cyclopropanation of **26** with $CHBr_3$ gave **28b-*anti*** (42% yield) and **28b-*syn*** (12% yield) as a separable mixture, while cyclopropanation of **26** with $FCHBr_2$ gave **28c-*anti*** (36% yield) and **28c-*syn*** (16% yield) as a separable mixture. Treatment of **28b-*anti*** with *n*-BuLi, followed by trapping with MeI, resulted in **28d-*anti*** (91% yield), stereochemistry of which was determined by the NOE correlation between the 7-methyl and 5-H as described in Figure 1. Deprotection of the *p*-methoxybenzyl moiety of **28a-*anti*** with $BF_3{\cdot}OEt_2$-anisole was followed by removal of the chlorines of **29a** through reduction with tin hydride, resulting in a separable mixture consisting of an *exo*-isomer **29e** (28% yield) and an *endo*-isomer **29f** (53% yield). Deprotection of **28c-*anti*** with $BF_3{\cdot}OEt_2$-anisole

Table 1. Inhibitory activities of 2-azabicyclo[4.1.0]heptan-3-imines against hiNOS, heNOS and their isoform selectivity[f]

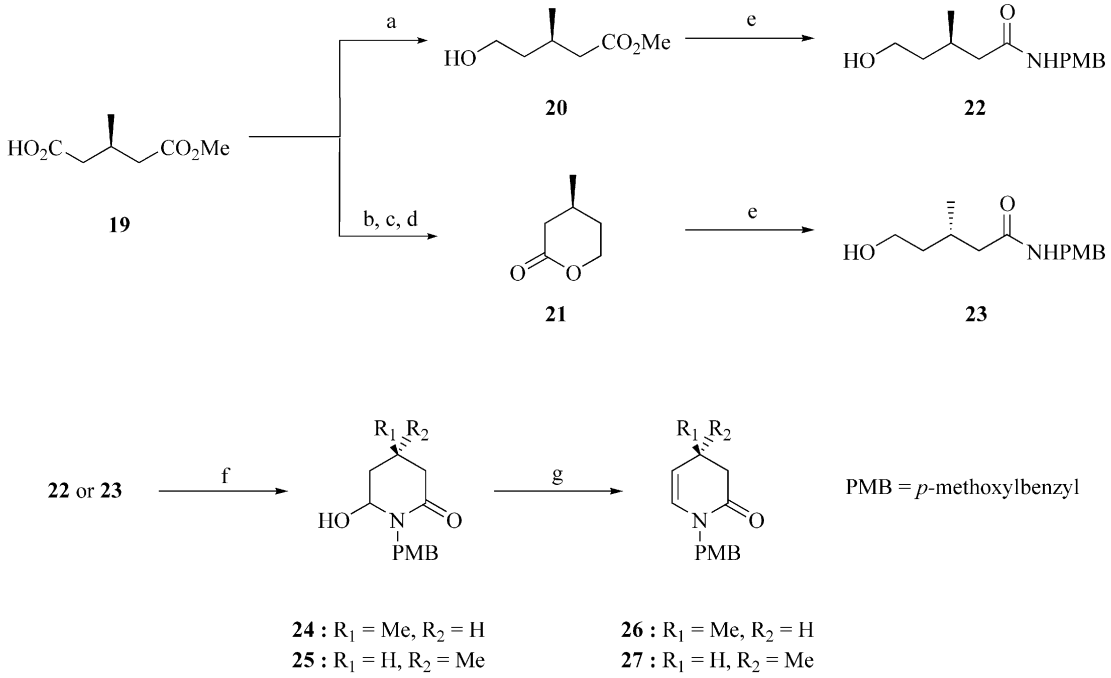
Structure	Compound	hiNOS IC_{50} (μM)	heNOS IC_{50} (μM)	Selectivity heNOS/ hiNOS
	**2** $R_1=R_2=Cl$[a]	0.020	0.16	8.0
	3 $R_1=Cl$, $R_2=H$[a]	0.40	0.62	1.6
	4 $R_1=H$, $R_2=Cl$[a]	0.011	0.12	10.9
	5 $R_1=H$, $R_2=F$[a]	0.031	0.10	3.2
	6 $R_1=R_2=Me$[b]	0.22	0.77	3.5
	7 $R_1=Me$, $R_2=H$[b]	0.39	0.68	1.7
	8 $R_1=H$, $R_2=Me$[b]	0.093	0.57	6.1
	9 $R_1=H$, $R_2=Me$[a]	0.040	0.53	13.3
	10 $R_1=H$, $R_2=Et$[b]	0.17	0.59	3.5
	11 $R_1=$vinyl, $R_2=H$[b]	1.8	NT[c]	NT[c]
	12 $R_1=H$, $R_2=n$-Bu[b]	3.6	NT[c]	NT[c]
	**13** $R_1=R_2=Cl$[a]	0.25	2.20	8.8
	14 $R_1=Cl$, $R_2=H$[a]	0.51	(>5)[d]	ND[e]
	15 $R_1=H$, $R_2=Cl$[a]	0.043	0.34	7.9
	16 $R_1=H$, $R_2=F$[a]			
		0.060	0.32	5.3

[a]Chiral.
[b]Racemic.
[c]NT: not tested.
[d]Less than 50% inhibition at 5 μM.
[e]ND: not determined.
[f]All compounds were prepared as their hydrochlorides.

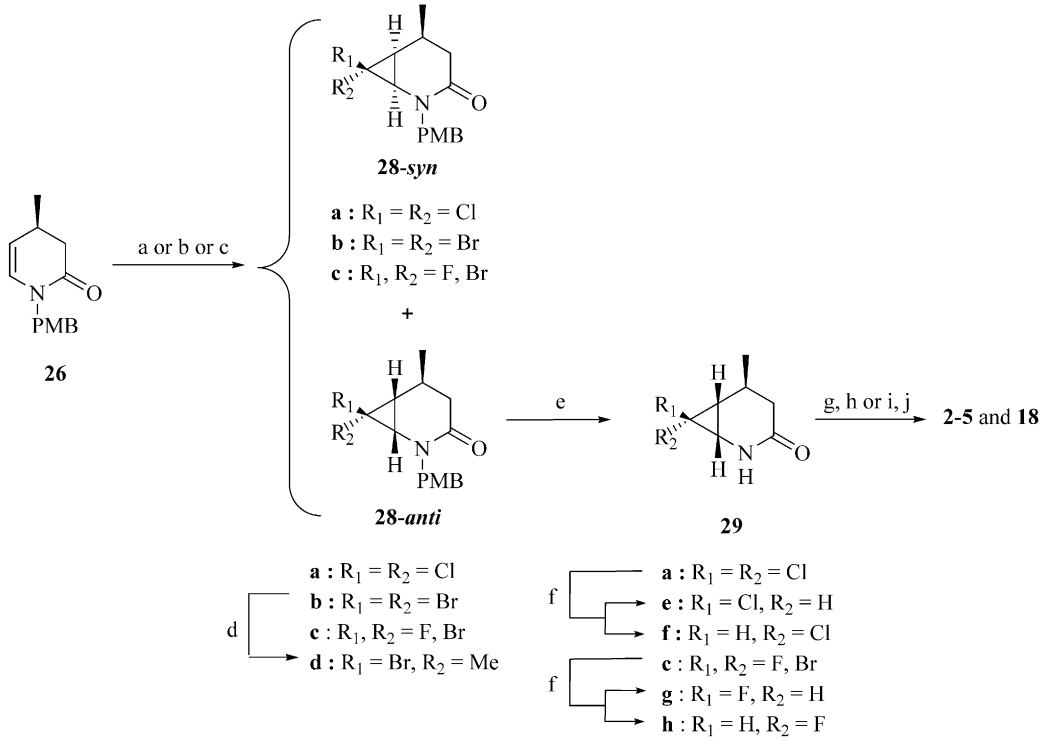
Table 2. Inhibitory activities of **17** and **18** against hiNOS, heNOS and their isoform selectivity[d]

Structure	Compound	hiNOS IC_{50} (μM)	heNOS IC_{50} (μM)	Selectivity heNOS/ hiNOS
	**17**[b]	0.90	NT[c]	NT[c]
	**18**[a]	>50	NT[c]	NT[c]

[a]Chiral.
[b]Racemic.
[c]NT: not tested.
[d]All compounds were prepared as their hydrochlorides.



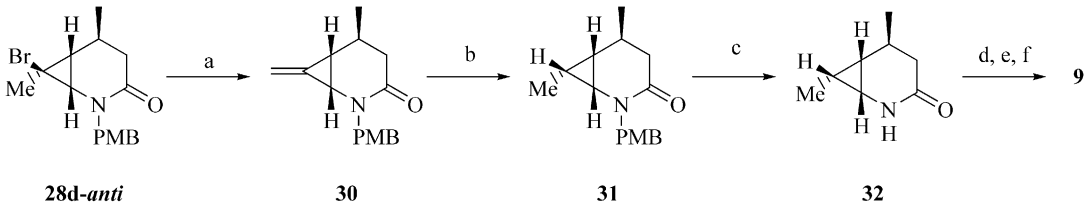
Scheme 1. Synthesis of optically active analogues **26** and **27**. Reagents: (a) $BH_3{\cdot}SMe_2$, THF, 0 °C (94%); (b) LiOH aq room temperature; (c) $LiBH_4$, THF, 50 °C; (d) *p*-TsOH·H_2O, benzene, reflux (90% in three steps); (e) $PMBNH_2$, toluene, reflux (**22**: 97%, **23**: 96%); (f) SO_3·pyridine, DMSO, Et_3N, room temperature (**24**: 57%, **25**: 43%); (g) *p*-TsOH·H_2O, toluene, reflux (**26**: 60%, **27**:·65%).



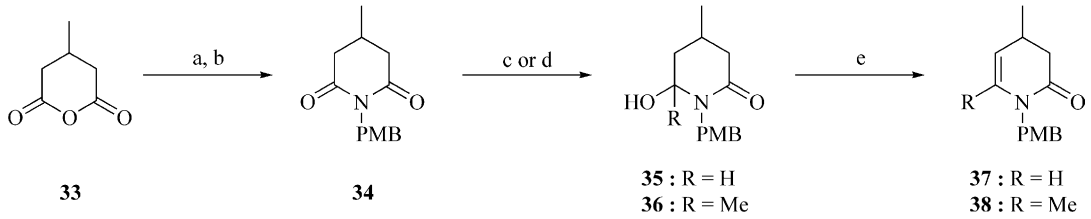
Scheme 2. Synthesis of **2**–**5** and **18**. Reagents: (a) $CHCl_3$, 50% NaOH aq, aliquat-336 (**28a-*anti***: 62%, **28a-*syn***: 12%); (b) $CHBr_3$, 50% NaOH aq, aliquat-336 (**28b-*anti***: 42%, **28b-*syn***: 12%); (c) $FCHBr_2$, 50% NaOH aq, $PhCH_2NEt_3Cl$ (**28c-*anti***: 36%, **28c-*syn***: 16%); (d) MeI, *n*-BuLi, THF, −78 °C (91%); (e) $BF_3{\cdot}OEt_2$, anisole, 100 °C (75–88%); (f) Ph_3SnH, AIBN, benzene, 80 °C (**29e**: 28%, **29f**: 53%; **29g**: 41%, **29h**: 44%); (g) $Et_3O^+BF_4^-$, CH_2Cl_2; (h) NH_3, EtOH; (i) $PhCH_2NH_2$, EtOH; (j) 4 M HCl dioxane (28–57% in three steps).

was followed by selective removal of the bromine of **29c** through reduction with tin hydride, resulting in a separable mixture consisting of an *exo*-isomer **29g** (41% yield) and an *endo*-isomer **29h** (44% yield). Compounds **29a**, **29e**, **29f** and **29h** were then converted to their corresponding amidines **2**–**5** and **18** by the usual procedure for amidine synthesis.

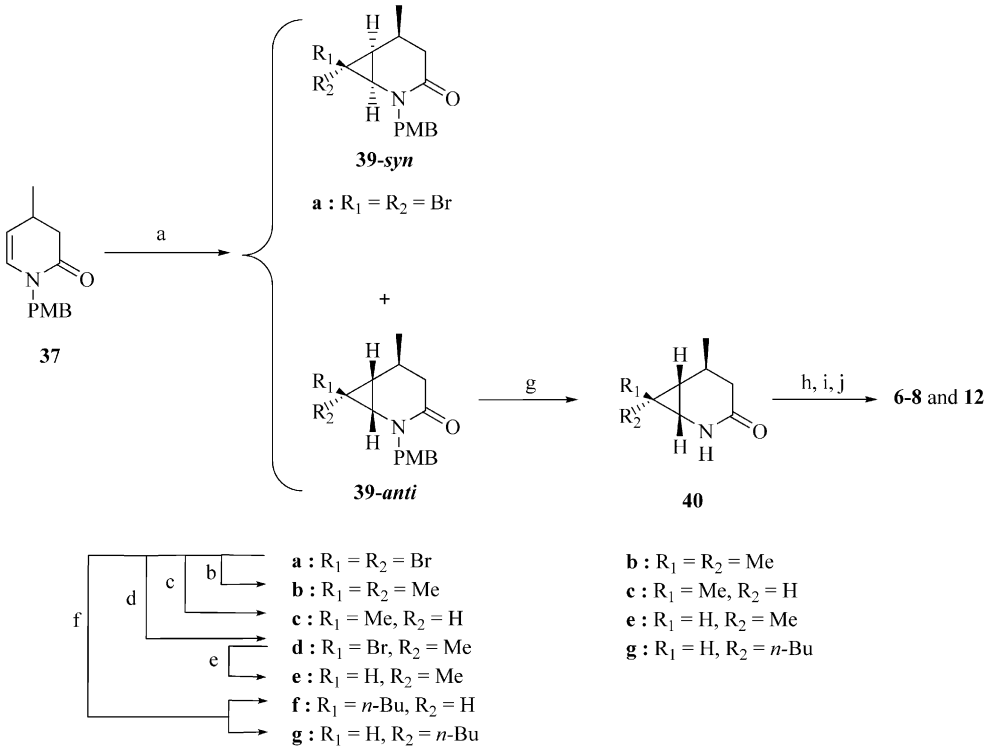
Preparation of compound **9** is described in Scheme 3. Treatment of **28d-*anti*** with *t*-BuOK gave **30**[15] at a 35%



Scheme 3. Synthesis of **9**. Reagents: (a) *t*-BuOK, THF, room temperature (35%); (b) 10% Pd/C, EtOAc (71%); (c) $BF_3{\cdot}OEt_2$, anisole, 100 °C (57%); (d) $Et_3O^+BF_4^-$, CH_2Cl_2; (e) NH_3, EtOH; (f) 4 M HCI dioxane (4% in three steps).



Scheme 4. Synthesis of racemic analogues **37** and **38**. Reagents: (a) $PMBNH_2$, toluene, room temperature; (b) Ac_2O, Et_3N, 80 °C (95% in two steps); (c) $NaBH_4$, EtOH. 0 °C (95%); (d) MeLi, THF, −78 °C (99%); (e) *p*-TsOH·H_2O, toluene, reflux (**37**: 60%, **38**: 99%).

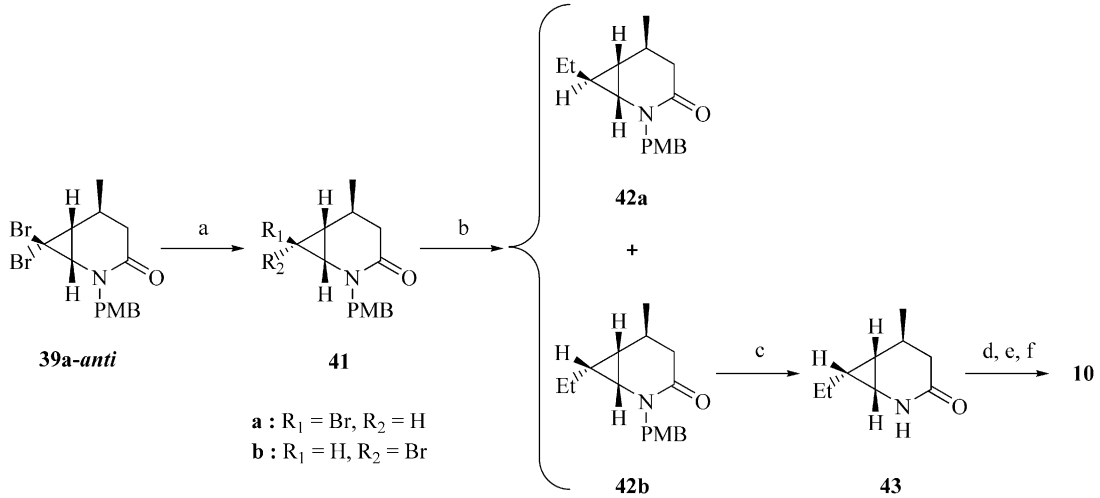


Scheme 5. Synthesis of **6**–**8** and **12**. Reagents: (a) $CHBr_3$, 50% NaOH aq, aliquat-336 (**39a-*anti***: 38%, **39a-*syn***: 13%); (b) CuSCN, MeLi, Et_2O–HMPA, then MeI (73%); (c) CuSCN, MeLi Et_2O–HMPA, then NH_4Cl aq (39%); (d) MeI, *n*-BuLi, THF, −78 °C (73%); (e) CuI, *n*-BuLi, THF, then 4 M HCl dioxane (36%); (f) CuSCN, *n*-BuLi, Et_2O–HMPA, then NH_4Cl aq (**39f-*anti***: 18%, **39g-*anti***: 39%); (g) $BF_3{\cdot}OEt_2$, anisole, 100 °C (47–78%); (h) $Et_3O^+BF_4^-$, CH_2CI_2; (i) NH_3, EtOH; (j) 4 M HCl dioxane (25–74% in three steps).

