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ATROPISOMERIC AND CONFORMATIONAL PROPERTIES OF 6*N*-BENZOYL- AND 6*N*-*p*-TOSYL-1,6-BENZODIAZOCINES: COMPARISON WITH THOSE OF 1,5-BENZODIAZEPINES

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Abstract – The atropisomeric and conformational properties of the eight-membered 1,6-benzodiazocines (**2**) with 6*N*-benzoyl (**A**) and 6*N*-*p*-tosyl (**B**) groups were examined by comparing them with those of the seven-membered 1,5-benzodiazepine congeners (**1**) (**A**, **B**). The conformation (orientation) of the benzene ring in the benzoyl and tosyl groups differed depending on the ring size (7/8) and *N*-substituent (-CO-/-SO_2-). The activation free-energy barrier to rotation of the axes in *N*-*p*-tosyl derivatives (**B**) was shown to be much higher than those of the benzoyl derivatives (**A**).

INTRODUCTION

Benzo-fused seven-membered-ring nitrogen-heterocycles are found as the scaffolds of many biologically active molecules[1] Since these heterocycles possess relatively flexible rings, the ring often changes its conformation so as to exert biological activity. It should be noted that, although often overlooked, atropisomerisms[2] are latent in these heterocycles. Thus far, we have investigated the conformations of several seven-membered-ring nitrogen-heterocycles and their relationships with their biological activities.[3] 5*N*-Benzoyl derivatives of 1,5-benzodiazepine (**1A**),[3d] which form the core structure of the vaptan class of arginine-vasopressin (VP) receptor ligands, were our first target.[3d,i,k] The (a*R*)- and (a*S*)-atropisomers[4] caused by the Ar–N(CO) (sp^2–sp^2) axis are present in **1A**, and, although the conformational change in the compound of **1A** type without a substituent at the *ortho*-position (*C*6) on the benzene ring was too rapid for isolation of the isomers at rt, the molecules with a substituent (Me) at *C*6 were conformationally "frozen" and could be separated into relatively stable isomers (Figure 1). Interestingly, the VP antagonistic activity was revealed to reside in the (a*S*)-isomer. Recently, we have investigated the congener 5*N*-*p*-toluenesulfonyl (tosyl) derivatives (**1B**)[3h] and revealed that they also possess the atropisomeric properties caused by the Ar–N(SO_2) axis[5] similar to the *N*-benzoyl derivatives (Figure 1). Interestingly, however, the properties were shown in some points to be very different between **1A** and **1B**, *e.g.*, **1B** showed an extraordinarily high activation free-energy barrier to rotation between the (a*R*)- and (a*S*)-isomers ($\Delta G^{\ddagger}$ = 132 kJ/mol) compared with that of **1A** (104 kJ/mol).[3h] That prompted us to investigate the atropisomeric and conformational properties of the related heterocycles with *N*-benzoyl and *N*-tosyl groups in more detail. In this paper, we deal with the eight-membered 1,6-benzodiazocines (**2**) with 6*N*-benzoyl (**A**-series) and 6*N*-tosyl (**B**-series) groups by comparing them with the seven-membered 1,5-benzodiazepine congeners (**1**) (**A**, **B**) (Figure 1).

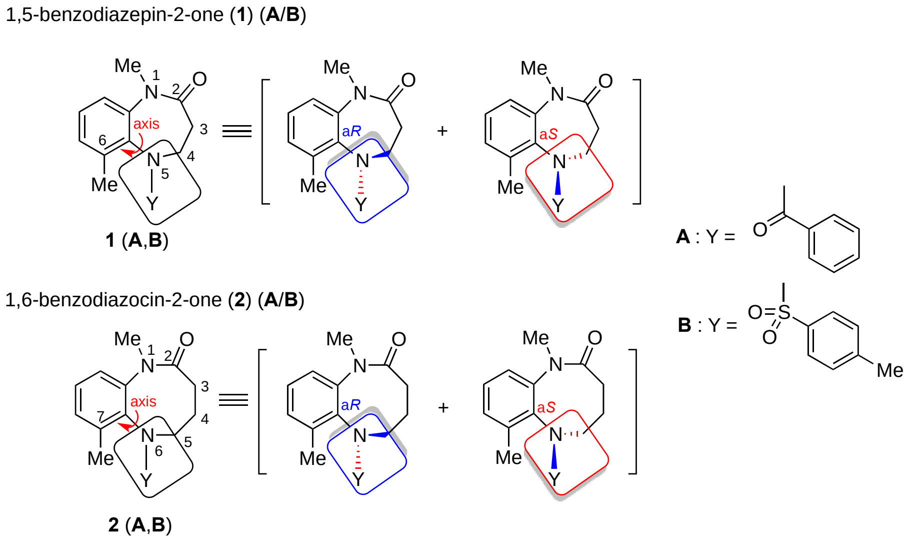


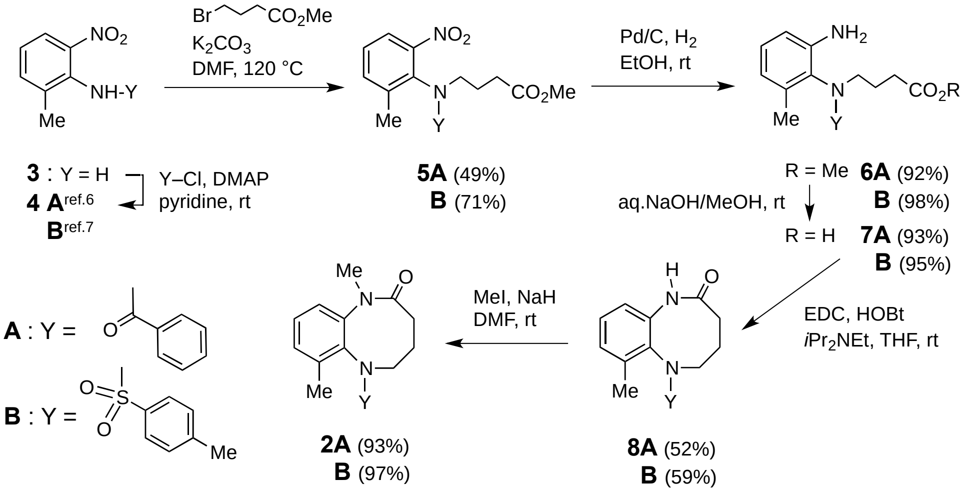
Figure 1. Atropisomers (a*R*/a*S*) in 1,5-benzodiazepin-2-one (**1**) and 1,6-benzodiazocin-2-one (**2**) with *N*-benzoyl (**A**) and *N*-tosyl (**B**) groups

RESULTS AND DISCUSSION

1. Preparation

N-Benzoyl- and *N*-tosyl-1,6-benzodiazocin-2-ones (**2A** and **2B**) were prepared starting from 3-nitro-6-methylaniline (**3**), as shown in Scheme 1. Reaction of the aniline (**3**) with benzoyl chloride and *p*-toluenesulfonyl chloride in pyridine followed by *N*-alkylation of the products (**4A**[6]/**B**[7]) with methyl 4-bromobutyrate in the presence of K_2CO_3 in DMF at 120 °C afforded the nitro-esters (**5A**/**B**).

