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Isolation and Characterization of Atropisomers of Seven-Membered-Ring Benzolactams

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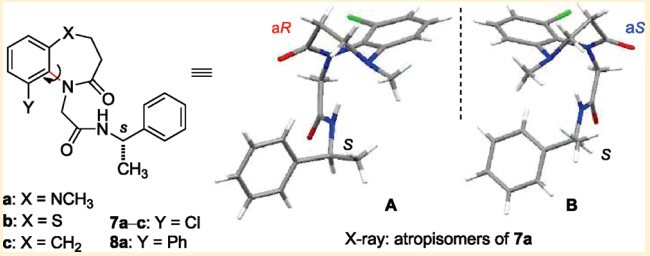
Supporting Information

ABSTRACT: The atropisomeric properties of seven-membered-ring benzolactams (**7a**−**c** and **8a**) [1,5-benzodiazepin-2-one (**a**), 1,5-benzothiazepin-4-one (**b**), and 1-benzazepin-2-one (**c**)] were examined. The atropisomers were isolated as the diastereomers with an (*S*)-phenethylamide moiety, which were characterized by X-ray crystallography, and the barriers to their interconversion were clarified.



INTRODUCTION

Seven-membered-ring benzolactams (**I**) (Figure 1) have been used as the core structures of various biologically active molecules. Lofendazam (**I**: X = NH),[1] diltiazem (**I**: X = S)[2] and benazepril (**I**: X = CH_2)[3] are the typical therapeutic agents developed using these structures. Thus far, the conformation of these heterocycles has been extensively investigated to gain insight into the structures of these relatively flexible heterocycles.[4] In essence, the important point is that compound **I** adopts chiral conformations because of an sp^2-sp^2 axis at Ar−N(C═O) to form the atropisomeric structures **A** and **B** (Figure 1)[5] and the target molecules (receptors or enzymes) may recognize **A** and **B** for biological activity. However, there has been little discussion about the conformation from the viewpoint of the atropisomerism.[6]

In our previous papers,[7] we described the atropisomeric properties of dibenzo[*b*,*d*]azepin-6-one (**II**:**a**−**c**), which is the core structure of a γ-secretase inhibitor, LY-411575[8] (Figure 2). Compound **II** (**a**−**c**) was shown to exist as a racemate of the atropisomers **II-A** and **II-B** with an activation free-energy barrier to rotation ($\Delta G^{\ddagger}$) of 98−122 kJ/mol. X-ray analysis of the enantiomers of **IIc** revealed the presence of two sp^2-sp^2 axes of Ar−Ar and Ar−N(C═O), although they exist only as a pair of enantiomers [**A** (a^1R,a^2S) and **B** (a^1S,a^2R)] without the presence of diastereomers [(a^1R,a^2R) and (a^1S,a^2S)]. We assumed that this phenomenon occurred because the two axes move together like a gear. However, since the axial chirality at the aryl−amide bond has not been studied thoroughly[9] compared with the biphenyl chirality, this is often regarded merely as a consequence of the biphenyl chirality and may not be fully confirmed. Herein we report the conformation of the seven-membered-ring benzolactams (**I**) to reveal and confirm the atropisomerism occurring at the Ar−N(C═O) axis.

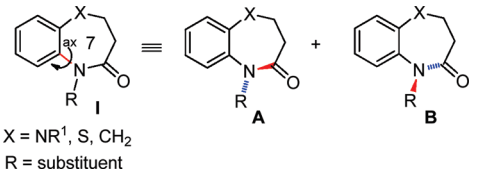
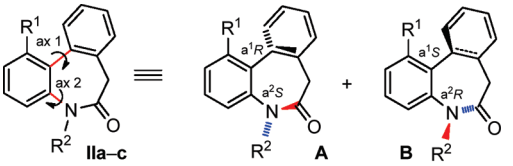


Figure 1. Seven-membered-ring benzolactams (**I**) and atropisomeric structures **A** and **B**.



	R^1	R^2	$\Delta G^{\ddagger}$ (kJ/mol)
a	H	CH_3	98
b	H	*i*Pr	106
c	CH_3	CH_3	122

Figure 2. Conformation and thermodynamic stability of the atropisomers of dibenzo[*b*,*d*]azepin-6-one (**IIa**−**c**: **A**, **B**).

RESULTS AND DISCUSSION

Synthesis of Seven-Membered-Ring Benzolactams. The seven-membered-ring benzolactams (**I**) prepared are the 1,5-benzodiazepin-2-ones (**a** series: X = NCH_3), 1,5-benzothiazepin-4-ones (**b** series: X = S), and 1-benzazepin-2-ones (**c** series: X = CH_2). The NH-lactams [**1a**−**c** (Y = H), **2a**−**c** (Y = Cl)] were prepared from the corresponding benzene precursors with

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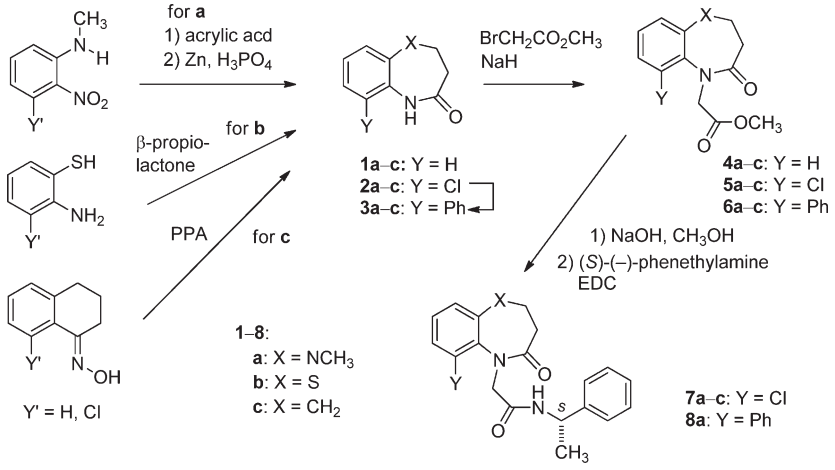
Scheme 1. Preparation of Seven-Membered-Ring Benzolactam Derivatives



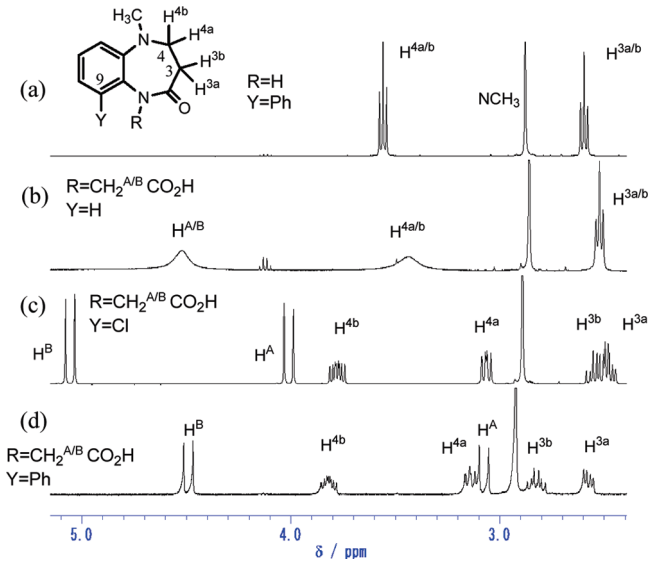


Figure 3. ^{1}H NMR (400 MHz, $CDCl_3$) spectra of **3a** (a), **4a**-COOH (b), **5a**-COOH (c), and **6a**-COOH (d).

$NHCH_3$, SH, and CH_2 moieties, respectively, as shown in Scheme 1. The compounds without a substituent at the ortho position on the benzene ring (Y = H) (**1a**–**c**) are the known compounds,[10−12] and compounds **2a**–**c**, which have a chloro substituent at the ortho position (Y = Cl), were prepared according to the modified methods reported for the synthesis of **1a**–**c**. It should be noted that the Beckmann rearrangement of 8-chloro-3,4-dihydronaphthalen-1-(2*H*)-one oxime with polyphosphoric acid (PPA) gave 9-chloro-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one (**2c**) and its regioisomer (1-one isomer) in a ratio of 53:47, whose stereochemistry was determined by the ^{1}H NMR (chemical shift of the *C*3-methylene protons: δ 2.38 (t, J = 7.2 Hz, 2H) for **2c** and 3.11 (br, 2H) for the isomer). Compounds **3a**–**c** with a phenyl group on the benzene ring were prepared in good yields in the Suzuki–Miyaura reaction of **2a**–**c**. The benzolactams with *N*-substituents [R = $CH_2CO_2CH_3$ (**4**–**6**) and $CH_2CONH(S)CH(CH_3)Ph$ (**7**, **8**)] were prepared from the corresponding NH-lactams (**1**–**3**) using conventional methods, i.e., *N*-alkylation with methyl bromoacetate followed by hydrolysis and amidation with (*S*)-phenethylamine (Scheme 1). The intermediary compounds **4**–**6** are useful for preparation of the biologically active molecules. The ortho-substituent (Y = Cl, Ph) is introduced in the nuclei to provide a higher rotation barrier for the axis, which may result in freezing the conformation of the molecules.