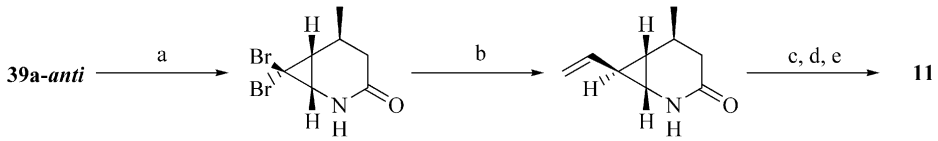
yield. Hydrogenation of **30** only afforded *endo*-isomer **31** at a 71% yield. Deprotection of **31** gave **32** (57% yield), which was converted to **9** according to the usual procedure.

Preparation of racemic compounds **37** and **38** is outlined in Scheme 4. Aminolysis of **33** with *p*-methoxybenzylamine, followed by formation of an imide with acetic anhydride, resulted in **34** (95% yield). Partial reduction of **34** with sodium borohydride afforded **35** (95% yield), while methylation of **34** with methyl lithium provided **36** (99% yield). Dehydration of **35** and **36** with *p*-toluenesulfonic acid produced **37** and **38** (60 and 99% yield, respectively).

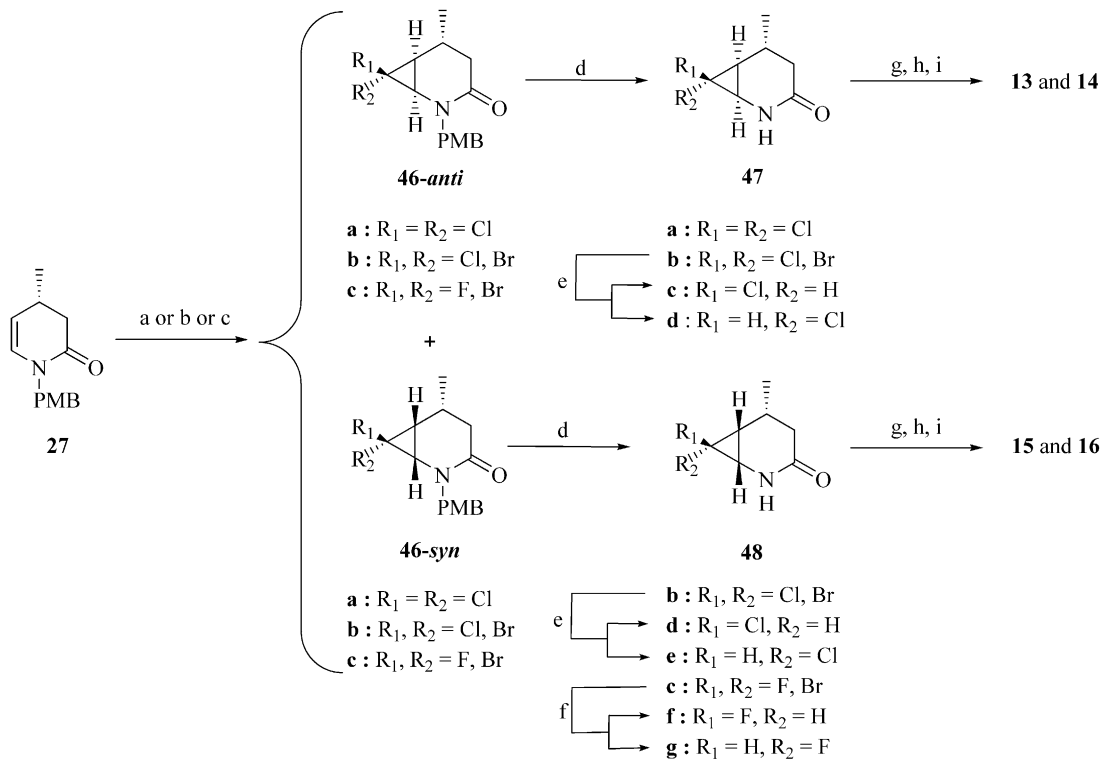
Synthesis of racemic compounds **6**–**8** and **12** is outlined in Scheme 5. Cyclopropanation of racemic compound **37** with $CHBr_3$ provided **39a-*anti*** (38% yield) and **39a-*syn*** (13% yield). Dimethylation of **39a-*anti*** with methyl lithium, followed by trapping with methyl iodide, afforded



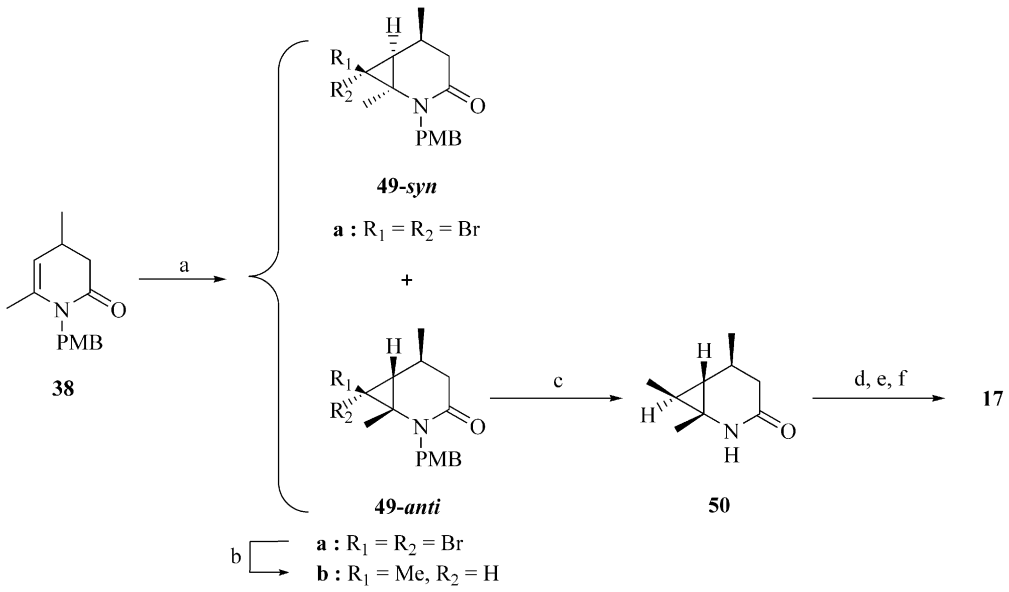
Scheme 6. Synthesis of **10.** Reagents: (a) *n*-Bu_3SnH, toluene, −10 °C (78%, **41a**:**41b** = 1:3); (b) CuI, *n*-BuLi, THF, then EtI (**42a**: 20%, **42b**: 18%); (c) $BF_3{\cdot}OEt_2$, anisole, 100 °C (39%); (d) $Et_3O^+BF_4^-$, CH_2Cl_2; (e) NH_3, EtOH; (f) 4 M HCl dioxane (88% in three steps).



Scheme 7. Synthesis of **11**. Reagents: (a) $BF_3{\cdot}OEt_2$, anisole, 100 °C (91%); (b) CuI, $CH_2{=}CHMgBr$, Et_2O–THF (59%); (c) $Et_3O^+BF_4^-$, CH_2Cl_2; (d) NH_3, EtOH; (e) 4 M HCl dioxane (6% in three steps).



Scheme 8. Synthesis of **13**–**16**. Reagents: (a) $CHCl_3$, 50% NaOH aq, aliguat-336 (**46a-*anti***: 53%, **46a-*syn***: 14%); (b) $ClCHBr_2$, 50% NaOH aq, $PhCH_2NEt_3Cl$ (**46b-*anti***: 64%, **46b-*syn***: 18%); (c) $FCHBr_2$, 50% NaOH aq, $PhCH_2NEt_3Cl$ (**46c-*syn***: 15%); (d) $BF_3{\cdot}OEt_2$, anisole, 100 °C (75–96%); (e) $(TMS)_3SiH$, BEt_3, toluene, room temperature (**47c**: 44%, **47d**: 28%; **48d**: 42%, **48e**: 54%); (f) Ph_3SnH, AIBN, benzene, 80 °C (**48g:** 22%); (g) $Et_3O^+BF_4^-$, CH_2Cl_2; (h) NH_3, EtOH; (i) 4 M HCl dioxane (9–48% in three steps).



Scheme 9. Synthesis of **17**. Reagents: (a) $CHBr_3$, 50% NaOH aq, aliquat-336 (**49a-*anti***: 26%, **49a-*syn***: 7%); (b) CuSCN, MeLi, Et_2O–HMPA, then NH_4Cl aq (65%); (c) $BF_3{\cdot}OEt_2$, anisole, 100 °C (90%); (d) $Et_3O^+BF_4^-$, CH_2Cl_2; (e) NH_3, EtOH; (f) 4 M HCl dioxane (48% in three steps).

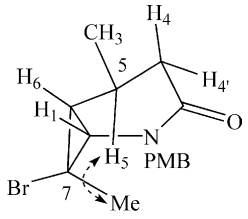


Figure 1. The NOE correlation between 7-methyl and 5-H in **28d**–***anti***.

39b-*anti* at a 73% yield. Monomethylation of **39a-*anti*** was carried out with methyl lithium, followed by trapping of the anion thus formed with aqueous ammonium chloride, to give *exo*-isomer **39c-*anti*** at a 39% yield. Treatment of **39a-*anti*** with *n*-BuLi, followed by trapping with methyl iodide, resulted in **39d-*anti*** (73% yield), the remaining bromine of which was successfully removed to gave **39e-*anti*** at a 36% yield. Treatment of **39a-*anti*** with *n*-BuLi in the presence of CuSCN produced a separable mixture of *exo*-isomer **39f-*anti*** and *endo*-isomer **39g-*anti*** at a yield of 18 and 39%, respectively. Deprotection of the *p*-methoxybenzyl moiety of **39b-*anti***, **39c-*anti***, **39e-*anti*** and **39g-*anti*** with $BF_3{\cdot}OEt_2$-anisole provided **40b**, **40c**, **40e** and **40g**, respectively. Compounds **40b**, **40c**, **40e** and **40g** were then converted to their corresponding amidines **6**–**8** and **12** by the usual amidine synthesis procedure.

Preparation of compound **10** is described in Scheme 6. Reductive removal of one of the bromines of **39a-*anti*** afforded *exo*-isomer **41a** and *endo*-isomer **41b** (**41a**:**41b** = 1:3), respectively. Ethylation of **41a** and **41b** gave a separable mixture of **42a** and **42b** at a yield of 20 and 18%, respectively. Deprotection of **42b** resulted in **43**, which was converted to **10** according to the usual procedure. Compound **11** was prepared as described in Scheme 7. Deprotection of **39a-*anti*** under the usual conditions afforded **44** (91% yield), which was converted to the vinyl intermediate **45** (59% yield). Application of the usual amidine synthesis procedure to **45** gave **11**.

The preparation of compounds **13**–**16** is outlined in Scheme 8. The optically active starting material **27** was converted to a separable mixture of **46a-c-*anti*** and**46a-c-*syn*** by a cyclopropanation procedure similar to that described above. Deprotection of **46a-*anti*** and **46b-*anti*** gave **47a** and **47b**, respectively. Reductive debromination of **47b** afforded *endo*-isomer **47c** and *exo*-isomer **47d** at a yield of 44 and 28%, respectively. Compounds **47a** and **47c** were then converted to amidine analogues **13** and **14**, respectively, according to the usual procedure.

Deprotection of **46b-*syn*** and **46c-*syn*** afforded **48b** and **48c**, respectively. Reductive debromination of **48b** gave a separable mixture of *exo*-isomer **48d** and *endo*-isomer **48e** at a yield of 42 and 54%, respectively, while reductive debromination of **48c** resulted in a separable mixture of **48f** and **48g**. Compounds **48e** and **48g** were then converted to **15** and **16**.

Preparation of compound **17** is described in Scheme 9. The racemic starting material **38** was transformed to **49a-*anti*** (26% yield) and **49a-*syn*** (7% yield) by the usual cyclopropanation procedure, as described above. Methylation of **49a-*anti*** provided **49b-*anti*** at a 65% yield, while the deprotection of **49b-*anti*** afforded **50** (90% yield). Compound **50** was then converted to amidine analogue **17** by the usual procedure.

Because of its stereochemical complexity, the structure of **4** was investigated by X-ray crystallographic analysis in addition to the usual spectral analyses.[16] As shown in Figure 2, the results of X-ray crystallography support the structure described in Table 1.

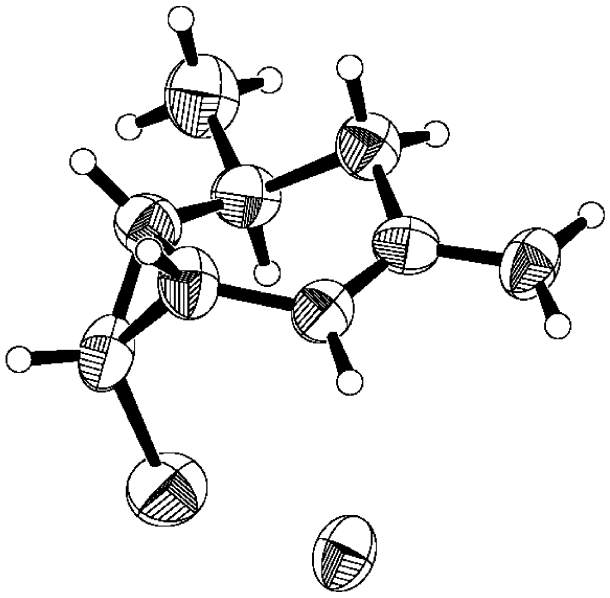


Figure 2. X-ray crystallographic analysis of **4**.

Results and Discussion

As described in previous papers,[13,17] compounds **2**–**18** were synthesized and biologically evaluated for their ability to inhibit the two isoforms of human NOS: hiNOS and heNOS. Isoform selectivity was determined from the ratio of the IC_{50} value for these two isoforms (i.e., heNOS/hiNOS).

The *gem*-dichloro analogues **2** and **13** were initially synthesized as optically active forms and evaluated. The *anti*-isomer **2** was more potent than **13** in the hiNOS inhibition assay and showed an 8-fold greater isoform selectivity.

Then biological evaluation of their optically active compounds **3** and **4** was carried out. The biological profile of optically active compound **4** was improved in all evaluations (hiNOS inhibition, heNOS inhibition and isoform selectivity) as compared with that of compound **3**. The fluoro analogue **5**, which corresponds to **4**, was prepared as an optically active form and evaluated. Replacement of the chloro group in **4** with a fluoro group gave **5**, which showed a slight reduction in the potency of hiNOS inhibition and slightly stronger heNOS inhibition. As a result, the isoform selectivity of fluoro analogue **5** was nearly 3-fold less than that of **4**.

Compound **14**, the enantiomer of **4**, was also prepared and biologically evaluated, but it showed reduced inhibitory activity against both isoforms when compared with **4**. Compounds **15** and **16** were also evaluated. The chloro analogue **15** demonstrated slightly stronger hiNOS inhibition as compared with **16**, while its heNOS inhibitory activity was unchanged. As a result, improved isoform selectivity was obtained by replacement of the fluoro group on the cyclopropane ring with a chloro group, as illustrated in the conversion of **16** to **15**.

Replacement of the fluoro group on the fused cyclopropane ring with a chloro group increased the isoform selectivity because of increased potency in hiNOS inhibition without a change of heNOS inhibition, as illustrated in the conversion of **5** to **4** or **16** to **15**.

The effect of adding an alkyl substituent to the fused cyclopropane ring was also studied. Replacement of the *gem*-dichloro group with a *gem*-dimethyl group gave **6**, which showed a 10-fold reduction in inhibitory activity against hiNOS and reduced isoform selectivity. Monomethyl analogues **7** and **8** showed less inhibitory activity against both isoforms as well as less isoform selectivity.

Compound **9**, the optically active form of the more potent monomethyl analogue **8**, was prepared and evaluated. The potency of hiNOS inhibition by **9** was nearly 2-fold greater than by its racemic mixture **8**, while heNOS inhibition remained unchanged. As a result, the isoform selectivity of **9** was improved when compared with that of **8**. In order to assess the possibility of further chemical modifications to the newly introduced methyl group, compounds **10**–**12** were prepared and biologically evaluated. Replacement of the methyl group in **8** with an ethyl group afforded **10**, which showed a 1.8-fold reduction in the potency of hiNOS inhibition but no change of heNOS inhibition. As a result, its isoform selectivity was nearly half that of **8**. Introduction of a higher alkyl group at the same position did not improve hiNOS inhibition irrespective of the stereochemistry, as illustrated in **11** and **12**.

Introduction of another methyl group at one of the ring junctions in **7** provided **17**, which showed more than 2-fold reduction in the potency of hiNOS inhibition. *N*-Benzylation of the 3-imino group of **4** afforded **18**, which showed a marked reduction of hiNOS inhibition.

