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Article

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Stereochemistry of *N*-Benzoyl-5-substituted-1-benzazepines Revisited: Synthesis of the Conformationally Biased Derivatives and Revision of the Reported Structure

Hidetsugu Tabata,[†] Tetsuya Yoneda,[†] Tomohiko Tasaka,[‡] Shigekazu Ito,[§] Tetsuta Oshitari,[†] Hideyo Takahashi,[†] and Hideaki Natsugari[†,*]

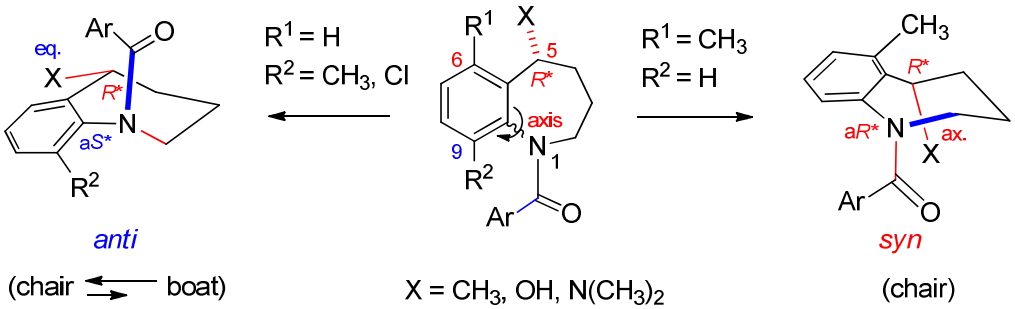
[†]Faculty of Pharma Sciences, Teikyo University, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan

[‡]Affinity Science Corporation, 1-11-1 Nishigotanda, Shinagawa-ku, Tokyo 141-0031, Japan

[§]Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8552, Japan

ABSTRACT: The *syn* (a*R**,5*R**) and *anti* (a*S**,5*R**) diastereomers of *N*-benzoyl-C5-substituted-1-benzazepines originating in the chiralities at C5 and the Ar–N(C=O) axis were

first stereoselectively synthesized by biasing the conformation with a substituent at C6 and C9, respectively. Detailed examination of the stereochemistry (i.e., conformation and configuration) of these *N*-benzoyl-1-benzazepines by X-ray crystallographic analysis, VT NMR, and DFT calculations revealed new physicochemical aspects of these heterocycles including revision of the stereochemistry previously reported.



INTRODUCTION

The 1-benzazepine nucleus has been used as the core structure of various biologically active molecules.[1] In recent years, the vasopressin (VP) receptor ligands with the 1-benzazepine nucleus (e.g., mozavaptan,[2] tolvaptan[3]) (Figure 1) have been developed as agents for the treatment of hyponatremia, congestive heart failure, etc.

Many of the vaptan class of drugs contain a preserved structure, i.e., a benzo-fused seven-membered-ring nitrogen heterocycle (e.g., 1-benzazepine, 1,4-benzodiazepine) linked

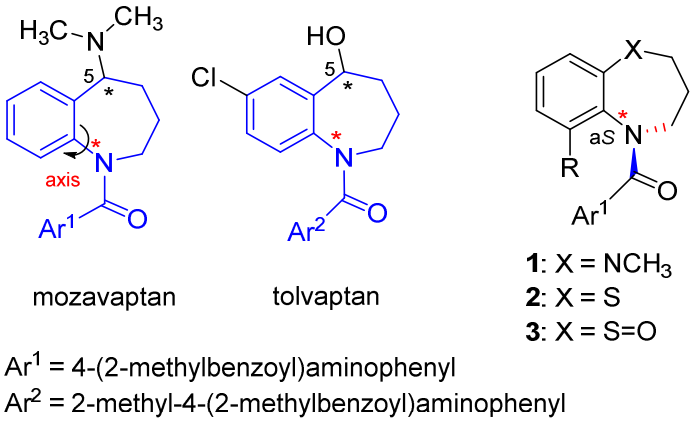


Figure 1. Non-peptide VP receptor antagonists.

through *N*-1 to a substituted benzoyl group. In our previous papers,[4] new VP receptor ligands with 1,5-benzodiazepine (**1**)[4a] and 1,5-benzothiazepine nuclei (**2**, **3**)[4b] (Figure 1) were described to reveal the importance of the stereochemistry around the seven-membered ring for exerting their biological activity. In particular, the axial chirality (a*S*/a*R*) based on the Ar–N(C=O) (sp^2–sp^2) axis[5] was clarified to be crucial by freezing the conformation in molecules with an *ortho* substituent (e.g., R = CH_3, Cl); the (a*S*) form was the eutomer (active enantiomer). Those studies also implied that, although often overlooked, such chirality may exist in the latent form in many biologically active molecules, and the active form of the *N*-benzoyl-1-benzazepine-type VP ligands (mozavaptan and tolvaptan) should also be (a*S*). In this regard, an understanding of the stereochemistry of the *N*-acyl-1-benzazepines is important.

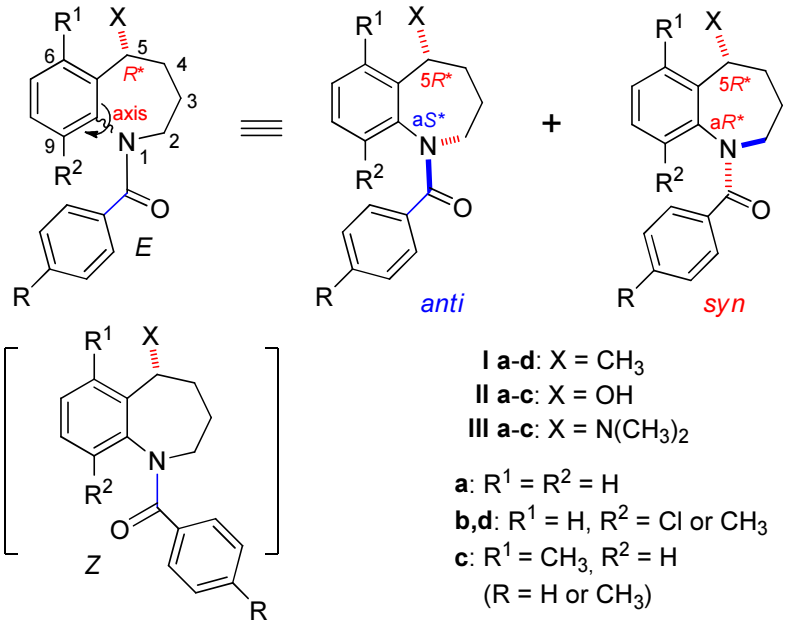


Figure 2. *Anti*/*syn* diastereomers originating in the (5*R**) central chirality and (a*R**)/(a*S**) axial chirality in *E*-*N*-benzoyl-1-benzazepines (**Ia**–**d**, **IIa**–**c**, and **IIIa**–**c**). For the *E*/*Z*-amide isomer, the Z isomer shown in brackets was negligible in the ^{1}H NMR spectrum.

Thus far, the pioneering conformational study on *N*-acyl-1-benzazepines by A. Hassner et al.,[6] followed by the excellent analysis of *N*-benzoyl-5-methyl-1-benzazepine (**Ia**) by M. Qadir et al.[7] have been reported. Compound **Ia** possesses a stereogenic center at C5 in addition to the chirality due to the axis at Ar–N(C=O).[8] thus forming the *anti* and *syn* diastereomers; the description "*anti*/*syn*" is used for the relative arrangement of the C5 substituent and the *N*-benzoyl group, i.e., *anti* and *syn* denote the arrangement on the opposite (a*S**,5*R**) and the same side (a*R**,5*R**), respectively (Figure 2). The reported structure of **Ia**, however, is interesting in that **Ia** takes predominantly the *syn* form in solution with a ratio of *syn*/*anti* = 1:0.25 (by NMR

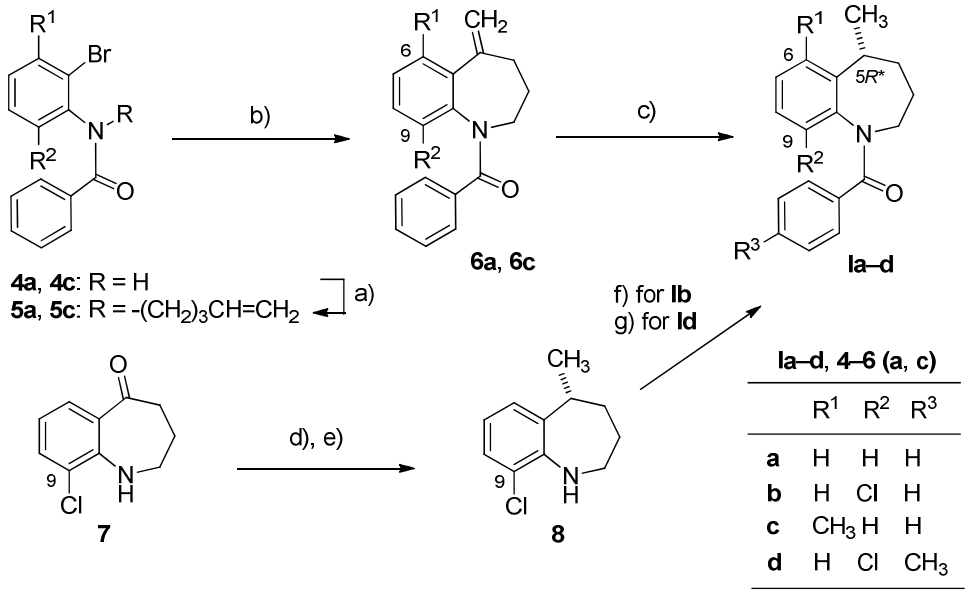
analysis), whereas in the solid state (by X-ray crystal analysis) it takes the *anti* form,[7,9] which stimulated us to revisit the stereochemistry of **Ia** and related compounds (**IIa**, **IIIa**). This paper deals with the detailed stereochemistry (conformation and configuration) of *N*-benzoyl-5-substituted-1-benzazepines (**I**–**III**), including a revision of the stereochemistry of **Ia** in the solution state previously reported.

RESULTS AND DISCUSSION

Synthesis of *N*-Benzoyl-5-substituted-1-benzazepines (I–III).

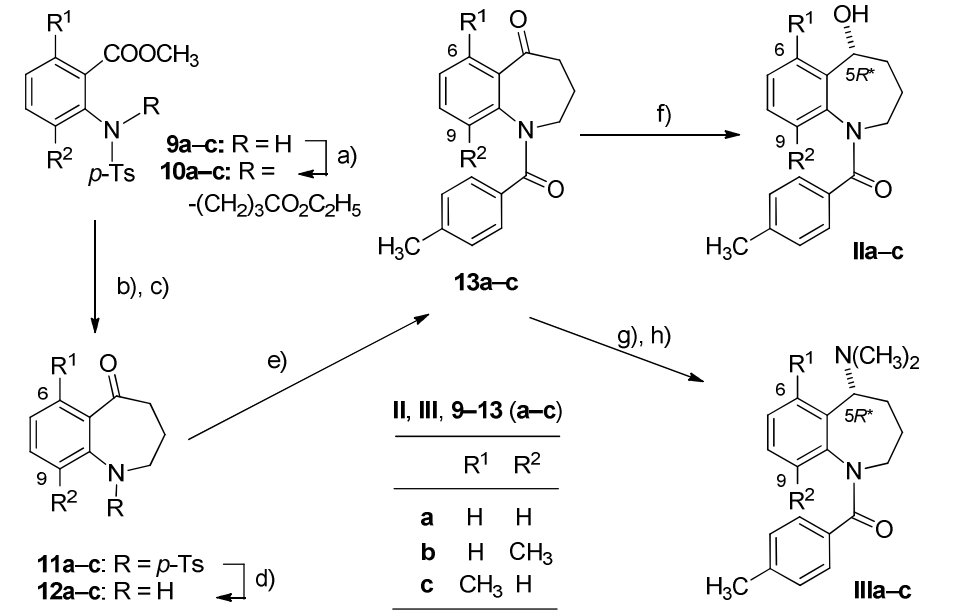
N-Benzoyl-5-substituted-1-benzazepines (**Ia**–**d, IIa**–**c, and IIIa**–**c**) were prepared from 5-substituted *N*-benzoyl-1-benzazepines (**6a, 6c**, **8**, and **13a**–**c**) using procedures similar to those previously reported[2,3,7] as shown in Scheme 1 and 2, i.e., compounds **Ia**[7] and **Ic** were prepared by reduction of the corresponding 5-methylene derivatives (**6a** and **6c**), respectively, and **Ib** and **Id** were prepared by *N*-acylation of methyl-1-benzazepine (**8**), which was prepared from **7** by reaction with MeMgBr followed by reduction with Et_3SiH (Scheme 1). Compounds **IIa**–**c** and **IIIa**–**c** were prepared by reduction of 5-oxo-1-benzazepine derivatives (**13a**–**c**) with $NaBH_4$ and by reductive amination with $NaBH_3CN$ (or $NaBH_4$) and CH_3NH_2 followed by *N*-methylation, respectively (Scheme 2).[2,3]

Scheme 1. Synthesis of *N*-Benzoyl-5-methyl-1-benzazepines (Ia–d)[a]



[a]Reagents and conditions: (a) NaH, pent-4-enyl tosylate, rt; (b) $Pd(OAc)_2$, DMF, PPh_3, LiCl, 120 °C; (c) Pd/C, H_2, CH_3OH, rt; (d) MeMgBr, THF, rt; (e) Et_3SiH, THF, rt; (f) BzCl, NaH, THF, rt; (g) *p*-Toluoyl chloride, NaH, THF, rt.