Conformation of Seven-Membered-Ring Benzolactams (1–6). First, the conformations of compounds **1**–**6** were examined. The methylene protons of all the NH-lactams **1**–**3** (**a**–**c**) showed sharp signals with AA′XX′-type splitting patterns in the ^{1}H NMR spectra, reflecting the rapid ring-flipping including the axis at aryl–NH(CO) (Figure 3a for **3a**). On the other hand, compounds **4**–**6** which bear the *N*-methoxycarbonylmethyl moiety showed a different pattern in the ^{1}H NMR spectra. In compounds **4a**–**c**, which are unsubstituted on the benzene ring (Y = H), the methylene protons of the lactam ring were observed as broad peaks without separation of the peaks of the geminal protons, and the methylene protons of the *N*-substituent also appeared as a broad signal (Figure 3b for **4a**-COOH). Attempted separation of the atropisomers of **4a**–**c** at room temperature using chiral HPLC failed. These results suggest that the axial chirality caused by the Ar–N(C=O) (sp^2–sp^2) axis is present, though the ring flipping occurs rather fast at room temperature.[13] In contrast, in the ^{1}H NMR spectra compounds of **5a**–**c** (Y = Cl) and **6a**–**c** (Y = Ph), all the methylene protons of the lactam ring were observed as separated sharp peaks (ABXY-type splitting) and the methylene protons of the *N*-substituent as AB-quartet peaks (Figure 3c for **5a**-COOH and Figure 3d for **6a**-COOH), which indicate that the rotation around the Ar–N(C=O) axis is restricted by the chloro and phenyl groups to separate the protons as diastereotopic ones. The upper field shift of the AB-quartet peaks in **6a**-COOH compared to those of **5a**-COOH is obviously ascribed to the effect of the *C*9-phenyl ring in **6a**-COOH. As was expected from the ^{1}H NMR spectra, the atropisomers of **5a**–**c** and **6a**–**c** could be separated at room temperature using chiral HPLC. Compound **5b** (X = S, Y = Cl) was subjected to X-ray structure analysis, which revealed that the lactam ring takes a boatlike conformation and **5b** exists as a racemate in the crystals; the a*R* and a*S*[14] atropisomers are present in a unit cell (space group $P2_1/n$) (Figure 4).

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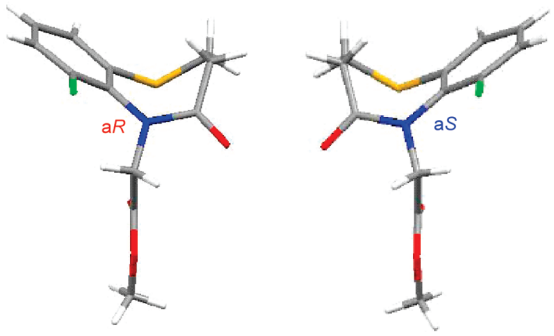

Figure 4. X-ray crystal structure of **5b** (racemate): (a*R*)-form (left) and (a*S*)-form (right) in a unit cell.

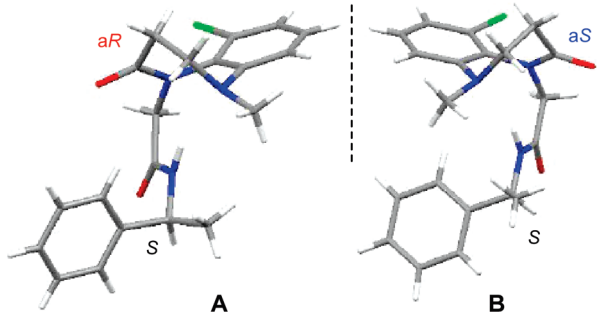

Figure 5. X-ray crystal structures of **7a-A** (a*R*, *S*) (left) and **7a-B** (a*S*, *S*) (right).

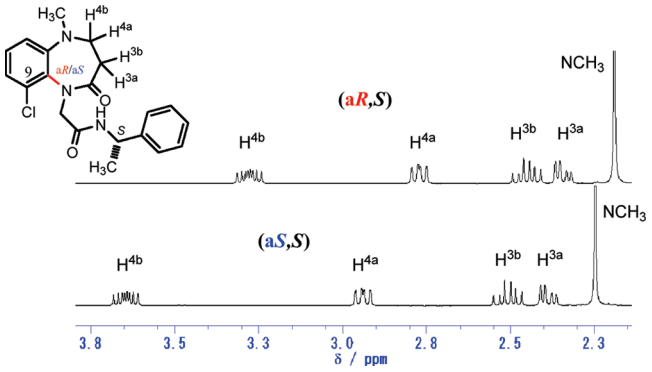

Figure 6. ^{1}H NMR spectra of **7a-A** (a*R*, *S*) (above) and **7a-B** (a*S*, *S*) (below).

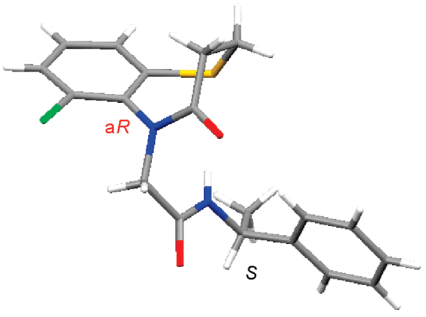

Figure 7. X-ray crystal structure of **7b-A** (a*R*, *S*).

Isolation and Structure Analysis of Atropisomers of Seven-Membered-Ring Benzolactams (7a−c and 8a). For isolation and characterization of the atropisomers, (*S*)-phenethylamide derivatives of **5a**−**c** and **6a** (**7a**−**c** and **8a**) (Y = Cl and Ph) were prepared to separate the atropisomers as diastereomers (Scheme 1).

Compound **7a** (X = NCH_3, Y = Cl) was obtained from **5a** via the carboxylic acid as a mixture of the diastereomers (**A** and **B**) (80% yield) in a ratio of 1:0.7 (by ^{1}H NMR), which were separated on column chromatography using SiO_2 to afford **7a-A** and **7a-B** as crystals. Investigation of the reaction (amidation) using HPLC showed that the ratio immediately after the reaction was 1:1, indicating that the ratio of 1:0.7 is not the result of a kinetically controlled reaction, but the result of equilibrium after thermodynamic conversion.

Both isomers were subjected to X-ray structure analysis to reveal that the benzolactam moiety exists in a boat-like form, and the absolute stereochemistry at the axis is a*R* for **7a-A** and a*S* for **7a-B** (Figure 5).[14,15] As shown in Figure 5, the isomers adopt antipode forms at the benzolactam moiety, and the phenyl group of the phenethylamide moiety of **7a-A** locates *anti* to the benzene ring of the benzolactam moiety (extended form), whereas that of **7a-B** adopts the *syn* (folded form). The extended form seemed to be thermodynamically more stable than the folded form to result in the preferred formation of **7a-A**. In the ^{1}H NMR spectra of **7a-A** and **7a-B** (Figure 6), the same coupling patterns of the ring methylene protons were observed, which indicates that both diastereomers have the same ring conformation (antipode form) in solution ($CDCl_3$). As shown in Figure 6, the ^{1}H NMR spectra are diagnostic for determining the stereochemistry. Thus, the methylene protons of **7a-A** appear in a higher field compared with those of **7a-B**: H^{3a}, H^{3b}, H^{4a}, H^{4b}: δ (ppm) 2.34, 2.43, 2.70, 3.28 for **7a-A**, and 2.39, 2.51, 2.94, 3.65 for **7a-B**, respectively. These data may easily be explained as due to the methylene protons of the lactam ring of **7a-A** locating over the benzene ring in the phenethylamide moiety to appear at a higher field.