Among the compounds tested, **2** and **4**[17] were selected for further biological and pharmacodynamic evaluation because of their excellent biological profile, including safety data. Additional in vitro activities of **2** and **4** as well as L-NMMA and aminoguanidine, were evaluated, including the IC_{50} for mouse iNOS, the K_i values for hiNOS and heNOS and the isoform selectivity determined from the two K_i values (Table 3).[17] The K_i value of **4** indicated that it was the most potent iNOS inhibitors among the compounds tested. Compound **4** also showed more iNOS selectivity than compound **2**. A non-selective inhibitor, L-NMMA, showed eNOS selectivity. Aminoguanidine showed far less activity than the other three inhibitors, while it showed quite a good iNOS selectivity (heNOS/hiNOS = 4.8-fold). In order to evaluate the above-mentioned two compounds **2** and **4** for their ability to inhibit iNOS in vivo, mice were administered the two test compounds subcutaneously (sc) at 3 h after lipopolysaccharide (LPS) injection. Then plasma NO_x accumulation from 3 to 6 h after LPS injection was determined. As shown in Table 3, compounds **2** and **4** inhibited NO_x accumulation in plasma and their ID_{50} values were 0.023 and 0.010 mg/kg, sc, respectively. To assess the acute toxicity of each compounds, the maximum tolerated dose (MTD) was determined. As shown in Table 3, the MTD values of **2** and **4** were 20 and 30 mg/kg, respectively, when a single

Table 3. Biological profiles of **2** and **4**

	IC_{50}	K_i values[a]		iNOS selectivity[b]	Acute toxicity	Mouse NO_x
	miNOS	hiNOS	heNOS	heNOS/hiNOS	MTD (mg/kg, iv)	ID_{50} (mg/kg, sc)
2	5.6 (nM)	5.20 (nM)	43.0 (nM)	8.3	20	0.023
4	4.0 (nM)	1.88 (nM)	18.8 (nM)	10.0	30	0.010
L-NMMA	3.5 (μM)	847 (nM)	250 (nM)	0.3	3000	26
Aminoguanidine	19.6 (μM)	39.9 (μM)	190 (μM)	4.8	NT[c]	NT[c]

[a]Each K_i value was determined from three separate experiments..[17]
[b]The iNOS selectivity is calculated by the formulation; K_i of heNOS/K_i of hiNOS.
[c]NT: not tested.

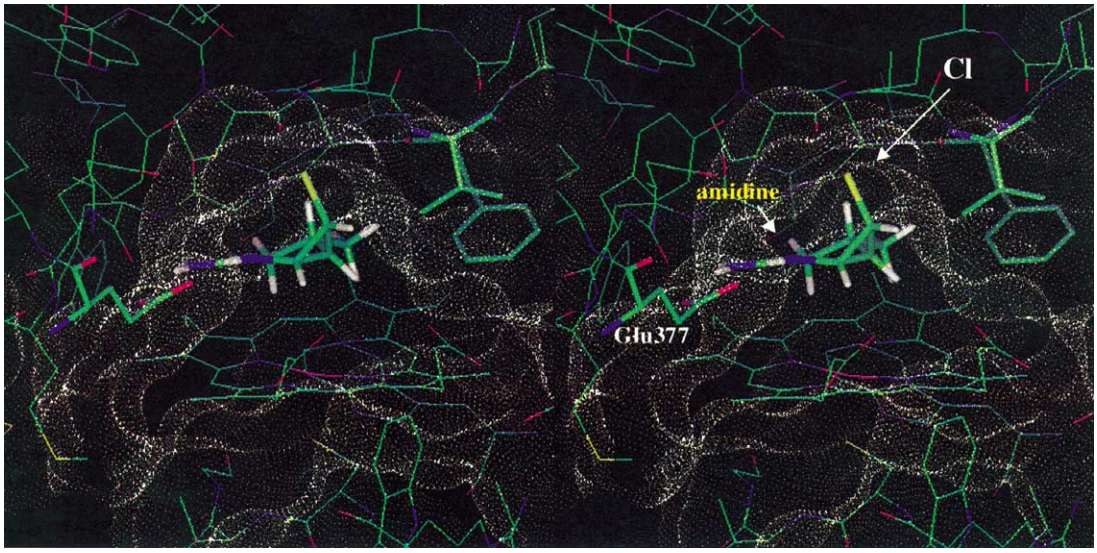


Figure 3. Stereo view of a docking model of compound **4** with human iNOS (PDB code 2NSI).

intravenous (iv) dose was given to normal mice. The MTD values of these two compounds indicated a much higher potency than that of L-NMMA (3000 mg/kg), but the MTD/ID_{50} ratio for NO_x accumulation in mice was 870 for **2** and 3000 for **4**. Oral bioavailability of **2** and **4** was excellent in rats (**2**: 52–100% and **4**: 62–83%) and dogs (**2**: 57% and **4**: 100%).

Figure 3 demonstrates a stereo view of a docking study of **4** with human iNOS (PDB code 2NSI). This study was performed using Insight II/Discover molecular modeling package (Accelrys, San Diego, CA) with CVFF force field on a SGI Octane 2 workstation with R12000 processors. Clear-cut interaction between the basic amidine moiety with acidic Glu377 residue and insertion of the chlorine moiety into a small pocket of the enzyme were observed.

Summary

In summary, we explored the SAR for a series of 2-iminopiperidines fused to a substituted cyclopropane ring and obtained a significant increase of hiNOS inhibition as well as better isoform selectivity in both in vitro and in vivo experiments. Among the compounds tested, **2** and **4** showed excellent profiles in both the biological and pharmacodynamic evaluations. The structure of **4** was finally determined by X-ray crystallographic analysis. Computer aided docking study of **4** with the enzyme was also performed. Accordingly, these two compounds could be useful tools to help elucidate the role of iNOS in various disease states and may also have potential as novel drugs.

Experimental

General directions

Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned structures. All ^1H NMR spectra were obtained on a Varian Gemini-200, VXR-200s spectrometer. Fast atom bombardment mass spectra (FAB-MS) and electron ionization (EI) were obtained on a Jeol JMS-DX303HF or PerSeptive Voyager Elite spectrometer. Atmospheric pressure chemical ionization (APCI) was determined on a Hitachi M1200H spectrometer. Matrix assisted laser desorption ionization-time of flight high-resolution mass spectra (MALDI-TOF HR-MS) were obtained on a PerSeptive Voyager Elite spectrometer. IR spectra were measured on a Perkin–Elmer FT-IR 1760X or Jasco FT/IR-430 spectrometer. Elemental analyses for carbon, hydrogen and nitrogen were carried out on a Perkin–Elmer PE2400 SeriesII CHNS/O analyzer. Optical rotations were measured using a Jasco DIP-1000 polarimeter. Melting points

(mp) were determined by Yanaco micro melting point apparatus MP-500D and are uncorrected. Column chromatography was carried out on silica gel (Merck silica gel 60 (0.063–0.200 mm) or Wako Gel C200 or Fuji Silysia FL60D). Thin layer chromatography was performed on silica gel (Merck TLC plate, silica gel 60 F_{254}).

Starting materials

Compounds **19**, **20** and **21** were synthesized according to the literature[14a–c]. Compound **33** is commercially available.

(3*R*)-5-Hydroxy-*N*-(4-methoxybenzyl)-3-methylpentanamide (22). To a stirred solution of **20** (5.0 g, 34 mmol) in toluene (60 mL) was added *p*-methoxybenzylamine (4.6 mL, 35.2 mmol) and stirred for 3 h at reflux temperature. After cooling up to room temperature, the reaction mixture was evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (EtOAc to EtOAc/MeOH, 8/1) to afford **22** as a pale yellow solid (8.3 g, 97%). TLC R_f 0.20 ($CHCl_3$/MeOH, 10/1); optical rotation $[\alpha]_D^{25}$ −4.1 (*c* 1.14, $CHCl_3$); IR (KBr) 3277, 2930, 1717, 1637, 1549, 1514, 1459, 1378, 1302, 1250, 1177, 1111, 1034, 816, 555, 526, 419 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.25–7.16 (m, 2H), 6.91–6.82 (m, 2H), 5.98 (brs, 1H), 4.36 (d, $J=5.6$ Hz, 2H), 3.79 (s, 3H), 3.66 (t, $J=6.0$ Hz, 2H), 2.60 (brs, 1H), 2.29–2.00 (m, 3H), 1.63–1.30 (m, 2H), 0.98 (d, $J=6.4$ Hz, 3H); MS (APCI, Pos.) *m*/*z* 252 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{21}N_1O_3+H^+$: 252.1560; found: 252.1583.

(4*R*)-6-Hydroxy-1-(4-methoxybenzyl)-4-methylpiperidin-2-one (24). To a stirred solution of **22** (6.1 g, 24.3 mmol) in DMSO (35 mL) were added Et_3N (17 mL, 122 mmol) and sulfur trioxide pyridine complex (19.4 g, 121.9 mmol) at 0 °C under an argon atmosphere. After stirring for 4.5 h at room temperature, the reaction was quenched with water. Then the mixture was treated with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1/1) to afford **24** as a white crystal (3.3 g, 57%). TLC R_f 0.50 (EtOAc); mp 88–89 °C; IR (KBr) 3258, 2951, 2841, 1627, 1514, 1479, 1439, 1413, 1312, 1297, 1281, 1249, 1182, 1170, 1100, 1065, 1026, 974, 931, 903, 838, 818, 768, 742, 701, 619, 582, 528 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.26–7.18 (m, 2H), 6.89–6.80 (m, 2H), 5.02–4.90 (m, 2H), 4.32 (d, $J=14.6$ Hz, 1H), 3.79 (s, 3H), 2.71–2.54 (m, 2H), 2.44–2.20 (m, 1H), 2.09–1.86 (m, 2H), 1.47 (ddd, $J=13.6$, 12.8, 3.6 Hz, 1H), 1.01 (d, $J=6.6$ Hz, 3H); MS (APCI, Pos.) *m*/*z* 250 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{19}N_1O_3+H^+$: 250.1443; found: 250.1432.

(4*S*)-1-(4-Methoxybenzyl)-4-methyl-3,4-dihydropyridin-2-one (26). A solution of **24** (3.4 g, 13.6 mmol) and *p*-toluenesulfonic acid monohydrate (150 mg, 0.8 mmol) in toluene (70 mL) was stirred for 1.5 h at reflux temperature. After cooling at room temperature, the reaction mixture was diluted with EtOAc and washed sequentially with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1/5–1/3) to afford **26** as a pale yellow oil (1.9 g, 60%). TLC R_f 0.55 (EtOAc/*n*-hexane, 1/1); optical rotation $[\alpha]_D^{25}$ −103.5 (*c* 1.05, $CHCl_3$); IR (neat) 3404, 2957, 2836, 1667, 1585, 1514, 1456, 1412, 1386, 1303, 1248, 1212, 1176, 1148, 1105, 1034, 965, 946, 877, 822, 764, 718, 580, 519 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.22–7.13 (m, 2H), 6.89–6.80 (m, 2H), 5.96 (dd, $J=7.8$, 1.4 Hz, 1H), 5.06–4.99 (m, 1H), 4.64 (d, $J=14.6$ Hz, 1H), 4.57 (d, $J=14.6$ Hz, 1H), 3.79 (s, 3H), 2.63 (dd, $J=17.6$, 6.4 Hz, 1H), 2.68–2.49 (m, 1H), 2.29 (dd, $J=17.6$, 11.4 Hz, 1H), 1.05 (d, $J=6.8$ Hz, 3H); MS (APCI, Pos.) *m*/*z* 232 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{17}N_1O_2+H^+$: 232.1338; found: 232.1358.

(3*S*)-5-Hydroxy-*N*-(4-methoxybenzyl)-3-methylpentanamide (23). Compound **23** was prepared from **21** in 96% yield according to the same procedure as described for the preparation of **22** from **20**. Pale yellow solid; TLC R_f 0.28 (EtOAc); optical rotation $[\alpha]_D^{25}$ +4.0 (*c* 1.05, $CHCl_3$); IR (KBr) 3276, 2930, 2312, 1718, 1637, 1549, 1514, 1460, 1379, 1302, 1250, 1177, 1111, 1052, 1035, 816, 760, 594, 526, 473, 444 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.21 (d, $J=8.8$ Hz, 2H), 6.87 (d, $J=8.8$ Hz, 2H), 5.84 (brs, 1H), 4.38 (d, $J=5.6$ Hz, 2H), 3.80 (s, 3H), 3.70–3.60 (m, 2H), 2.30–2.05 (m, 3H), 1.60–1.50 (m, 2H), 0.99 (d, $J=6.6$ Hz, 3H); MS (APCI, Pos.) *m*/*z* 252 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{21}N_1O_3+H^+$: 252.1600; found: 252.1585.

(4*S*)-6-Hydroxy-1-(4-methoxybenzyl)-4-methylpiperidin-2-one (25). Compound **25** was prepared from **23** in 43% yield according to the same procedure as described for the preparation of **24** from **22**. White crystal; TLC R_f 0.50 (EtOAc); mp 136–137 °C; IR (KBr) 3260, 2951, 1627, 1514, 1479, 1439, 1249, 1182, 1100, 1065, 1026, 974, 903, 838, 818, 742, 620, 582, 528 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.23 (d, $J=8.8$ Hz, 2H), 6.85 (d, $J=8.8$ Hz, 2H), 4.95 (d, $J=14.2$ Hz, 1H), 5.00–4.88 (m, 1H), 4.34 (d, $J=14.2$ Hz, 1H), 3.79 (s, 3H), 2.70–2.52 (m, 1H), 2.40–2.18 (brs, 1H), 2.10–1.80 (m, 2H), 1.65–1.36 (m, 2H), 1.00 (d, $J=6.6$ Hz, 3H); MS (APCI, Pos.) *m*/*z* 250 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{19}N_1O_3+H^+$: 250.1443; found: 250.1469.

(4*R*)-1-(4-Methoxybenzyl)-4-methyl-3,4-dihydropyridin-2-one (27). Compound **27** was prepared from **25** in 65% yield according to the same procedure as described for the preparation of **26** from **24**. Pale yellow oil; TLC R_f 0.55 (EtOAc/*n*-hexane, 1/1); optical rotation $[\alpha]_D^{25}$ +104.1 (*c* 1.06, $CHCl_3$); IR (neat) 2958, 2836, 1668, 1612, 1585, 1513, 1442, 1408, 1384, 1304, 1248, 1212, 1176, 1147, 1109, 1034, 946, 822, 717, 643, 572, 518 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.17 (d, $J=8.8$ Hz, 2H), 6.84 (d, $J=8.8$ Hz, 2H), 5.96 (dd, $J=7.7$, 1.5 Hz, 1H), 5.03 (dd, $J=7.7$, 3.4 Hz, 1H), 4.61 (d, $J=2.6$ Hz, 2H), 3.79 (s, 3H), 2.70–2.50 (m, 2H), 2.40–2.15 (m,

1H), 1.05 (d, $J=6.8$ Hz, 3H); MS (APCI, Pos.) m/z 232 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{17}N_1O_2+H^+$: 232.1338; found: 232.1317.

General procedure for cyclopropanation

(1*S*,5*S*,6*R*)-7,7-Dichloro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (28a-*anti*) and (1*R*,5*S*,6*S*)-7,7-dichloro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (28a-*syn*). To a stirred solution of **26** (1.2 g, 5.2 mmol) in $CHCl_3$ (12.5 mL, 156 mmol) were added aliquat-336 (0.1 mL, 0.22 mmol) and 50% aqueous sodium hydroxide (2.6 g) under an argon atmosphere. The reaction mixture was stirred for 22 h at room temperature. After completing the reaction, the mixture was treated with saturated aqueous ammonium chloride and extracted with Et_2O. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5–1:3) to afford **28a-*anti*** as a pale yellow oil (1.0 g, 62%) and **28a-*syn*** as a pale yellow oil (196 mg, 12%).

28a-*anti*: TLC R_f 0.36 (EtOAc/*n*-hexane, 1/2); optical rotation $[\alpha]_D^{25}$ +26.3 (*c* 1.00, $CHCl_3$); IR (neat) 2963, 2836, 1668, 1612, 1513, 1443, 1415, 1384, 1303, 1248, 1176, 1079, 1033, 890, 854, 822, 766, 731, 575, 512 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.24 (m, 2H), 6.93–6.85 (m, 2H), 5.44 (d, $J=14.4$ Hz, 1H), 3.81 (s, 3H), 3.81 (d, $J=4.4$ Hz, 1H), 2.95 (d, $J=9.8$ Hz, 1H), 2.39–2.02 (m, 3H), 1.76 (dd, $J=9.8$, 5.0 Hz, 1H), 1.25 (d, $J=6.4$ Hz, 3H); MS (APCI, Pos.) m/z 316 $(M+H, {}^{35}Cl, {}^{37}Cl)^+$, 314 $(M+H, {}^{35}Cl, {}^{35}Cl)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Cl_2N_1O_2+H^+$: 314.0715; found: 314.0695.

28a-*syn*: TLC R_f 0.18 (EtOAc/*n*-hexane, 1/2); optical rotation $[\alpha]_D^{25}$ +30.9 (*c* 0.88, $CHCl_3$); IR (neat) 3447, 2964, 2932, 2837, 1734, 1651, 1513, 1458, 1417, 1392, 1342, 1303, 1250, 1177, 1109, 1035, 929, 891, 845, 821, 712, 630, 584, 522 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35–7.26 (m, 2H), 6.95–6.85 (m, 2H), 4.87 (d, $J=14.6$ Hz, 1H), 4.57 (d, $J=14.6$ Hz, 1H), 3.81 (s, 3H), 3.20 (d, $J=10.4$ Hz, 1H), 2.62–2.16 (m, 3H), 1.97 (dd, $J=10.0$, 6.0 Hz, 1H), 1.26 (d, $J=6.4$ Hz, 3H); MS (APCI, Pos.) m/z 316 $(M+H, {}^{35}Cl, {}^{37}Cl)^+$, 314 $(M+H, {}^{35}Cl, {}^{35}Cl)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Cl_2N_1O_2+H^+$: 314.0715; found: 314.0728.