Scheme 2. Synthesis of *N*-Benzoyl-5-substituted-1-benzazepines (IIa–c and IIIa–c)[a]



[a]Reagents and conditions: (a) Ethyl 4-bromobutylate, K_2CO_3, DMF, 120 °C; (b) *t*-BuOK, toluene, 120 °C; (c) AcOH, conc. HCl, H_2O, reflux; (d) PPA, 100 °C; (e) *p*-Toluoyl chloride, Et_3N, THF, 0 °C; (f) $NaBH_4$, CH_3OH, rt; (g) $NaBH_3CN$ or $NaBH_4$, CH_3NH_2, MS4A, CH_3OH, 90 °C → rt; (h) 37% HCHO, AcOH, $NaBH_3CN$, CH_3OH, rt.

Computational Studies. To study the conformational preferences of the *N*-benzoyl-5-substituted-1-benzazepines, the following computational studies were carried out. First, the conformation ensembles of **Ia**, **Ib**, **Ic**, **IIa**, **IIc**, and **IIIa** were generated from 2D chemical structures as the initial structures for the density functional theory (DFT) calculations. These conformations were optimized within RDKit[10] using the universal force field (UFF) and clustered using a tolerance of 0.2 Å root-mean-square deviation. For each conformer, the Hartree-Fock(HF)/DFT calculations were carried out to obtain optimized geometries and energies at the RHF/6-31G(d,p), and RB3LYP/6-31G(d,p) and RB3LYP/6-311+G(d,p) levels. For a set of stable conformers, the geometry optimizations and frequency analyses were carried out at the RB3LYP/6-311+G(d,p) level. As a representative of the results obtained by these computational studies, the selected conformers of **Ia** are illustrated below (in Figure 9).

Stereochemistry of *N*-Benzoyl-5-methyl-1-benzazepines (Ia–d: X = CH_3). In general, the *N*-benzoyl-5-substituted-1-benzazepines (**I**–**III**) theoretically have *E*/*Z*-amide isomers[11] around the N–C(=O) bond and (a*S*)/(a*R*)-axial isomers[12] based on the Ar–N(C=O) (sp^2–sp^2) axis (Figure 2), and thus four stereoisomers (conformers) may exist in the molecules. For the *E*/*Z*-amide isomers, however, compounds **I**–**III** all exist predominantly in the *E* form, and the *Z* isomer was negligible in the ^{1}H NMR spectrum.[13] Thus, compounds **I**–**III** exist only as a

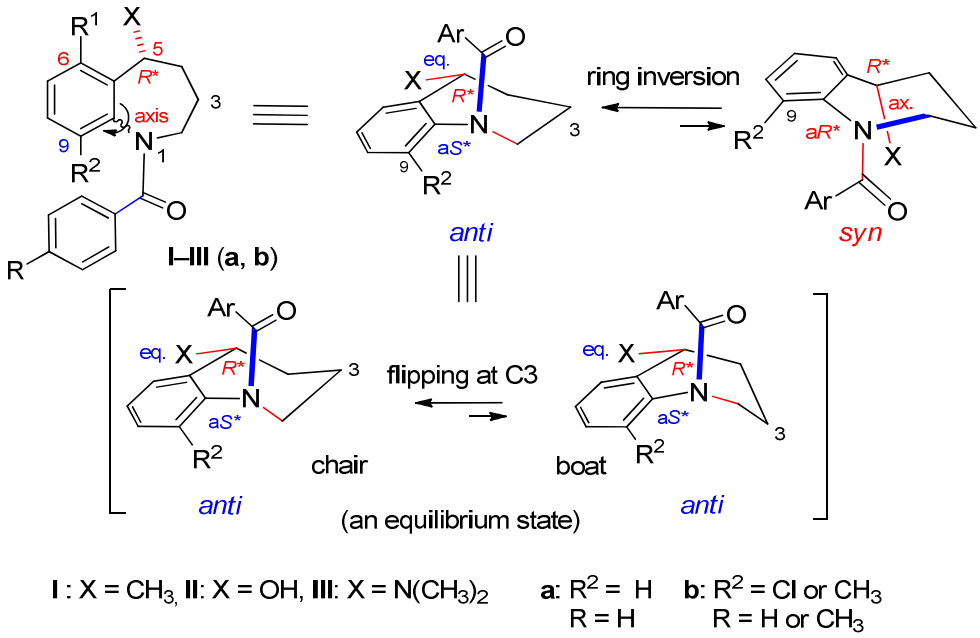


Figure 3. Conformation of *anti*/*syn* diastereomers of **I–III** (**a**, **b**). Azepine ring takes an equilibrium state between the chair and boat (in brackets); both forms are observed separately at lower temperatures (~183 K) in a ratio of 1:0.3 (**Ia**) in CD_2Cl_2.

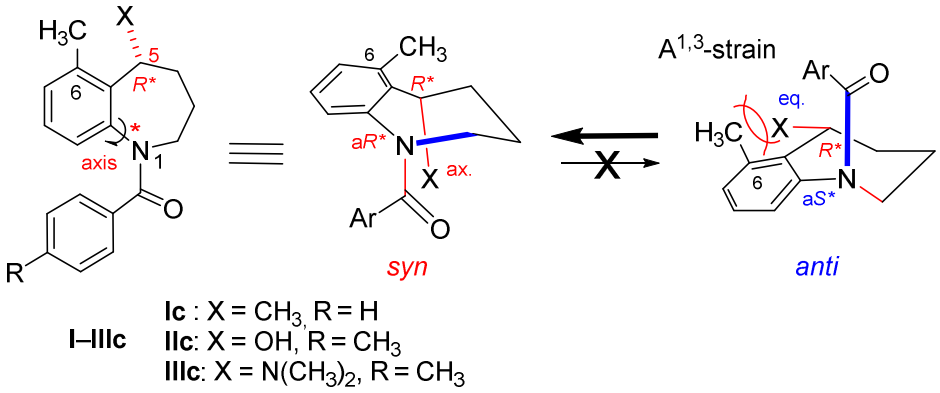


Figure 4. *Syn* formation in 6-methyl derivatives (**I-IIIc**): because of the steric hindrance ($A^{1,3}$-strain), the 5-substituent adopts a sterically less hindered axial (ax.) orientation to form the *syn* isomer.

mixture of diastereomers (*anti/syn* isomers) originating in the two stereogenic elements at C5 and the axis (Figure 2).[8] The *anti* form and *syn* form possess the C5 substituent disposed in a equatorial (eq.) and axial (ax.) orientation, respectively.

Figures 3 and 4 show schematic drawings of the stereochemistry of **I**–**III** (**a**–**c**). First, the conformation was examined in detail using 5-methyl derivatives **Ia**–**d** (X = CH_3). In compound **Ia**, the ring inversion via rotation around the Ar–N(C=O) axis readily occurs to form inseparable *anti*/*syn* diastereomers, whereas in **Ib** the rotation around the axis is restricted by the *ortho* substituent (R^2) to form separable *anti*/*syn* diastereomers (Figure 3). On the other hand, in compound **Ic** (Figure 4), because of the steric hindrance caused by the C6 methyl group (allylic 1,3-strain),[8a] the C5 methyl group is confined so as to adopt a sterically less hindered ax. orientation forming a *syn* isomer stereoselectively (Figure 4). The DFT calculation study of **Ic** confirmed that the *syn*-chair structure exists as the lowest-energy conformer, e.g., more stable by 15.5 kJ/mol than the *anti*-chair structure of **Ic**.

The ^{1}H NMR spectra (in $CDCl_3$, 296 K) of **Ia**, **Ib**, and **Ic** are shown in Figure 5. The spectrum of **Ia** is the same as that reported by M. Qadir et al.,[7] in which the diastereomers were observed in a ratio of 1:0.25 [Figure 5 (a)].

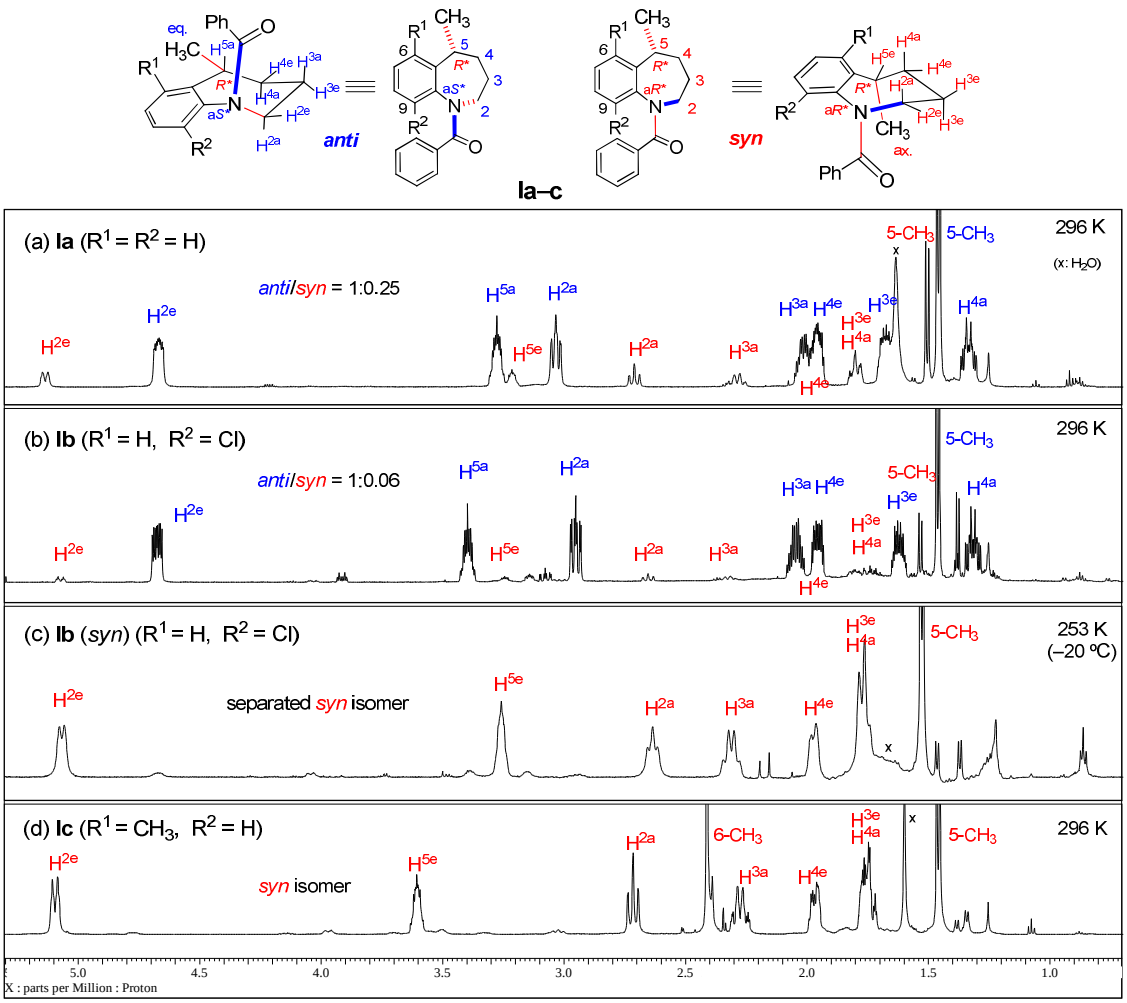


Figure 5. ^{1}H NMR spectra (600 MHz in $CDCl_3$): (a) **Ia**, (b) **Ib** (before separation of the *anti*/*syn* isomers), (c) **Ib** (*syn* isomer after separation by preparative HPLC), and (d) **Ic**. The descriptors a and e are used for the stereochemical arrangement of the proton, axial and equatorial orientation, respectively. The assignment of the signals from the *anti* and *syn* isomers are shown in blue and red, respectively.