Conventional catalytic reduction of the nitro group in **5A/B** afforded the amino-esters (**6A/B**), which were hydrolyzed to the amino-carboxylic acids (**7A/B**). Cyclization of **7A/B** to the eight-membered lactams (**8A/B**) was performed with *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) in the presence of HOBt and *i*Pr$_2$NEt in THF at rt. *N*-Methylation of the lactams with MeI in the presence of NaH in DMF at rt afforded the 6*N*-benzoyl- and 6*N*-*p*-tosyl-1,7-dimethyl-1,6-benzodiazocin-2-ones (**2A** and **2B**).



Scheme 1. Preparation of 1,6-benzodiazocin-2-one derivatives (**2A** and **2B**)

2. Conformation

First, the structures of the 1,6-benzodiazocine derivatives (**2A** and **2B**) in solution and solid states were examined using ^{1}H NMR (Figure 2) and X-ray crystallographic analysis (Figure 3) by comparing them with those of the previously reported 1,5-benzodiazepine derivatives (**1A**[3d] and **1B**[3h]). The *N*-benzoyl-1,5-benzodiazepine (**1A**) has the *cis*- and *trans*-amide rotamers[8] around the N–C(=O) bond in addition to the axial isomers based on the Ar–N(CO) (sp^2–sp^2) axis. In the NMR spectrum of **1A**, a *cis*/*trans* ratio of *ca*. 1:0.1 was observed (Figure 2A), whereas these isomers could not be separated and in crystal only the *cis*-isomer was obtained (see the X-ray analysis) (Figure 3). The preference for the *cis*-isomer in **1A** can be explained as attributable to the strong π–π-interaction between the two benzene rings.[9] On the other hand, the eight-membered congener *N*-benzoyl-1,6- benzodiazocine (**2A**) showed the *cis*/*trans* ratio of *ca*. 1:0.3. The increase in the *trans*-isomer (= decrease in the *cis*-isomer) in **2A** presumably reflects the decreased π–π-interaction between the two benzene rings compared with **1A** as shown in the X-ray analysis. It should be noted that the *cis*/*trans* isomers were not observed in the *N*-tosyl derivatives (**1B**/**2B**) (Figure 2B).

As shown in Figure 2, the chemical shift of the two methyl groups (*N*-Me and Ar-Me) provided good information on the conformation (orientation) of the benzene ring in the *N*-substituent in solution. The

N-Me group in *cis*-**2A** was observed at a higher field (δ 2.53 ppm) compared with that in *cis*-**1A** (δ 3.51 ppm), and the Ar-Me group in *cis*-**2A** was observed at a lower field (δ 2.45 ppm) compared with that in *cis*-**1A** (δ 1.97 ppm) (Figure 2A). The higher chemical shift of *N*-Me in **2A**, and that of Ar-Me in **1A** can be explained as due to the Me locating over the benzene ring of the benzoyl group (anisotropy effect), and the results were supported by the X-ray crystal structures of **1A** and **2A**, as indicated by broken arrows in Figure 3. Meanwhile, as shown in Figure 2B, in the *N*-tosyl derivatives (**1B**/**2B**), the chemical shift of the two methyl groups (*N*-Me and Ar-Me) showed the opposite movement from that of the *N*-benzoyl derivatives (**1A**/**2A**) described above, and the conformation was proven to be similar both in the solution and solid states.

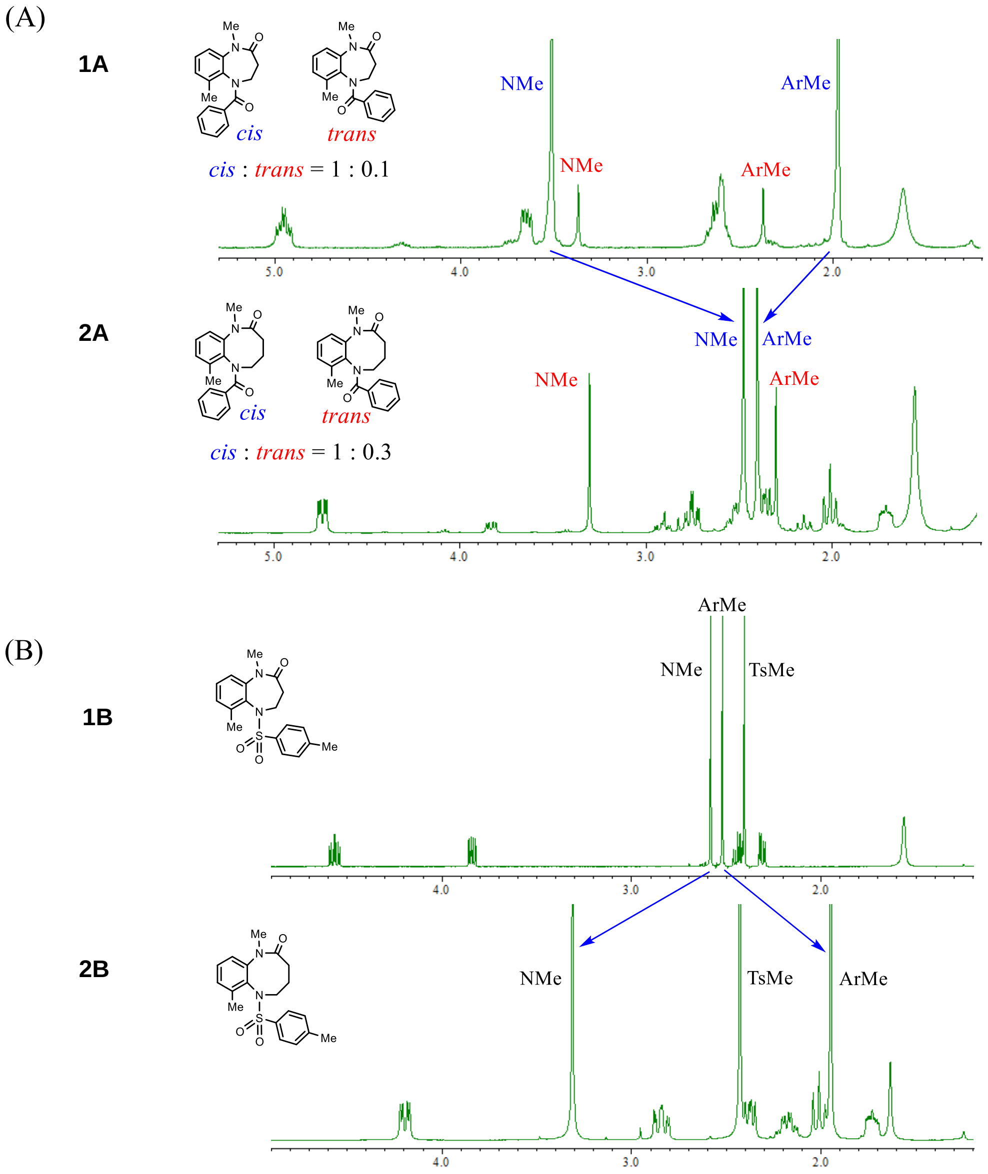


Figure 2. ^{1}H NMR ($CDCl_3$) spectra: (A) **1A** and **2A**, (B) **1B** and **2B**. *Cis*/*trans* isomers do not occur in **1B**/**2B**.