(1*S*,5*S*,6*R*)-7,7-Dibromo-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (28b-*anti*) and (1*R*,5*S*,6*S*)-7,7-dibromo-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (28b-*syn*). To a stirred solution of **26** (2 g, 8.6 mmol) in $CHBr_3$ (25 mL, 286 mmol) were added aliquat-336 (0.1 mL, 0.22 mmol) and 50% aqueous sodium hydroxide (6.4 g) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 10 h at 0 °C. After completing the reaction, the mixture was treated with saturated aqueous ammonium chloride and extracted with Et_2O. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1/5 to 1/3) to afford **28b-*anti*** as a pale yellow oil (1.5 g, 42%) and **28b-*syn*** as a pale yellow oil (416 mg, 12%).

28b-*anti*: TLC R_f 0.38 (EtOAc/*n*-hexane, 1/2); optical rotation $[\alpha]_D^{25}$ +15.1 (*c* 1.00, $CHCl_3$); IR (neat) 2961, 2959, 2836, 1667, 1513, 1460, 1415, 1248, 1178, 1032, 845, 764 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (d, $J=8.4$ Hz, 2H), 6.90 (d, $J=8.4$ Hz, 2H), 5.47 (d, $J=14.8$ Hz, 1H), 3.81 (d, $J=14.8$ Hz, 1H), 3.81 (s, 3H), 2.98 (d, $J=9.8$ Hz, 1H), 2.45–2.00 (m, 3H), 1.77 (dd, $J=9.8$, 5.4 Hz, 1H), 1.26 (m, 3H); MS (APCI, Pos.) m/z 404 $(M+H, {}^{79}Br, {}^{81}Br)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Br_2N_1O_2+H^+$: 401.9704; found: 401.9725.

28b-*syn*: TLC R_f 0.18 (EtOAc/*n*-hexane, 1/2); optical rotation $[\alpha]_D^{25}$ +31.6 (*c* 0.63, $CHCl_3$); IR (neat) 2963, 2835, 1651, 1512, 1456, 1415, 1388, 1302, 1248, 1176, 1107, 1033, 849, 773 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (d, $J=8.6$ Hz, 2H), 6.92 (d, $J=8.6$ Hz, 2H), 4.93 (d, $J=14.2$ Hz, 1H), 4.54 (d, $J=14.2$ Hz, 1H), 3.82 (s, 3H), 3.27 (d, $J=10.2$ Hz, 1H), 2.50–2.43 (m, 3H), 2.20–2.10 (m, 1H), 1.28 (d, $J=6.2$ Hz, 3H); MS (APCI, Pos.) m/z 404 $(M+H, {}^{79}Br, {}^{81}Br)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Br_2N_1O_2+H^+$: 401.9704; found: 401.9708.

(1*S*,5*S*,6*R*)-7-Bromo-7-fluoro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (28c-*anti*) and (1*R*,5*S*,6*S*)-7-bromo-7-fluoro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (28c-*syn*). To a stirred solution of **26** (200 mg, 0.86 mmol) in CH_2Cl_2 (1 mL) were added $FCHBr_2$ (0.33 mL, 4.3 mmol), benzyltriethylammonium chloride (5.9 mg, 0.03 mmol) and 50% aqueous sodium hydroxide (1 g) at 0 °C under an argon atmosphere. The reaction mixture was warmed up to room temperature and stirred for 48 h. After completing the reaction, the mixture was treated with water and extracted with Et_2O. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:10–1:5) to afford **28c-*anti*** as a pale yellow oil (107 mg, 36%) and **28c-*syn*** as a pale yellow oil (47 mg, 16%).

28c-*anti*: TLC R_f 0.45 (EtOAc/*n*-hexane, 1:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.24 (d, $J=9.5$ Hz, 1H) and 7.23 (d, $J=9.5$ Hz, 1H), 6.95 (d, $J=9.5$ Hz, 1H) and 6.94 (d, $J=9.5$ Hz, 1H), 5.47 (d, $J=14.2$ Hz, 0.5H) and 5.19 (d, $J=14.2$ Hz, 0.5H), 4.00 (d, $J=14.2$ Hz, 0.5H) and 3.79 (d, $J=14.2$ Hz, 0.5H), 3.81 (s, 1.5H) and 3.80 (s, 1.5H), 3.02–2.83 (m, 1H), 2.40–2.00 (m, 3H), 1.82–1.60 (m, 1H), 1.25 (d, $J=6.0$ Hz, 1.5H) and 1.24 (d, $J=6.0$ Hz, 1.5H); MS (APCI, Pos.) m/z 342 $(M+H)^+$, 344.

28c-*syn*: TLC R_f 0.40 (EtOAc/*n*-hexane, 1/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.28–7.21 (m, 2H), 6.95–6.82 (m, 2H), 4.99 (d, $J=14.3$ Hz, 0.5H) and 4.72 (d, $J=7.4$ Hz, 0.5H), 4.41 (d, $J=14.3$ Hz, 0.5H) and 3.80 (d, $J=7.4$ Hz, 0.5H), 3.81 (s, 3H), 3.22–3.02 (m, 1H), 2.85–2.30

(m, 3H), 1.80–1.60 (m, 1H), 1.24 (d, $J=7.2$ Hz, 1.5H) and 1.23 (d, $J=6.6$ Hz, 1.5H); MS (APCI, Pos.) m/z 342 $(M+H)^+$, 344.

(1*S*,5*S*,6*R*,7*S*)-7-Bromo-2-(4-methoxybenzyl)-5,7-dimethyl-2-azabicyclo[4.1.0]heptan-3-one (28d-*anti*). To a stirred solution of **28b-*anti*** (1.4 g, 3.5 mmol), MeI (1.1 mL, 18 mmol) in THF (30 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 2.8 mL, 4.5 mmol) at −78 °C under an argon atmosphere and stirred for 30 min. The reaction mixture was treated with 1 M HCl, warmed up to room temperature and extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5–1:3) to afford **28d-*anti*** as a pale yellow oil (1.1 g, 91%). TLC R_f 0.45 (EtOAc/*n*-hexane, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (d, $J=8.8$ Hz, 2H), 6.87 (d, $J=8.8$ Hz, 2H), 4.94 (d, $J=14.2$ Hz, 1H), 4.08 (d, $J=14.2$ Hz, 1H), 3.80 (s, 3H), 2.93 (d, $J=9.4$ Hz, 1H), 2.31–1.97 (m, 2H), 1.81 (m, 1H), 1.56 (dd, $J=9.4$, 6.4 Hz, 1H), 1.42 (s, 3H), 1.18 (d, $J=6.6$ Hz, 3H); MS (APCI, Pos.) m/z 338 $(M+H)^+$.

(1*S*,5*S*,6*R*)-7,7-Dichloro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-one (29a). To a stirred solution of **28a-*anti*** (993 mg, 3.2 mmol) in anisole (1.7 mL, 15.6 mmol) was added $BF_3{\cdot}OEt_2$ (4.0 mL) and the reaction mixture was stirred for 35 h at 100 °C under an argon atmosphere. Then the mixture was quenched with water and then treated with 5 M NaOH under cooling in an ice bath. The resulting mixture was extracted with $CHCl_3$, and washed with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:2–2:1) to afford **29a** as a white powder (466 mg, 75%). TLC R_f 0.36 (EtOAc/*n*-hexane, 2/1); mp 98–99 °C; optical rotation $[\alpha]_D^{25}$ +69.6 (*c* 1.09, $CHCl_3$); IR (KBr) 3203, 2971, 1661, 1628, 1480, 1352, 1198, 1141, 1077, 1033, 892, 833, 721, 565, 552, 494, 473, 445 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.59 (brs, 1H), 3.19 (dd, $J=9.8$, 1.2 Hz, 1H), 2.25 (dd, $J=12.8$, 3.2 Hz, 1H), 2.21–2.02 (m, 1H), 2.04 (d, $J=12.8$ Hz, 1H), 1.79 (ddd, $J=9.8$, 5.0, 0.6 Hz, 1H), 1.30 (d, $J=6.4$ Hz, 3H); MS (APCI, Pos.) m/z 198 (M + H, ^{37}Cl, ^{37}Cl)$^+$, 196 (M + H, ^{37}Cl, ^{35}Cl)$^+$, 194 (M + H, ^{35}Cl, ^{35}Cl)$^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_9Cl_2N_1O_1+H^+$: 194.0139; found: 194.0150.

(1*S*,5*S*,6*R*,7*S*)-7-Chloro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-one (29e) and (1*S*,5*S*,6*R*,7*R*)-7-chloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (29f). To a stirred mixture of **29a** (1.0 g, 5.2 mmol) in benzene (6.6 mL) were added Ph_3SnH (2.0 g, 5.7 mmol) and azobisisobutylonitrile (42 mg, 0.26 mmol). The reaction mixture was stirred with heating at 80 °C for 4 h under an argon atmosphere. Under cooling in an ice bath, the reaction mixture was diluted with EtOAc and then washed with 10% aqueous potassium fluoride. The resulting insoluble substance was removed by filtration. The organic layer was washed with brine and dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5–2:1) to afford **29e** as a white powder (232 mg, 28%) and **29f** as a white powder (440 mg, 53%).

29e: TLC R_f 0.41 (EtOAc/*n*-hexane, 5/1); mp 117–120 °C; optical rotation $[\alpha]_D^{25}$ +7.1 (*c* 0.35, $CHCl_3$); IR (KBr) 3197, 2961, 1677, 1456, 1411, 1381, 1353, 1233, 1077, 997, 834, 724, 543, 479 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.40–6.20 (brs, 1H), 2.94 (dt, $J=9.2$, 2.0 Hz, 1H), 2.85 (dd, $J=3.6$, 2.0 Hz, 1H), 2.25–1.90 (m, 3H), 1.50–1.38 (m, 1H), 1.26 (d, $J=6.6$ Hz, 3H); MS (APCI, Pos.) m/z 160 (M + H, ^{35}Cl)$^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{10}Cl_1N_1O_1+H^+$: 160.0529; found: 160.0538.

29f: TLC R_f 0.27 (EtOAc/*n*-hexane, 5/1); mp 136–137 °C; optical rotation $[\alpha]_D^{25}$ +95.0 (*c* 1.06, $CHCl_3$); IR (KBr) 3466, 3231, 2968, 2877, 1638, 1474, 1422, 1388, 1358, 1278, 1228, 1199, 1068, 1012, 935, 878, 792, 732, 684, 555 489 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.10–5.80 (brs, 1H), 3.26 (dd, $J=7.8$, 5.2 Hz, 1H), 2.86 (dd, $J=5.2$, 1.2 Hz, 1H), 2.28–2.03 (m, 3H), 1.36–1.25 (m, 1H), 1.23 (d, $J=6.4$ Hz, 3H); MS (APCI, Pos.) m/z 160 (M + H, ^{35}Cl)$^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{10}Cl_1N_1O_1+H^+$: 160.0529; found: 160.0556.

(1*S*,5*S*,6*R*)-7-Bromo-7-fluoro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-one (29c). Compound **29c** was prepared from **28c-*anti*** in 88% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.38 (EtOAc/*n*-hexane, 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.70–6.40 (brs, 1H), 3.20–3.08 (m, 1H), 2.32–1.90 (m, 3H), 1.85–1.62 (m, 1H), 1.30–1.25 (m, 3H); MS (APCI, Pos.) m/z 224 $(M+H)^+$, 222.

(1*S*,5*S*,6*R*,7*S*)-7-Fluoro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-one (29g) and (1*S*,5*S*,6*R*,7*R*)-7-fluoro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (29 h). Compounds **29g** and **29h** were prepared from **29c** in 41 and 44% yield, respectively according to the same procedure as described for the preparation of **29e** and **29f** from **29a**.

29g: Pale yellow powder; TLC R_f 0.21 (EtOAc/*n*-hexane, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.45–6.20 (brs, 1H), 4.28 (dd, $J=61.6$, 2.2 Hz, 1H), 3.10–2.97 (m, 1H), 2.62–2.20 (m, 3H), 2.60–2.40 (m, 1H), 1.25 (d, $J=6.6$ Hz, 3H); MS (APCI, Pos.) m/z 144 $(M+H)^+$.

29h: Pale yellow powder; TLC R_f 0.36 (EtOAc/*n*-hexane, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.80–5.60 (brs, 1H), 4.48 (ddd, $J=64.8$, 6.6, 4.2 Hz, 1H), 2.70–2.61 (m, 1H), 2.29–2.02 (m, 3H), 1.23 (d, $J=6.2$ Hz, 3H), 1.20–1.00 (m, 1H); MS (APCI, Pos.) m/z 144 $(M+H)^+$.

(1*S*,5*S*,6*S*)-2-(4-Methoxybenzyl)-5-methyl-7-methylene-2-azabicyclo[4.1.0]heptan-3-one (30). To a stirred solution of **28d-*anti*** (1 g, 3 mmol) in THF (10 mL) was added *t*-BuOK (1 g, 9 mmol) at room temperature. The reaction mixture was stirred for 2 h. After completing the reaction, the reaction mixture was diluted with

water and extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:3–1:1) to afford **30** as a pale yellow oil (270 mg, 35%). TLC R_f 0.29 (EtOAc/*n*-hexane, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.39 (t, J = 1.8 Hz, 1H), 5.24 (t, J = 1.8 Hz, 1H), 4.69 (d, J = 14.6 Hz, 1H), 4.59 (d, J = 14.6 Hz, 1H), 3.80 (s, 3H), 3.02 (d, J = 6.2 Hz, 1H), 2.30–2.00 (m, 3H), 1.80–1.65 (m, 1H), 1.15 (d, J = 6.6 Hz, 3H); MS (APCI, Pos.) m/z 258 $(M+H)^+$.

(1*R*,5*S*,6*S*,7*R*)-2-(4-Methoxybenzyl)-5,7-dimethyl-2-azabicyclo[4.1.0]heptan-3-one (31). Catalytic hydrogenation of **30** (772 mg, 3 mmol) was carried out in EtOAc (4 mL) in the presence of 10% palladium carbon (80 mg). The catalyst was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:4) to afford **31** as a pale yellow oil (552 mg, 71%). TLC R_f 0.61 (EtOAc/*n*-hexane, 1/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 5.21 (d, J = 14.2 Hz, 1H), 3.73 (s, 3H), 3.60 (d, J = 14.2 Hz, 1H), 2.42 (dd, J = 8.4, 6.4 Hz, 1H), 2.21 (dd, J = 15.2, 4.6 Hz, 1H), 2.07 (dd, J = 15.2, 12.0 Hz, 1H), 1.74 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H), 1.00–0.79 (m, 2H), 0.82 (d, J = 5.6 Hz, 3H); MS (APCI, Pos.) m/z 260 $(M+H)^+$.

(1*R*,5*S*,6*S*,7*R*)-5,7-Dimethyl-2-azabicyclo[4.1.0]heptan-3-one (32). Compound **32** was prepared from **31** in 57% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.38 (EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.86 (brs, 1H), 2.66 (m, 1H), 2.17 (dd, J = 15.2, 5.0 Hz, 1H), 2.05 (dd, J = 15.2, 13.0 Hz, 1H), 1.90–1.65 (m, 1H), 1.17 (d, J = 6.6 Hz, 3H), 1.07–0.85 (m, 5H); MS (APCI, Pos.) m/z 140 $(M+H)^+$.

1-(4-Methoxybenzyl)-4-methylpiperidine-2,6-dione (34). To a stirred solution of 3-methylglutaric anhydride (**33**) (20 g, 156 mmol) in THF (300 mL) was added *p*-methoxybenzylamine (23 g, 168 mmol) at room temperature and stirred for 30 min. After completing the reaction, the mixture was evaporated and the residue was diluted with EtOAc. The resulting mixture was treated with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated to afford a residue, which was used for the subsequent reaction without further purification.

To a stirred solution of the compound obtained above in Ac_2O (100 mL) was added Et_3N (20 mL) at room temperature. The reaction mixture was heated at 80 °C for 1 h. After completing the reaction, the mixture was cooled to room temperature and evaporated. The residue was diluted with EtOAc and water. The organic layer was washed with 1 M HCl, saturated aqueous sodium bicarbonate, brine and dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 10:1–1:1) to afford **34** as a pale yellow solid (37 g, 95%). TLC R_f 0.82 (EtOAc/*n*-hexane, 1:1); mp 50–51 °C; IR (KBr) 3368, 2968, 2871, 1719, 1671, 1611, 1514, 1469, 1428, 1387, 1339, 1291, 1347, 1218, 1175, 1142, 1109, 1062, 1029, 970, 937, 886, 832, 806, 776, 646, 628, 595, 562, 518 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 4.88 (s, 2H), 3.77 (s, 3H), 2.80–2.65 (m, 2H), 2.40–2.12 (m, 3H), 1.04 (d, J = 6.2 Hz, 3H); MS (APCI, Pos.) m/z 248 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{17}N_1O_3+H^+$: 248.1287; found: 248.1259.