The ^{13}C NMR spectrum of **Ia** also exhibited the presence of the two isomers. The spectrum of **Ib** before the separation procedure was that of a mixture of the diastereomers (ca. 1:0.06) [Figure 5 (b)], from which the minor isomer was successfully separated by preparative HPLC.

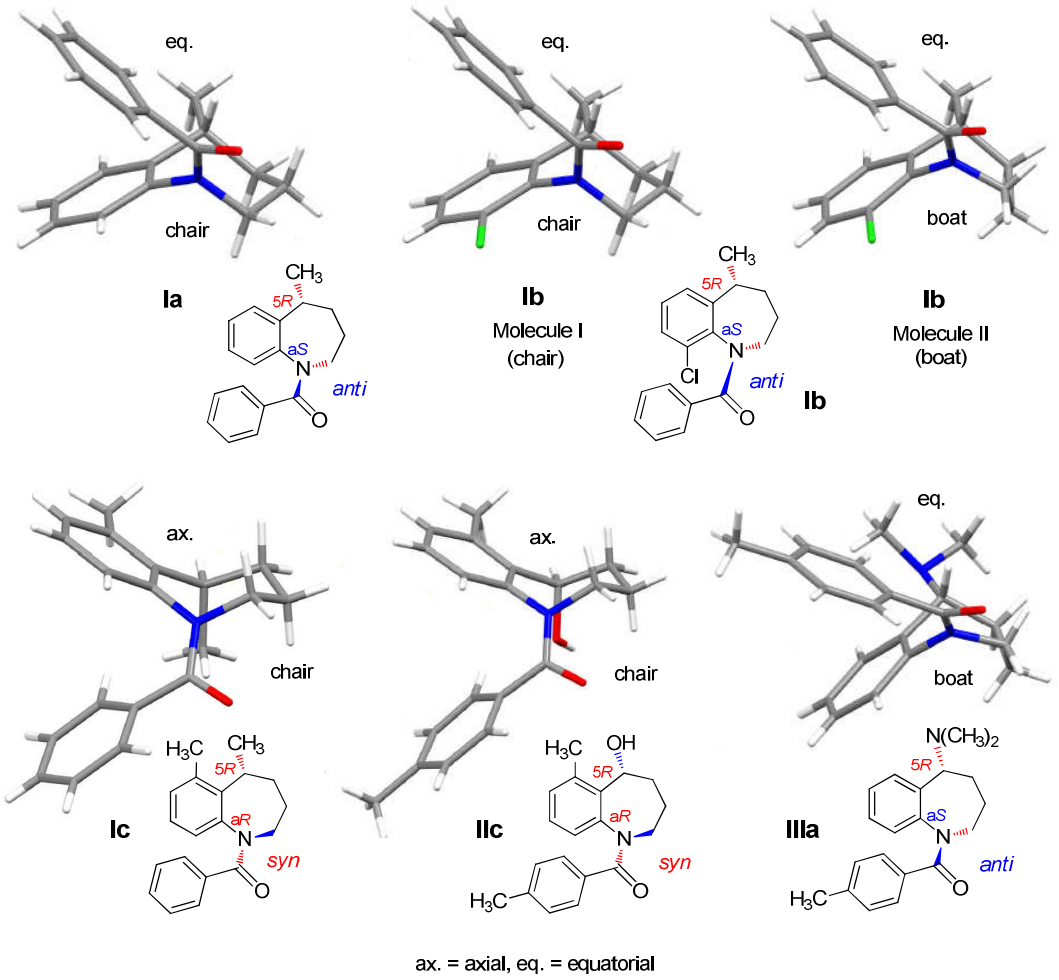


Figure 6. X-ray crystal structures of **Ia** (ref. 6), **Ib**, **Ic**, **IIc**, and **IIIa**. The structures with the 5*R* stereochemistry were extracted from the CIF data of the racemates. Compound **Ib** possesses chair and boat forms (Molecules I and II) in a unit cell.

The spectrum of the separated minor isomer of **Ib** [Figure 5 (c)] was measured at low temperature (253 K), since its relative instability prompts isomerization into the major isomer at rt. Very importantly, compound **Ic** exhibited ^{1}H NMR signals [Figure 5 (d)] similar to those of the minor forms of **Ia** and **Ib.** From these ^{1}H NMR analyses, it is clear that the structural features of the major isomer of **Ia** is similar to those of the major isomer of **Ib**, and the minor

isomer of **Ia** has the structural features similar to those of the minor isomer of **Ib** [Figure 5 (c)] and compound **Ic** [Figure 5 (d)]. Through detailed inspection of the 2D-NMR spectra (NOESY, COSY, and HMQC) the stereochemistry of **Ib** (major isomer) and **Ic** in solution was deduced to be *E-anti* and *E-syn*, respectively. The *E-anti* form of **Ib** (major isomer) was supported by the ^{1}H NMR spectrum, in which the vicinal couplings (^{3}J) observed for 5-H proton (δ 3.36–3.43 ppm) are consistent with the axial orientation of the proton: the ^{3}J values (Hz), 3.4 (H^{5ax}, H^{4eq}) and 10.3 (H^{5ax}, H^{4ax}), correspond well with the values estimated from the torsion angles obtained from the X-ray crystal structure, *i.e.*, the torsion angles: $\angle H^{5ax}$-C5-C4-H^{4eq} = 50 ° and $\angle H^{5ax}$-C5-C4-H^{4ax} = 180 °.[14]

Furthermore, the diagnostic data for supporting the *E-anti* structure of **Ib** (major) in solution were obtained by the nuclear Overhauser enhanced differential spectroscopy (NOEDS) of the major isomer of *N-p*-toluoyl analogue of **Ib** (**Id**) (Figure 7),[15] *i.e.*, NOE enhancement and correlation were observed between the 5-CH_3 protons and 6-H proton, and between 5-H proton and 2'-H (in Ar), 4-H^{eq}, and 3-H^{ax} protons as shown in Figure 7, indicating the *anti* structure with the 5-CH_3 group in an equatorial orientation and 5-H proton in an axial one.

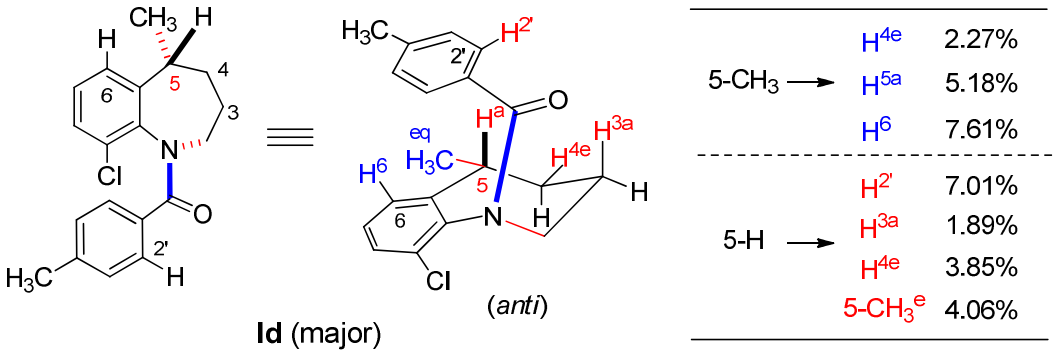
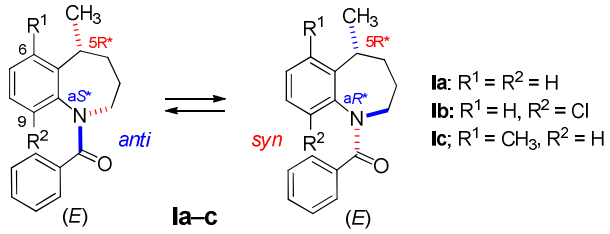


Figure 7. NOEDS experiment on **Id** (major isomer) after irradiation at the 5-CH_3 and 5-H protons (600 MHz, CD_2Cl_2): % enhancement after irradiation is shown in Table.

Table 1. *Anti*/*syn* equilibrium ratio of Ia–c measured by ^{1}H NMR, energy difference calculated from the equilibrium ratio and by DFT calculation, and energy barrier



	R^1	R^2	*anti* : *syn* ratio (^{1}H NMR in $CDCl_3$ at 296 K)	Energy difference (kJ/mol) [a] experimental ΔG_{TC}	Energy difference (kJ/mol) [a] calculated (DFT) ΔG_{298}	Energy barrier experimental ($\Delta G^{\ddagger}$ kJ/mol)
Ia	H	H	1 : 0.25[b] (1 : 0.25 at 298 K)[d]	3.4 (3.8)[d]	4.0 (5.0)[d,e]	69.5 (Tc = 383 K)[c] (63.4)[d]
Ib	H	Cl	1 : 0.06[f]	7.2	5.9	NA[g]
Ic	CH_3	H	—[h] : 1	—[i]	15.5	NA[g]

[a]Comparison between the *anti* and *syn* isomers with the chair-like form. [b]Almost the same ratio was observed in CD_3OD and DMSO-d_6. [c]Estimated from the coalescence VT ^{1}H NMR spectra measured in DMSO-d_6: Tc = coalescence temperature. [d]Data in Ref 7. [e]By molecular mechanics calculation. [f]The ratio in CD_2Cl_2 was 1:0.08. [g]NA: not analyzed. [h]The *anti* isomer was not confirmed in the ^{1}H NMR spectrum. [i]Not determined.

The deduced structures of **Ib** (major) and **Ic** were also obtained by the X-ray crystal analysis, as shown in Figure 6. It is noteworthy that the lowest-energy conformers of **Ib** (*E*-*anti*-chair) and **Ic** (*E*-*syn*-chair) obtained by the DFT calculations coincide with the X-ray crystal structures. Thus, the stereochemistry of the major and minor isomers of **Ia** in both solid and solution state was unambiguously assigned to be *anti* and *syn*, respectively, and these results clearly indicate that the previously reported[7] structure of the major diastereomer of **Ia** in solution state (*syn*) was misassigned.[9]

The activation free energy barrier to rotation ($\Delta G^{\ddagger}$) between the *anti*/*syn* isomers of **Ia** was estimated using variable-temperature ^{1}H NMR (VT ^{1}H NMR) in DMSO-d_6 (see Figure S3 in the Supporting Information); the coalescence spectra yielded a $\Delta G^{\ddagger}$ value[16] of ca. 69.5 kJ/mol (Table 1). The energy difference (ΔG) between the *anti*/*syn* isomers was calculated by DFT to be 4.0 kJ/mol, which is in good agreement with the experimental value of 3.4 kJ/mol [calculated from the equilibrium ratio (1:0.25)] (Table 1).

Furthermore, very unexpectedly, the VT ^{1}H NMR study of **Ia** at lower temperatures (243 K to 183 K in CD_2Cl_2) unveiled another interesting conformational aspect of *N*-benzoyl-5-methyl-1-benzazepines (Figure 8, Table 2): by lowering the temperature, each diastereotopic methylene proton signal in the major *anti* isomer of **Ia** split into paired signals

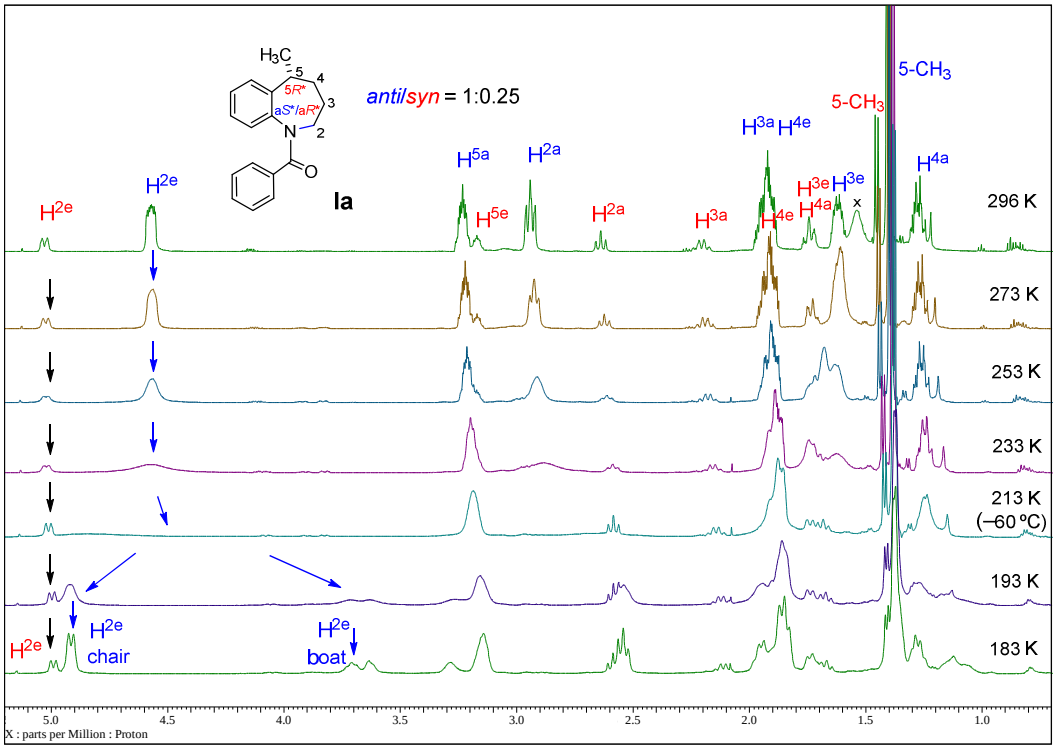
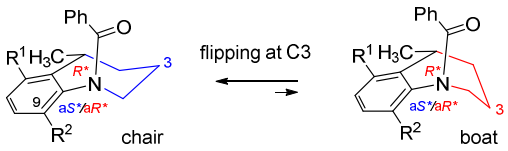


Figure 8. VT ^{1}H NMR spectra of **Ia** in CD_2Cl_2 at lower temperatures (296–183 K): the signals of the *anti* isomer split into a pair of signals with a ratio of 1:0.3, whereas those of the *syn* isomer apparently did not.[ref.17] As for the descriptors a and e, see the caption of Figure 5. The diagnostic signals, H^{2e} in the *anti* isomer and H^{2e} in the *syn* isomer, are indicated by arrows.