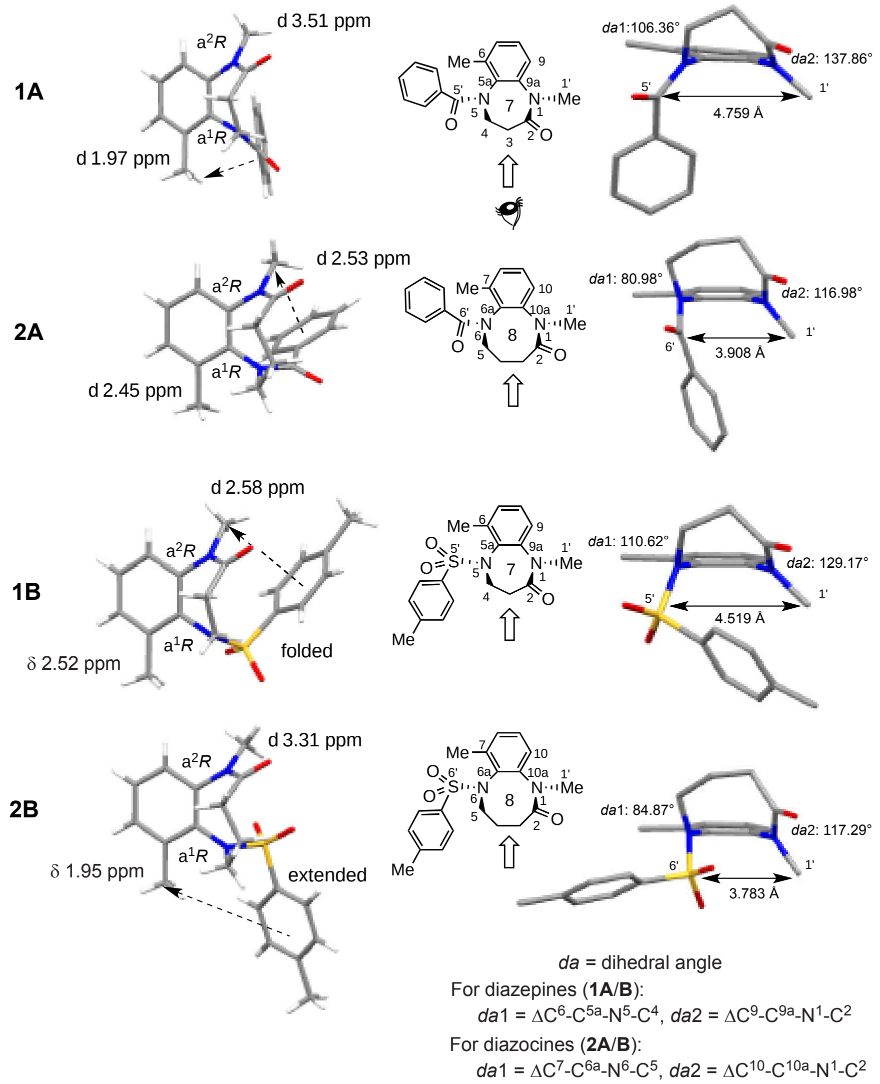


Figure 3. X-Ray crystal structures of **1A**, **2A**, **1B**, and **2B**. As for **2A** and **2B**, the structures with the a^1*R* stereochemistry were extracted from the CIF data of the racemates.

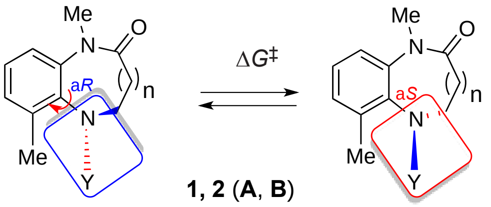
It should be noted that, in addition to the axial chirality due to the sp^2–sp^2 axis of Ar–N(CO)/Ar–SO$_2$ (a^1), the compounds (**1A**, **2A**, **1B**, and **2B**) have another axial chirality due to the sp^2–sp^2 axis of Ar–N^1(C^{2}O) (a^2). These axes, however, move together like a gear forming only a stable diastereomer with a relative stereochemistry of (a^1*R**, a^2*R**), as shown in Figure 3;[10] the other diastereomer (a^1*R**, a^2*S**) appears not to form because of ring strain.[11]

On the right side of Figure 3, the molecular shapes of **1A**, **2A**, **1B**, and **2B** viewed from the chain-side of the ring are shown. All have a cage (boat-like) structure, and the conformation of the diazepine ring is similar between **1A** and **1B** regardless of the *N*-substituent, and that of the diazocine ring in **2A** and **2B** is also similar. The dihedral angles (*da*) of C^6-C^{5a}-N^5-C^4 (*da*1) and C^9-C^{9a}-N^1-C^2 (*da*2) for 1,5-benzodiazepin-2-ones (**1A/1B**) are larger than those of C^7-C^{6a}-N^6-C^5 (*da*1) and C^{10}-C^{10a}-N^1-C^2 (*da*2) for 1,6-benzodiazocin-2-ones (**2A/2B**), meaning that, compared with the ring of the diazepine **1A/1B**, that of the diazocine **2A/2B** has a more caged form and the distance between $C^{1'}$ and $C^{6'}$ (or $S^{6'}$) in **2A/2B** is shorter than that between $C^{1'}$ and $C^{5'}$ (or $S^{5'}$) in **1A/1B**.