6-Hydroxy-1-(4-methoxybenzyl)-4-methylpiperidin-2-one (35). To a stirred solution of **34** (14 g, 56.6 mmol) in EtOH (300 mL) was added $NaBH_4$ (4.2 g, 111 mmol) at 0 °C. The reaction mixture was stirred for 2 h at room temperature. After completing the reaction, the resulting mixture was cooled to 0 °C and treated with 1 M HCl to adjust the pH value to 7. After removal of the solvent by evaporation, the resulting mixture was extracted with EtOAc and washed with brine. The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:1) to afford **35** as a white crystal (13.4 g, 95%). TLC R_f 0.24 (EtOAc/*n*-hexane, 1:1); mp 130–131 °C; IR (KBr) 3259, 2952, 1626, 1514, 1479, 1413, 1299, 1249, 1170, 1101, 1065, 1025, 974, 902, 838, 819, 767, 742, 619, 583, 528 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 5.10–4.70 (m, 2H), 4.40–4.25 (m, 1H), 3.75 (s, 3H), 2.80–2.05 (m, 3H), 1.95–1.60 (m, 2H), 1.47 (ddd, J = 13.6, 12.8, 3.6 Hz, 1H), 1.04 (d, J = 6.6 Hz, 3H); MS (APCI, Pos.) m/z 250 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{19}N_1O_3+H^+$: 250.1443; found: 250.1437.

1-(4-Methoxybenzyl)-4-methyl-3,4-dihydropyridin-2-one (37). Compound **37** was prepared from **35** in 60% yield according to the same procedure as described for the preparation of **26** from **24**. Pale yellow oil; TLC R_f 0.55 (EtOAc/*n*-hexane, 1:1); IR (neat) 3421, 2957, 2836, 1668, 1612, 1585, 1513, 1457, 1409, 1385, 1304, 1248, 1212, 1176, 1147, 1105, 1034, 946, 822, 717, 580, 518 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 5.96 (dd, J = 7.8, 1.5 Hz, 1H), 5.03 (dd, J = 7.8, 3.3 Hz, 1H), 4.70–4.50 (m, 2H), 3.79 (s, 3H), 2.80–2.05 (m, 3H), 1.05 (d, J = 6.8 Hz, 3H); MS (APCI, Pos.) m/z 232 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{17}N_1O_2+H^+$: 232.1337; found: 232.1313.

6-Hydroxy-1-(4-methoxybenzyl)-4,6-dimethylpiperidin-2-one (36). To a stirred solution of **34** (40 g, 162 mmol) in THF (600 mL) was added MeLi (1 M in Et_2O, 174 mL, 174 mmol) at −78 °C under an argon atmosphere. After completing the reaction, the mixture was diluted with Et_2O and saturated aqueous ammonium chloride was added. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1/1) to afford

36 as a white solid (42 g, 99%). TLC R_f 0.13 (EtOAc/*n*-hexane, 1:1); mp 66–68 °C; IR (KBr) 3309, 2963, 1704, 1633, 1548, 1515, 1459, 1370, 1304, 1252, 1173, 1160, 1036, 830, 696, 589 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20 (d, $J=8.8$ Hz, 2H), 6.86 (d, $J=8.8$ Hz, 2H), 5.85 (br, 1H), 4.36 (d, $J=5.6$ Hz, 2H), 3.80 (s, 3H), 2.63–2.00 (m, 5H), 2.13 (s, 3H), 1.00 (d, $J=6.4$ Hz, 3H); MS (APCI, Pos.) m/z 264 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{21}N_1O_3+ H^+$: 264.1600; found: 264.1585.

1-(4-Methoxybenzyl)-4,6-dimethyl-3,4-dihydropyridin-2-one (38). Compound **38** was prepared from **36** in 99% yield according to the same procedure as described for the preparation of **26** from **24**. Colorless oil; TLC R_f 0.58 (EtOAc/*n*-hexane, 1/1); IR (neat) 2957, 2836, 1674, 1614, 1513, 1457, 1388, 1248, 1176, 1110, 1034, 959, 891, 819, 772, 659, 548 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.11 (d, $J=8.8$ Hz, 2H), 6.84 (d, $J=8.8$ Hz, 2H), 4.92 (d, $J=15.8$ Hz, 1H), 4.89 (s, 1H), 4.70 (d, $J=15.8$ Hz, 1H), 3.78 (s, 3H), 2.80–2.20 (m, 3H), 1.85 (s, 3H), 1.04 (d, $J=7.0$ Hz, 3H); MS (APCI, Pos.) m/z 246 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{19}N_1O_2+ H^+$: 246.1494; found: 246.1477.

(*dl*)-(1*S*,5*S*,6*R*)-7,7-Dibromo-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (39a-*anti*) and (*dl*)-(1*R*,5*S*,6*S*)-7,7-dibromo-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (39a-*syn*). Compounds **39a-*anti*** and **39a-*syn*** were prepared from **37** in 38 and 13% yield, respectively according to the same procedure as described for the preparation of **28b-*anti*** and **28b-*syn*** from **26**.

39a-*anti*: pale yellow oil; TLC R_f 0.38 (EtOAc/*n*-hexane, 1:2); IR (neat) 2961, 2836, 1667, 1612, 1513, 1415, 1379, 1248, 1175, 1075, 1033, 845, 764, 721, 581, 503 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.29 (d, $J=8.4$ Hz, 2H), 6.89 (d, $J=8.4$ Hz, 2H), 5.47 (d, $J=14.8$ Hz, 1H), 3.81 (d, $J=14.8$ Hz, 1H), 3.81 (s, 3H), 2.98 (d, $J=9.8$ Hz, 1H), 2.40–2.00 (m, 3H), 1.77 (dd, $J=9.8$, 5.4 Hz, 1H), 1.26 (m, 3H); MS (APCI, Pos.) m/z 404 ($M+H$, ^{79}Br, $^{81}Br)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Br_2N_1O_2+ H^+$: 401.9704; found: 401.9717.

39a-*syn*: pale yellow oil; TLC R_f 0.18 (EtOAc/*n*-hexane, 1:2); IR (neat) 2962, 2836, 1652, 1513, 1456, 1415, 1389, 1341, 1303, 1249, 1176, 1108, 1033, 885, 849, 773, 582, 545 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (d, $J=8.6$ Hz, 2H), 6.91 (d, $J=8.6$ Hz, 2H), 4.93 (d, $J=14.2$ Hz, 1H), 4.54 (d, $J=14.2$ Hz, 1H), 3.82 (s, 3H), 3.27 (d, $J=10.2$ Hz, 1H), 2.50–2.45 (m, 3H), 2.20–2.10 (m, 1H), 1.28 (d, $J=6.2$ Hz, 3H); MS (APCI, Pos.) m/z 404 ($M+H$, ^{79}Br, $^{81}Br)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Br_2N_1O_2+ H^+$: 401.9704; found: 401.9703.

(*dl*)-(1*S*,5*S*,6*S*)-2-(4-Methoxybenzyl)-5,7,7-trimethyl-2-azabicyclo[4.1.0]heptan-3-one (39b-*anti*). To a stirred suspension of CuSCN (4.8 g, 40 mmol) in Et_2O (30 mL) was added MeLi (1 M in Et_2O, 80 mL, 80 mmol) at −78 °C under an argon atmosphere. The reaction mixture was warmed up to −15 °C over 1.5 h and then cooled to −20 °C. A solution of **39a-*anti*** (2.0 g, 5.0 mmol) in Et_2O (40 mL) and HMPA (1.4 mL, 8 mmol) was added to the mixture and stirred for 1.5 h. Then the reaction mixture was cooled to −50 °C and treated with MeI (10 mL, 161 mmol). After stirring for 30 min, the reaction was quenched with saturated aqueous ammonium chloride and the resulting precipitates were removed by filtration. The filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5–1:3) to afford **39b-*anti*** as a pale yellow oil (1.0 g, 73%). TLC R_f 0.55 (EtOAc/*n*-hexane, 1:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.22 (d, $J=8.8$ Hz, 2H), 6.85 (d, $J=8.8$ Hz, 2H), 5.14 (d, $J=14.0$ Hz, 1H), 3.79 (d, $J=14.0$ Hz, 1H), 3.79 (s, 3H), 2.29–2.01 (m, 3H), 1.78 (m, 1H), 1.10 (d, $J=6.6$ Hz, 3H), 1.00 (s, 3H), 0.86 (s, 3H), 0.69 (dd, $J=8.6$, 6.2 Hz, 1H); MS (APCI, Pos.) m/z 274 $(M+H)^+$.

(*dl*)-(1*R*,5*S*,6*S*,7*S*)-2-(4-Methoxybenzyl)-5,7-dimethyl-2-azabicyclo[4.1.0]heptan-3-one (39c-*anti*). To a stirred suspension of CuSCN (6.0 g, 50 mmol) in Et_2O (35 mL) was added MeLi (1 M in Et_2O, 100 mL, 100 mmol) at −78 °C under an argon atmosphere. The reaction mixture was warmed up to −15 °C in 1.5 h and then cooled to −20 °C. A solution of **39a-*anti*** (2.5 g, 6.2 mmol) in Et_2O (45 mL) and HMPA (1.7 mL, 10 mmol) was added to the mixture. After stirring for 1.5 h, the reaction mixture was cooled to −50 °C, then quenched with saturated aqueous ammonium chloride and warmed up to room temperature. After stirring for 30 min, the resulting precipitates were removed by filtration. The filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5–1:3) to afford **39c-*anti*** as a pale yellow oil (627 mg, 39%). TLC R_f 0.38 (EtOAc/*n*-hexane, 1:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.23 (d, $J=8.8$ Hz, 2H), 6.85 (d, $J=8.8$ Hz, 2H), 4.76 (d, $J=14.2$ Hz, 1H), 4.36 (d, $J=14.2$ Hz, 1H), 3.80 (s, 3H), 2.28–2.04 (m, 3H), 1.73 (m, 1H), 1.13 (d, $J=6.6$ Hz, 3H), 0.91 (d, $J=6.2$ Hz, 3H), 0.68 (m, 1H), 0.57 (m, 1H); MS (APCI, Pos.) m/z 260 $(M+H)^+$.

(*dl*)-(1*S*,5*S*,6*R*,7*S*)-7-Bromo-2-(4-methoxybenzyl)-5,7-dimethyl-2-azabicyclo[4.1.0]heptan-3-one (39d-*anti*). Compound **39d-*anti*** was prepared from **39a-*anti*** in 73% yield according to the same procedure as described for the preparation of **28d-*anti*** from **28b-*anti***. Pale yellow oil; TLC R_f 0.45 (EtOAc/*n*-hexane, 2:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.28 (d, $J=8.8$ Hz, 2H), 6.89 (d, $J=8.8$ Hz, 2H), 4.94 (d, $J=14.2$ Hz, 1H), 4.08 (d, $J=14.2$ Hz, 1H), 3.80 (s, 3H), 2.93 (d, $J=9.4$ Hz, 1H), 2.35–1.95 (m, 2H), 1.81 (m, 1H), 1.56 (dd, $J=9.4$, 6.4 Hz, 1H), 1.42 (s, 3H), 1.18 (d, $J=6.5$ Hz, 3H); MS (APCI, Pos.) m/z 338 $(M+H)^+$.

(*dl*)-(1*R*,5*S*,6*S*,7*R*)-2-(4-Methoxybenzyl)-5,7-dimethyl-2-azabicyclo[4.1.0]heptan-3-one (39e-*anti*). To a stirred suspension of CuI (2.4 g, 12.8 mmol) in THF (50 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 16 mL, 25.6

mmol) at −78 °C under an argon atmosphere. The reaction mixture was warmed up to −45 °C over 1 h and then cooled to −78 °C. A solution of **39d-*anti*** (866 mg, 2.6 mmol) in THF (5 mL) was added to the mixture, and stirred for 1 h at −78 °C. After stirring at −78 °C for 1 h, the mixture was quenched with 4 M HCl/EtOAc, and warmed up to room temperature. After stirred for 30 min, the reaction mixture was treated with water and extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:6–2:1) to afford **39e-*anti*** as a pale yellow oil (243 mg, 36%). TLC R_f 0.61 (EtOAc/*n*-hexane, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 5.21 (d, J = 14.2 Hz, 1H), 3.73 (s, 3H), 3.60 (d, J = 14.2 Hz, 1H), 2.42 (dd, J = 8.4, 6.4 Hz, 1H), 2.21 (dd, J = 15.2, 4.6 Hz, 1H), 2.07 (dd, J = 15.2, 12.0 Hz, 1H), 1.74 (m, 1H), 1.05 (d, J = 6.6 Hz, 3H), 1.00–0.75 (m, 2H), 0.82 (d, J = 5.6 Hz, 3H); MS (APCI, Pos.) m/z 260 $(M+H)^+$.

(*dl*) - (1*R*,5*S*,6*S*,7*S*) - 7 - Butyl - 2 - (4 - methoxybenzyl) - 5-methyl-2-azabicyclo[4.1.0]heptan-3-one (39f-*anti*) and (*dl*) - (1*R*,5*S*,6*S*,7*R*) - 7 - butyl - 2 - (4 - methoxybenzyl) - 5 - methyl-2-azabicyclo[4.1.0]heptan-3-one (39g-*anti*). To a stirred suspension of CuSCN (5.1 g, 42 mmol) in Et_2O (70 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 51 mL, 82 mmol) at −78 °C under an argon atmosphere and warmed up to −10 °C. After stirring for 1.5 h, the reaction mixture was cooled to −78 °C. A solution of **39a-*anti*** (2.1 g, 5.2 mmol) in Et_2O (30 mL) and HMPA (2 mL, 11.5 mmol) was added to the mixture. After stirring for 1 h, the reaction mixture was poured into saturated aqueous ammonium chloride under stirring. The reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5) to afford **39f-*anti*** as a pale yellow oil (282 mg, 18%) and **39g-*anti*** as a pale yellow oil (611 mg, 39%).

39f-*anti*: TLC R_f 0.32 (EtOAc/*n*-hexane, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.22 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.92 (d, J = 14.2 Hz, 1H), 4.20 (d, J = 14.2 Hz, 1H), 3.80 (s, 3H), 2.30–2.05 (m, 3H), 1.75 (m, 1H), 1.27–1.00 (m, 6H), 1.14 (d, J = 6.6 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H), 0.73–0.58(m, 2H); MS (APCI, Pos.) m/z 302 $(M+H)^+$.

39g-*anti*: TLC R_f 0.40 (EtOAc/*n*-hexane, 1:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.33 (d, J = 14.0 Hz, 1H), 3.79 (s, 3H), 3.63 (d, J = 14.0 Hz, 1H), 2.49 (t, J = 7.0 Hz, 1H), 2.32–2.04 (m, 2H), 1.77 (m, 1H), 1.46–1.20 (m, 6H), 1.13 (d, J = 6.4 Hz, 3H), 0.99–0.80 (m, 5H); MS (APCI, Pos.) m/z 302 $(M+H)^+$.

(*dl*) - (1*S*,5*S*,6*S*) - 5,7,7 - Trimethyl - 2 - azabicyclo[4.1.0]-heptan-3-one (40b). Compound **40b** was prepared from **39b-*anti*** in 49% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.15 (EtOAc/*n*-hexane, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.80 (brs, 1H), 2.36 (d, J = 8.4 Hz, 1H), 2.14 (dd, J = 14.0, 4.0 Hz, 1H), 1.98 (dd, J = 14.0, 2.0 Hz, 1H), 1.73 (m, 1H), 1.15 (d, J = 6.6 Hz, 3H), 1.04 (s, 3H), 0.99 (s, 3H), 0.71 (dd, J = 8.4, 6.0 Hz, 1H); MS (APCI, Pos.) m/z 154 $(M+H)^+$.

(*dl*) - (1*R*,5*S*,6*S*,7*S*) - 5,7 - Dimethyl - 2 - azabicyclo[4.1.0]-heptan-3-one (40c). Compound **40c** was prepared from **39c-*anti*** in 78% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.09 (EtOAc/*n*-hexane, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.12 (brs, 1H), 2.32 (ddd, J = 8.4, 3.0, 1.8 Hz, 1H), 2.14 (dd, J = 15.0, 5.8 Hz, 1H), 2.01 (d, J = 15.0 Hz, 1H), 1.86 (m, 1H), 1.18 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 5.8 Hz, 3H), 0.81 (m, 1H), 0.71 (m, 1H); MS (APCI, Pos.) m/z 140 $(M+H)^+$.

(*dl*) - (1*R*,5*S*,6*S*,7*R*) - 5,7 - Dimethyl - 2 - azabicyclo[4.1.0]-heptan-3-one (40e). Compound **40e** was prepared from **39e-*anti*** in 68% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.14 (EtOAc/*n*-hexane, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.80–5.60 (brs, 1H), 2.70–2.60 (m, 1H), 2.20–1.90 (m, 2H), 1.85–1.55 (m, 1H), 1.16 (d, J = 6.6 Hz, 3H), 1.05–0.97 (m, 5H); MS (APCI, Pos.) m/z 140 $(M+H)^+$.

(*dl*)-(1*R*,5*S*,6*S*,7*R*)-7-Butyl-5-methyl-2-azabicyclo[4.1.0]-heptan-3-one (40g). Compound **40g** was prepared from **39g-*anti*** in 47% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.16 (EtOAc/*n*-hexane, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.97 (brs, 1H), 2.80–2.70 (m, 2H), 2.49–2.04 (m, 1H), 1.75 (m, 1H), 1.46–1.20 (m, 6H), 1.18 (d, J = 6.6 Hz, 3H), 0.99–0.80 (m, 5H); MS (APCI, Pos.) m/z 182 $(M+H)^+$.