Table 2. Chair/boat equilibrium in Ia–c measured by ^{1}H NMR and energy difference



Ia: $R^1 = R^2 = H$, **Ib**: $R^1 = H$, $R^2 = Cl$, **Ic**: $R^1 = CH_3$, $R^2 = H$

	chair:boat ratio at 183 K[a]	Energy difference (kJ/mol)		Energy barrier ($\Delta G^{\ddagger}$ kJ/mol) (Tc = 223 K)[b]
		experimental ΔG_{TC}	calculated (DFT) ΔG_{298}	
Ia (for a*R**, *S**)[c]	1 : 0.3	1.7	3.6	40.4
Ib (for a*R**, *S**)[d]	1 : 0.2	2.4	4.0	40.6
Ic (a*S**, *S**)[e]	1 : —[f]	—[g]	9.1	NA[h]

[a]Measured by ^{1}H NMR in CD_2Cl_2. [b]Tc = coalescence temperature. [c]The major *anti* isomer of **Ia**. [d]The major *anti* isomer of **Ib**. [e]*Syn* form. [f]The boat form was not confirmed. [g]Not determined. [h]NA: not analyzed.

showing the appearance of two new conformers (with a ratio of 1:0.3), although that in the minor *syn* isomer of **Ia** apparently did not show any change (Figure 8).[17] The energy barrier ($\Delta G^{\ddagger}$) between the split conformers estimated by VT NMR was 40.4 kJ/mol (Tc = 223 K in CD_2Cl_2). The energy difference (ΔG) between the conformers was 1.7 kJ/mol (calculated from the equilibrium ratio at 183 K). Compound **Ib** (major *anti* isomer) also exhibited two conformers in NMR at lower temperatures (see Figure S6 in the Supporting Information), whereas compound **Ic** (*syn* form) apparently did not show any change in the spectrum.[17] The appearance of the two conformers from the *anti* isomers (major isomers of **Ia** and **Ib**) at lower temperatures was unanticipated, since thus far the *anti* isomer is believed to take a chair form.[6,7] The conformers observed at lower temperatures were most probably chair and boat forms, and thus the signals appearing in the NMR spectrum at rt may be the population-weighted average ones between the chair and boat forms (in brackets in Figure 3). In addition, it is noteworthy that, in the X-ray crystallographic analysis of **Ib** (Figure 6), two independent molecules [Molecule I (chair) and Molecule II (boat)] are present in a unit cell, which may support the assumption.

The relatively small energy difference (ΔG) between the chair and boat forms in the *anti* isomers calculated by DFT is also consistent with this phenomenon: ΔG_{298} value, 3.6 kJ/mol

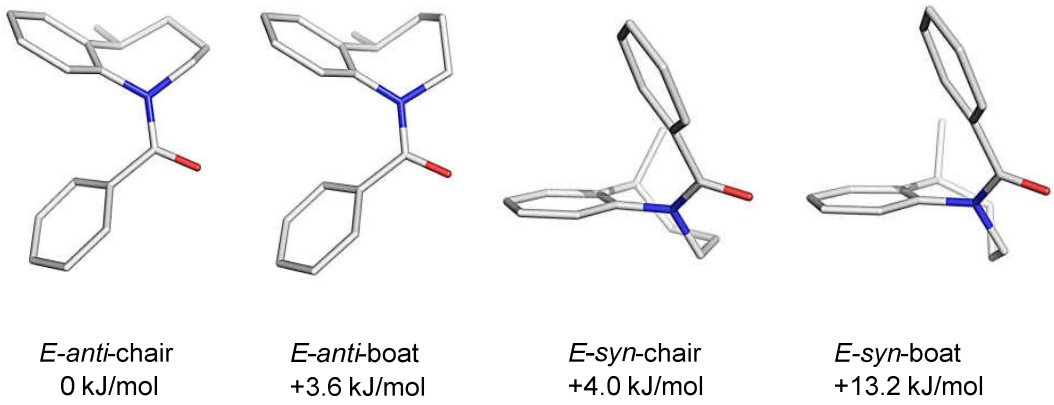


Figure 9. Four selected conformers of **Ia** (*E*-amide isomer) and the free energy difference (ΔG_{298}) as calculated by the DFT method.

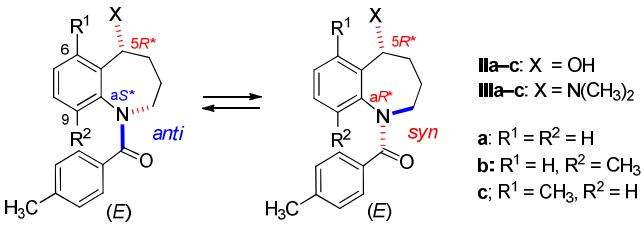
for **Ia**; and 4.0 kJ/mol for **Ib** (Table 2, Figure 9). In contrast, in the *syn* isomers of **Ia**–**Ic**, large energy differences between the chair and boat forms were calculated, i.e., the ΔG_{298} values (kJ/mol) calculated by DFT were 9.2, 7.3, and 9.1 for **Ia**, **Ib**, and **Ic**, respectively. The reason why the *syn* isomers apparently did not show any change at lower temperatures in the ^{1}H NMR spectrum may be the large energy differences between the conformers.[17]

Stereochemistry of 5-Hydroxy- and 5-(*N*,*N*-Dimethylamino)-*N*-(*p*-toluoyl)-1-benzazepines [IIa–c: X = OH and IIIa–c: X = N(CH$_3$)$_2$]. Next, the stereochemistry of the *N*-benzoyl-1-benzazepines with 5-hydroxy (**IIa**–**c**) and 5-*N*,*N*-dimethylamino (**IIIa**–**c**) groups (see Figures 3, 4 and Table 3) was examined. Compounds **IIa**–**c** and **IIIa**–**c** are the basic structure of tolvaptan[3] and mozavaptan[2] (see Figure 1), respectively. The *anti*/*syn* stereochemistry of these drugs has previously received little attention and has not been analyzed, although the *E*/*Z*-amide

isomer has been discussed (i.e., the *E* isomer is predominant).[2] In essence, **IIa**–**c** and **IIIa**–**c** showed structural features similar to those of **Ia**–**c**. The *anti*/*syn* stereochemistry of **IIa**–**c** and **IIIa**–**c** in the solution state was determined by the 2D-NMR spectra (NOESY, COSY, and HMQC). Similarly to **Ia**–**c**, the *anti* form is predominant in **IIa**,**b** and **IIIa**,**b**, and only the *syn* form is observed in **IIc** and **IIIc**. The ^{1}H NMR spectra of **a**–**c**-series of compounds are compared as shown in Figures S1 and S2 (in the Supporting Information). The X-ray crystallographic structures of **IIc** and **IIIa** are shown in Figure 6, in which **IIc** revealed a *syn*-chair (ax. OH) form as expected, whereas that of **IIIa** unexpectedly showed a boat form with the $N(CH_3)_2$ group in *anti* (eq.) form. The *anti*/*syn* ratio, energy barrier, and energy difference for **IIa**–**c** and **IIIa**–**c** are summarized in Table 3 (cf., Table 1 for **Ia**–**c**).

For the *anti*/*syn* ratio of **IIa**–**c** and **IIIa**–**c** in the solution state, it is interesting to note that, in the **a**-series ($R^1 = R^2 = H$) of compounds (**IIa** and **IIIa**), the *syn* proportion increased compared with that of **Ia** (*anti*/*syn* ratio: 1:0.25). i.e., the *anti*/*syn* ratio of **IIa** is 1:0.30, and that of **IIIa** is 1:0.43–1:0.82 (Tables 3). The increase in the *syn* isomer in **IIa** and **IIIa** may be explained by the steric bulk of the substituent, which confers a labile nature due to the steric repulsion between C6-H and C5-substituent to increase the *syn* isomer with the substituent in

Table 3. *Anti*/*syn* equilibrium ratio of IIa–c and IIIa–c measured by ^{1}H NMR, energy difference calculated from the equilibrium ratio and by DFT calculation, and energy barrier



	X	R^1	R^2	*anti* : *syn* ratio (^{1}H NMR at 296 K)[a]	Energy difference (kJ/mol) experimental ΔG_{TC}	Energy difference (kJ/mol) calculated (DFT) ΔG_{298}	Energy barrier experimental ($\Delta G^{\ddagger}$ kJ/mol)
IIa	OH	H	H	1 : 0.30[b]	3.0	4.2	68.8 (Tc = 333 K)[c]
IIb	OH	H	CH_3	1 : 0.15	4.7	NA[d]	NA[d]
IIc	OH	CH_3	H	—[e] : 1	—[f]	10.8	NA[d]
IIIa	$N(CH_3)_2$	H	H	1 : 0.82	0.5	3.4	71.0 (Tc = 353 K)[c]
				1 : 0.50 in CD_2Cl_2	1.8		
				1 : 0.43 in CD_3OD	2.1		
				1 : 0.43 in THF-d_8	2.1		
IIIb	$N(CH_3)_2$	H	CH_3	1 : 0.16	4.5	NA[d]	NA[d]
IIIc	$N(CH_3)_2$	CH_3	H	—[e] : 1	—[f]	NA[d]	NA[d]

[a]In DMSO-d_6 unless otherwise stated. [b]Almost the same ratio was observed in $CDCl_3$, CD_2Cl_2, and CD_3OD. [c]Estimated from the coalescence VT ^{1}H NMR spectra measured in DMSO-d_6: Tc = coalescence temperature. [d]NA: not analyzed. [e]The *anti* form was not confirmed. [f]Not determined.

the axial position. The high proportion of the *syn* isomer (*anti*/*syn* = 1:0.82) of **IIIa** in DMSO-d_6 was unexpected, because the ratios for **Ia** and **IIa** were unchanged regardless of the solvent used, and the energy difference (ΔG) between the *anti* and *syn* forms in **IIIa** obtained by DFT calculation was 3.4 kJ/mol. This unexpected ratio observed in **IIIa** may be caused by stabilization of the *syn* form in DMSO, although the mechanism of the solvent effect is not clear at present. On the other hand, similar to **Ib** and **Ic**, the **b**-series (R^1 = H, R^2 = CH_3) of compounds (**IIb** and **IIIb**) predominantly formed the *anti* isomer, and the **c**-series (R^1 = CH_3, R^2 = H) of

compounds (**IIc** and **IIIc**) existed only as the *syn* isomer. The DFT calculation study of **IIc** also supported the hypothesis that the *syn*-chair structure exists as the most stable conformer, i.e., more stable by 10.8 kJ/mol than the *anti*-chair structure.

CONCLUSION

The *syn* and *anti* diastereomers of *N*-benzoyl-5-substituted-1-benzazepines (**I**–**III**) was first prepared stereoselectively by biasing the conformation with a substituent at C6 (for **Ic**–**IIIc**) and C9 (for **Ib**–**IIIb**), respectively, and the stereochemistry of **I**–**III** was examined in detail to reveal new physicochemical aspects of these heterocycles including revision of the previously reported stereochemistry of **Ia** in the solution state. The results may not only shed light on the active form of the vaptan class of VP ligands (e.g., mozavaptan and tolvaptan), but also may provide useful information for future drug design when these heterocycles are used as the scaffold.

EXPERIMENTAL SECTION

General experimental procedure.