Similarly, compound **8a** (Y = Ph) was obtained as a mixture of the diastereomers in a ratio of **A**:**B** = 1:0.9, which were separated by column chromatography (SiO_2). The stereochemistry was assigned on the basis of the chemical shifts of the methylene protons as described above.

Compound **7b** (X = S, Y = Cl) was obtained as a mixture of the diastereomers in a ratio of 1:0.9, which were separated by crystallization to afford **7b-A** as crystals (yield 37%). From the mother liquor, the isomer **7b-B** (in 85% de) was obtained as an oily substance. The stereochemistry was clarified by X-ray structure analysis of **7b-A** (Figure 7), which showed that the thiazepinone ring takes a boatlike form similar to **7a**; the stereochemistry at the axis of **7b-A** is a*R*,[15] and hence, that of **7b-B** was determined to be a*S*. The same tendency of the chemical shifts of the methylene protons in the ^{1}H NMR spectra of **7b-A** and **B** as those in **7a-A** and **B** were observed, e.g., H^{2a}: δ (ppm) 3.15 for **7b-A**, and 3.27 for **7b-B**.[16]

Compound **7c** (X = CH_2) was also obtained as a mixture of diastereomers in a ratio of 1:0.8, which were separated by column chromatography (SiO_2) to afford **7c-A** (yield 36%) and **7c-B** (yield 31%) as crystals. The stereochemistry was deduced by comparing the chemical shifts of the methylene protons in the ^{1}H NMR spectra as discussed above, e.g., H^{3a}, H^{3b}: δ (ppm) 2.37, 2.84 for **7c-A**, and 2.65, 3.44 for **7c-B**.

Stereochemical Stability of Atropisomers of Seven-Membered-Ring Benzolactams (7a−c and 8a). The stereochemical

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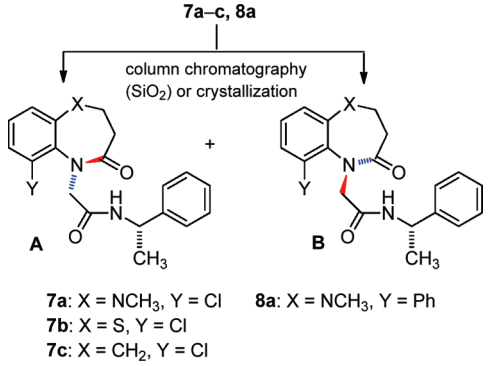
Table 1. Separation of the Atropisomers (A and B) and Their Stereochemical Stability



compd (axial chirality[a])	mp (°C)	$\Delta G^{\ddagger}$ kJ/mol	conditions for isomerization[b]	equilibrium ratio (A:B)
7a-A (a*R*)	173−175	102.5	37 °C, 10 h[c]	1:0.7
B (a*S*)	124−127	99.4	37 °C, 8 h	
8a-A (a*S*)	196−198	106.9	50 °C, 14 h[d]	1:0.9
B (a*R*)	196−198	105.8	50 °C, 12 h[e]	
7b-A (a*R*)	142−144	100.8	37 °C, 8 h	1:0.9
B (a*S*)	oil[f]	99.2	37 °C, 7 h	
7c-A (a*R*)	52−54	101.9	37 °C, 9 h	1:0.8
B (a*S*)	78−80	99.8	37 °C, 8 h	

[a] See ref 14. [b] To the equilibrium state in toluene. [c] At 50 °C, 2 h. [d] At 37 °C after 7 h, isomerized to 71% de. [e] At 37 °C after 7 h, isomerized to 60% de. [f] 85% de.

stability of these separated diastereomers of **7a**−**c** and **8a** was next examined at 37 °C (or 50 °C) in toluene. The activation free energy barrier to rotation ($\Delta G^{\ddagger}$)[17] and the conditions required for isomerization to the equilibrium state are shown in Table 1. The diastereomers **7a-A** and **B** showed $\Delta G^{\ddagger}$ values of 102.5 and 99.4 kJ/mol, respectively, which may reflect the equilibrium ratio of 1:0.7. The higher stereochemical stability of **8a-A** (106.9 kJ/mol) compared with **7a-A** (102.5 kJ/mol) is well explained because of the steric bulkiness of phenyl vs Cl. The stability of benzolactams **7b** (**A**/**B**) and **7c** (**A**/**B**) was revealed to be almost the same as that of **7a** (**A**/**B**), which reached the equilibrium state at 37 °C for 7 to 10 h. Here again, the energy barrier to rotation of type **A** was shown to be slightly higher than that of type **B**.

CONCLUSION

In conclusion, atropisomers of seven-membered-ring benzolactams (**I**) (1,5-benzodiazepin-2-one, 1,5-benzothiazepin-4-one, and 1-benzazepin-2-one) were separated as diastereomers, and the conformation was first clarified from the viewpoint of the atropisomerism. The axial chirality at the aryl−amide bond is often overlooked, although it exists in various forms as observed in the dibenzo[*b*,*d*]azepin-6-ones (**II**). These results may support our assumption that the two axial chiralities exist in **II** and move together like a gear and may prove the relevance of the atropisomeric structures of these heterocycles to the biological activity. We hope that this work provides useful information for future drug design.

EXPERIMENTAL SECTION

The NH-lactams 5-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**1a**),[10] 2,3-dihydro-1,5-benzo[*b*][1,4]thiazepine-4(5*H*)-one (**1b**),[11] and 1,3,4,5-tetrahydro-2*H*-1-benzoazepin-2-one (**1c**)[12] were prepared according to the reported procedure, which were used for the preparation of the benzolactams with a chloro substituent at the ortho position of the benzene ring (**2a**, **2b**, and **2c**) as described below.

9-Chloro-5-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (2a). (1) Concentrated H_2SO_4 (98%, 15 mL) was added by portions to a mixture of 3-chloro-*N*-methyl-2-nitroaniline[18] (5.75 g, 30.8 mmol) and acrylic acid (25 mL, 308 mmol) in H_2O (27 mL). The mixture was stirred at 80 °C for 5 h. After being cooled to room temperature, the mixture was extracted with EtOAc. The extract was washed with H_2O and brine and dried. Removal of the solvent gave yellow crystals which were collected and washed with *i*-Pr_2O to afford *N*-(3-chloro-2-nitrophenyl)-*N*-methyl-*β*-alanine (5.59 g, 70%): mp 126−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (t, J = 7.3 Hz, 2H), 2.77 (s, 3H), 3.34 (t, J = 7.3 Hz, 2H), 7.16 (dd, J = 0.9, 8.0 Hz, 1H), 7.17 (dd, J = 0.9, 8.3 Hz, 1H), 7.34 (dd, J = 8.0, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6, 42.3, 51.4, 121.1, 124.6, 125.8, 130.8, 145.6, 176.6; IR (KBr) 2966, 1714, 1594 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{10}N_2O_4Cl$ 257.0335 $(M - H)^-$, found 257.0349.

(2) To a stirred solution of *N*-(3-chloro-2-nitrophenyl)-*N*-methyl-*β*-alanine (250 mg, 0.97 mmol) in 1,4-dioxane (2.4 mL) and H_3PO_4 (85%, 0.57 mL) was added Zn powder (474 mg, 7.25 mmol) by portions at 80 °C. The mixture was refluxed for 5 h. After being cooled to room temperature, the mixture was filtered. The filtrate was poured into aq $NaHCO_3$, and the aqueous mixture was extracted with EtOAc. The extract was washed with H_2O and brine and dried. Removal of the solvent gave colorless crystals that were collected and washed with *i*-Pr_2O to afford **2a** (114 mg, 56%): mp 159−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, J = 7.3 Hz, 2H), 2.84 (s, 3H), 3.54 (t, J = 7.3 Hz, 2H), 6.95 (dd, J = 1.7, 7.3 Hz, 1H), 7.07 (dd, J = 1.7, 8.0 Hz, 1H), 7.09 (dd, J = 7.3, 8.0 Hz, 1H), 7.22 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.7, 41.5, 58.2, 118.1, 122.7, 125.9, 126.1, 129.4, 144.0,

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172.4; IR (KBr) 3178, 1680 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{12}N_2OCl$ 211.0633 $(M + H)^+$, found 211.0632.