(*dl*) - (1*S*,5*S*,6*R*,7*S*) - 7 - Bromo - 2 - (4 - methoxybenzyl) - 5-methyl-2-azabicyclo[4.1.0]heptan-3-one (41a) and (*dl*)-(1*S*,5*S*,6*R*,7*R*)-7-bromo-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (41b). To a stirred solution of **39a-*anti*** (8.0 g, 19.8 mmol) in toluene (70 mL) was added *n*-Bu_3SnH (6.4 mL, 23.8 mmol) at −10 °C. After stirring for 15 h at −10 °C, the reaction was quenched with 10% aqueous potassium fluoride and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5–2:1) to afford **41a** and **41b** as an inseparable mixture (5.0 g, 78% yield, **41a**:**41b** = 1:3).

41a: Pale yellow oil; TLC R_f 0.35 (EtOAc/*n*-hexane, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.27 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.76 (d, J = 14.0 Hz, 1H), 4.42 (d, J = 14.0 Hz, 1H), 3.80 (s, 3H), 2.98 (dd, J = 10.0, 1.0 Hz, 1H), 2.44 (dd, J = 3.0, 1.0 Hz, 1H), 2.30–2.10 (m, 2H), 1.82 (m, 1H), 1.46 (m, 1H), 1.21 (d, J = 6.6 Hz, 3H); MS (APCI, Pos.) m/z 324 $(M+H)^+$.

41b: Pale yellow oil; TLC R_f 0.38 (EtOAc/*n*-hexane, 1:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, J = 8.8 Hz,

2H), 6.85 (d, $J=8.8$ Hz, 2H), 5.52 (d, $J=14.0$ Hz, 1H), 3.79 (s, 3H), 3.64 (d, $J=14.0$ Hz, 1H), 3.27 (dd, $J=7.8$, 5.0 Hz, 1H), 2.64 (dd, $J=9.4$, 5.0 Hz, 1H), 2.48–2.02 (m, 3H), 1.80 (m, 1H), 1.20 (d, $J=6.6$ Hz, 3H); MS (APCI, Pos.) m/z 324 $(M+H)^+$.

(*dl*)-(1*R*,5*S*,6*S*,7*R*)-7-Ethyl-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (42b). To a stirred suspension of CuI (7.2 g, 37.8 mmol) in THF (120 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 47 mL, 75.6 mmol) at −78 °C under an argon atmosphere. The reaction mixture was warmed up to −45 °C over 1 h. A solution of **41a** and **41b** (2.4 g, 7.4 mmol) in THF (45 mL) was added to the mixture and stirred for 1 h at −45 °C. Then the reaction mixture was treated with EtI (15 mL, 188 mmol). After stirring for 30 min, the reaction was quenched with saturated aqueous ammonium chloride and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:6–2:1) to afford **42b** as a pale yellow oil (404 mg, 20%). TLC R_f 0.50 (EtOAc/*n*-hexane, 2:3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (d, $J=8.0$ Hz, 2H), 6.84 (d, $J=8.0$ Hz, 2H), 5.34 (d, $J=14.0$ Hz, 1H), 3.79 (s, 3H), 3.62 (d, $J=14.0$ Hz, 1H), 2.49 (dd, $J=8.2$, 6.6 Hz, 1H), 2.31–2.04 (m, 2H), 1.77 (m, 1H), 1.50–1.16 (m, 2H), 1.13 (d, $J=6.6$ Hz, 3H), 0.99 (t, $J=7.0$ Hz, 3H), 0.99–0.85 (m, 2H); MS (APCI, Pos.) m/z 274 $(M+H)^+$.

(*dl*)-(1*R*,5*S*,6*S*,7*R*)-7-Ethyl-5-methyl-2-azabicyclo[4.1.0]-heptan-3-one (43). Compound **43** was prepared from **42b** in 39% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. White powder; TLC R_f 0.26 (EtOAc/*n*-hexane, 3:2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.67 (brs, 1H), 2.68 (dd, $J=8.0$, 6.0 Hz, 1H), 2.16 (dd, $J=15.0$, 5.6 Hz, 1H), 2.01 (d, $J=15.0$ Hz, 1H), 1.75 (m, 1H), 1.32 (m, 2H), 1.17 (d, $J=6.6$ Hz, 3H), 1.03–0.84 (m, 2H), 0.96 (t, $J=7.0$ Hz, 3H); MS (APCI, Pos.) m/z 154 $(M+H)^+$.

(*dl*)-(1*S*,5*S*,6*R*)-7,7-Dibromo-5-methyl-2-azabicyclo[4.1.0]-heptan-3-one (44). Compound **44** was prepared from **39a-*anti*** in 91% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.43 (EtOAc/*n*-hexane, 4:1); mp 106–109 °C; IR (KBr) 3205, 3099, 2960, 1656, 1474, 1452, 1407, 1365, 1352, 1286, 1200, 1121, 1096, 1072, 1015, 933, 884, 774, 717, 553 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.55 (brs, 1H), 3.21 (d, $J=9.4$ Hz, 1H), 2.30–1.94 (m, 3H), 1.83 (dd, $J=9.4$, 5.2 Hz, 1H), 1.32 (d, $J=6.0$ Hz, 3H); MS (APCI, Pos.) m/z 284 $(M+H,\ ^{79}Br,\ ^{81}Br)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_9Br_2N_1O_1+\ H^+$: 281.9129; found: 281.9130.

(*dl*)-(1*R*,5*S*,6*S*,7*S*)-5-Methyl-7-vinyl-2-azabicyclo[4.1.0]-heptan-3-one (45). To a stirred suspension of CuI (3.1 g, 16 mmol) in Et_2O (13 mL) was added vinyl magnesium bromide (1 M in THF, 32 mL, 32 mmol) at −40 °C under an argon atmosphere and stirring was continued for 1 h. To this solution was added a solution of **44** (1.2 g, 4.2 mmol) in THF (25 mL) and the reaction mixture was warmed up to −15 °C over 1 h. After completing the reaction, the reaction was quenched with saturated aqueous ammonium chloride and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:2–1:1) to afford **45** as a pale yellow powder (375 mg, 59%). TLC R_f 0.23 (EtOAc/*n*-hexane, 2:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.95 (brs, 1H), 5.46 (ddd, $J=17.0$, 10.3, 4.1 Hz, 1H), 5.03 (ddd, $J=17.0$, 1.5, 0.8 Hz, 1H), 4.94 (dd, $J=10.3$, 1.5 Hz, 1H), 2.65 (ddd, $J=8.5$, 2.7, 1.9 Hz, 1H), 2.27–1.86 (m, 3H), 1.49 (ddd, $J=8.5$, 4.8, 2.5 Hz, 1H), 1.22 (d, $J=6.4$ Hz, 3H), 1.13 (m, 1H); MS (APCI, Pos.) m/z 152 $(M+H)^+$.

(1*R*,5*R*,6*S*)-7,7-Dichloro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (46a-*anti*) and (1*S*,5*R*,6*R*)-7,7-dichloro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo [4.1.0]heptan-3-one (46a-*syn*). Compounds **46a-*anti*** and **46a-*syn*** were prepared from **27** in 53 and 14% yield, respectively according to the same procedure as described for the preparation of **28a-*anti*** and **28a-*syn*** from **26**.

46a-*anti*: pale yellow oil; TLC R_f 0.36 (EtOAc/*n*-hexane, 1:2); optical rotation $[\alpha]_D^{25}$ −27.5 (*c* 1.03, $CHCl_3$); IR (neat) 2964, 2932, 2874, 2837, 1669, 1613, 1586, 1515, 1445, 1416, 1384, 1363, 1303, 1280, 1248, 1196, 1176, 1112, 1080, 1033, 970, 890, 855, 823, 766, 731, 703, 626, 575, 511 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (d, $J=8.6$ Hz, 2H), 6.89 (d, $J=8.6$ Hz, 2H), 5.44 (d, $J=14.0$ Hz, 1H), 3.81 (s, 3H), 3.81 (d, $J=14.0$ Hz, 1H), 2.95 (d, $J=10.0$ Hz, 1H), 2.37–2.05 (m, 3H), 1.76 (dd, $J=10.2$, 5.4 Hz, 1H), 1.25 (d, $J=6.2$ Hz, 3H); MS (APCI, Pos.) m/z 316 $(M+H,\ ^{35}Cl,\ ^{37}Cl)^+$, 314 $(M+H,\ ^{35}Cl,\ ^{35}Cl)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Cl_2N_1O_2+\ H^+$: 314.0715; found: 314.0686.

46a-*syn*: pale yellow oil; TLC R_f 0.18 (EtOAc/*n*-hexane, 1:2); optical rotation $[\alpha]_D^{25}$ −29.7 (*c* 1.00, $CHCl_3$); IR (neat) 2964, 1652, 1513, 1456, 1417, 1392, 1249, 1176, 1034, 891, 820, 763, 520 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31 (d, $J=8.8$ Hz, 2H), 6.89 (d, $J=8.8$ Hz, 2H), 4.87 (d, $J=14.4$ Hz, 1H), 4.57 (d, $J=14.4$ Hz, 1H), 3.81 (s, 3H), 3.20 (d, $J=10.2$ Hz, 1H), 2.60–2.25 (m, 3H), 2.00–1.90 (m, 1H), 1.27 (d, $J=10.0$ Hz, 3H); MS (APCI, Pos.) m/z 314 $(M+H,\ ^{35}Cl,\ ^{35}Cl)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Cl_2N_1O_2+\ H^+$: 314.0715; found: 314.0708.

(1*R*,5*R*,6*S*)-7-Bromo-7-chloro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (46b-*anti*) and (1*S*,5*R*,6*R*)-7-bromo-7-chloro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (46b-*syn*). Compounds **46b-*anti*** and **46b-*syn*** were prepared from **27** in 64 and 18% yield, respectively according to the same procedure as described for the preparation of **28a-*anti*** and **28a-*syn*** from **26** by using $ClCHBr_2$ and $PhCH_2NEt_3Cl$ instead of $CHCl_3$ and aliquat-336.

46b-*anti*: pale yellow oil; TLC R_f 0.49 (EtOAc/*n*-hexane, 1:1); optical rotation $[\alpha]_D^{25}$ −12.4 (*c* 1.07, $CHCl_3$); IR

(neat) 2963, 2931, 2836, 1668, 1613, 1585, 1513, 1443, 1415, 1381, 1303, 1280, 1248, 1175, 1112, 1077, 1033, 964, 885, 848, 817, 793, 765, 727, 576, 508 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.29 (d, $J=8.8$ Hz, 2H), 6.90 (d, $J=8.8$ Hz, 2H), 5.48 (d, $J=14.4$ Hz, 0.5H) and 5.43 (d, $J=14.4$ Hz, 0.5H), 3.84 (d, $J=9.8$ Hz, 0.5H) and 3.80 (d, $J=14.4$ Hz, 0.5H), 3.81 (s, 3H), 3.04 (d, $J=9.8$ Hz, 0.5H) and 2.88 (d, $J=9.8$ Hz, 0.5H), 2.20–2.05 (m, 3H), 1.84 (dd, $J=14.6$, 5.2 Hz, 0.5H) and 1.69 (dd, $J=10.0$, 5.2 Hz, 0.5H), 1.30–1.20 (m, 3H); MS (APCI, Pos.) m/z 360, 358 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Br_1Cl_1N_1O_2+H^+$: 358.0209; found: 358.0205.

46b-*syn*: pale yellow oil; TLC R_f 0.40 (EtOAc/*n*-hexane, 1:1); optical rotation $[\alpha]_D^{25}$ −25.1 (*c* 1.15, $CHCl_3$); IR (neat) 2963, 1652, 1514, 1456, 1416, 1392, 1342, 1303, 1250, 1177, 1111, 1032, 889, 836, 763, 712, 523 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32 (d, $J=8.8$ Hz, 2H), 6.91 (d, $J=8.8$ Hz, 2H), 4.97 (d, $J=14.4$ Hz, 0.5H) and 4.84 (d, $J=14.4$ Hz, 0.5H), 4.63 (d, $J=14.4$ Hz, 0.5H) and 4.49 (d, $J=14.4$ Hz, 0.5H), 3.82 (s, 1.5H) and 3.80 (s, 1.5H), 3.29 (d, $J=10.3$ Hz, 0.5H) and 3.16 (d, $J=10.3$ Hz, 0.5H), 2.65–2.20 (m, 3H), 2.10–1.90 (m, 1H), 1.30–1.25 (m, 3H); MS (APCI, Pos.) m/z 360, 358 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{15}H_{17}Br_1Cl_1N_1O_2+H^+$: 358.0209; found: 358.0196.

(1*S*,5*R*,6*R*)-7-Bromo-7-fluoro-2-(4-methoxybenzyl)-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (46c-*syn*). Compound **46c-*syn*** was prepared from **27** in 15% yield according to the same procedure as described for the preparation of **28a-*anti*** and **28a-*syn*** from **26**. Pale yellow oil; TLC R_f 0.40 (EtOAc/*n*-hexane, 1:1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.29 (d, $J=8.6$ Hz, 2H), 6.88 (d, $J=8.6$ Hz, 2H), 4.99 (d, $J=14.3$ Hz, 0.5H) and 4.71 (d, $J=14.3$ Hz, 0.5H), 4.41 (d, $J=7.4$ Hz, 0.5H) and 3.78 (d, $J=7.4$ Hz, 0.5H), 3.81 (s, 3H), 3.23–3.04 (m, 1H), 2.65–2.30 (m, 3H), 2.08–1.80 (m, 1H), 1.24 (d, $J=6.4$ Hz, 1.5H) and 1.22 (d, $J=6.4$ Hz, 1.5H); MS (APCI, Pos.) m/z 342 $(M+H)^+$.

(1*R*,5*R*,6*S*)-7,7-Dichloro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-one (47a). Compound **47a** was prepared from **46a-*anti*** in 79% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.36 (EtOAc/*n*-hexane, 1:2); mp 100–101 °C; optical rotation $[\alpha]_D^{25}$ −70.5 (*c* 1.09, $CHCl_3$); IR (KBr) 3436, 2972, 1662, 1630, 1481, 1403, 1373, 1353, 1205, 1078, 1034, 893, 833, 720, 566, 504 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.37 (brs, 1H), 3.19 (dd, $J=9.8$, 1.4 Hz, 1H), 2.30–1.94 (m. 3H), 1.84–1.74 (m, 1H), 1.30 (d, $J=6.2$ Hz, 3H); MS (APCI, Pos.) m/z 194 $(M+H, {}^{35}Cl, {}^{35}Cl)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_9Cl_2N_1O_1+H^+$: 194.0139; found: 194.0146.

(1*R*,5*R*,6*S*)-7-Bromo-7-chloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (47b). Compound **47b** was prepared from **46b-*anti*** in 95% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.33 (EtOAc/*n*-hexane, 2:1); mp 97–99 °C; optical rotation $[\alpha]_D^{25}$ −56.9 (*c* 0.88, $CHCl_3$); IR (KBr) 3200, 2968, 1660, 1631, 1477, 1455, 1400, 1367, 1351, 1280, 1235, 1197, 1136, 1076, 1026, 938, 888, 784, 744, 717, 551, 499, 472 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.30–6.15 (brs, 1H), 3.29 (dd, $J=9.6$, 1.4 Hz, 0.5H) and 3.11 (dd, $J=9.6$, 1.4 Hz, 0.5H), 2.30–2.00 (m, 3H), 1.88 (ddd, $J=9.7$, 5.4, 1.0 Hz, 0.5H) and 1.73 (ddd, $J=9.7$, 5.4, 1.0 Hz, 0.5H), 1.33–1.29 (m, 3H); MS (APCI, Pos.) m/z 241, 239 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_9Br_1Cl_1N_1O_1+H^+$: 237.9634; found: 237.9662.

(1*R*,5*R*,6*S*,7*S*)-7-Chloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (47c) and (1*R*,5*R*,6*S*,7*R*)-7-chloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (47d). To a stirred mixture of **47b** (1.0 g, 4.2 mmol) in toluene (5 mL) were added $(TMS)_3SiH$ (2.0 mL, 6.5 mmol) and BEt_3 (1 M in THF, 0.1 mL) and stirring was continued at room temperature. After completing the reaction, the reaction mixture was diluted with EtOAc (10 mL) and washed with brine (10 mL), dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane, 1:5–1:1) to afford **47c** as a white powder (295 mg, 44%) and **47d** as a white powder (188 mg, 28%), respectively.

47c: TLC R_f 0.28 (EtOAc); mp 135–136 °C; optical rotation $[\alpha]_D^{25}$ −94.5 (*c* 1.05, $CHCl_3$); IR (KBr) 3464, 3230, 2974, 2878, 1646, 1475, 1423, 1389, 1358, 1295, 1278, 1229, 1199, 1112, 1069, 1013, 937, 879, 793, 770, 734, 686, 616, 557, 540, 491, 442 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.00–5.70 (brs, 1H), 3.27 (dd, $J=7.8$, 5.2 Hz, 1H), 2.87 (ddd, $J=9.4$, 5.2, 1.2 Hz, 1H), 2.30–2.00 (m, 3H), 1.36–1.25 (m, 1H), 1.24 (d, $J=6.4$ Hz, 3H); MS (APCI, Pos.) m/z 160 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{10}Cl_1N_1O_1+H^+$: 160.0529; found: 160.0540.

47d: TLC R_f 0.42 (EtOAc); mp 118–120 °C; optical rotation $[\alpha]_D^{25}$ −7.5 (*c* 0.40, $CHCl_3$); IR (KBr) 3195, 3049, 2961, 2928, 1677, 1456, 1411, 1382, 1353, 1291, 1233, 1077, 997, 834, 725, 543, 480 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.50–6.30 (brs, 1H), 2.94 (dt, $J=9.2$, 1.9 Hz, 1H), 2.90–2.82 (m, 1H), 2.26–1.90 (m, 3H), 1.55–1.40 (m, 1H), 1.26 (d, $J=6.4$ Hz, 3H); MS (APCI, Pos.) m/z 160 $(M+H)^+$.