All reagents were purchased from commercial suppliers and used as received. Reaction mixtures were stirred magnetically, and the reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates. Column chromatography was performed using silica gel (45–60 μm). Extracted solutions were dried over anhydrous $MgSO_4$ or Na_2SO_4. Solvents were evaporated under reduced pressure. NMR spectra were recorded on a spectrometer at 400 MHz or 600 MHz for ^1H NMR, and 100 MHz or 150 MHz for ^{13}C NMR at 296 K unless otherwise stated. Chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as an internal standard, and coupling constants (*J*) are reported in Hertz (Hz). Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). The high-resolution mass spectra (HRMS) were recorded using an ESI/TOF mass spectrometer. IR spectra were recorded on a FT-IR spectrometer equipped with ATR (Diamond). Melting points were recorded on a melting point apparatus and are uncorrected.

1-Benzoyl-5-methyl-2,3,4,5-tetrahydro-*1H*-1-benzazepine (Ia). Compound **Ia** was prepared according to the procedure previously reported.[7] Colorless crystals: mp 88–89 °C (lit.[7] mp 87.8–88.6 °C). The spectroscopic data of **Ia** was identical to those of the compound reported. The ^1H NMR spectrum in $CDCl_3$ is shown in Figure 5, which indicates that the *anti*/*syn* ratio is 1:0.25:

^{1}H NMR ($CDCl_3$, 600 MHz) ***anti*** (**equatorial**)**-isomer** (= reportedly[7] **axial-isomer**): δ 1.30–1.37 (m, 1H, H^{4a}), 1.46 (d, *J* = 7.6 Hz, 3H, CH_3), 1.64–1.72 (m, 1H, H^{3e}), 1.92–2.06 (m, 2H, H^{3a} and H^{4e}), 3.00–3.08 (m, 1H, H^{2a}), 3.24–3.32 (m, 1H, H^{5a}), 4.67 (ddd, *J* = 3.4, 6.9, 13.1 Hz, 1H, H^{2e}), 6.62 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.90 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.09–7.31 (m, 7H, Ar-H). ***syn*** (**axial**)**-isomer** (= reportedly[7] **equatorial-isomer**): δ 1.51 (d, *J* = 6.9 Hz, 3H, 5-CH_3), 1.76–1.84 (m, 2H, H^{3e} and H^{4a}), 1.92–2.06 (m, 1H, H^{4e}), 2.23–2.35 (m, 1H, H^{3a}), 2.66–2.75 (m, 1H, H^{2a}), 3.17–3.26 (m, 1H, H^{5e}), 5.14 (m, 1H, H^{2e}), 6.54 (d, *J* = 7.6 Hz, 1H, Ar-H), 6.85 (dt, *J* = 1.3, 7.6 Hz, 1H, Ar-H),7.07 (t, *J* = 7.6 Hz, 1H, Ar-H), other aromatic protons overlapped by resonances of the *anti*-isomer; ^{13}C NMR ($CDCl_3$, 150 MHz) ***anti*-isomer**: δ 20.0 (CH_3), 27.0 (*C*-3), 34.4 (*C*-4), 34.8 (*C*-5), 47.0 (*C*-2), 125.3 (Ar-C), 126.6 (Ar-C), 127.3 (Ar-C), 127.7 (Ar-C), 128.1 (Ar-C), 128.5 (Ar-C), 129.5 (Ar-C), 136.2 (Ar-C), 141.9 (Ar-C), 142.6 (Ar-C), 169.5 (CO). ***syn*-isomer**; δ 18.7 (CH_3), 24.1 (*C*-3), 32.3 (*C*-4), 40.9 (*C*-5), 48.4 (*C*-2), 126.7 (Ar-C), 127.1 (Ar-C), 127.5 (Ar-C), 128.9 (Ar-C), 129.4 (Ar-C), 129.5 (Ar-C), 130.6 (Ar-C), 136.2 (Ar-C), 142.1 (Ar-C), 143.0 (Ar-C), carbonyl peak not observed.

9-chloro-5-methyl-2,3,4,5-tetrahydro-*1H*-1-benzazepine (8). To a stirred solution of 9-chloro-5-oxo-2,3,4,5-tetrahydro-*1H*-1-benzazepine (**7**)[3] (150 mg, 0.77 mmol) in THF (11 mL) at 25 °C under an atmosphere of argon was added methyl magnesium iodide (1 M in THF, 3

mL, 3.08 mmol). The mixture was stirred at 25 °C for 6 h, and evaporated. To the residue was added saturated NH_4Cl (aq), and the mixture was extracted with diethyl ether. The extract was washed with brine, dried, and concentrated to give 9-chloro-5-hydroxy-5-methyl-2,3,4,5-tetrahydro-*1H*-1-benzazepine, which was used in the next reaction without further purification. To the crude product (109 mg) were added TFA (0.4 mL, 5.0 mmol) and Et_3SiH (0.8 mL, 5.0 mmol). After being stirred at 25 °C for 4 h, the mixture was treated with saturated $NaHCO_3$ (aq), and then extracted with ethyl acetate. The extract was washed with brine, dried, and concentrated. The concentrate was purified by column chromatography on silica gel (hexane/ethyl acetate = 20:1) to give **8** as a colorless oil (102 mg, 0.52 mmol, 68%): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.31 (d, *J* = 7.6 Hz, 3H), 1.53–1.60 (m, 1H), 1.72–1.80 (m, 2H), 1.87–1.95 (m, 1H), 3.05–3.13 (m, 3H), 4.51 (br, 1H), 6.75 (t, *J* = 7.6 Hz, 1H), 7.04 (dd, *J* = 1.4, 7.6 Hz, 1H), 7.16 (dd, *J* = 1.4, 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 19.6, 27.5, 33.5, 38.7, 48.1, 120.7, 124.1, 126.7, 127.0, 138.9, 145.8; IR(ATR) 778, 1138, 1273, 3473 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{14}NCl$ 196.0888 $(M+H)^+$, found 196.0888.

1-Benzoyl-9-chloro-5-mthyl-2,3,4,5-tetrahydro-*1H*-1-benzazepine (Ib). To a stirred solution of **8** (50 mg, 0.26 mmol) in THF (3 mL) at 0 °C under an atmosphere of argon was added sodium hydride (60% in oil) (15 mg, 0.38 mmol). The mixture was stirred at 25 °C for

30 min, cooled to 0 °C, and treated with benzoyl chloride (0.09 mL, 0.77 mmol). After being stirred at 25 °C for 3 h, the mixture was treated with H_2O, extracted with ethyl acetate. The extract was washed with brine, dried, and concentrated. The concentrate was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1) to afford **Ib** as a white powder (74 mg, 0.25 mmol, 95%). Signals of a mixture of *anti*/*syn* (= 1:0.06) diastereomers were observed in the ^{1}H NMR and ^{13}C NMR spectra; ***anti* isomer** (major isomer), ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.28–1.35 (m, *J* = 4.1, 9.6, 10.3, 13.6 Hz, 1H, H^{4a}), 1.46 (d, *J* = 6.9 Hz, 3H, 5-CH_3), 1.59–1.66 (m, *J* = 3.4, 4.1, 6.9, 6.9, 14.1 Hz, 1H, H^{3e}), 1.92–1.99 (m, *J* = 3.4, 4.1, 6.9, 13.6 Hz, 1H, H^{4e}), 2.00–2.09 (m, *J* = 4.1, 4.1, 9.6, 9.6, 14.1 Hz, 1H, H^{3a}), 2.91–2.99 (m, *J* = 3.4, 9.6, 13,2 Hz, 1H, H^{2a}), 3.36–3.43 (m, *J* = 3.4, 6.9, 10.3 Hz, 1H, H^{5a}), 4.64–4.70 (m, *J* = 4.1, 6.9, 13.2 Hz, 1H, H^{2e}), 7.04 (dd, *J* = 1.4, 8.3 Hz, 1H, Ar-H), 7.10–7.16 (m, 2H, Ar-H), 7.19–7.25 (m, 3H, Ar-H), 7.48 (t, *J* = 8.3 Hz, 1H, Ar-H), 8.11 (dd, *J* = 1.4, 7.6 Hz, 1H, Ar-H) (see, Tables S1–3 in the Supporting Information for the detailed analysis of the methylene protons by ^{1}H NMR) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.1, 26.9, 34.3, 35.3, 45.9, 123.6, 127.3, 127.5, 127.9, 128.7, 129.8, 132.2, 136.0, 139.7, 145.2, 169.3; ***syn* isomer** (minor isomer) ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.53 (d, *J* = 7.6 Hz, 3H), 1.69–1.84 (m, 2H), 1.94–2.00 (m, 1H), 2.27–2.36 (m, 1H), 2.66, (t, *J* = 12.4 Hz, 1H), 3.20–3.28 (m, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.08–7.16 (m, 3H), 7.20 (d, *J* = 6.9 Hz, 1H), 7.26–7.29

(m, 1H), 7.64 (t, J = 7.6 Hz, 2H) [the ^{1}H NMR spectral data of the *syn* (minor) isomer described above are those assigned using the separated *syn* isomer (isolated as a colorless oil) at 253K.]; ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.3, 29.4, 33.8, 34.9, 49.3, 123.7, 126.5, 126.8, 127.1, 127.7, 128.5, 128.8, 129.6, 136.4, 145.4, 170.5; IR(ATR) 1643 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{18}NOCl$ 300.1150 $(M+H)^+$, found 300.1150. The *anti*/*syn* isomers of **Ib** were separable by HPLC. The separation condition is as follows: CHIRALPAK IA (1.0 cmϕ × 25 cm); Eluent, hexane/ethanol (19 /1); Flow rate, 2.0 mL/min; Temperature, 23 ºC; Detection, 254 nm. Minor peak: retention time = 16.0 min, 18.7 min; Major peak: retention time = 20.5 min, 21.9 min. The two minor peaks (= the same diastereomer) were collected by HPLC using the chiral column and combined to subject to the ^{1}H NMR analysis [Figure 5 (c)]. Crystals suitable for X-ray crysatallography were obtained by recrystallization of the *anti*/*syn* (= 1:0.06) mixture from hexane/ethyl acetate.

***N*-(2-Bromo-6-methylphenyl)-*N*-(pent-4-en-1-yl)benzamide (5c).** To a solution of *N*-(2-bromo-3-methylphenyl)benzamide (**4c**)[18] (538 mg, 1.85 mmol) in THF (15 mL) was added sodium hydride (60% in oil) (84 mg, 2.11 mmol) at 0 °C under an atmosphere of argon. After the mixture was stirred at 25 °C for 1 h, and pent-4-enyl tosylate (371 mg, 1.54 mmol) was added. After being stirred at 25 °C for 8 h, the mixture was treated with H_2O, and extracted

with ethyl acetate. The extract was washed with brine, dried, and concentrated. The concentrate was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to afford **5c** (515 mg, 93%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.61–1.69 (m, 1H), 1.81–1.88 (m, 1H), 2.06–2.17 (m, 2H), 2.37 (s, 3H), 3.38–3.43 (m, 1H), 4.23–4.28 (m, 1H), 4.95 (d, *J* = 9.6 Hz, 1H), 5.01 (d, *J* = 17.1 Hz, 1H), 5.77–5.84 (m, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 7.02–7.04 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 2H), 7.18–7.20 (m, 1H), 7.31 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.9, 26.5, 31.3, 48.9, 115.0, 126.0, 127.2, 127.6, 127.9, 129.2, 129.5, 129.8, 136.3, 137.9, 140.3, 142.2, 170.6; IR (ATR) 1652 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}NOBr$ 380.0620 $(M+Na)^+$, found 380.0622.

1-Benzoyl-6-methyl-5-methylene-2,3,4,5-tetrahydro-*1H*-1-benzazepine (6c). To a suspension of Pd $(OAc)_2$ (12.7 mg, 5 mol%) in DMF (5 mL) were added PPh_3 (59.5 mg, 20 mol%), LiCl (52.9 mg, 1.25 mmol), and Et_3N (0.32 mL, 2.27 mmol) under an atmosphere of argon. After the mixture was stirred at 25 °C for 15 min, a solution of *N*-(2-bromo-6-methylphenyl)-*N*-(pent-4-en-1-yl)benzamide (**5c**) (409 mg, 1.14 mmol) in DMF (3 mL) was added to the mixture. After being stirred at 130 °C for 20 h, the mixture was cooled to rt and filtered through Celite. The filtrate was washed with H_2O, brine and dried, and concentrated. The concentrate was purified by column chromatography on silica gel (hexane/ethyl acetate =

8:1) to give **6c** as colorless crystals (247 mg, 79%): mp 90–92 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.85–1.91 (m, 1H), 2.01–2.06 (m, 1H), 2.22 (ddd, *J* = 3.4, 11.0, 13.0 Hz, 1H), 2.33 (s, 3H), 2.68–2.70 (m, 1H), 2.94 (ddd, *J* = 2.7, 11.0, 11.6 Hz, 1H), 4.85 (ddd, *J* = 3.4, 13.0, 13.6 Hz, 1H), 5.04 (d, *J* = 1.3 Hz, 1H), 5.48 (br, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.4, 29.0, 34.7, 47.2, 116.5, 125.8, 126.9, 127.5, 127.9, 129.2, 129.2, 135.9, 136.5, 139.9, 147.0, 169.5; IR (ATR) 2918, 1639 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NO$ 278.1539 $(M+H)^+$, found 278.1540.