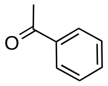
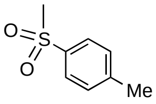
3. Atropisomers

Similar to the seven-membered 1,5-benzodiazepines (**1A**, **1B**), the 8-membered 1,6-benzodiazocines (**2A**, **2B**) could be separated into the (a*R*)- and (a*S*)-enantiomers using HPLC on a chiral column. Table 1 shows the physicochemical properties of the enantiomers. The absolute stereochemistry of the enantiomers of **2A** and **2B** was deduced by the (+)/(−)-angle of optical rotation compared with that of the **1A** and **1B**,[12] and the structure of (−)-**2B** was definitively confirmed to be (a*S*) by X-ray crystal analysis (Figure 4).[13]

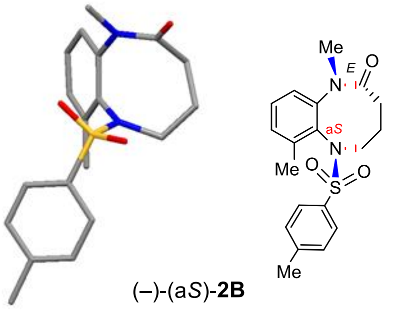
Table 1. Physicochemical Properties of the Atropisomers of **1A**, **2A**, **1B**, and **2B**



1, 2 (**A**, **B**)

	Y	n	$[a]_D^{20}$ (MeOH)		DG‡ (kJ/mol)	Racemization 1)
1A	 **A**	1	(a*R*) –115.0	(a*S*) +113.1	104	50 °C, 5 h in toluene
2A		2	(a*R*) –416.1 2)	(a*S*) +422.1 2)	118	80 °C, 8 h 3) in toluene
1B	 **B**	1	(a*R*) +159.7	(a*S*) –155.2	132	150 °C, 2 h in DMF 4)
2B		2	(a*R*) +152.1	(a*S*) –161.6	129	140 °C, 1 h in DMF

1)Conditions required for racemization. 2)The absolute stereochemistry of (+)/(–)-2**A** is tentatively assigned as shown in the Table.[ref.12] 3)40% was isomerized (see, Supporting Inf.). 4)At 80 °C in toluene, not isomerized after 4 h.



(–)-(a*S*)-**2B**

Figure 4. X-Ray crystal structure of (−)-(a*S*)-**2B**

The activation free-energy barriers to rotation ($\Delta G^{\ddagger}$) were estimated experimentally from the conversion profiles between the (a*R*)- and (a*S*)-enantiomers.[14] Table 1 shows the $\Delta G^{\ddagger}$ values and conditions required for racemization of the enantiomers. In the course of racemization, the cage structure should also be inverted. As described above, compared with the seven-membered ring of **1A**/**1B**, the eight-membered ring of 1,6-benzodiazocin-2-ones (**2A**/**2B**) has more deeply caged conformations. Thus, it is reasonable to assume that **2A**/**2B** has greater resistance to the inversion of the ring system, including the axis, than **1A**/**1B**.[15,16] The assumption coincided for the *N*-benzoyl derivatives (**1A**/**2A**); the $\Delta G^{\ddagger}$ value of **1A** was 104 kJ/mol and that of **2A** was 118 kJ/mol, with an energy difference of 14 kJ/mol.

Contrary to our expectation, however, in the *N*-tosyl derivatives (**1B**/**2B**), high $\Delta G^{\ddagger}$ values at a similar level were observed, *i.e.*, 132 kJ/mol for **1B** and 129 kJ/mol for **2B**. Although the reason for this difference between **1B**/**2B** and **1A**/**2A** is not apparent, this unexpected result may be ascribed to the intrinsic properties of the Ar–N(SO_2) axis. The N–S plane in **1B** and **2B** possesses a bulky *S*-substituent (*i.e.*, SO_2-aryl). Because of the bulky substituent, the steric hindrance between the $C^{6\ (\mathrm{or}\ 7)}$-Me group is enhanced and the rotation around the Ar–N(SO_2) axis is highly hindered compared with that around the Ar–N(CO) axis, resulting in an the extraordinarily high energy barrier to rotation (~130 kJ/mol) to **1B**/**2B**. Thus, since the energy barrier to rotation around the axis is too high, the difference in the ring size (7/8) between **1B** and **2B** induces little effect on the energy barrier to rotation.

4. Computational study of 1B and 2B

It is interesting that the orientation of the benzene ring of the tosyl moiety differs between **1B** and **2B**, as shown in Figure 3. That is, the benzene ring of **1B** locates over the diazepine ring (folded form), whereas that of **2B** locates *anti* to the diazocine ring (extended form). To obtain information on the difference, the stable conformation of the *N*-tosyl derivatives **1B** and **2B** were analyzed by DFT calculation.

The 12 conformers of **1B** were generated starting from the 2D chemical structures of **1B** using the RDKit.[17] Among them, the six conformers with a^1R stereochemistry were analyzed to obtain the stable conformations by DFT calculation at 298 K in solution state (CH_2Cl_2)[18] using Gaussian 09[19] at the RB3LYP/6-31+G (d,p) level. The calculation yielded **1B** with the folded form as the lowest-energy conformer (for the structure, see Figure S2 in Supporting Inf.), which was in good agreement with the X-ray structure of **1B** shown in Figure 3. The energy level of the extended form was shown to be unstable by 2.97 kJ/mol (ΔG) compared with that of the lowest (folded) conformer. On the other hand, similar analysis of the stability of the conformers of **2B** (22 conformers generated with a^1R stereochemistry) identified the extended form as the lowest one (for the structure, see Figure S3 in Supporting Inf.), which was again in good agreement with the X-ray structure of **2B** shown in Figure 3. The second lowest-energy conformer of **2B** was shown to have the orientation of the folded form with a ΔG value of 1.76 kJ/mol.

The preference for the folded form in **1B** and the extended form in **2B** may well be explained by the difference in the distance between $C^{1'}$–$S^{5'}$ in **1B** (4.519 Å) and $C^{1'}$–$S^{6'}$ in **2B** (3.783 Å) (Figure 3). The shorter distance in **2B** may cause a steric hindrance to the $C^{1'}H_3$, which forces the bulky substituent (-SO_2-*p*-tolyl) to locate *anti* to the diazocine ring to give the extended form as the stable conformer.

5. Conclusion

The atropisomeric and conformational properties of the 1,5-benzodiazepines (**1**)/1,6-benzodiazocines (**2**) with *N*-benzoyl (**A**) and *N*-tosyl (**B**) groups were examined to reveal that the conformation (orientation) of the benzene ring in the benzoyl and tosyl groups differs depending on the ring size (7/8) and *N*-substituent (-CO-/-SO_2-), and is similar both in the solution and solid states. The activation free-energy barrier to rotation of the axis in *N*-tosyl derivatives (**B**) was shown to be much higher than those of the benzoyl derivatives (**A**). These findings may be useful for understanding the chemical properties of the related compounds with medium-sized ring systems and for future drug design of biologically active compounds.

EXPERIMENTAL

General remarks: 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 obtained with an ionization mode of ESI. IR spectra were recorded on an FT-IR spectrometer equipped with ATR (Diamond). Optical rotations were determined with a digital polarimeter. Melting points were recorded on a melting point apparatus and are uncorrected.