(1*S*,5*R*,6*R*)-7-Bromo-7-chloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (48b). Compound **48b** was prepared from **46b-*syn*** in 96% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.21 (EtOAc/*n*-hexane, 2/1); mp 125–126 °C; optical rotation $[\alpha]_D^{25}$ +20.2 (*c* 0.11, $CHCl_3$); IR (KBr) 3139, 3035, 2349, 1717, 1637, 1402, 1344, 1178, 886, 813, 712, 524, 473, 464, 438 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.10–7.80 (brs, 1H), 3.50 (dd, $J=10.4$, 4.0 Hz, 0.5H) and 3.36 (dd, $J=10.4$, 4.0 Hz, 0.5H), 3.10–1.90 (m, 4H), 1.40–1.20 (m, 3H); MS (APCI, Pos.) m/z 241, 239 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_9Br_1Cl_1N_1O_1+H^+$: 237.9634; found: 237.9668.

(1*S*,5*R*,6*R*,7*S*)-7-Chloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (48d) and (1*S*,5*R*,6*R*,7*R*)-7-chloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (48e). Compounds **48d**

and **48e** were prepared from **48b** in 42 and 54% yield, respectively according to the same procedure as described for the preparation of **47c** and **47d** from **47b**.

48d: pale yellow powder; TLC R_f 0.35 (EtOAc); mp 86–88 °C; optical rotation $[\alpha]_D^{25}$-53.9 (*c* 0.52, $CHCl_3$); IR (KBr) 3187, 3063, 2962, 1685, 1489, 1396, 1350, 1206, 1050, 997, 886, 786, 519, 501 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.10–6.80 (brs, 1H), 3.04–2.92 (m, 1H), 2.70–2.24 (m, 2H), 1.80–1.60 (m, 2H), 1.30–0.90 (m, 1H), 1.16 (d, J = 6.6 Hz, 3H); MS (APCI, Pos.) m/z 160 $(M+H)^+$.

48e: pale yellow powder; TLC R_f 0.20 (EtOAc); mp 89–91 °C; optical rotation $[\alpha]_D^{25}$ +15.1 (*c* 0.15, $CHCl_3$); IR (KBr) 3434, 2964, 1638, 1487, 1397, 1353, 1064, 722 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.70–6.50 (brs, 1H), 3.22 (dd, J = 8.3, 5.7 Hz, 1H), 3.01 (ddd, J = 9.8, 5.7, 4.2 Hz, 1H), 2.65–2.45 (m, 1H), 2.45–2.30 (m, 2H), 1.55–1.40 (m, 1H), 1.24 (d, J = 6.4 Hz, 3H); MS (APCI, Pos.) m/z 160 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{10}Cl_1N_1O_1+H^+$: 160.0529; found: 160.0519.

(1*S*,5*R*,6*R*)-7-Bromo-7-fluoro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (48c). Compound **48c** was prepared from **46c-*syn*** in 75% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow powder; TLC R_f 0.23 (EtOAc/*n*-hexane, 3:1); ^1H NMR (200 MHz, $CDCl_3$) δ 6.70–6.55 (brs, 1H), 3.42 (dd, J = 10.2, 4.4 Hz, 0.5H) and 3.27 (dd, J = 10.4, 4.2 Hz, 0.5H), 2.55–1.00 (m, 4H), 1.32 (d, J = 6.2 Hz, 3H); MS (APCI, Pos.) m/z 224 $(M+H)^+$, 222.

(1*S*,5*R*,6*R*,7*R*)-7-Fluoro-5-methyl-2-azabicyclo[4.1.0]heptan-3-one (48g). Compound **48g** was prepared from **48c** in 22% yield according to the same procedure as described for the preparation of **29h** from **29c**. Pale yellow powder; TLC R_f 0.51 ($CHCl_3$/MeOH, 10:1); ^1H NMR (200 MHz, $CDCl_3$) δ 6.65–5.30 (brs, 1H), 4.57 (ddd, J = 64.0, 6.4, 4.6 Hz, 1H), 2.78 (m, 1H), 2.65–2.33 (m, 2H), 2.16–1.95 (m, 1H), 1.33–1.13 (m, 1H), 1.21 (d, J = 6.2 Hz, 3H); MS (APCI, Pos.) m/z 144 $(M+H)^+$, 124 $(M-F)^+$.

(*dl*)-(1*S*,5*S*,6*R*)-7,7-Dibromo-2-(4-methoxybenzyl)-1,5-dimethyl-2-azabicyclo[4.1.0]heptan-3-one (49a-*anti*) and (*dl*)-(1*R*,5*S*,6*S*)-7,7-dibromo-2-(4-methoxybenzyl)-1,5-dimethyl-2-azabicyclo[4.1.0]heptan-3-one (49a-*syn*). Compounds **49a-*anti*** and **49a-*syn*** were prepared from **38** in 26 and 7% yield, respectively according to the same procedure as described for the preparation of **28b-*anti*** and **28b-*syn*** from **26**.

49a-*anti*: pale yellow solid; TLC R_f 0.40 (EtOAc/*n*-hexane, 1:2); mp 118–119 °C; IR (KBr) 3435, 2965, 1655, 1512, 1438, 1305, 1243, 1182, 1033, 856, 756, 588, 512 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.24 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.37 (d, J = 15.4 Hz, 1H), 3.83 (d, J = 15.4 Hz, 1H), 3.79 (s, 3H), 2.40–2.00 (m, 3H), 1.61–1.40 (m, 1H), 1.50 (s, 3H), 1.31 (d, J = 6.2 Hz, 3H); MS (APCI, Pos.) m/z 420 $(M+H, {}^{81}Br, {}^{81}Br)^+$, 418 $(M+H, {}^{79}Br, {}^{81}Br)^+$, 416; HR-MS (MALDI-TOF, Pos.) calcd for $C_{16}H_{19}Br_2N_1O_2+H^+$: 415.9861; found: 415.9845.

49a-*syn*: pale yellow oil; TLC R_f 0.31 (EtOAc/*n*-hexane, 1:2); IR (neat) 2961, 2835, 1652, 1514, 1455, 1404, 1304, 1248, 1177, 1108, 1034, 808, 759, 648, 540 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.28 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.17 (d, J = 15.6 Hz, 1H), 4.29 (d, J = 15.6 Hz, 1H), 3.80 (s, 3H), 2.80–2.30 (m, 3H), 1.70–1.50 (m, 1H), 1.66 (s, 3H), 1.31 (d, J = 6.4 Hz, 3H); MS (APCI, Pos.) m/z 420 $(M+H, {}^{81}Br, {}^{81}Br)^+$, 418 $(M+H, {}^{79}Br, {}^{81}Br)^+$, 416; HR-MS (MALDI-TOF, Pos.) calcd for $C_{16}H_{19}Br_2N_1O_2+H^+$: 415.9861; found: 415.9868.

(*dl*)-(1*R*,5*S*,6*S*,7*S*)-2-(4-Methoxybenzyl)-1,5,7-trimethyl-2-azabicyclo[4.1.0]heptan-3-one (49b-*anti*). Compound **49b-*anti*** was prepared from **49a-*anti*** in 65% yield according to the same procedure as described for the preparation of **39c-*anti*** from **39a-*anti***. Pale yellow oil; TLC R_f 0.24 (EtOAc/*n*-hexane, 1:3); ^1H NMR (200 MHz, $CDCl_3$) δ 7.21 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.94 (d, J = 14.6 Hz, 1H), 4.21 (d, J = 14.6 Hz, 1H), 3.79 (s, 3H), 2.30–2.02 (m, 2H), 1.70–1.40 (m, 1H), 1.25 (s, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.2 Hz, 3H), 0.48 (m, 1H), 0.33 (t, J = 5.8 Hz, 1H); MS (APCI, Pos.) m/z 274 $(M+H)^+$.

(*dl*)-(1*R*,5*S*,6*S*,7*S*)-1,5,7-Trimethyl-2-azabicyclo[4.1.0]heptan-3-one (50). Compound **50** was prepared from **49b-*anti*** in 90% yield according to the same procedure as described for the preparation of **29a** from **28a-*anti***. Pale yellow oil; TLC R_f 0.36 (EtOAc); ^1H NMR (200 MHz, $CDCl_3$) δ 6.08 (brs, 1H), 2.22–1.86 (m, 3H), 1.32 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.2 Hz, 3H), 0.89 (m, 1H), 0.41 (t, J = 4.6 Hz, 1H); MS (APCI, Pos.) m/z 154 $(M+H)^+$.

General procedure for preparation of compounds 2–18

(1*S*,5*S*,6*R*)-7,7-Dichloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (2). To a stirred solution of **29a** (390 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) was added triethyloxonium tetrafluoroborate (2 M in CH_2Cl_2, 1.5 mL, 3.0 mmol) under an argon atmosphere, and the reaction mixture was stirred at room temperature for 20 h. Concentration of the reaction mixture under reduced pressure gave a residue, which was used for the subsequent reaction without further purification. To a stirred solution of the compound obtained above in EtOH (5 mL) was added saturated ethanolic ammonia (5 mL) under an argon atmosphere at room temperature and stirring was continued for an additional 40 h. The reaction mixture was diluted with $CHCl_3$ (25 mL) and the resulting precipitates were removed by filtration. The filtrate was concentrated under reduced pressure. The reaction mixture was treated with 2 M NaOH (30 mL) and extracted with $CHCl_3$. The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was converted to its hydrochloride with 4 M HCl/EtOAc–EtOH at 0 °C and further purified by column chromatography on silica gel ($CHCl_3$/MeOH, 5:1) to afford **2** as a beige powder (137 mg, 30%). TLC R_f 0.35 ($CHCl_3$/MeOH/AcOH, 10/1/1); mp 214–216 °C; optical rotation $[\alpha]_D^{25}$ +44.6 (*c* 0.44, MeOH); IR (KBr)

3231, 3050, 1678, 1521, 1454, 1418, 1385, 1354, 1330, 1286, 1245, 1206, 1174, 1093, 1047, 1021, 986, 933, 894, 862, 827, 720, 560, 543, 489, 457, 435 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 10.41 (brs, 1H), 9.70 (brs, 1H), 7.25 (brs, 1H), 3.55 (d, $J=9.8$ Hz, 1H), 2.53 (dd, $J=15.6$, 5.0 Hz, 1H), 2.36 (dd, $J=15.6$, 11.8 Hz, 1H), 2.12 (dd, $J=9.8$, 5.4 Hz, 1H), 2.03–1.80 (m, 1H), 1.27 (d, $J=6.6$ Hz, 3H); MS and HR-MS analysis showed only the ion from $C_7H_{10}Cl_2N_2$ corresponding to the loss of HCl, MS (FAB, Pos.) m/z 193 $(M+H)^+$, 157 $(M-Cl)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{10}Cl_2N_2+H^+$: 193.0299; found: 193.0323.

(1*S*,5*S*,6*R*,7*S*)-7-Chloro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-imine hydrochloride salt (3). Compound **3** was prepared from **29e** in 57% yield according to the same procedure as described for the preparation of **2** from **29a**. Brown oil; TLC R_f 0.33 ($CHCl_3$/MeOH/AcOH, 10:1:1); optical rotation $[\alpha]_D^{25}$ −5.92 (*c* 0.39, MeOH); IR (neat) 3391, 2971, 2360, 2342, 1695, 1682, 1652, 1634, 1520, 1456, 1435, 1385, 1356, 1297, 1243, 1072, 932, 890, 860, 792, 762, 668, 523 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 10.10–9.85 (brs, 1H), 9.20–9.00 (brs, 1H), 8.80–8.60 (brs, 1H), 3.58 (dd, $J=3.9$, 2.0 Hz, 1H), 3.19 (dd, $J=9.4$, 2.0 Hz, 1H), 2.45–2.38 (m, 1H), 2.36–2.05 (m, 2H), 1.75–1.56 (m, 1H), 1.10 (d, $J=6.4$ Hz, 3H); MS and HR-MS analysis showed only the ion from $C_7H_{11}Cl_1N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 159 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{11}Cl_1N_2+H^+$: 159.0689; found: 159.0667.

(1*S*,5*S*,6*R*,7*R*)-7-Chloro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-imine hydrochloride salt (4). Compound **4** was prepared from **29f** in 53% yield according to the same procedure as described for the preparation of **2** from **29a**. White powder; TLC R_f 0.33 ($CHCl_3$/MeOH/AcOH, 10:1:1); mp 234–235 °C; optical rotation $[\alpha]_D^{25}$ +68.1 (*c* 1.00, MeOH); IR (KBr) 3130, 2873, 2155, 2086, 2043, 1690, 1456, 1422, 1390, 1361, 1297, 1276, 1234, 1204, 1127, 966, 929, 917, 879, 841, 796, 771, 713, 684, 600, 536, 523, 481, 423 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.80–9.65 (brs, 1H), 9.30–9.10 (brs, 1H), 8.80–8.60 (brs, 1H), 3.64 (dd, $J=7.7$, 5.5 Hz, 1H), 3.04 (dd, $J=8.9$, 5.5 Hz, 1H), 2.41 (d, $J=8.2$ Hz, 2H), 1.90–1.70 (m, 1H), 1.55–1.40 (m, 1H), 1.21 (d, $J=6.8$ Hz, 3H); MS and HR-MS analysis showed only the ion from $C_7H_{11}Cl_1N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 159 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{11}Cl_1N_2+H^+$: 159.0689; found: 159.0690; anal. calcd for $C_7H_{12}Cl_2N_2$; C, 43.10%, H, 6.20%, N, 14.36%, Cl, 36.34%; found; C, 43.08%; H, 6.25%, N, 14.24%.

X-ray crystallography of 4

Colorless platelet crystals of **4** were obtained from EtOH/EtOAc (6:1) solution. A suitable crystal of **4** having the approximate dimension of 0.10×0.20×0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC5R diffractometer with graphite monochromated Cu-K_α radiation and a RU-200 rotating anode X-ray generator. Of the 9156 reflections that were collected, 4523 were unique. Equivalent reflections were merged. An empirical absorption correction was applied.

The program package teXsan[18] was used for analysis and drawing figures. The positions of all the non-H atoms were determined by the program SHEXLS86,[19] and the H atoms of calculated from the coordinates of non-H atoms and confirmed by the difference Fourier synthesis.

Crystal data: orthorombic, space group $P2_12_12_1$, $a=7.31(3)$, $b=23.23(3)$, $c=5.63(1)$ Å, $Z=4$, 1910 measured reflections, 1280 with $I>3.00\sigma(I)$, $2\theta<130.02°$, $R=0.063$. Full information on the crystal structure can be ordered from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, upon request quoting the deposition number CCDC 191009.

(1*S*,5*S*,6*R*,7*R*)-7-Fluoro-5-methyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (5). Compound **5** was prepared from **29h** in 53% yield according to the same procedure as described for the preparation of **2** from **29a**. White powder; TLC R_f 0.21 ($CHCl_3$/MeOH/AcOH, 10:1:1); mp 157–158 °C; optical rotation $[\alpha]_D^{25}$ +57.5 (*c* 0.16, MeOH); IR (KBr) 3089, 2876, 1684, 1627, 1454, 1424, 1365, 1343, 1332, 1233, 1157, 1046, 1032, 1013, 908, 869, 773, 736, 708, 603, 567, 491, 425 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 10.10–9.90 (brs, 1H), 9.50–9.20 (brs, 1H), 9.15–8.80 (brs, 1H), 4.78 (ddd, $J=65.6$, 6.2, 4.4 Hz, 1H), 3.05–2.80 (m, 1H), 2.60–2.28 (m, 2H), 2.12–1.82 (m, 1H), 1.45–1.15 (m, 1H), 1.18 (d, $J=6.6$ Hz, 3H); MS and HR-MS analysis showed only the ion from $C_7H_{11}F_1N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 143 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{11}F_1N_2+H^+$: 143.0985; found: 143.0974.

(*dl*)-(1*S*,5*S*,6*S*)-5,7,7-Trimethyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (6). Compound **6** was prepared from **40b** in 25% yield according to the same procedure as described for the preparation of **2** from **29a**. White powder; TLC R_f 0.46 ($CHCl_3$/MeOH/AcOH, 15:2:1); mp 125–126 °C; IR (KBr) 2956, 1677, 1456, 1234, 1071, 969, 881, 691 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.40 (brs, 1H), 8.99 (brs, 1H), 8.71 (brs, 1H), 2.74 (dd, $J=15.0$, 3.0 Hz, 1H), 2.45 (d, $J=8.0$ Hz. 1H), 2.10 (m, 1H), 1.74 (m, 1H), 1.22 (d, $J=6.6$ Hz, 3H), 1.07 (s, 3H), 0.99 (s, 3H), 0.83 (dd, $J=8.0$, 6.0 Hz, 1H); MS and HR-MS analysis showed only the ion from $C_9H_{16}N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 153 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_9H_{16}N_2+H^+$: 153.1392; found: 153.1373.