1-Benzoyl-5,6-dimethyl-2,3,4,5-tetrahydro-*1H*-1-benzazepine (Ic). To a solution of **6c** (193 mg, 0.697 mmol) in ethanol (6 mL) was added 10% Pd/C (139 mg). The susupension was stirred at 25 °C under a hydrogen atmosphere for 20 h. The mixture was then filtered through a thin pad of Celite, which was washed with ethyl acetate. The collected filtrate was evaporated, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 8:1) to afford **Ic** as colorless crystals (128 mg, 65%): mp 76–78 °C; in the ^{1}H NMR spectrum, signals due to the *syn* diastereomer were observed and those of the *anti* isomer were negligible; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.45 (d, *J* = 7.5 Hz, 3H), 1.74–1.77 (m, 2H), 1.95–1.99 (m, 1H), 2.23–2.31 (m, 1H), 2.41 (s, 3H), 2.69–2.73 (m, 1H), 3.58–3.63 (m, 1H), 5.07–5.11 (m, 1H),

6.42 (d, *J* = 8.2 Hz, 1H), 6.73 (dd, *J* = 7.5, 8.2 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 7.11–7.14 (m, 2H), 7.20–7.24 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.3, 21.1, 23.9, 31.8, 33.1, 48.4, 125.9, 127.4(x2), 127.6, 128.9(x2), 129.3, 129.4, 135.8, 136.7, 140.5, 143.4, 168.5. IR (ATR) 2938, 1633 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}NO$ 302.1515 $(M+Na)^+$, found 302.1520.

1-Benzoyl-6-chloro-5-methyl-2,3,4,5-tetrahydro-*1H*-1-benzazepine (Id). Sodium hydride (60% in oil) (8.3 mg, 0.21 mmol) was added to a stirred solution of **8** (20.3 mg, 0.104 mmol) in THF (1 mL) at 0 °C under an atmosphere of argon. The mixture was stirred at 25 °C for 30 min, cooled to 0 °C, and treated with *p*-toluoyl chloride (41 μL, 0.31 mmol). After being stirred at 25 °C for 9 h, the mixture was treated with H_2O and then extracted with ethyl acetate. The extract was washed with brine, dried, and concentrated. The concentrate was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1) to afford **Id** as pale yellow crystals (28.9 mg, 89%): mp 121–123 °C; Signals of a mixture of *anti*/*syn* (= 1:0.07) diastereomers were observed in the ^{1}H NMR and ^{13}C NMR spectra; ***anti* isomer** (major isomer), ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26–1.35 (m,1H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.56–1.65 (m, 1H), 1.91–2.08 (m, 2H), 2.24 (s, 3H), 2.93 (ddd, J = 2.7, 9.1, 12.8 Hz, 1H), 3.38 (ddq, *J* = 3.2, 6.8, 13.7 Hz, 1H), 4.66 (ddd, *J* = 3.6, 6.8, 12.8 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 2H), 7.05 (dd, *J* = 1.3, 7.8 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 1.3, 7.8 Hz, 1H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 20.0, 21.3, 26.8, 34.2, 35.2, 45.8, 126.8, 127.8, 127.9, 127.9, 128.5, 129.1, 130.1, 132.2, 133.0, 139.8, 139.9, 145.1, 169.4; ***syn* isomer** (minor isomer) (only the distinguishable peaks are described), ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.05 (d, J = 7.7 Hz, 0.21H), 2.25 (s, 0.21H), 2.58–2.66 (m, 0.07H), 3.21–3.25 (m, 0.07H), 5.05–5.09 (m, 0.07H), 7.36–7.38 (m, 0.07H), 7.52 (d, J = 8.2 Hz, 0.14H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.2, 21.7, 23.7, 32.2, 41.0, 47.5, 49.2, 126.8, 127.7, 128.3, 128.8, 129.0, 129.1, 132.4, 143.3, 144.3, 170.8; IR (ATR) 2933, 1644 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}NO$ 336.1126 $(M+Na)^+$ found 336.1131.

5-Oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-*1H*-1-benzazepine (11a) and 5-oxo-2,3,4,5-tetrahydro-*1H*-1-benzazepine (12a). Compound **11a** was prepared according to the reported method[19] shown in Scheme 2 starting from methyl 2-(*N*-*p*-toluenesulfonyl)aminobenzote (**9a**). Removal of the *p*-toluenesulfonyl group with polyphosphric acid (PPA) afforded **12a**.[19]

Methyl 3-Methyl-2-(*N*-*p*-toluenesulfonyl)aminobenzoate (9b). To a solution of methyl 2-amino-3-methylbenzote (3.14 g, 19 mmol) in pyridine (20 mL) was added *p*-TsCl (4.3 g, 22.8 mmol). After being stirred at 25 °C for 18 h, the mixture was poured into ice-water. The resultant precipitates were collected by filtration. The solid obtained was dissolved in CH_2Cl_2, and the solution was washed with dil. HCl, H_2O, dried, and evaporated. The residue was purified by recrystallization (CH_2Cl_2/hexane) to give **9b** as white solids (5.81 g, 95%): mp

137–139 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.61 (s, 3H), 3.46 (s, 3H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 8.50 (br, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.5, 21.4, 51.9, 125.8, 126.5, 127.8, 127.9, 129.1, 135.3, 135.9, 136.2, 139.6, 143.4, 167.4; IR (ATR) 3223, 1695, 1294, 1150 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}NO_4S$ 320.0951 $(M+H)^+$, found 320.0960.

Methyl 6-Methyl-2-(*N*-*p*-toluenesulfonyl)aminobenzoate (9c). Compound **9c** was prepared from methyl 2-amino-6-methylbenzote (1.42 g, 8.63 mmol) according to a similar procedure described for the preparation of **9b** from methyl 2-amino-3-methylbenzote. White solids (2.71 g, 98%): mp 67–69 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.37 (s, 3H), 3.74 (s, 3H), 6.96 (d, *J* = 8.2 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 9.02 (br, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 22.3, 52.0, 120.2, 121.4, 127.1, 127.7, 129.5, 131.9, 136.6, 137.7, 139.5, 143.6, 168.8; IR (ATR) 3088, 1667, 1295, 1156 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{17}NO_4S$ 320.0951 $(M+H)^+$, found 320.0952.

Methyl 3-Methyl-2-[N-(3-ethoxycarbonyl)propyl-*N*-*p*-toluenesulfonyl]aminobenzoate (10b). To a solution of **9b** (3.49 g, 10.9 mmol) in DMF (27 mL) were added ethyl 4-bromobutylate (1.75 mL, 12 mmol) and K_2CO_3 (4.2 g, 30 mmol). After being stirred at 120 °C

for 8 h, the mixture was poured into ice-water, and then extracted with ethyl acetate. The organic layer was washed with H_2O, brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 7:1) to afford **10b** (4.7 g, 99%) as white solids: mp 97–99 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (t, *J* = 6.8 Hz, 3H), 1.92-2.05 (m, 2H), 2.13 (s, 3H), 2.26–2.36 (m, 2H), 2.41 (s, 3H), 3.57 (s, 3H), 3.72 (t, *J* = 8.2 Hz, 2H), 4.09 (q, *J* = 6.8 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 19.1, 21.4, 24.3, 31.7, 51.8, 51.9, 60.3, 127.3, 128.1, 129.2, 129.4, 132.7, 135.0, 136.6, 138.0, 140.9, 142.9, 166.8, 172.8; IR (ATR) 2947, 1733, 1342, 1156 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{27}NO_6S$ 456.1451 $(M+Na)^+$, found 456.1463.

Methyl 6-Methyl-2-[N-(3-ethoxycarbonyl)propyl-*N*-*p*-toluenesulfonyl]aminobenzoate (10c). Compound **10c** was prepared from **9c** (1.76 g, 5.5 mmol) according to a similar procedure described for the preparation of **10b** from **9b**. White solids (2.39 g, 99%): mp 79–80 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.23 (t, *J* = 6.8 Hz, 3H), 1.80 (br, 2H), 2.32–2.38 (m, 2H), 2.37 (s, 3H), 2.43 (s, 3H), 3.36 (br, 1H), 3.71 (br, 1H), 3.89 (s, 3H), 4.09 (q, *J* = 6.8 Hz, 2H), 6.60–6.62 (m, 1H), 7.18–7.21 (m, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 20.1, 21.5, 23.3, 31.2, 51.3, 52.1, 60.3, 125.6, 128.0, 129.4,

129.6, 130.4, 135.5, 135.9, 136.8, 137.4, 143.5, 167.9, 173.0; IR (ATR) 2946, 1740, 1351. 1163 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{27}NO_6S$ 456.1451 $(M+Na)^+$, found 456.1459.

9-Methyl-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-*1H*-1-benzazepine (11b). To a stirred solution of *t*-BuOK (1.4 g, 12.5 mmol) in toluene (60 mL) at 70 °C was added portion-wise **10b** (2.7 g, 6.23 mmol). After the addition was completed, the mixture was heated under reflux for 2 h. The mixture was cooled to room temperature, and then poured into ice-water. The mixture was extracted with CH_2Cl_2, and the organic layer was dried, and concentrated to afford a crude mixture of methyl and ethyl esters of 9-methyl-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-1*H*-1-benzazepine-4-carboxylic acid. To the crude mixture thus obtained were added AcOH (10 mL), conc. HCl (3.4 mL) and H_2O (1 mL). The mixture was heated under reflux for 5 h and poured into ice-water. The pH was adjusted to about 7–8 by adding dil. NaOH (aq). The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 7/1) to give **11b** as white solids (1.48 g, 72%): mp 137–139 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.50–1.62 (m, 1H), 1.78–1.84 (m, 1H), 2.25–2.34 (m, 1H), 2.43 (s, 3H), 2.46 (s, 3H), 3.60 (ddd, *J* = 1.4, 5.0, 5.5 Hz, 1H), 3.88–3.96 (m, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 7.34–7.40 (m, 2H), 7.49–7.53 (m, 1H), 7.52 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 18.4, 21.6, 21.8, 38.3, 47.5, 126.8, 127.3, 129.1, 129.8, 134.2, 135.3, 137.0, 138.8, 141.1, 143.9, 204.2; IR (ATR) 2940, 1684, 1345, 1158 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_3S$ 330.1158 $(M+H)^+$, found 330.1161.

6-Methyl-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-*1H*-1-benzazepine (11c). Compound **11c** was prepared from **10c** (1.15 g, 2.64 mmol) according to a similar procedure described for the preparation of **11b** from **10b**. White solids (432 mg, 50%): mp 146–148 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 1.80 (tt, *J* = 5.9, 6.0 Hz, 2H), 2.28 (s, 3H), 2.30–2.33 (m, 2H), 2.42 (s, 3H), 3.71 (t, *J* = 5.9 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.2, 2H), 7.33 (dd, *J* = 7.8, 7.9 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.6, 21.5, 22.4, 39.9, 48.5, 127.3, 127.3, 129.6, 130.9, 131.4, 135.7, 137.0, 137.7, 137.7, 143.7, 205.7; IR (ATR) 2926, 1688, 1341, 1158 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_3S$ 330.1158 $(M+H)^+$, found 330.1168.

9-Methyl-5-oxo-2,3,4,5-tetrahydro-*1H*-1-benzazepine (12b). To PPA (2.4 g) (preheated at 100 °C) was added 9-methyl-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-*1H*-1-benzazepine (**11b**) (330 mg, 1.0 mmol). The mixture was stirred for 2 h at the same temperature, then poured into ice-water. After the pH was adjusted to about 8–9 with aq NaOH, the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated. The residue was

purified by column chromatography on silica gel (hexane/ethyl acetate = 8:1) to give **12b** as pale brown crystals (134 mg, 76%): mp 120–122 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.20 (tt, *J* = 6.8, 7.3 Hz, 2H), 2.25 (s, 3H), 2.84 (t, *J* = 7.3 Hz, 2H), 3.31 (t, *J* = 6.8 Hz, 2H), 4.68 (br, 1H), 6.75 (dd, *J* = 6.8, 7.8 Hz, 1H), 7.16 (d, *J* = 6.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.4, 32.2, 41.0, 47.9, 117.9, 123.3, 125.1, 127.6, 133.2, 151.8, 203.3; IR (ATR) 3389, 1652 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}NO$ 176.1070 $(M+H)^+$, found 176.1074.