Methyl 4-*N*-benzoyl-*N*-(2-methyl-6-nitrophenyl)aminobutyrate (5A). To a solution of *N*-(2-methyl-6-nitrophenyl)benzamide (**4A**)[6] (481 mg, 1.88 mmol) in DMF (5.0 mL) was added methyl bromobutyrate (441 mg, 2.44 mmol) and potassium carbonate (778 mg, 5.63 mol). After the mixture was stirred for 6 h at 120 °C, cooled to 0 °C, water was added to the mixture. The aqueous solution was extracted with EtOAc, and the combined organic layer was washed with H_2O and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (silica gel, EtOAc/hexane = 1/9) to afford **5A** as a pale yellow oil (329 mg, 49%): ^1H NMR (600 MHz, $CDCl_3$)

(*cis*:*trans* = 1:0.25) (*cis*-form) δ 1.91–1.98 (m, 1H), 2.00–2.06 (m, 1H), 2.28 (s, 3H), 2.33–2.44 (m, 2H), 3.56 (ddd, *J* = 5.2, 11.0, 13.5 Hz, 1H), 3.65 (s, 3H), 3.94 (ddd, *J* = 5.2, 11.0, 13.5 Hz, 1H), 7.13 (dd, *J* = 7.6, 7.9 Hz, 2H), 7.23–7.31 (m, 4H), 7.38 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.69 (dd, *J* = 1.0, 7.9 Hz, 1H); (*trans*-form) δ 1.72–1.76 (m, 0.5H), 2.04–2.08 (m, 0.5H), 2.45 (s, 0.75H), 3.33–3.38 (m, 0.25H), 3.53 (s, 0.75H), 3.54–3.57 (m, 0.25H), 7.41–7.44 (m, 0.25H), 7.47–7.49 (m, 0.75H), 7.57–7.61 (m, 0.75H), 7.92 (d, *J* = 7.5 Hz, 0.25H); ^{13}C NMR (150 MHz, $CDCl_3$) (*cis*-form) δ 18.6, 22.6, 31.5, 50.2, 51.6, 123.5, 126.3, 127.6, 127.7, 128.2, 128.7, 130.2, 135.3, 135.9, 139.0, 170.1, 173.2; (*trans*-form) δ 18.2, 23.5, 30.9, 51.3, 123.6, 128.3, 129.9, 135.4, 135.9, 147.2; IR (ATR) 2952, 1739, 1674, 1523 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_2O_5$ 379.1264 $(M+Na)^+$, found 379.1265.

Methyl 4-*N*-[(4-methylphenyl)sulfonyl]-*N*-(2-methyl-6-nitrophenyl)aminobutyrate (5B). To a solution of 4-methy-*N*-(2-methyl-6-nitrophenyl)benzenesulfonamide (**4B**)[7] (761 mg, 2.49 mmol) in DMF (6.0 mL) was added methyl bromobutyrate (496 mg, 2.74 mmol) and potassium carbonate (1.0 g, 7.47 mol). After the mixture was stirred for 18 h at 120 °C, cooled to 0 °C, water was added to the mixture. The aqueous solution was extracted with EtOAc, and the combined organic layer was washed with H_2O and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (silica gel, EtOAc/hexane = 1/20) to afford **5B** as colorless crystals (720 mg, 71%): mp 89–91 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.91–2.01 (m, 2H), 2.23 (s, 3H), 2.33 (t, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 3.64 (s, 3H), 3.65–3.68 (m, 2H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.65 (dd, *J* = 0.9, 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.1, 21.5, 23.8, 31.2, 51.1, 51.6, 123.3, 127.4, 128.8, 129.7, 130.8, 135.6, 136.8, 142.7, 143.9, 150.3, 173.1; IR (ATR) 1748, 1533 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}N_2O_4S$ 429.1091 $(M+Na)^+$, found 429.1093.

Methyl 4-*N*-benzoyl-*N*-(6-amino-2-methylphenyl)aminobutyrate (6A). To a solution of **5A** (662 mg, 1.86 mmol) in EtOH (19 mL) was added 10% palladium on carbon (63 mg). After the mixture was stirred at 25 °C for 3 h under a hydrogen atmosphere, the mixture was filtered. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography (silica gel, EtOAc/hexane = 1/4) to afford **6A** as a white solid (555 mg, 92%): mp 73–75 °C: ^{1}H NMR (600 MHz, $CDCl_3$) (*cis*:*trans* = 1:0.2) (*cis*-form) δ 1.97–2.10 (m, 2H), 1.99 (s, 3H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.92 (s, 3H), 3.71 (ddd, *J* = 5.6, 10.3, 13.0 Hz, 1H), 3.79 (ddd, *J* = 5.5, 10.4, 13.0 Hz, 1H), 3.96 (br, 2H), 6.42 (dd, *J* = 0.8, 7.9 Hz, 1H), 6.54 (dd, *J* = 0.8, 7.9 Hz, 1H), 6.92 (t, *J* = 7.9 Hz, 1H), 7.12–7.15 (m, 2H), 7.23–7.26 (m, 1H), 7.38–7.40 (m, 2H); (*trans*-form) δ 2.74 (s, 0.6H), 2.97–2.98 (m, 0.2H), 3.10–3.12 (m, 0.2H), 3.51 (s, 0.6H), 4.46–4.49 (m, 0.4H), 7.05 (d, *J* = 7.5 Hz, 0.2H), 7.19 (dd, *J* = 7.5, 7.5 Hz, 0.2H), 7.50–7.53 (m, 0.6H), 7.67–7.68 (m, 0.6H); ^{13}C NMR (150 MHz, $CDCl_3$) (*cis*-form) δ 18.2, 23.3, 26.8, 31.9, 48.3, 51.6, 113.6, 120.5, 127.3, 127.4, 128.1, 128.6, 129.6, 130.0, 135.6, 136.3, 142.8, 171.5, 173.4; (*trans*-form) δ 18.6, 26.8, 30.4, 44.9, 51.6, 127.0, 128.3, 128.7, 129.4, 172.4; IR (ATR) 3364, 1740, 1624 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}N_2O_3$ 349.1523 (M+Na)$^+$, found 349.1524.

Methyl 4-*N*-[(4-methylphenyl)sulfonyl]-*N*-(6-amino-2-methylphenyl)aminobutyrate (6B). To a solution of **5B** (1.01 g, 2.48 mmol) in EtOH (24 mL) was added 10% palladium on carbon (84 mg). After the mixture was stirred at 25 °C for 9 h under a hydrogen atmosphere, the mixture was filtered. The filtrate was concentrated under vacuum, and the residue was purified by column chromatography (silica gel, EtOAc/hexane = 1/4) to afford **6B** as a white solid (914 mg, 98%): mp 75–77 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.78 (s, 3H), 1.86 (quin, *J* = 7.4 Hz, 2H), 2.35 (dt, *J* = 1.8, 7.4 Hz, 2H), 2.42 (s, 3H), 3.34 (dt, *J* = 7.4, 14.1 Hz, 1H), 3.63 (s, 3H), 3.76 (dt, *J* = 7.4, 14.1 Hz, 1H), 6.52 (dd, *J* = 0.9, 7.9 Hz, 1H), 6.57 (dd, *J* = 0.9, 7.9 Hz, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.3, 21.5, 24.6, 31.2, 49.6, 51.5 114.7, 121.0, 123.8, 127.4, 129.1, 129.7, 137.2, 139.2, 143.6, 146.5, 173.3; IR (ATR) 3380, 1738 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{24}N_2O_4S$ 377.1530 (M+H)$^+$, found 377.1532.