5-Methyl-9-phenyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (3a). To a stirred solution of **2a** (594 mg, 2.82 mmol) in a mixture of *N*,*N*-dimethylacetamide (DMA) (17.1 mL) and H_2O (0.9 mL) were added tris(dibenzylideneacetone)dipalladium (0) ($Pd_2(dba)_3$) (65 mg, 2.5 mol %), 2-dicyclohexcylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (81 mg, 6 mol %), and K_2CO_3 (779 mg, 5.64 mmol). After being stirred at 25 °C for 1 h under argon, the mixture was treated with phenylboronic acid (1.03 g, 8.46 mmol) and stirred at 100 °C for 7 h under argon. After being cooled to room temperature, the mixture was filtered through Celite. The filtrate was poured into H_2O, and the aqueous mixture was extracted with EtOAc. The extract was washed with brine and dried. After removal of the solvent, the residue was purified by column chromatography (silica gel, EtOAc/hexane = 1/3) to afford **3a** as colorless crystals (656 mg, 92%): mp 127−130 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.60 (t, J = 7.0 Hz, 2H), 2.88 (s, 3H), 3.56 (t, J = 7.0 Hz, 2H), 6.71 (br,1H), 6.98 (dd, J = 1.4, 7.5 Hz, 1H), 7.07 (dd, J = 1.2, 8.0 Hz, 1H), 7.24 (dd, J = 7.3, 7.8 Hz, 1H), 7.30−7.32 (m, 2H), 7.35−7.39 (m, 1H), 7.41−7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9, 41.6, 58.5, 118.9, 123.8, 126.0, 127.8, 128.8, 129.2, 134.7, 137.9, 143.0, 172.9; IR (KBr) 3055, 1670 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{17}N_2O$ 253.1335 $(M + H)^+$, found 253.1333.

6-Chloro-2,3-dihydro-1,5-benzo[*b*][1,4]thiazepine-4(5*H*)-one (2b). To a stirred solution of 2-amino-3-chlorothiophenol[19] (0.80 g, 5.0 mmol) in pyridine (6.0 mL) was added β-propiolactone (0.31 mL, 5.0 mmol) at 25 °C, and the mixture was stirred for 30 min. To the mixture was added acetic anhydride (6.0 mL) dropwise over a period of 1 h with stirring. After being stirred at 5 °C for 14 h, the mixture was concentrated. To the concentrate was added EtOAc, and the mixture was washed successively with H_2O, 2 N HCl, H_2O, aq $NaHCO_3$, and H_2O and dried. The organic layer was evaporated to afford **2b** as colorless crystals (755 mg, 3.53 mmol, 71%): mp 168−170 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.64 (t, J = 6.9 Hz, 2H), 3.45 (t, J = 6.9 Hz, 2H), 7.10 (t, J = 7.9 Hz, 1H), 7.30(s, 1H), 7.42 (dd, J = 1.4, 7.9 Hz, 1H), 7.51 (dd, J = 1.4, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.7, 34.5, 126.6, 127.2, 128.6, 130.3, 134.1, 138.8, 172.2; IR (KBr) 3112, 1672 cm^{-1}; HRMS (ESI) m/z calcd for C_9H_8ClNOS 214.0080 $(M + H)^+$, found 214.0088.

2,3-Dihydro-6-phenyl-1,5-benzo[*b*][1,4]thiazepine-4(5*H*)-one (3b). To a stirred solution of **2b** (106 mg, 0.5 mmol) in a mixture of DMA (3.0 mL) and H_2O (0.16 mL) were added $Pd_2(dba)$ (46 mg, 10 mol %), Xphos (57 mg, 24 mol %), and K_2CO_3 (138 mg, 1.0 mmol). After being stirred at room temperature for 1 h under argon atmosphere, the mixture was treated with phenylboronic acid (487 mg, 4.0 mmol) and stirred at 100 °C for 7 h under argon atmosphere. After being cooled to room temperature, the mixture was filtered through Celite. The filtrate was poured into H_2O. The aqueous mixture was extracted with EtOAc, and the extract was washed with H_2O and dried. After removal of the solvent, the oily residue was purified by column chromatography (silica gel, EtOAc/hexane = 1:3) to give **3b** as colorless crystals (123 mg, 97%): mp 175−177 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.74 (t, J = 6.8 Hz, 2H), 3.48 (t, J = 6.8 Hz, 2H), 6.86 (br, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.28−7.34 (m, 3H), 7.36−7.47 (m, 3H), 7.63 (dd, J = 1.4, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.7, 34.3, 100.5, 126.2, 127.2, 128.1, 128.9, 129.0, 131.1, 134.7, 135.9, 138.6, 172.4; IR (KBr) 2918, 1674 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{13}NOS$ 256.0791 $(M + H)^+$, found 256.0793.

9-Chloro-1,3,4,5-tetrahydro-2*H*-1-benzoazepin-2-one (2c) and 2c-Regioisomer via the Beckmann Rearrangement of 8-Chloro-3,4-dihydronaphthalen-1(2*H*)-one Oxime. (1) A mixture of 8-chloro-3,4-dihydro-1(2*H*)-naphthalenone[20] (6.30 g, 34.9 mmol), hydroxylamine hydrochloride (7.20 g, 104 mmol), sodium acetate (8.64 g, 105 mmol), and EtOH (350 mL) was refluxed for 1.5 h. After being cooled to room temperature, the mixture was poured into ice−water. Pale yellow crystals separated were collected by filtration and washed with H_2O and hexane to afford 8-chloro-3,4-dihydronaphthalen-1(2*H*)-one oxime (6.30 g, 92%): mp 159−161 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79 (tt, J = 6.1, 6.8 Hz, 2H), 2.65 (t, J = 6.1 Hz, 2H), 2.87 (t, J = 6.8 Hz, 2H), 7.07 (dd, J = 0.7, 7.5 Hz, 1H), 7.14 (dd, J = 7.5, 8.0 Hz, 1H), 7.32 (dd, J = 0.7, 8.0 Hz, 1H), 9.30 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.8, 31.0, 126.4, 128.8, 128.9, 129.5, 131.4, 143.8, 153.9; IR (KBr) 3231 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{10}ClNO$ 196.0524 $(M + H)^+$, found 196.0524. The oxime thus obtained is the sole isomer, whose stereochemistry is presumed to be (*E*).

(2) The mixture of the oxime (6.00 g, 30.6 mmol) and polyphosphoric acid (PPA) (104 g) was stirred at 95 °C for 1 h and then cooled to room temperature. The mixture was poured into ice−water and extracted with EtOAc. The extract was washed successively with H_2O, saturated $NaHCO_3$, and H_2O and dried. Removal of the solvent gave a white solid, which was purified by column chromatography (silica gel, EtOAc/hexane = 1/4 to 1/1) to afford **2c** (3.10 g, 52%) and 9-chloro-2,3,4,5-tetrahydro-1*H*-2-benzoazepin-1-one (**2c**-regio isomer) (2.80 g, 47%) as colorless crystals. Data for **2c**: mp 162−164 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (quin, J = 6.8, 7.2 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 6.8 Hz, 2H), 7.08 (t, J = 7.8 Hz, 1H), 7.14 (dd, J = 1.4, 7.8 Hz, 1H), 7.22 (1H, b), 7.31 (dd, J = 1.4, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 30.8, 32.8, 125.8, 126.0, 127.8, 128.2, 134.8, 136.0, 173.7; IR (KBr) 3190, 1656 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{10}ClNO$ 196.0524 $(M + H)^+$, found 196.0524. Data for **2c**-regioisomer: mp 192−195 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (br, 2H), 2.83 (br, 2H), 3.11 (br, 2H), 6.51 (br, 1H), 7.10 (dd, J = 0.8, 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.37 (dd, J = 0.8, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 30.3, 39.0, 126.7, 128.9, 131.0, 132.4, 132.9, 139.4, 169.5; IR (KBr) 3190, 1656 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{10}ClNO$ 196.0524 $(M + H)^+$, found 196.0526.