6-Methyl-5-oxo-2,3,4,5-tetrahydro-*1H*-1-benzazepine (12c). Compound **12c** was prepared from 6-methyl-5-oxo-2,3,4,5-tetrahydro-1-*p*-toluenesulfonyl-*1H*-1-benzazepine (**11c**) (350 mg, 1.1 mmol) according to a similar procedure described for the preparation of **12b** from **11b**. Pale brown crystals **(**156 mg, 84%): mp 95–96 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.14 (tt, *J* = 6.4, 6.8 Hz, 2H), 2.42 (s, 3H), 2.79 (t, *J* = 6.8 Hz, 2H), 3.23 (t, *J* = 6.4 Hz, 2H), 4.63 (br, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.3 Hz, 1H), 7.05 (dd, *J* = 7.3, 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7, 32.3, 42.0, 46.7, 115.2, 121.8, 124.9, 130.5, 139.3, 152.4, 205.6; IR (ATR) 3357, 1652 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{13}NO$ 176.1070 $(M+H)^+$, found 176.1072.

5-Oxo-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine (13a). Sodium hydride (60% in oil) (84 mg, 2.11 mmol) was added to a stirred solution of **12a** (170 mg, 1.06 mmol) in THF (6 mL) at 0 °C under an atmosphere of argon. The mixture was stirred at 25 °C for 30 min, cooled

to 0 °C, and treated with *p*-toluoyl chloride (0.42 mL, 3.17 mmol). After being stirred at 25 °C for 8 h, the mixture was treated with H_2O and then extracted with ethyl acetate. The extract was washed with brine, dried, and concentrated. The concentrate was purified by column chromatography on silica gel (hexane/ethyl acetate = 6:1) to afford **13a** as pale yellow crystals (261 mg, 88%): mp 136–138 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.96–2.28 (br, 2H), 2.26 (s, 3H), 2.91 (t, *J* = 6.1 Hz, 2H), 3.07–4.01 (br, 1H), 4.09–5.26 (br, 1H), 6.73 (d, *J* = 1.3, 7.5 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 2H), 7.13 (d, *J* = 7.5 Hz, 2H), 7.21 (dt, *J* = 2.0, 7.5 Hz, 1H), 7.25 (dt, *J* = 1.3, 7.5 Hz, 1H), 7.86 (dd, *J* = 2.0, 7.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 22.7, 40.1, 47.5, 127.0, 128.6, 128.7, 129.0, 129.4, 132.3, 132.9, 134.3, 140.6, 143.3, 170.6, 202.0; IR (ATR) 1677, 1636 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}NO_2$ 280.1332 $(M+H)^+$, found 280.1341.

9-Methyl-5-oxo-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine (13b). Compound **13b** was prepared from **12b** (222 mg, 1.27 mmol) according to a similar procedure described for the preparation of **13a** from **12a**. Colorless crystals (367 mg, 89%): mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79–1.90 (m, 1H), 1.97 (s, 3H), 2.18–2.26 (m, 1H), 2.22 (s, 3H), 2.70–2.85 (m, 2H), 3.23 (ddd, *J* = 2.7, 6.4, 12.8 Hz, 1H), 4.82 (ddd, *J* = 6.8, 10.9, 12.8 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 7.17 (dd, *J* = 1.3, 7.7 Hz, 1H), 7.24 (t, *J* = 7.7 Hz,

1H), 7.56 (dd, *J* = 1.3, 7.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 17.3, 21.3, 21.3, 39.6, 44.8, 126.7, 128.3, 128.3, 128.3, 132.3, 135.3, 135.8, 137.5, 139.0, 140.5, 171.0, 204.8; IR (ATR) 2970, 1741, 1641 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NO_2$ 294.1489 $(M+H)^+$, found 294.1491.

6-Methyl-5-oxo-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine (13c). Compound **13c** was prepared from **12c** (693 mg, 4.0 mmol) according to a similar procedure described for the preparation of **13a** from **12a**. Colorless crystals (1.05 g, 90%): mp 91–92 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.96–2.12 (br, 2H), 2.23 (S, 3H), 2.35 (s, 3H), 2.71 (t, *J* = 6.1 Hz, 2H), 3.33 (br, 1H), 4.56 (br, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.5 Hz, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.4, 21.3, 22.3, 41.0, 46.6, 126.4, 128.4, 128.5, 130.2, 130.6, 132.5, 137.0, 137.0, 139.5, 140.2, 171.5, 207.8 ; IR (ATR) 2951, 1687, 1640 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NO_2$ 316.1308 $(M+Na)^+$, found 316.1318.

5-Hydroxy-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine (IIa). To a solution of **13a** (57 mg, 0.24 mmol) in methanol (2.4 mL) was added $NaBH_4$ (14 mg, 0.36 mmol) at room temperature. The mixture was stirred for 1h, and concentrated. To the concentrate was added CH_2Cl_2, and the mixture was washed with H_2O, brine, dried, and concentrated. The concentrate

was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1) to afford **IIa** as colorless crystals (67 mg, 99%): mp 130–132 °C; signals of a mixture of *anti*/*syn* (= 1:0.30) diastereomers were observed in the ^{1}H NMR and ^{13}C NMR spectra; ***anti* isomer** (major isomer), ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.48, (br, 1H), 1.71 (br, 1H), 1.89 (br, 1H), 2.10 (br, 1H), 2.18 (s, 3H), 2.62 (br, 1H), 4.65 (d, *J* = 13.0 Hz, 1H), 4.90 (d, *J* = 9.9 Hz, 1H), 5.56 (br, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.90–6.94 (m, 1H), 6.96 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 20.9, 26.1, 35.7, 46.3, 69.8, 125.1, 127.0, 127.8, 128.0, 128.3, 128.7, 133.5, 139.3, 140.5, 142.6, 168.1; ***syn* isomer** (minor isomer) (only the distinguishable peaks are described), ^{1}H NMR δ 4.83-4.86 (br, 0.6H), 5.39 (br, 0.3H), 6.53 (d, *J* = 7.6 Hz, 0.3H), 7.06 (t, *J* = 7.2 Hz, 0.3H), 7.27 (d, *J* = 7.2 Hz, 0.3H), 7.29 (d, *J* = 7.7 Hz, 0.6H); ^{13}C NMR δ 22.9, 32.9, 47.6, 73.1, 126.6, 128.0, 129.2, 130.2, 134.1, 138.5, 139.9, 143.1; IR (ATR) 3222, 1623 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NO_2$ 282.1489 $(M+H)^+$, found 282.1496.

5-Hydroxy-9-methyl-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine (IIb). Compound **IIb** was prepared from **13b** (40 mg, 0.14 mmol) according to a similar procedure described for the preparation of **IIa** from **13a**. Colorless crystals (31 mg, 77%): mp 157–159 °C; signals of a mixture of *anti*/*syn* (= 1:0.15) diastereomers were observed in the ^{1}H NMR and ^{13}C NMR

spectra; ***anti* isomer** (major isomer), ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.42–1.49 (m, 1H), 1.64–1.69 (m, 1H), 1.76 (s, 3H), 1.91–1.97 (m, 1H), 2.07–2.09 (m, 1H), 2.19 (s, 3H), 2.53–2.57 (m, 1H), 4.59–4.63 (m, 1H), 4.96–4.98 (m, 1H), 5.54 (d, *J* = 4.5 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 7.16 (dd, *J* = 7.5, 7.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H): ^{13}C NMR (150 MHz, DMSO-d_6) δ 17.4, 20.9, 26.0, 36.0, 45.8, 69.9, 122.8, 127.6, 127.7, 128.1, 129.1, 133.3, 133.3, 138.9, 139.8, 143.7, 167.3; ***syn* isomer** (minor isomer) (only the distinguishable peaks are described), ^{1}H NMR δ 1.53–1.59 (m, 0.15H), 1.69 (s, 0.45 H), 2.07–2.09 (m, 0.15H), 2.18 (s, 0.45H), 4.84–4.86 (m, 0.15H), 5.38 (d, *J* = 3.7 Hz, 0.15H), 6.87 (d, *J* = 7.9 Hz, 0.3H), 7.03–7.06 (m, 0.15H), 7.12–7.16 (m, 0.15H), 7.33 (d, *J* = 7.9 Hz, 0.3H), 7.41–7.43 (m, 0.15H); ^{13}C NMR δ 17.6, 21.1, 22.7, 33.2, 47.4, 73.1, 126.5, 127.5, 127.9, 128.9, 129.2, 130.2, 138.8, 167.6; IR (ATR) 3372, 1612 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}NO_2$ 296.1645 $(M+H)^+$, found 296.1653.

5-Hydroxy-6-methyl-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine (IIc). Compound **IIc** was prepared from **13c** (70 mg, 0.24 mmol) according to a similar procedure described for the preparation of **IIa** from **13a**. Colorless crystals (67.1 mg, 95%): mp 184–186 °C; in the ^{1}H NMR spectrum, signals due to the *syn* diastereomer were observed and those of the *anti* isomer were negligible; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.55–1.60 (m, 2H), 2.06–2.09 (m, 1H), 2.18

(s, 3H), 2.24–2.30 (m, 1H), 2.36 (s, 3H), 2.61–2.65 (m, 1H), 4.76–4.80 (m, 1H), 5.26 (br, 1H), 5.27 (br, 1H), 6.37 (d, *J* = 7.6 Hz, 1H), 6.78 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 20.1, 20.9, 22.7, 39.5, 47.6, 66.1, 127.1, 127.4, 127.9, 128.7, 129.0, 134.3, 136.1, 138.4, 143.5, 168.0; IR (ATR) 3398, 1607 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}NO_2$ 296.1645 $(M+H)^+$, found 296.1651.

5-(*N*,*N*-Dimethylamino)-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine (IIIa). A mixture of **13a** (157 mg, 0.56 mmol), 40% methylamine in methanol (2 mL), MS4A (360 mg), and methanol (2 mL) was refluxed for 6 h. After being cooled to room temperature, the mixture was treated with $NaBH_4$ (30 mg, 0.79 mmol), and stirred overnight at room temperature. The insoluble material was removed by filtration, and the filtrate was concentrated. To the concentrate was added CH_2Cl_2, and the mixture was washed with H_2O, brine, dried, and concentrated to give 5-(*N*-methylamino)-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine (168 mg), which was used for in the next reaction without further purification. To a mixture of the crude product, 37% HCHO (0.18 mL), $NaBH_3CN$ (46 mg, 0.73 mmol), and methanol (2 mL) was added acetic acid (0.12 mL, 1.97 mmol) at 0 °C. After being stirred for 6 h at room temperature, the mixture was poured into 10% K_2CO_3 (aq), extracted with ethyl acetate, dried,

and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3:1) to afford **IIIa** as colorless crystals (157 mg, 90%): mp 109–110 °C; signals of a mixture of *anti*/*syn* diastereomers were observed in the ^{1}H NMR and ^{13}C NMR spectra, and the ratio differed depending to the solvent used (see Table 3 in the main text); the data in DMSO-d_6 (*anti*/*syn* = 1:0.82) are as follows (in the NMR, only the distinguishable peaks are described); ***anti* isomer**, ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.07–1.13 (m, 1H), 1.24–1.30 (m, 1H), 1.77–1.82 (m, 1H), 2.05–2.11 (m, 1H), 2.18 (s, 3H), 2.34 (s, 6H), 3.02 (br, 1H), 3.25–3.32 (m, 1H), 3.94–3.98 (m, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.90–7.07 (m, 4H), 7.18–7.21 (m, 1H), 7.48 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 20.9, 23.2, 28.2, 43.5, 44.8, 46.0, 64.8, 126.0, 127.3, 127.9, 128.4, 128.7, 132.2, 133.6, 138.5, 139.4, 168.7; ***syn* isomer**, ^{1}H NMR δ 1.53–1.59 (m, 0.8H), 1.64–1.67 (m, 0.8H), 2.05–2.11 (m, 0.8H), 2.09 (s, 4.8H), 2.18 (s, 2.4H), 2.20–2.25 (m, 0.8H), 2.34 (s, 2.4H), 2.57–2.62 (m, 0.8H), 3.56 (br, 0.8H), 4.84–4.89 (m, 0.8H), 6.76 (d, *J* = 6.7 Hz, 0.8H), 6.90-7.07 (m, 3.2H), 7.18–7.21 (m, 0.8H), 7.28 (d, *J* = 6.3 Hz, 1.6H); ^{13}C NMR δ 23.9, 29.3, 40.2, 43.5, 47.4, 71.7, 126.3, 127.8, 128.0, 128.2, 130.3, 134.5, 138.6, 143.1, 18.9; IR (ATR) 2951, 1641 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{24}N_2O$ 309.1961 $(M+H)^+$, found 309.1968.