4-*N*-(6-Amino-2-methylphenyl)-*N*-benzoylaminobutyric acid (7A). To a solution of **6B** (300 mg, 0.842 mmol) in MeOH (8.0 mL) was added 1N *aq.* NaOH (4.0 mL). After being stirred at 25 °C for 2 h, the mixture was acidified with 1N HCl, and extracted with EtOAc. The extract was dried, and concentrated to afford **7A** as a white solid (243 mg, 93%): mp 243–245 °C: ^{1}H NMR (600 MHz, $CDCl_3$) (*cis*:*trans* = 1:0.2) (*cis*-form) δ 1.93–2.09 (m, 2H), 1.99 (s, 3H), 2.46 (dt, *J* = 2.0, 7.4 Hz, 2H), 3.47 (br, 2H), 3.72 (ddd, *J* = 5.6, 9.5, 13.2 Hz, 1H), 3.86 (ddd, *J* = 6.0, 9.5, 13.2 Hz, 1H), 6.43 (dd, *J* = 1.3, 7.5 Hz, 1H), 6.56 (dd, *J* = 1.3, 7.9 Hz, 1H), 6.93 (dd, *J* = 7.5, 7.9 Hz, 1H), 7.13–7.16 (m, 2H), 7.24–7.27 (m, 1H), 7.38–7.40 (m, 2H); (*trans*-form) δ 2.12–2.14 (m, 0.4H), 2.30–2.31 (m, 0.2H), 2.73 (s, 0.6H), 4.46–4.48 (m, 0.4H), 7.06 (d, *J* = 7.5 Hz, 0.2H), 7.20, (dd, *J* = 7.5, 8.2 Hz, 0.2H), 7.49–7.50 (m, 0.6H), 7.64–7.66 (m, 0.4H), 7.68 (d, *J* = 8.2 Hz, 0.2H); ^{13}C NMR (150 MHz, $CDCl_3$) (*cis*-form) δ 18.2, 23.3, 31.9, 48.2, 113.7, 120.6, 127.4, 127.5, 127.9, 128.7, 129.9, 130.3, 135.2, 136.1, 142.7, 171.9, 176.2; (*trans*-form) δ 18.6, 26.6, 30.2, 44.9, 117.8, 126.0; IR (ATR) 2932, 1732, 1608 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_2O_3$ 311.1401 (M–H)$^-$, found 311.1403.

4-*N*-(6-Amino-2-methylphenyl)-*N*-[(4-methylphenyl)sulfonyl]aminobutyric acid (7B). To a solution of **6B** (88 mg, 0.234 mmol) in MeOH (2.4 mL) was added 1N *aq.* NaOH (1.2 mL). After being stirred at 25 °C for 1 h, the mixture was acidified with 1N HCl, and extracted with EtOAc. The extract was dried, and concentrated to afford **7B** as a white solid (80 mg, 95%): mp 170–172 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.75 (s, 3H), 1.81–1.89 (m, 2H), 2.41–2.45 (m, 2H), 2.42 (s, 3H), 3.34 (dt, *J* = 6.3, 14.0 Hz, 1H), 3.79 (dt, *J* = 7.7, 14.0 Hz, 1H), 4.60 (br, 2H), 6.53 (dd, *J* = 1.1, 7.7 Hz, 1H), 6.59 (dd, *J* = 1.1, 7.7 Hz, 1H), 6.99 (dd, J = 7.7, 7.7 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.2, 21.5, 24.4, 31.2, 49.6, 114.9, 121.3, 123.9, 127.4, 129.1, 129.7, 137.1, 139.1, 143.7, 146.5, 177.4; IR (ATR) 2929, 1704, 1327 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{22}N_2O_4S$ 363.1373 $(M+H)^+$, found 363.1374.

6-Benzoyl-7-methyl-3,4,5,6-tetrahydro-1,6-benzodiazocin-2-one (8A). To a solution of **7A** (164 mg, 0.53 mmol) in CH_2Cl_2 (5.3 mL) was added Et_3N (0.22 mL, 1.58 mmol) and EDC (403 mg, 2.1 mmol). After the mixture was stirred at 25 °C for 20 h, the mixture was concentrated, and diluted with EtOAc. The organic layer was washed with saturated *aq.* $NaHCO_3$, 1N HCl and saturated *aq.* NH_4Cl, and dried over $MgSO_4$. The filtrate was concentrated to give **8A** as a white solid (81 mg, 52%): mp 233–234 °C: ^{1}H NMR (600 MHz, $CDCl_3$) (*cis*:*trans* = 1:0.12) (*cis*-form) δ 1.80–1.85 (m, 1H), 2.10 (ddd, J = 1.4, 12.7, 12.7 Hz, 1H), 2.41–2.45 (m, 1H), 2.48 (s, 3H), 2.56–2.64 (m, 1H), 2.82 (ddd, J = 4.2, 13.0, 13.0 Hz, 1H), 4.78 (ddd, J = 1.1, 4.9, 13.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.91 (br, 1H), 7.09–7.13 (m, 3H), 7.15–7.21 (m, 4H); (*trans*-form) δ 1.97–2.01 (m, 0.12H), 2.20 (ddd, J = 1.5, 12.8, 12.8 Hz, 0.12H), 2.37 (s, 0.36H), 3.01 (ddd, J = 4.5, 12.9, 14.7 Hz, 0.12H), 3.96 (ddd, J = 0.9, 5.6, 14.7 Hz, 0.12H), 7.28–7.30 (m, 0.24H), 7.43–7.47 (m, 0.6H); ^{13}C NMR (150 MHz, $CDCl_3$) (*cis*-form) δ 18.2, 22.7, 32.1, 49.2, 123.4, 126.7, 127.6, 128.7, 129.8, 129.8, 135.2, 135.5, 136.8, 139.5, 169.9, 174.8; (*trans*-form) δ 17.8, 26.5, 31.2, 50.4, 124.0, 126.0, 129.5, 130.4; IR (ATR) 2925, 1669, 1644 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{18}N_2O_2$ 295.1441 $(M+H)^+$, found 295.1444.