9-Phenyl-1,3,4,5-tetrahydro-2*H*-1-benzoazepin-2-one (3c). To a stirred solution of **2c** (81 mg, 0.41 mmol) in a mixture of DMA (2.8 mL) and H_2O (0.25 mL) were added $Pd_2(dba)_3$ (57 mg, 0.060 mmol), Xphos (74 mg, 0.015 mmol), and K_2CO_3 (114 mg, 0.830 mmol). After being stirred at 25 °C for 1 h under argon atmosphere, the mixture was treated with phenylboronic acid (91 mg, 0.75 mmol) and stirred at 100 °C for 50 h under argon atmosphere. After being cooled to room temperature, the mixture was filtered through Celite, and the filtrate was poured into H_2O. The aqueous mixture was extracted with EtOAc, and the extract was washed with brine, dried, and evaporated. After removal of the solvent, the residue was purified by column chromatography (silica gel, EtOAc/hexane = 1/6) to afford **3c** as a white solid (87 mg, 88%): mp 148−149 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (tt, J = 7.0, 7.3 Hz, 2H), 2.45 (t, J = 7.3 Hz, 2H), 2.84 (t, J = 7.0 Hz, 2H), 6.83 (br, 1H), 7.20−7.25 (m, 3H), 7.29−7.31 (m, 2H), 7.35−7.39 (m, 1H), 7.41−7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.4, 30.6, 32.8, 125.5, 127.6, 128.6, 128.7, 128.9, 134.3, 134.6, 134.7, 137.7, 174.0; IR (KBr) 3054, 1664 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{15}NO$ 238.1226 $(M + H)^+$, found 238.1237.

Preparation of Methyl (1,5-Benzodiazepin-1-yl)acetates 4a, 5a, and 6a: Methyl (5-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)acetate (4a). To a solution of **1a**[10] (1.00 g, 5.67 mmol) in DMF (16 mL) was added NaH (60%, 681 mg, 17 mmol) at −20 °C, and the mixture was stirred at −20 °C for 15 min. Then methyl bromoacetate (2.7 mL, 28.4 mmol) was added to the mixture, and stirring was continued at −20 °C for 2.5 h. After being warmed to room temperature, the mixture was poured into H_2O. The aqueous mixture was extracted with EtOAc, and the combined organic layer was washed with H_2O and dried. After removal of the solvent, the residue was purified by column chromatography (silica gel, EtOAc/dichloromethane =1:5) to give **4a** as a colorless oil (1.26 g, 89%): ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (t−br, J = 6.8 Hz, 2H), 2.81 (s, 3H),

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3.43 (br, 2H), 3.80 (s, 3H), 4.41 (br, 2H), 7.01−7.06 (m, 2H), 7.14 (dd, J = 1.4, 7.8 Hz, 1H), 7.22 (ddd, J = 1.4, 7.8, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.0, 41.0, 50.9, 52.4, 58.7, 119.3, 122.3, 122.8, 137.5, 143.2, 170.0, 172.3; IR (neat) 3489, 1752, 1676 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{17}N_2O_3$ 249.1234 $(M + H)^+$, found 249.1235.

Compounds **5a** and **6a** were prepared from the corresponding 1,5-benzodiazepinones (**2a**, **3a**) according to a similar procedure described for the preparation of **4a** from **1a**.

Methyl (9-chloro-5-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)acetate (5a): colorless oil (97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (ddd, J = 1.2, 5.6, 12.9 Hz, 1H), 2.57 (ddd, J = 7.0, 12.9, 13.1 Hz, 1H), 2.84 (s, 3H), 3.09 (ddd, J = 1.2, 7.0, 10.0 Hz, 1H), 3.70 (s, 3H), 3.74 (ddd, J = 5.6, 10.0, 13.1 Hz, 1H,), 4.24 (d, J = 17.0 Hz, 1H), 4.53 (d, J = 17.0 Hz, 1H), 7.00 (dd, J = 1.4, 8.0 Hz, 1H), 7.12 (dd, J = 1.4, 8.0 Hz, 1H), 7.19 (dd, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.6, 41.1, 49.6, 52.0, 58.2, 118.2, 124.4, 128.2, 130.4, 133.9, 146.6, 168.6, 173.1; IR (neat) 3355, 1750, 1681 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{16}N_2O_3Cl$ 283.0844 $(M + H)^+$, found 283.0830.

Methyl (5-methyl-2-oxo-9-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)acetate (6a): colorless crystals (82%); mp 157−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (dd, J = 5.3, 12.7 Hz, 1H), 2.84 (ddd, J = 7.3, 12.7, 13.1 Hz, 1H), 2.90 (s, 3H), 3.18 (d, J = 17.0 Hz, 1H), 3.20 (dd, J = 7.3, 10.0 Hz, 1H), 3.52 (s, 3H), 3.81 (ddd, J = 5.3, 10.0, 13.1 Hz, 1H), 4.15 (d, J = 17.0 Hz, 1H), 7.04 (dd, J = 1.4, 7.5 Hz, 1H), 7.09 (dd, J = 0.9, 8.3 Hz, 1H), 7.31−7.37 (m, 4H), 7.40−7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.1, 41.1, 49.4, 51.7, 58.2, 118.7, 125.0, 127.7, 127.9, 128.4, 128.9, 134.0, 136.6, 139.0, 145.4, 168.6, 173.5; IR (KBr) 2949, 1737, 1669 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{21}N_2O_3$ 325.1547 $(M + H)^+$, found 325.1531.

Preparation of Methyl (1,5-Benzothiazepinyl)acetate: 4b, 5b, and 6b. Compounds **4b**, **5b**, and **6b** were prepared from the corresponding 1,5-benzothiazepinones (**1b**,[11] **2b**, **3b**) according to a similar procedure described for the preparation of **4a** from **1a**.

Methyl (3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2*H*)-yl)acetate (4b): colorless oil (97%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.65 (br, 2H), 3.40 (br, 2H), 3.80 (s, 3H), 4.00 (br, 1H), 4.90 (br, 1H), 7.22 (ddd, J = 1.3, 7.4, 7.4 Hz, 1H), 7.33 (dd, J = 1.3, 7.4 Hz, 1H), 7.41 (ddd, J = 1.6, 7.4, 7.4 Hz, 1H), 7.62 (dd, J = 1.6, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 34.1, 51.0, 52.4, 123.6, 127.2, 127.7, 130.7, 135.7, 146.8, 169.7, 171.7; IR (neat) 2953, 1750, 1672 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{13}NO_3S$ 252. 0685 $(M + H)^+$, found 252.0694.

Methyl (6-chloro-3,4-dihydro-4-oxo-1,5-benzothiazepin-5(2*H*)-yl)acetate (5b): colorless crystals (98%); mp 93−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (ddd, J = 7.6, 12.4, 12.6 Hz, 1H), 2.67 (ddd, J = 1.8, 6.0, 12.6 Hz, 1H), 3.29−3.41 (m, 2H), 3.73 (s, 3H), 4.29 (d, J = 16.8 Hz, 1H), 4.54 (d, J = 16.8 Hz, 1H), 7.22 (dd, J = 7.5, 8.0 Hz, 1H), 7.49 (dd, J = 1.2, 8.0 Hz, 1H), 7.59 (dd, J = 1.2, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.4, 33.9, 49.4, 52.0, 128.5, 129.9, 131.8, 132.1, 134.7, 168.2, 172.1; IR (KBr) 2951, 1761, 1735 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3SCl$ 308.0119 $(M + Na)^+$, found 308.0107. This compound was subjected to X-ray crystallographic analysis.

Methyl (3,4-dihydro-4-oxo-6-phenyl-1,5-benzothiazepin-5(2*H*)-yl)acetate (6b): white solid (76%); mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (ddd, J = 1.9, 6.3, 12.4 Hz, 1H), 2.84 (ddd, J = 7.0, 12.4, 12.4 Hz, 1H), 3.23 (d, J = 16.8 Hz, 1H), 3.39 (ddd, J = 6.3, 12.4, 12.4 Hz, 1H), 3.47 (ddd, J = 1.9, 7.0, 12.4 Hz, 1H), 3.55 (s, 3H), 4.16 (d, J = 16.8 Hz, 1H), 7.29−7.46 (m, 7H), 7.66 (dd, J = 1.7, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.7, 33.8, 49.5, 51.7, 127.9, 128.1, 128.1, 129.1, 130.7, 132.3, 135.1, 137.5, 138.3, 168.3, 172.5; IR (KBr) 2957, 1737, 1670 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{17}NO_3S$ 328.1002 $(M + H)^+$, found 328.1000.

Preparation of Methyl (1-Benzoazepinyl)acetate: 4c, 5c, and 6c. Compounds **4c**, **5c**, and **6c** were prepared from the corresponding 1-benzoazepinones (**1c**,[12] **2c**, **3c**) according to a similar procedure described for the preparation of **4a** from **1a**.