(*dl*)-(1*R*,5*S*,6*S*,7*S*)-5,7-Dimethyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (7). Compound **7** was prepared from **40c** in 74% yield according to the same procedure as described for the preparation of **2** from **29a**. Pale yellow oil; TLC R_f 0.40 ($CHCl_3$/MeOH/AcOH, 15:2:1); IR (neat) 2961, 1677, 1514, 1462, 1384, 1356, 1060, 669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.80 (brs, 1H), 9.22 (brs, 1H), 8.72 (brs, 1H), 2.66 (dd,

J = 16.0, 4.0 Hz, 1H), 2.43 (dd, J = 8.0, 3.0 Hz, 1H), 2.29 (dd, J = 16.0, 9.0 Hz, 1H), 1.91 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 5.2H, 3H), 0.96 (m, 1H), 0.85 (m, 1H); MS and HR-MS analysis showed only the ion from $C_8H_{14}N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 139 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_8H_{14}N_2 + H^+$: 139.1235; found: 139.1225.

(*dl*)-(1*R*,5*S*,6*S*,7*R*)-5,7-Dimethyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (8). Compound **8** was prepared from **40e** in 30% yield according to the same procedure as described for the preparation of **2** from **29a**. White powder; TLC R_f 0.15 ($CHCl_3$/MeOH/AcOH, 20:1:1); mp 183–184 °C; IR (KBr) 3258, 3085, 2964, 1676, 1630, 1458, 1418, 1342, 1204, 1086, 781, 747, 706 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.75 (brs, 1H), 8.97 (brs, 1H), 8.77 (brs, 1H), 2.66 (dd, J = 8.0, 6.0 Hz, 1H), 2.30 (dd, J = 15.5, 4.0 Hz, 1H), 2.19 (dd, J = 15.5, 11.5 Hz, 1H), 1.56 (m, 1H), 1.08 (d, J = 6.5 Hz, 3H), 1.12–1.02 (m, 1H), 1.00–0.88 (m, 1H), 0.79 (d, J = 6.0 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_8H_{14}N_2$ corresponding to the loss of HCl, MS (FAB, Pos.) m/z 139 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_8H_{14}N_2 + H^+$: 139.1235; found: 139.1206.

(1*R*,5*S*,6*S*,7*R*)-5,7-Dimethyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (9). Compound **9** was prepared from **32** in 4% yield according to the same procedure as described for the preparation of **2** from **29a**. Beige powder; TLC R_f 0.50 ($CHCl_3$/MeOH/AcOH, 5:1:1); mp 182–184 °C; optical rotation $[\alpha]_D^{25}$ +17.2 (c 0.10, MeOH); IR (KBr) 3357, 3083, 1680, 1627, 1511, 1459, 1423, 1343, 1282, 1245, 1204, 1180, 1100, 1095, 1070, 978, 712, 528 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.70–9.65 (brs, 1H), 9.20–9.00 (brs, 1H), 8.70–8.60 (brs, 1H), 2.73 (t, J = 7.5 Hz, 1H), 2.45–2.15 (m, 2H), 1.80–1.50 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 1.20–0.90 (m, 2H), 0.85 (d, J = 6.4 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_8H_{14}N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 139 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_8H_{14}N_2 + H^+$: 139.1235; found: 139.1228.

(*dl*)-(1*R*,5*S*,6*S*,7*R*)-7-Ethyl-5-methyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (10). Compound **10** was prepared from **43** in 88% yield according to the same procedure as described for the preparation of **2** from **29a**. Off-white powder; TLC R_f 0.48 ($CHCl_3$/MeOH/AcOH, 15:2:1); mp 180–181 °C; IR (KBr) 3089, 1678, 1629, 1418, 1358, 1308, 1205, 889, 801, 761, 701 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.64 (brs, 1H), 9.35 (brs, 1H), 8.90 (brs, 1H), 2.90–2.70 (m, 2H), 2.15 (dd, J = 16.0, 12.0 Hz, 1H), 1.77 (m, 1H), 1.40–1.20 (m, 2H), 1.24 (d, J = 6.6 Hz, 3H), 1.12–0.96 (m, 2H), 1.01 (t, J = 6.8 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_9H_{16}N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 153 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_9H_{16}N_2 + H^+$: 153.1392; found: 153.1372.

(*dl*)-(1*R*,5*S*,6*S*,7*S*)-5-Methyl-7-vinyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (11). Compound **11** was prepared from **45** in 6% yield according to the same procedure as described for the preparation of **2** from **29a**. Pale yellow oil; TLC R_f 0.35 ($CHCl_3$/MeOH/AcOH, 20:4:1); IR (neat) 3122, 1679, 1636, 1525, 1458, 1430, 1382, 1355, 1215, 1185, 1084, 988, 907, 861, 649 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 10.07 (brs, 1H), 9.01 (brs, 1H), 8.61 (brs, 1H), 5.49 (ddd, J = 17.2, 10.2, 8.4 Hz, 1H), 5.08 (dd, J = 17.2, 1.8 Hz, 1H), 4.95 (dd, J = 10.2, 1.8 Hz, 1H), 2.88 (dt, J = 8.4, 3.0 Hz, 1H), 2.54 (m, 1H), 2.28 (dd, J = 16.0, 7.0 Hz, 1H), 2.11 (m, 1H), 1.82 (m, 1H), 1.29 (m, 1H), 1.09 (d, J = 6.6 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_9H_{14}N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 151 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_9H_{14}N_2 + H^+$: 151.1235; found: 151.1230.

(*dl*)-(1*R*,5*S*,6*S*,7*R*)-7-Butyl-5-methyl-2-azabicyclo[4.1.0]-heptan-3-imine hydrochloride salt (12). Compound **12** was prepared from **40g** in 34% yield according to the same procedure as described for the preparation of **2** from **29a**. Beige powder; TLC R_f 0.53 ($CHCl_3$/MeOH/AcOH, 15:2:1); mp 187–188 °C; IR (KBr) 3015, 2927, 2858, 1678, 1631, 1459, 1419, 1349, 1100, 748, 602 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.62 (brs, 1H), 9.15 (brs, 1H), 9.01 (brs, 1H), 2.81–2.71 (m, 2H), 2.17 (dd, J = 16.0, 12.0 Hz, 1H), 1.73 (m, 1H), 1.42–1.25 (m, 6H), 1.23 (d, J = 6.6 Hz, 3H), 1.12–1.00 (m, 2H), 0.91 (t, J = 6.2 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_{11}H_{20}N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) m/z 181 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{11}H_{20}N_2 + H^+$: 181.1705; found: 181.1710.

(1*R*,5*R*,6*S*)-7,7-Dichloro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-imine hydrochloride salt (13). Compound **13** was prepared from **47a** in 24% yield according to the same procedure as described for the preparation of **2** from **29a**. Beige powder; TLC R_f 0.35 ($CHCl_3$/MeOH/AcOH, 10:1:1); mp 213–214 °C; optical rotation $[\alpha]_D^{25}$ −45.6 (c 0.45, MeOH); IR (KBr) 3234, 3068, 1678, 1522, 1452, 1418, 1385, 1355, 1330, 1245, 1207, 1093, 1022 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 9.66 (brs, 3H), 3.55 (d, J = 9.6 Hz, 1H), 2.57–2.28 (m, 2H), 2.11 (dd, J = 10.0, 5.6 Hz, 1H), 2.01–1.84 (m, 1H), 1.27 (d, J = 6.6 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_7H_{10}Cl_2N_2$ corresponding to the loss of HCl, MS (FAB, Pos.) m/z 193 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{10}Cl_2N_2 + H^+$: 193.0299; found: 193.0309.

(1*R*,5*R*,6*S*,7*S*)-7-Chloro-5-methyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (14). Compound **14** was prepared from **47c** in 48% yield according to the same procedure as described for the preparation of **2** from **29a**. Beige powder; TLC R_f 0.33 ($CHCl_3$/MeOH/AcOH, 10:1:1); mp 231–232 °C; optical rotation $[\alpha]_D^{25}$ −66.9 (c 0.25, MeOH); IR (KBr) 3257, 3031, 2873, 1682, 1628, 1459, 1422, 1390, 1362, 1296, 1276, 1234, 1204, 1071, 1011, 879, 770, 716, 684, 541 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ10.05–9.90 (brs, 1H), 9.50–9.30 (brs, 1H), 9.00–8.80 (brs, 1H), 3.64 (dd, J = 7.8, 5.6 Hz, 1H), 3.05 (dd, J = 8.8, 5.6 Hz, 1H), 2.55–2.30 (m, 2H), 1.96–1.72 (m, 1H), 1.56–1.40 (m, 1H), 1.20 (d, J = 6.6 Hz, 3H); MS

and HR-MS analysis showed only the ion from $C_7H_{11}Cl_1N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) *m/z* 159 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{11}Cl_1N_2+ H^+$: 159.0689; found: 159.0697.

(1*S*,5*R*,6*R*,7*R*)-7-Chloro-5-methyl-2-azabicyclo[4.1.0]-heptan-3-imine hydrochloride salt (15). Compound **15** was prepared from **48e** in 13% yield according to the same procedure as described for the preparation of **2** from **29a**. Beige amorphous; TLC R_f 0.30 ($CHCl_3$/MeOH/AcOH, 10:1:1); mp 76–78 °C; Optical rotation $[\alpha]_D^{25}$ +24.8 (*c* 0.10, MeOH); IR (KBr) 3289, 3108, 2965, 2876, 1679, 1530, 1511, 1456, 1413, 1376, 1355, 1279, 1249, 1061, 1004, 920, 875, 835, 810, 722, 609, 546, 484, 450, 424 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ10.50–10.20 (brs, 1H), 9.20–8.90 (brs, 1H), 8.90–8.60 (brs, 1H), 3.59 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.40–3.10 (m, 1H), 2.70 (dd, *J* = 16.7, 6.2 Hz, 1H), 2.50–2.30 (m, 1H), 2.20 (dd, *J* = 16.7, 11.0 Hz, 1H), 1.80-1.60 (m, 1H), 1.16 (d, *J* = 6.6 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_7H_{11}Cl_1N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) *m/z* 159 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{11}Cl_1N_2+ H^+$: 159.0689; found: 159.0676.

(1*S*,5*R*,6*R*,7*R*)-7-Fluoro-5-methyl-2-azabicyclo[4.1.0]heptan-3-imine hydrochloride salt (16). Compound **16** was prepared from **48g** in 9% yield according to the same procedure as described for the preparation of **2** from **29a**. Beige amorphous; TLC R_f 0.28 ($CHCl_3$/MeOH/AcOH, 20:4:1); optical rotation $[\alpha]_D^{25}$ +8.9 (*c* 0.10, MeOH); IR (KBr) 3430, 2925, 2853, 1734, 1678, 1453, 1151, 756, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.8–10.3 (brs, 1H), 8.81 (brs, 2H), 4.67 (m, 1H), 3.12–2.75 (m, 2H), 2.45–2.10 (m, 2H), 1.50–1.25 (m, 1H), 1.26 (3H, d, *J* = 6.0 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_7H_{11}F_1N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) *m/z* 143 $(M+H)^+$, 123 $(M-F)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_7H_{11}F_1N_2+ H^+$: 143.0985; found: 143.0987.

(*dl*)-(1*R*,5*S*,6*S*,7*S*)-1,5,7-Trimethyl-2-azabicyclo[4.1.0]-heptan-3-imine hydrochloride salt (17). Compound **17** was prepared from **50** in 48% yield according to the same procedure as described for the preparation of **2** from **29a**. Brown oil; TLC R_f 0.35 ($CHCl_3$/MeOH/AcOH, 20:1:1); IR (neat) 2962, 1681, 1532, 1456, 1430, 1393, 1335, 1277, 1210, 1049, 751 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 10.17 (brs, 1H), 8.89 (brs, 1H), 8.46 (brs, 1H), 2.42 (dd, *J* = 16.4, 5.4 Hz, 1H), 2.24 (dd, *J* = 16.4, 7.4 Hz, 1H), 1.98 (m, 1H), 1.31 (s, 3H), 1.20–0.90 (m, 1H), 1.02 (m, 6H), 0.62 (m, 1H); MS and HR-MS analysis showed only the ion from $C_9H_{16}N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) *m/z* 153 $(M+H)^+$, 97; HR-MS (MALDI-TOF, Pos.) calcd for $C_9H_{16}N_2+ H^+$: 153.1392; found: 153.1363.

***N*-[(1*S*,3*E*,5*S*,6*R*,7*R*)-7-Chloro-5-methyl-2-azabicyclo [4.1.0]hept-3-ylidene]-1-phenylmethanamine hydrochloride salt (18).** Compound **18** was prepared from **29f** in 28% yield according to the same procedure as described for the preparation of **2** from **29a** using benzylamine instead of saturated ethanolic ammonia. Brown oil; TLC R_f 0.24 ($CHCl_3$/MeOH, 5:1); optical rotation $[\alpha]_D^{25}$ +6.6 (*c* 0.48, MeOH); IR (neat) 3626, 3585, 3333, 3040, 2970, 2934, 2879, 1661, 1586, 1499, 1486, 1456, 1428, 1382, 1361, 1296, 1280, 1254, 1218, 1072, 870, 752, 697, 522 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 10.40–10.20 (brs, 1H), 10.05–9.90 (brs, 1H), 7.50–7.30 (m, 5H), 4.53 (m, 2H), 3.71 (dd, *J* = 7.7, 5.6 Hz, 1H), 3.12 (dd, *J* = 9.2, 5.6 Hz, 1H), 2.70–2.40 (m, 2H), 2.00–1.80 (m, 1H), 1.60–1.45 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H); MS and HR-MS analysis showed only the ion from $C_{14}H_{17}Cl_1N_2$ corresponding to the loss of HCl, MS (APCI, Pos.) *m/z* 249 $(M+H)^+$; HR-MS (MALDI-TOF, Pos.) calcd for $C_{14}H_{17}Cl_1N_2+ H^+$: 249.1159; found: 249.1131.

Biological assays

Preparation of partially purified enzyme and determination of K_i values. Human eNOS was overexpressed in Sf-21 cells, by infecting the cells with baculovirus carrying heNOS cDNA. The hiNOS was overexpressed in A549 by stimulation with LPS (10 μg/mL) plus cytokines (10 ng/mL TNF-α, 5 ng/mL IL-1β and 100 ng/mL interferon-γ). Human eNOS and iNOS were partially purified by chromatography on 2′,5′-ADP-Sepharose gels. NOS activity was determined by the method for the conversion of [^{14}C]-L-arginine to L-citrulline with a minor modification. The conversion rates for various concentrations of the test compounds and L-arginine were measured. Dixon and lineweaver-Bulk plots were constructed to determine the K_i values and the mode of inhibition. Selectivity was evaluated as the rate of the IC_{50} values for heNOS and hiNOS.

Enzyme assay with recombinant mouse iNOS. Recombinant mouse iNOS was purchased from Cayman Chemical (Cat. No. 60862) and the inhibitory activities of the test compounds were evaluated by measuring the conversion rate from [^{14}C]-L-arginine to [^{14}C]-L-citrulline, and then the IC_{50} values were determined.

The ID_{50} value was determined from a log–logit transformation of the dose–response curves (**2** and **4**; 3, 10, 30 μg/kg, sc, L-NMMA; 10, 30 and 100 mg/kg, sc). The ID_{50} value was defined as the concentration of test compound that produced a 50% inhibition in the NO_x accumulation induced by LPS treatment alone.[17] The MTD was defined as the maximum dose at which no death was observed within 24 h after an intravenous injection administration. The doses used were 10, 20, 30, 40, and 50 mg/kg for **2** and **4** and 1000, 2000, 3000, 4000, and 5000 mg/kg for L-NMMA.

Inhibition of NO_x accumulation and the maximum tolerated dose (MTD) in mice. The test compounds or saline were administered subcutaneously at 3 h after LPS (10 mg/kg, iv) injection into 7 week old Balb/c mice (Charles River Japan, Inc.). Blood was collected by venipuncture from the abdominal aorta under light anesthesia at 6 h after LPS treatment. Plasma was obtained by centrifugation and the concentration of accumulated NO_x over 3 h was determined by the

method described below. To evaluate the acute toxicity, the MTD (iv maximum dose where no death was observed within 24 h after the administration) of the test compound was determined.

Measurement of nitrite/nitrate. Nitrite and nitrate, the oxidized form of nitric oxide that accumulated in the culture medium and plasma were determined by the use of nitrite/nitrate colorimetric assay kit (Cayman Chemical, Cat. No. 780001). Basically, the nitrate in the sample was reduced to nitrite with a nitrate reductase contained in the assay kit; nitrite levels were then determined spectrophotometrically as the total NO_x concentration.

Docking study. Docking study was performed using InsightII/Discover molecular modeling package (Accelrys, San Diego, CA) with CVFF force field on a SGI Octane2 workstation with R12000 processors. Simulated-annealing procedure in gas phase was used to search the complex model of the lowest-energy. Initial protein structure of hiNOS (PDB code 2NSI) was obtained from the Protein Data Bank. All the hydrogens were added and their positions were energetically optimized. During simulation, all the heavy atoms were fixed (dielectric constant: $\varepsilon = 4r$).

First of all, a complex model of low-energy, consisting of **4** with hiNOS was constructed, in which **4** was put near the Glu377 residue of the enzyme to form a salt bridge with its amidine group. A complex model was first equilibrated by running dynamics (dielectric constant: $\varepsilon = 4r$) for 6 ps while increasing the temperature from 50 to 1200 K by time steps of 1 fs, after which the resulting conformations were sampled every 5000 steps over a span of 300 ps at 1200 K to yield 60 snapshots. Each snapshot was then equilibrated for 4 ps while decreasing the temperature from 1200 to 200 K, followed by 200 K simulation for 4 ps. Each annealed model was energetically optimized using the steepest descent method followed by the conjugate-gradient method to an energy difference of 0.001 kcal/mol between successive iterations.

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