6-[(4-Methylphenyl)sulfonyl]-7-methyl-3,4,5,6-tetrahydro-1,6-benzodiazocin-2-one (8B). To a solution of **7B** (80 mg, 0.22 mmol) in CH_2Cl_2 (3.0 mL) was added Et_3N (80 μL, 0.57 mmol) and EDC (64 mg, 0.33 mmol). After the mixture was stirred at 25 °C for 20 h, the mixture was concentrated, and diluted with EtOAc. The organic layer was washed with saturated *aq.* $NaHCO_3$, 1N HCl and saturated *aq.* NH_4Cl, and dried over $MgSO_4$. The filtrate was concentrated to give **8B** as a white solid (45 mg, 59%): mp 247–250 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.73–1.78 (m, 1H), 1.98 (ddd, J = 0.9, 12.4, 12.5 Hz, 1H), 2.04–2.11 (m, 1H), 2.13 (s, 3H), 2.32 (dd, J = 8.0, 12.4 Hz, 1H), 2.43 (s, 3H), 2.91 (ddd, J = 3.8, 12.7, 15.0 Hz, 1H), 4.39 (ddd, J = 1.1, 4.3, 15.0 Hz, 1H), 6.82 (br, 1H), 6.99 (dd, J = 0.6, 7.9 Hz, 1H), 7.18 (dd, J = 0.6, 7.9 Hz, 1H), 7.25 (t, J = 7.9 Hz, 1H), 7.26 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.2, 21.6, 26.1, 31.6, 50.6, 123.8, 127.3, 129.2, 129.6, 130.3, 135.8, 137.5, 138.1, 140.0, 143.6, 173.9; IR (ATR) 2926, 1653, 1331 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_2O_3S$ 345.1267 $(M+H)^+$, found 345.1270.

6-Benzoyl-1,7-dimethyl-3,4,5,6-tetrahydro-1,6-benzodiazocin-2-one (2A). To a solution of **8A** (76 mg, 0.26 mmol) in DMF (2.0 mL) was added sodium hydride (60% in oil) (21 mg, 0.52 mmol) at 0 °C under argon. The mixture was stirred for 30 min at 25 °C, cooled to 0 °C, and treated with MeI (48 μL, 0.77

mmol). After being stirred for 5 h at 25 °C, the mixture was treated with H_2O, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/hexane = 1/2) to afford **2A** as a white solid (74 mg, 93%): mp 160–162 °C: ^{1}H NMR (600 MHz, $CDCl_3$) (*cis*:*trans* = 1:0.3) (*cis*-form) δ 1.74–1.79 (m, 1H), 2.07 (ddd, *J* = 1.2, 12.7, 12.7 Hz, 1H), 2.41 (ddd, *J* = 0.9, 7.9, 12.7 Hz, 1H), 2.45 (s, 3H), 2.53 (s, 3H), 2.54–2.60 (m, 1H), 2.80 (ddd, *J* = 4.2, 13.0, 13.0 Hz, 1H), 4.78 (ddd, *J* = 0.9, 5.1, 13.0 Hz, 1H), 6.88 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.12–7.18 (m, 3H), 7.21–7.25 (m, 3H), 7.43–7.45 (m, 1H); (*trans*-form) δ 1.58–1.61 (m, 0.3H), 2.00–2.04 (m, 0.3H), 2.21 (ddd, *J* = 1.5, 12.8, 12.8 Hz, 0.3H), 2.34 (s, 0.9H), 2.37–2.39 (m, 0.3H), 2.96 (ddd, *J* = 4.8, 13.0, 14.7 Hz, 0.3H), 3.35 (s, 0.9H), 3.88 (ddd, *J* = 09, 5.6, 12.7 Hz, 0.3H), 7.12–7.18 (m, 0.9H), 7.21–7.25 (m, 0.6H), 7.28 (dd, *J* = 0.9, 76 Hz, 0.3H), 7.34 (dd, *J* = 7.6, 7.7 Hz, 0.3H), 7.43–7.45 (m, 0.3H); ^{13}C NMR (150 MHz, $CDCl_3$) (*cis*-form) δ 18.4, 22.7, 32.9, 35.6, 49.5, 123.0, 125.9, 127.6, 128.3, 129.4, 130.3, 134.3, 136.7, 139.5, 141.9, 168.6, 173.2; (*trans*-form) δ 17.7, 26.2, 31.8, 36.7, 50.1, 123.8, 128.6, 128.8, 128.9, 129.5, 130.2, 136.2, 136.2, 138.6, 142.3, 171.4, 173.2; IR (ATR) 1652, 1634 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_2O_2$ 309.1598 $(M+H)^+$, found 309.1600.

6-[(4-Methylphenyl)sulfonyl]-1,7-dimethyl-3,4,5,6-tetrahydro-1,6-benzodiazocin-2-one (2B). To a solution of **8B** (44 mg, 0.12 mmol) in DMF (1.5 mL) was added sodium hydride (60% in oil) (8.0 mg, 0.19 mmol) at 0 °C under argon. The mixture was stirred for 30 min at 25 °C, cooled to 0 °C, and treated with MeI (24 μL, 0.38 mmol). After being stirred for 2 h at 25 °C, the mixture was treated with H_2O, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography (silica gel, EtOAc/hexane = 1/2) to afford **2B** as a white solid (44 mg, 97%): mp 228–230 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.71–1.75 (m, 1H), 1.95 (s, 3H), 2.01 (dd, *J* = 0.8, 12.6 Hz, 1H), 2.14–2.19 (m, 1H), 2.37 (dd, *J* = 8.0, 12.6 Hz, 1H), 2.43 (s, 3H), 2.84 (ddd, *J* = 4.1, 13.1, 14.9 Hz, 1H), 3.31 (s, 3H), 4.19 (dd, *J* = 5.3, 14.9 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.15 (dd, *J* = 0.8, 7.8 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.1, 21.5, 26.5, 32.3, 37.2, 50.3, 123.5, 127.4, 129.2, 129.6, 129.9, 135.9, 137.7, 138.9, 143.5, 145.1, 172.5; IR (ATR) 1661, 1333 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}N_2O_3S$ 359.1424 $(M+H)^+$, found 359.1425.

Separation of enantiomers using chiral HPLC:

Atropisomers of 6-benzoyl-1,7-dimethyl-3,4,5,6-tetrahydro-1,6-benzodiazocin-2-one (2A).[12] CHIRAL ART Amylose-SA (0.46 cmϕ × 25 cm); eluent, hexane:EtOH (4:1); flow rate, 0.6 mL/min; temperature, 25 °C; detection, 254 nm. Former peak (a*S*)-**2A**: retention time = 15.4 min; $[\alpha]_D^{20}$ +422.1 (>99.9%ee, *c* 0.15, MeOH). Latter peak (a*R*)-**2A**: retention time = 23.6 min; $[\alpha]_D^{20}$ –416.1 (99.4%ee, *c* 0.15, MeOH).

Atropisomers of 6-[(4-methylphenyl)sulfonyl]-1,7-dimethyl-3,4,5,6-tetrahydro-1,6-benzodiazocin-2-one (2B). CHIRAL ART Amylose-SA (0.46 cmϕ × 25 cm); eluent, hexane:EtOH (9:1); flow rate, 0.7 mL/min; temperature, 25 °C; detection, 254 nm. Former peak (a*S*)-**2B**: retention time = 25.7 min; $[\alpha]_D^{20}$ –161.6 (99.7%ee, *c* 0.095, MeOH). Latter peak (a*R*)-**2B**: retention time = 28.9 min; $[\alpha]_D^{20}$ +152.1 (96.4%ee, *c* 0.095, MeOH).