Methyl (2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)acetate (4c): white solid (93%); mp 79−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (br, 2H), 2.35 (br-t, J = 6.8 Hz, 2H), 2.92 (br, 2H), 3.74 (s, 3H), 4.51 (s, 2H), 7.11−7.22 (m, 3H), 7.25−7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 29.8, 32.8, 49.8, 52.2, 122.0, 126.4, 127.4, 129.4, 135.8, 142.2, 169.6, 173.2; IR (KBr) 2954, 1746, 1672 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_3$ 234.1125 $(M + H)^+$, found 234.1125.

Methyl (9-chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)acetate (5c): white solid (90%); mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88−1.98 (m, 1H), 2.22−2.44 (m, 3H), 2.65 (dd, J = 6.5, 13.4 Hz, 1H), 3.48−3.72 (m, 1H), 3.69 (s, 3H), 4.11 (d, J = 17.3 Hz, 1H), 4.88 (d, J = 17.3 Hz, 1H), 7.14−7.20 (m, 2H), 7.34 (dd, J = 2.1, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 29.7, 32.2, 49.3, 52.0, 127.9, 128.3, 128.7, 129.0, 138.7, 140.0, 169.5, 173.5; IR (KBr) 2950, 1742, 1673 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{14}NO_3Cl$ 290.0554 $(M + Na)^+$, found 290.0554.

Methyl (2-oxo-9-phenyl-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl) acetate (6c): hite solid (97%); mp 150−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99−2.09 (m, 1H), 2.41−2.49 (m, 2H), 2.53−2.59 (m, 1H), 2.69 (dd, J = 6.3, 13.4 Hz, 1H), 3.11 (d, J = 17.3 Hz, 1H), 3.59 (s, 3H), 3.70 (ddd, J = 6.8, 7.0, 13.4 Hz, 1H), 4.17 (d, J = 17.3 Hz, 1H), 7.23 (dd, J = 2.6, 6.5 Hz, 1H), 7.27−7.32 (m, 4H), 7.34−7.38 (m, 1H), 7.41−7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.5, 29.7, 32.7, 49.6, 51.8, 127.5, 127.7, 128.2, 128.7, 129.0, 129.7, 136.0, 138.1, 138.9, 139.0, 169.4, 174.0; IR (KBr) 2952, 1755, 1666 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{19}NO_3$ 332.1257 $(M + Na)^+$, found 332.1272.

2-(9-Chloro-5-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)-*N*-[(1*S*)-1-phenylethyl]acetamide (7a) and the Atropisomers 7a-A and 7a-B. 1) To a solution of **5a** (1.00 g, 3.54 mmol) in MeOH (10 mL) was added 1 N NaOH aq (30 mL). After being stirred at 25 °C for 2 h, the mixture was acidified with 2 N HCl and extracted with EtOAc. The extract was dried and concentrated to afford 9-chloro-5-methyl-2-oxo-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)acetic acid (**5a**-CO_2H) as a white solid (662 mg, 70%): mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (ddd, J = 0.9, 6.1, 13.1 Hz, 1H), 2.54 (ddd, J = 7.3, 12.4, 13.1 Hz, 1H), 2.89 (s, 3H), 3.06 (ddd, J = 0.9, 7.3, 10.5 Hz, 1H), 3.78 (ddd, J = 6.1, 10.5, 12.4 Hz, 1H), 4.01 (d, J = 17.0 Hz, 1H), 5.06 (d, J = 17.0 Hz, 1H), 7.20 (dd, J = 2.6, 6.5 Hz, 1H), 7.37−7.42 (m, 2H), 12.43 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.9, 40.6, 50.1, 58.9, 118.5, 127.6, 129.8, 130.4, 134.4, 144.6, 169.1, 172.2; IR (KBr) 3334, 1750, 1683 cm^{-1}; HRMS (ESI) m/z calcd for 269.0687 $C_{12}H_{14}N_2O_3Cl$ $(M + H)^+$, found 269.0679.

(2) To a solution of **5a**-CO_2H (150 mg, 0.558 mmol) in THF (4.5 mL) were added *N*-hydroxybenzotriazole (HOBt) (82.9 mg, 0.614 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (321 mg, 1.67 mmol), and (*S*)-(−)-1-phenethylamine ((*S*)-PEA) (0.36 mL, 2.8 mmol). The mixture was stirred at 25 °C for 3 h. After removal of the solvent, the residue was poured into aq $NaHCO_3$. The aqueous solution was extracted with EtOAc, and the extract was washed successively with aq $NaHCO_3$, H_2O, dilute HCl, and H_2O and dried. Removal of the solvent gave a mixture of the diastereomers **7a-A** and **7a-B** (ratio 1: 0.67 determined by ^{1}H NMR) as a white foam (166 mg, 80%). The mixture was separated and purified by column chromatography (silica gel, EtOAc/hexane = 1:2) to give **7a-A** (a*R*,*S*) (isolated yield: 69 mg, 34%) and **7a-B** (a*S*,*S*) (isolated yield: 45 mg, 22%). **7a-A** (a*R*,*S*): colorless crystals; mp 173−175 °C; $[\alpha]^{21}_D$ +111.2 (*c* 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (d, J = 6.8 Hz, 3H), 2.19 (s, 3H), 2.34 (dd, J = 5.9, 12.9 Hz, 1H), 2.43 (ddd, J = 5.9, 7.3, 12.9 Hz, 1H), 2.70 (dd, J = 7.3, 10.3 Hz, 1H), 3.28 (ddd, J = 5.9, 10.3, 12.9 Hz, 1H), 4.02 (d, J = 17.3 Hz, 1H),

4.91 (d, J = 17.3 Hz, 1H), 5.17 (quin, J = 6.8 Hz, 1H), 6.99 (t, J = 4.6 Hz, 1H), 7.26−7.27 (m, 3H), 7.38−7.40 (m, 4H), 8.30 (br-d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 33.2, 40.2, 47.1, 51.9, 58.5, 118.1, 126.5, 127.2, 128.4, 128.9, 129.9, 134.3, 142.6, 145.4, 167.3, 171.8; IR (KBr) 3236, 1685, 1664 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{23}N_3O_2Cl$ 372.1473 (M + H)$^+$, found 372.1454. **7a-B** (a*S*,*S*): colorless crystals; mp 124−127 °C; $[\alpha]^{21}_D$ −44.9 (c 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (d, J = 7.1 Hz, 3H), 2.25 (s, 3H), 2.39 (dd, J = 5.6, 12.9 Hz, 1H), 2.51 (ddd, J = 5.6 7.3, 12.9 Hz, 1H), 2.94 (dd, J = 7.3, 10.5 Hz, 1H), 3.65 (ddd, J = 5.6, 10.5, 12.9 Hz, 1H), 4.08 (d, J = 17.3 Hz, 1H), 4.98 (d, J = 17.3 Hz, 1H), 5.15 (quin, J = 7.1 Hz, 1H), 6.92 (dd, J = 4.6, 8.8 Hz, 1H), 7.03−7.06 (m, 2H), 7.17−7.22 (m, 2H), 7.26−7.27 (m, 3H), 8.08 (br-d, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 33.3, 40.3, 47.5, 51.2, 59.2, 118.0, 126.2, 126.5, 127.0, 128.3, 128.8, 129.8, 133.9, 143.0, 145.4, 167.2, 171.8; IR (KBr) 3246, 1682, 1670 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{23}N_3O_2Cl$ 372.1473 (M + H)$^+$, found 372.1454.

2-(6-Chloro-3,4-dihydro-4-oxo-1*H*-1,5-benzothiazepin-1-yl)-*N*-[(1*S*)-1-phenylethyl]acetamide (7b) and the Atropisomers 7b-A and 7b-B. Compounds **7b** was prepared from the corresponding acetate (**5b**) via the carboxylic acid (**5b**-CO_2H) according to a similar procedure described for the preparation of **7a** from **5a**.