5-(*N*,*N*-Dimethylamino)-9-methyl-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine

(IIIb). Compound **IIIb** was prepared from **13b** (387 mg, 1.32 mmol) according to a similar procedure described for the preparation of **IIIa** from **13a**. Colorless crystals (320 mg, 75%): mp 84–85 °C; signals of a mixture of *anti*/*syn* (= 1:0.16) diastereomers were observed in the ^{1}H NMR and ^{13}C NMR spectra, ***anti* isomer** (major isomer), ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.96–1.03 (m, 1H), 1.94–1.26 (m, 1H), 1.74–1.78 (m, 1H), 1.76 (s, 3H), 2.03–2.13 (m, 1H), 2.18 (s, 3H), 2.34 (s, 6H), 3.14–3.17 (m, 1H), 3.55–3.58 (m, 1H), 4.00–4.04 (m, 1H), 6.91 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), ^{13}C NMR (150 MHz, DMSO-d_6) δ 17.6, 20.9, 23.4, 28.7, 44.7, 45.2, 65.1, 123.8, 125.8, 127.1, 127.9, 128.1, 129.0, 133.3, 138.4, 139.9, 168.0; ***syn* isomer** (minor isomer), ^{1}H NMR δ 2.08 (s, 0.96H), 2.21 (s, 0.48H), 2.34 (s, 0.48H), 4.83–4.86 (br, 0.6H), 5.39 (br, 0.3H), 6.53 (d, J = 7.6 Hz, 0.3H), 7.06 (t, J = 7.2 Hz, 0.3H), 7.27 (d, J = 7.2 Hz, 0.3H), 7.29 (d, J = 7.7 Hz, 0.6H); ^{13}C NMR δ 21.0, 23.4, 27.3, 44.0, 50.0, 63.3, 126.6, 128.1, 128.2, 128.8, 129.4, 135.3, 136.8, 138.7, 142.2, 170.0; IR (ATR) 2936, 1636, 1381 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{26}N_2O$ 345.1937 $(M+Na)^+$, found 345.1941.

5-(*N*,*N*-Dimethylamino)-6-methyl-1-(*p*-toluoyl)-2,3,4,5-tetrahydro-*1H*-1-benzazepine

(IIIc). Compound **IIIc** was prepared from **13c** (81 mg, 0.26 mmol) according to a similar procedure described for the preparation of **IIIa** from **13a**. A white powder (59 mg, 70%); in the

^{1}H NMR spectrum, signals due to the *syn* diastereomer were observed and those of the *anti* isomer were negligible; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.47 (t, J = 13.6 Hz, 1H), 1.61 (d, J = 12.5 Hz, 1H), 2.07 (s, 6H), 2.13–2.23 (m, 2H), 2.18 (s, 3H), 2.30 (s, 3H), 2.54 (t, J = 12.6 Hz, 1H), 3.47 (br, 1H), 4.79 (d, J = 13.0 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.87 (dd, J = 7.5, 7.6 Hz, 1H), 6.95 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 20.9, 21.2, 23.7, 28.8, 44.4, 47.8, 63.5, 127.0, 127.8, 128.4, 128.9, 129.1, 134.6, 137.5, 137.9, 138.3, 143.8, 168.7; IR (ATR) 2948, 1636, 1453 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{26}N_2O$ 345.1937 $(M+Na)^+$, found 345.1941.

X-ray Crystallographic Data. Crystal data of **Ia** is reported in the ref.6. (CCDC 251227).

Crystal data of Ib (CCDC 1443486): $C_{18}H_{18}ONCl$: mp 137–138 °C, *M*r = 299.80, CuKα (λ = 1.54187 Å), triclinic, *P*-1, colorless prism 0.20 × 0.20 × 0.10 mm, crystal dimensions a = 9.43615 (17) Å, b = 9.54443 (17) Å, c = 17.4522 (4) Å, α = 84.4167 (8)°, β = 89.6078 (9)°, γ = 78.8942 (9)°, T = 173 K, Z = 4, V = 1534.92 (5) Å^3, D_{calc} = 1.297 gcm^{-3}, μCuKα = 18.980 cm^{-1}, F_{000} = 632.00, GOF = 1.146, R_{int} = 0.0566, R_1 = 0.0518, wR_2 = 0.0772.

Crystal data of Ic (CCDC 1443487): $C_{19}H_{21}ON$: mp 76–78 °C, *M*r = 279.38, CuKα (λ = 1.54187 Å), monoclinic, $P2_1$, colorless prism 0.45 × 0.45 × 0.05 mm, crystal dimensions a = 7.7089 (3) Å, b = 11.7832 (4) Å, c = 17.4740 (6) Å, α = 90°, β = 10.653 (2)°, γ = 90°, T =

173 K, Z = 4, V = 1559.90 (8) Å^3, D_{calc} = 1.190 gcm^{-3}, μCuKα = 5.644 cm^{-1}, F_{000} = 600.00, GOF = 1.049, R_{int} = 0.0371, R_1 = 0.0325, wR_2 = 0.1006, Flack parameter = –0.0 (3).

Crystal data of IIc (CCDC 1443488): $C_{19}H_{21}O_2N_2$: mp 184–186 °C, *M*r = 309.39, CuKα (λ = 1.54187 Å), monoclinic, $P2_1/n$, colorless prism 0.40 × 0.35 × 0.05 mm, crystal dimensions a = 11.2708 (3) Å, b = 10.4765 (3) Å, c = 13.4089)3) Å, α = 90°, β = 99.427 (2)°, γ = 90°, T = 173 K, Z = 4, V = 1561.92 (6) Å^3, D_{calc} = 1.316 gcm^{-3}, μCuKα = 6.863 cm^{-1}, F_{000} = 660.00, GOF = 1.632, R_{int} = 0.0343, R_1 = 0.0491, wR_2 = 0.1637.

Crystal data of IIIa (CCDC 1443489): $C_{20}H_{24}ON_2$: mp 109–110 °C, *M*r = 308.42, CuKα (λ = 1.54187 Å), triclinic, *P*-1, colorless prism 0.25 × 0.25 × 0.20 mm, crystal dimensions a = 9.2514 (2) Å, b = 9.3547 (2) Å, c = 10.3366 (2) Å, α = 78.33 (1)°, β = 82.189 (1)°, γ = 75.906 (1)°, T = 173 K, Z = 2, V = 846.17 (3) Å^3, D_{calc} = 1.210 gcm^{-3}, μCuKα = 5.829 cm^{-1}, F_{000} = 332.00, GOF = 1.634, R_{int} = 0.0286, R_1 = 0.0501, wR_2 = 0.1600.

Computational Methodology. Conformer generations were performed for **Ia**, **Ib**, **Ic**, **IIa**, **IIc**, and **IIIa** using the RDkit[8] with UFF. All HF/DFT calculations were performed with Gaussian 09.[20] In HF/DFT calculations, geometry optimizations in the gas phase were carried out at the RHF/6-31G(d,p), RB3LYP/6-31G(d,p), and RB3LYP/6-31+G(d,p) levels. The SCF (self-consistent field) energies at the RB3LYP/6-31+G(d,p) level were compared with the stability

of conformers. The lowest-energy conformers showed good agreement with the X-ray structures.[21] For more accurate comparison of the stability at room temperature (298.15 K), Gibbs free energies were computed using vibrational analyses with B3LYP/6-311+G(d,p).

ASSOCIATED CONTENT

Supporting Information Available:

^{1}H, ^{13}C and 2D NMR (NOESY, COSY, and HMQC) spectra for new compounds, comparison of ^{1}H NMR spectra for **IIa**–**c** and **IIIa**–**c**, ^{1}H NMR analytical data of **Ib** (major), VT NMR at elevated temperatures for **Ia**, **IIa**, and **IIIa**, and VT NMR at lower temperatures for **Ib** and **Ic**, X-ray data (CIF) for compounds, **Ib**, **Ic**, **IIc**, and **IIIa**, and detailed DFT calculation results (energy differences and atomic coordinates) for compounds, **Ia**, **Ib**, **Ic**, **IIa**, **IIc**, and **IIIa**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

***E-mail:** natsu@pharm.teikyo-u.ac.jp

Notes

The authors declare no competing financial interest.

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(8) A reviewer has suggested that the two stereogenic elements are substituent tropicity and a tetrahedral atom with four different ligands. According to the suggestion, the diastereomers of (a*S*,5*R*) (*anti*) and (a*R*,5*R*) (*syn*) described in the text correspond to those of (g^+g^-,5*R*) and

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(9) Dr. M. Qadir et al. reported (See Reference 6) that the major isomer of **Ia** takes predominantly the *syn* form in solution (^{1}H NMR), whereas in the solid state (by X-ray crystal analysis) it takes the *anti* form, The *anti* form in the crystal state was explained by the result of a better crystal packing arrangement, since the energy barrier between the *anti*/*syn* conformers is fairly surmountable under ambient conditions ($\Delta G^{\ddagger}$ = 63.4 kJ/mol). The assignment in solution relied on the 2D-NOESY and NOE analyses,[7] which may raise the issue of uncertainty of NOESY analysis when the conformations of the compound in question are exchangeable as in **Ia**.

(10) RDKit: Open-source cheminformatics: http://www.rdkit.org.

(11) The description "*E*/*Z*" is used according to the IUPAC nomenclature around N–C(=O) bond of amide. The *E* isomer has the *cis* relative arrangement of the two benzene rings of *N*-benzoyl-1-benzazepines and the *Z* isomer has the *trans* one.

(12) The terms a*S* and a*R* are those of nomenclature based on the chiral axis, which correspond to *P* and *M* based on the helix nomenclature, respectively.

(13) Several very small peaks that may originate in the *Z* isomer were observed in the ^{1}H NMR spectrum; in particular, the small peaks were noticeable in compounds **Ib**, **IIb**, and **IIIb**, which bear a substituent (Cl or CH_3) at the C9 position (see, Figure 5, and Figures S1 and S2 in the Supporting Information). However, the peaks were not sufficient to assign the entire *Z* structure. The *E* stereochemistry was determined by the NOESY experiment on **IIb** and **IIIb**, in which the 9-CH_3 group showed a correlation with the protons of the benzoyl ring. Formation of the *E* structure in compounds **I**–**III** is consistent with the report that *N*-benzoyl-*N*-methylanilines exist in a *E* structure; Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 2833–2838. Preference for the *E*-amide isomer over the *Z* isomer was also supported by our DFT calculation studies, e.g., in the compound **Ia** shown in Figure 8, all the *Z* isomers of **Ia** exhibited higher energy values than the corresponding *E* isomers. The energy differences (ΔG_{298}) of the *E*/*Z* conformers in comparison with the lowest-energy conformer (*E*-*anti*-chair of **Ia**) determined by DFT calculation are as follows: *E*/*Z* (kJ/mol) = 0/+10.4 for *anti*-chair, +3.6/+14.6 for *anti*-boat, +4.0/+10.2 for *syn*-chair, and +13.2/+17.7 for *syn*-boat).

(14) See the Supporting Information for the detailed ^{1}H NMR analytical data of the methylene protons of **Ib** (major). The values of the vicinal coupling (^{3}J) correspond well with those

estimated from the torsion angles by the Karplus equation (Karplus, M. *J. Am. Chem. Soc.*, **1963**, *85*, 2870–2871).

(15) Compound **Id** (*N*-*p*-toluoyl analogue of **Ib**) was used for the NOEDS analysis in place of **Ib** (*N*-benzoyl derivative) to distinguish the aromatic proton signals easily.

(16) For determination of $\Delta G^{\ddagger}$ values by VT NMR, see: Boiadjiev, S. E.; Lightner, D. A. *Tetrahedron* **2002**, *58*, 7411–7421.

(17) Close inspection of the VT NMR images (Figure 8 for **Ia**, Figure S6 for **Ib**, and Figure S7 for **Ic**) indicated that the signal of H^{2e} in the *syn* isomer showed broadening at around 253 K, although similar sharp signals were observed at 296 K and 183 K. These phenomena may suggest that the *syn i*somer also exists as a mixture of chair and boat forms at low temperatures, although the content of the boat form is very small (e.g., < 2%). The large energy difference between the chair and boat forms in the *syn* isomer of **Ia**–**c** obtained by the DFT calculation (ΔG: 7.3–9.2 kJ/mol) also supports this suggestion.

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(21) One exception is the discrepancy observed for **IIIa,** which showed, as the the lowest-energy conformer, the *E*-*anti*-boat form in the X-ray analysis (Figure 6) and the *E*-*anti*-chair form by the DFT calculation (Table S6 in the Supporting Information). The *E*-*anti*-boat form was the second lowest-energy conformer in the calculation. Since the energy difference (ΔG) obtained by the calculation between both forms (chair/boat) is very small (0.38 kJ/mol), this could be caused by a crystal packing arrangement.