Crystal data of 2A, 2B and (a*S*)-2B:[20] All measurements were made on a Rigaku Raxis Rapid imaging plate area detector with graphite monochromated Cu-Kα radiation. The data were collected at a temperature of –100 °C. The structure was solved by direct method SIR92 and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. All calculations were performed using the Crystal Structure (Crystal Structure 4.0) crystallographic software package or SHELXL97.

Crystal data of 2A (CCDC: 1863265). $C_{19}H_{20}O_2N_2$: mp 160–162 °C, *M*r = 308.38, CuKα (λ = 1. 54187 Å), triclinic, *P*-1, colorless prism 0.40 × 0.25 × 0.15 mm, crystal dimensions a = 8.8115(2) Å, b = 9.5804(2) Å, c = 11.5539(3) Å, α = 74.007(2)°, β = 71.260(2)°, γ = 62.167(2)°, T = 173 K, Z = 2, V = 807.57(3) Å^3, D_{calc} = 1.268 gcm^{-3}, μCuKα = 6.635 cm^{-1}, F_{000} = 328.00, GOF = 1.666, R_{int} = 0.0288, R_1 = 0.0460, wR_2 = 0.1456.

Crystal data of 2B (CCDC: 1863266). $C_{19}H_{22}O_3N_2S$: mp 233–234 °C, *M*r = 358.45, CuKα (λ = 1.54187 Å), monoclinic, $P2_1/n$, colorless prism 0.40 × 0.15 × 0.10 mm, crystal dimensions a = 14.7145(3) Å, b = 7.5801(2) Å, c = 16.6248(3) Å, α = 90°, β = 110.571(1)°, γ = 90°, T = 173 K, Z = 4, V = 1736.05(6) Å^3, D_{calc} = 1.371 gcm^{-3}, μCuKα = 18.323 cm^{-1}, F_{000} = 760.00, GOF = 1.499, R_{int} = 0.0414, R_1 = 0.0474, wR_2 = 0.1403.

Crystal data of (a*S*)-2B (CCDC: 1863267). $C_{19}H_{22}O_3N_2S$: mp 154–155 °C, *M*r = 358.45, CuKα (λ = 1.54187 Å), hexagonal, $P6_5$, colorless prism 0.15 × 0.10 × 0.04 mm, crystal dimensions a = 8.23205(15) Å, b = 8.23205(15) Å, c = 45.2678(10) Å, α = 90°, β = 90°, γ = 120°, T = 173 K, Z = 6, V = 2656.67(9) Å^3, D_{calc} = 1.344 gcm^{-3}, μCuKα = 17.961 cm^{-1}, F_{000} = 1140.00, GOF = 1.243, R_{int} = 0.1348, R_1 = 0.0849, wR_2 = 0.1227, Flack parameter = 0.00(5).

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4. The terms a*S* and a*R* (chiral axis nomenclature) correspond to *P* and *M* (helix nomenclature), respectively.
5. In the >N–SO$_2$ moiety of the *N*-tosyl derivative (**1B**), the nitrogen atom possesses an sp^2-like nature (the sum of angles around the nitrogen atom shows *ca.* 360°) and the N–S has the double bond character, and thus the >N–S part forms a plane.[3h] The axis between the two planes (*i.e.*, benzene and the >N–S part), which are approximately orthogonally oriented, causes the chirality.
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7. F. Kipnis, N. Weiner, and P. Spoerri, *J. Am. Chem. Soc.*, 1944, **66**, 1989.
8. The description "*cis*/*trans*" is used for the relative arrangement of the two benzene rings.
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10. For convenience, only axis 1 (a^1) is discussed in the main text, except in Figure 3.
11. In the eight-membered ring conformers of (a^1*R*)-**2B**, two types of unexpected diastereomer appeared in the DFT calculation study. The first one was the unfavored diastereomers (a^1*R*, a^2*S*), which appeared in two of the 22 conformers of **2B** analyzed. However, the energy difference (ΔG) compared with the diastereomer (a^1*R*, a^2*R*) was shown to be very large (>82 kJ/mol). The second one had the *Z*-form around the lactam moiety (>N^1-C^2=O), which appeared in 10 of the 22 conformers of **2B** analyzed. These conformers, however, were also shown to be very unstable, with ΔG values of >74 kJ/mol, compared with the lowest conformer. The large energy differences suggest that these two types of diastereomer would not occur in practice. On the other hand, in the seven-membered ring conformers of **1B**, only the *E*-(a^1*R*, a^2*R*) conformer appeared in the calculation study. See the Supporting Information for the detailed computational studies of **1B**/**2B** (Figure S4).
12. As reported for the 7-, 8-, and 9-membered-ring dibenzolactams in reference 3c), the (+)/(–)-angle of optical rotation was diagnostic to determine the absolute stereochemistry of the (a*R*/a*S*)-enantiomers. The absolute stereochemistry of (+)/(–)-**2A** is tentatively assigned as shown in Table 1. Efforts are now underway to assign the stereochemistry definitely. The results will be reported in due course.
13. The absolute stereochemistry was determined based on the Flack parameter.
14. For determination of $\Delta G^{\ddagger}$ values, see: M. Petit, A. J. B. Lapierre, and D. P. Curran, *J. Am. Chem. Soc.*, 2005, **127**, 14994.
15. The conformation and sterochemical stability of the (a*R*)- and (a*S*)-atropisomers of 7-, 8-, and 9-membered-ring dibenzolactams were reported in reference 3c), in which the enantiomers of the 8-membered-ring lactam were shown to possess extreme stability toward racemization ($\Delta G^{\ddagger}$ = 112 kJ/mol) compared with those of 7- and 9-membered-ring lactams ($\Delta G^{\ddagger}$ = 98 and 102 kJ/mol, respectively).
16. The calculated relative energy of the 1-benzoyl derivative of (fully reduced)-1-benzazocine was reported to be greater than that of the (fully reduced)-1-benzazepine, see: M. Qadir, J. Cobb, P. W. Sheldrake, N. Whittall, A. J. P. White, K. K. (M.) Hii, P. N. Horton, and M. B. Hursthouse, *J. Org. Chem.*, 2005, **70**, 1552.
17. RDKit: Open-source cheminformatics, http://www.rdkit.org.
18. For predicting free energy in solution, the SMD (Standard Molecular Data) solvation model was used, see: A. V. Marenich, C. J. Cramer, and D. G. Truhlar, *J. Phys. Chem. B*, 2009, **113**, 6378. Conformational analysis in the gas phase was also performed, see the Supporting Information for the

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20. CCDC 1863265 (**2A**), CCDC 1863266 (**2B**), and CCDC 1863267 ((a*S*)-**2B**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.