(6-Chloro-3,4-dihydro-4-oxo-1*H*-1,5-benzothiazepin-1-yl)-acetic acid (5b-CO_2H): white solid (88%); mp 144−146 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.41 (ddd, J = 7.3, 12.8, 12.8 Hz, 1H), 2.51 (ddd, J = 1.1, 6.2, 12.8 Hz, 1H), 3.21 (ddd, J = 6.2, 11.7, 12.8 Hz, 1H), 3.33 (ddd, J = 1.1, 7.3, 11.7 Hz, 1H), 4.13 (d, J = 17.2 Hz, 1H), 4.17 (d, J = 17.2 Hz, 1H), 7.34 (dd, J = 7.6, 8.4 Hz, 1H), 7.61 (dd, J = 1.4, 7.6 Hz, 1H), 7.64 (dd, J = 1.4, 8.4 Hz, 1H), 12.4 (br, 1H); ^{13}C NMR (150 MHz, d-DMSO) δ 32.9, 33.5, 49.3, 128.9, 129.1, 131.2, 132.0, 134.7, 142.9, 168.5, 171.6; IR (KBr) 2918, 1747, 1632 cm^{-1}; HRMS (ESI) m/z calcd for $C_{11}H_{10}NO_3SCl$ 293.9962 (M + Na)$^+$, found 293.9947.

2-(6-Chloro-3,4-dihydro-4-oxo-1*H*-1,5-benzothiazepin-1-yl)-*N*-[(1*S*)-1-phenylethyl]acetamide (7b). The mixture (with a ratio of 1:0.9 determined by ^{1}H NMR) of the diastereomers of **7b-A** and **7b-B** was obtained as a colorless foam (yield 99%). The foam was treated with Et_2O to separate the diastereomers **7b-A** (a*R*,*S*) and **7b-B** (a*S*,*S*). The diastereomer **7b-A** was obtained as colorless crystals (isolated yield: 37%), and the diastereomer **7b-B** was obtained from the mother liquor as a colorless oily substance (isolated yield: 40% in a 85% de (**B**:**A** = 5.6:1)). **7b-A** (a*R*,*S*): colorless crystals; mp 142−144 °C; $[\alpha]^{25}_D$ −107.8 (c 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, J = 7.2 Hz, 3H), 2.46 (ddd, J = 7.2, 12.8, 12.8 Hz, 1H), 2.64 (ddd, J = 1.2, 5.6, 12.8 Hz, 1H), 3.15 (ddd, J = 5.6, 12.8, 12.8 Hz, 1H), 3.35 (ddd, J = 1.2, 7.2, 12.8 Hz, 1H), 4.07 (d, J = 16.6 Hz, 1H), 4.84 (d, J = 16.6 Hz, 1H), 5.11 (quin, J = 7.2 Hz, 1H), 7.25−7.30 (m, 2H), 7.33−7.36 (m, 4H), 7.55 (dd, J = 1.2, 8.2 Hz, 1H), 7.59 (dd, J = 1.2, 7.6 Hz, 1H), 7.90 (br-d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 33.1, 34.1, 48.9, 52.8, 126.2, 127.1, 128.4, 129.2, 132.8, 134.5, 166.5, 171.6; IR (KBr) 3305, 1673 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O_2SCl$ 397.0748 (M + Na)$^+$, found 397.0751. **7b-B** (a*S*,*S*) (85% de): colorless oil; $[\alpha]^{25}_D$ +21.099 (c 0.1, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J = 7.2 Hz, 3H), 2.46 (ddd, J = 7.4, 12.8, 12.8 Hz, 1H), 2.65 (ddd, J = 1.6, 6.1, 12.8 Hz, 1H), 3.27 (ddd, J = 6.1, 12.8, 12.8, 1H), 3.37 (ddd, J = 1.6, 7.4, 12.8 Hz, 1H), 4.07 (d, J = 16.6 Hz, 1H), 4.89 (d, J = 16.6 Hz, 1H), 5.10 (quin, J = 7.2 Hz, 1H), 7.18−7.35 (m, 6H), 7.52 (dd, J = 0.6, 8.4 Hz, 2H), 7.83 (br-d, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 33.2, 34.1, 49.0, 52.3, 126.2, 128.3, 129.0, 130.3, 130.4, 132.7, 134.4, 142.3, 142.9, 166.3, 171.6; IR (neat) 3316, 1680 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O_2SCl$ 397.0748 (M + Na)$^+$, found 397.0747.

2-(9-Chloro-2-oxo-2,3,4,5-tetrahydro-*1H*-1-benzoazepin-1-yl)-*N*-[(1*S*)-1-phenylethyl]acetamide (7c) and the Atropisomers (7c-A and 7c-B). Compounds **7c** was prepared from the corresponding acetate (**5c**) via the carboxylic acid (**5c**-CO_2H) according to a similar procedure described for the preparation of **7a** from **5a**.

(9-Chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)acetic acid (5c-CO_2H): white solid (90%); mp 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88−1.97 (m, 1H), 2.21−2.42 (m, 3H), 2.62 (dd, J = 6.5, 13.6 Hz, 1H), 3.57 (ddd, J = 7.3, 13.4, 13.6 Hz, 1H), 4.17 (d, J = 17.5 Hz, 1H), 4.83 (d, J = 17.5 Hz, 1H), 7.14 (dd, J = 1.7, 7.5 Hz, 1H), 7.19 (dd, J = 7.5, 7.8 Hz, 1H), 7.35 (dd, J = 1.7, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 29.8, 32.1, 49.5, 128.0, 128.5, 128.7, 129.0, 138.5, 139.8, 173.0, 174.1; IR (KBr) 2944, 1745, 1624 cm^{-1}; HRMS (ESI) m/z calcd for $C_{12}H_{12}NO_3Cl$ 276.0398 (M + Na)$^+$, found 276.0397.

2-(9-Chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzoazepin-1-yl)-*N*-[(1*S*)-1-phenylethyl]acetamide (7c). The mixture (with a ratio of 1:0.8 determined by ^{1}H NMR) of the diastereomers of **7c-A** and **7c-B** was obtained as a white foam (yield 87%). The foam was chromatographed on SiO_2 to separate the diastereomers **7c-A** (a*R*,*S*) and **7c-B** (a*S*,*S*). **7c-A** (a*R*,*S*): colorless crystals (isolated yield: 36%); mp 52−54 °C; $[\alpha]^{24}_D$ −19.1 (c 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, J = 7.0 Hz, 3H), 1.78−1.84 (m, 1H), 2.09−2.30 (m, 3H), 2.37 (dd, J = 7.3, 10.3 Hz, 1H), 2.84 (ddd, J = 5.9, 10.3, 12.9 Hz, 1H), 3.97 (d, J = 14.9 Hz, 1H), 4.69 (d, J = 14.9 Hz, 1H), 5.08 (quin, J = 7.0 Hz, 1H), 6.73 (br-d, J = 7.6 Hz, 1H), 7.05 (dd, J = 1.2, 7.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.23−7.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 28.3, 29.5, 32.2, 48.8, 52.2, 125.9, 126.0, 127.1, 127.6, 128.3, 128.4, 128.4, 128.7, 128.9, 138.8, 139.3, 142.8, 167.1, 174.3; IR (KBr) 3306, 2931, 1656 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_2Cl$ 379.1184 (M + Na)$^+$, found 379.1181. **7c-B** (a*S*,*S*): colorless crystals (isolated yield: 31%); mp 78−80 °C; $[\alpha]^{24}_D$ −217.4 (c 0.2, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, J = 7.0 Hz, 3H), 1.88−1.97 (m, 1H), 2.21−2.42 (m, 3H), 2.65 (dd, J = 7.3, 10.5 Hz, 1H), 3.44 (ddd, J = 5.6, 10.5, 12.9 Hz, 1H), 3.99 (d, J = 15.1 Hz, 1H), 4.61 (d, J = 15.1 Hz, 1H), 5.09 (quin, J = 7.0 Hz, 1H), 6.47 (br-d, J = 7.6 Hz, 1H), 7.12 (dd, J = 1.4, 7.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.22−7.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 28.4, 29.9, 32.3, 49.0, 52.4, 126.0, 127.2, 127.8, 125.5, 128.8, 128.9, 139.1, 139.5, 142.9, 167.4, 174.3; IR (KBr) 3309, 2942, 1654 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O_2Cl$ 357.1364 (M + H)$^+$, found 357.1370.

2-(5-Methyl-2-oxo-9-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)-*N*-[(1*S*)-1-phenylethyl]acetamide (8a) and the Atropisomers 8a-A and 8a-B. Compound **8a** was prepared from the corresponding acetate (**6a**) via the carboxylic acid (**6a**-CO_2H) according to a similar procedure described for the preparation of **7a** from **5a**.

(5-Methyl-2-oxo-9-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-yl)acetic acid (6a-CO_2H): white solid (94%); mp 179−183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (dd, J = 5.6, 12.9 Hz, 1H), 2.82 (ddd, J = 7.3, 12.7, 12.9 Hz, 1H), 2.92 (s, 3H), 3.08 (d, J = 18.0 Hz, 1H), 3.14 (dd, J = 7.3, 10.5 Hz, 1H), 3.82 (ddd, J = 5.6, 10.5, 12.7 Hz, 1H), 4.49 (d, J = 18.0 Hz, 1H), 7.25 (dd, J = 1.2, 8.0 Hz, 1H), 7.30−7.35 (m, 3H), 7.39−7.47 (m, 3H), 7.50 (dd, J = 7.8, 8.0 Hz, 1H), 12.5 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2, 40.6, 50.1, 59.0, 118.8, 128.1, 128.3, 128.5, 129.1, 129.5, 134.5, 136.9, 137.8, 143.1, 169.4, 172.8; IR (KBr) 3491, 1739, 1679 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O_3$ 311.1390 (M + H)$^+$, found 311.1387.

2-(5-Methyl-2-oxo-9-phenyl-2,3,4,5-tetrahydro-*1H*-1,5-benzodiazepin-1-yl)-*N*-[(1*S*)-1-phenylethyl]acetamide (8a). The mixture (with a ratio of 1:0.89 determined by ^{1}H NMR) of the diastereomers of **8a-A** and **8a-B** was obtained as a colorless form (yield 89%), which was chromatographed on SiO_2 to separate the diastereomers **8a-A** (a*S*,*S*) and **8a-B** (a*R*,*S*). **8a-A** (a*S*,*S*): colorless crystals (isolated yield: 39%); mp 196−198 °C; $[\alpha]^{21}_D$ +51.5 (c 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.8 Hz, 3H), 2.22 (s, 3H), 2.47 (dd, J = 5.3, 12.9 Hz, 1H), 2.75 (ddd, J = 5.3, 7.5, 12.9 Hz, 1H), 2.87 (dd, J = 7.5, 10.0 Hz, 1H), 3.08 (d, J = 17.3 Hz, 1H), 3.37 (ddd, J = 5.3, 10.0, 12.9 Hz, 1H), 4.22 (d, J = 17.3 Hz, 1H), 5.09 (quin, J = 6.8 Hz, 1H),

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7.06 (dd, J = 1.2, 8.0 Hz, 1H), 7.21 (dd, J = 1.4, 7.8 Hz, 1H), 7.27−7.30 (m, 1H), 7.33−7.46 (m, 10H), 8.33 (br-d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 33.7, 40.3, 47.1, 52.2, 58.6, 118.4, 126.4, 127.1, 128.1, 128.2, 128.4, 128.5, 129.2, 134.4, 137.1, 138.0, 142.7, 144.0, 167.5, 172.4; IR (KBr) 3246, 1676 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_3O_2$ 414.2176 $(M + H)^+$, found 414.2171. **8a-B** (a*R*,*S*): colorless crystals (isolated yield: 39%); mp 196−198 °C; $[\alpha]^{21}_D$ −46.2 (c 0.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, J = 7.3 Hz, 3H), 2.34 (s, 3H), 2.51 (dd, J = 5.3, 12.9 Hz, 1H), 2.82 (ddd, J = 5.3, 7.5, 12.9 Hz, 1H), 3.05 (dd, J = 7.5, 10.0 Hz, 1H), 3.07 (d, J = 17.3 Hz, 1H), 3.72 (ddd, J = 5.3, 10.0, 12.9 Hz, 1H), 4.31 (d, J = 17.3 Hz, 1H), 5.08 (quin, J = 7.3 Hz, 1H), 6.99−7.01(m, 3H), 7.17−7.22 (m, 4H), 7.33−7.45 (m, 6H), 8.10 (br-d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 33.8, 40.6, 47.4, 51.5, 59.3, 118.4, 126.1, 126.9, 127.1, 128.1, 128.2, 128.3, 128.4, 129.2, 134.0, 137.1, 138.0, 143.1, 144.0, 167.3, 172.5. IR (KBr) 3275, 1678 cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{28}N_3O_2$ 414.2176 $(M + H)^+$, found 414.2171.

Single-Crystal X-ray Analysis. 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 Crystal Structure (Crystal Structure 3.8) crystallographic software package. Typical crystal data are as follows.

Cryatal Data for 5b. $C_{12}H_{12}O_3NClS$: mp 93−96 °C; M_r = 285.74, Cu Kα (λ = 1.54187 Å), monoclinic, $P2_1/n$, colorless prism 0.60 × 0.50 × 0.30 mm, crystal dimensions a = 9.31754(17) Å, b = 11.0378(2) Å, c = 24.8795(5) Å, α = 90°, β = 91.2800(7)°, γ = 90°, T = 173 K, Z = 8, V = 2558.10(8) Å^3, D_{calc} = 1.484 gcm^{-3}, μCu Kα = 41.854 cm^{-1}, F_{000} = 1184.00, GOF = 1.227, R_{int} = 0.058, R_1 = 0.0468, wR_2 = 0.1304.

Crystal Data for 7a-A (a*R*,*S*). $C_{20}H_{22}O_2N_3Cl$: mp 173−175 °C, M_r = 371.87, Cu Kα (λ = 1.54187 Å), orthorhombic, $P2_12_12_1$, colorless prism 0.50 × 0.40 × 0.20 mm, crystal dimensions a = 8.18197(15) Å, b = 12.6373(2) Å, c = 17.1203(3) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1875.71(6) Å^3, D_{calc} = 1.315 gcm^{-3}, μCu Kα = 19.565 cm^{-1}, F_{000} = 784.00, GOF = 0.648, R_{int} = 0.136, R_1 = 0.0471, wR_2 = 0.1054, Flack parameter = 0.04(6).

Crystal Data for 7a-B (a*S*,*S*). $C_{20}H_{22}O_2N_3Cl$: mp 124−127 °C, M_r = 371.87, Cu Kα (λ = 1.54187 Å), orthorhombic, $P2_12_12_1$, colorless prism 0.25 × 0.20 × 0.10 mm, crystal dimensions a = 8.18197(15) Å, b = 8.69418(16) Å, c = 26.3682(5) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1875.71(6) Å^3, D_{calc} = 1.317 gcm^{-3}, μCu Kα = 19.583 cm^{-1}, F_{000} = 784.00, GOF = 0.737, R_{int} = 0.040, R_1 = 0.0286, wR_2 = 0.0660, Flack parameter = 0.003(14).

Crystal Data for 7b-A (a*R*,*S*). $C_{19}H_{19}O_2N_2ClS$: mp 142−144 °C, M_r = 374.88, Cu Kα (λ = 1.54187 Å), monoclinic, $P2_1$, colorless prism 0.60 × 0.40 × 0.40 mm, crystal dimensions a = 8.3785(4) Å, b = 12.3205(4) Å, c = 8.5550(3) Å, α = 90°, β = 90.842(3)°, γ = 90°, T = 173 K, Z = 2, V = 1875.71(6) Å^3, D_{calc} = 1.3410 gcm^{-3}, μCu Kα = 31.449 cm^{-1}, F_{000} = 392.00, GOF = 0.737, R_{int} = 0.045, R_1 = 0.0385, wR_2 = 0.0906, Flack parameter = 0.00(2)

Stereochemical (Thermodynamic) Stability of Diastereomeric Atropisomers (A/B of 7a−c and 8a). The $\Delta G^{\ddagger}$ value was determined on the basis of the time-dependent conversion rate (% de) estimated from chiral or nonchiral HPLC analysis of a solution of the diastereomeric atropisomers (**A** and **B**) after the compounds were allowed to stand at designated temperatures.[17]

■ ASSOCIATED CONTENT

Supporting Information. General experimental procedure, ^{1}H NMR and ^{13}C NMR spectra for new compounds, figures of thermal isomerization rate of enantiomers of **7a**−**c** and **8a**, X-ray data (CIF) for compounds **5b**, **7a-A**, **7a-B**, and **7b-A**, and ^{1}H NMR spectra of the temperature dependent analysis for **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Note that the definition of the axial chirality (a*S* and a*R*) leads to reversed stereochemical designations between **5**, **7** (Y = Cl) and **6**, **8** (Y = Ph) according to the priority rule. The terms a*S* and a*R* (chiral axis nomenclature) correspond to *P* and *M* (helix nomenclature), respectively.

(15) The absolute stereochemistry was determined based on the Flack parameter (Cu Kα radiation was used for the measurement).

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