JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

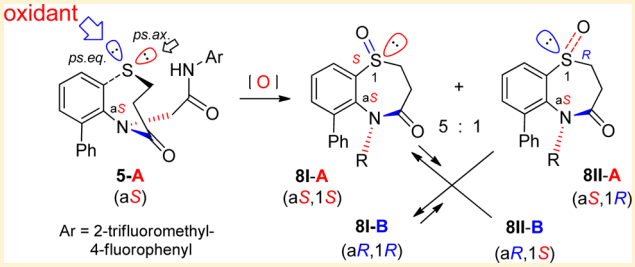
Stereochemistry of 1,5-Benzothiazepin-4-one *S*-Oxide: Insight into the Stereogenic Elements at the Sulfur Atom and Axis

Hidetsugu Tabata, Tetsuya Yoneda, Tetsuta Oshitari, Hideyo Takahashi, and Hideaki Natsugari*

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

Supporting Information

ABSTRACT: Oxidation of 1,5-benzothiazepin-4-one (**5-A**) stereoselectively afforded the *S*-oxide **8I-A** (a*S*,1*S*) in preference to the diastereomer **8II-A** (a*S*,1*R*) affected by the remote stereogenic axis. All the enantiomers (**8I-A**/**8I-B** and **8II-A**/**8II-B**) were separated and isolated, and the interconversion between **8I** and **8II** (equilibrium ratio ≈5:1) was unequivocally verified to be caused by the rotation around the axis.



INTRODUCTION

The 1,5-benzothiazepin-4-one nucleus (**1**) has been used as the core structure of various biologically active molecules (Figure 1).

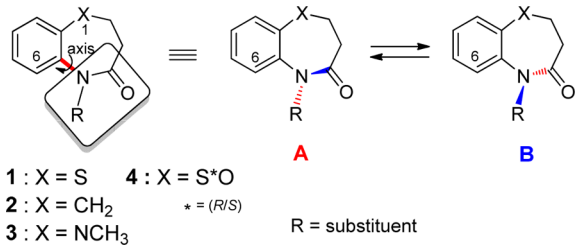


Figure 1. Seven-membered-ring benzolactams (**1**−**4**) and atropisomeric structures **A** and **B**.

Diltiazem,[1] with antihypertensive and antianginal activity, and thiazesim,[2] with antidepressant activity, are the typical therapeutic agents developed using the nucleus. The *S*-oxide derivatives (**4**) have also been shown to display biological activities, such as growth hormone secretagogue activity[3] and the inhibition of angiotensin converting enzyme,[4] human leukocyte elastase,[5] and HIV-reverse transcriptase.[6] Thus, the stereochemical and physicochemical analyses of these relatively flexible heterocycles are important and should provide useful information for future drug design.

As part of our research on atropisomerism in biologically active molecules,[7] we have recently reported the atropisomeric properties of pharmaceutically important seven-membered-ring benzolactams [**1** (X = S), **2** (X = CH_2), and **3** (X = NCH_3)] (Figure 1) due to an sp^2−sp^2 axis at Ar−N(C═O) (a conformational stereogenic axis)[8a] by introducing a substituent at the 6-position[9] to freeze the conformation, which led to the successful discovery of the potent new acyl-CoA cholesterol acyltransferase (ACAT) inhibitors **5**, **6**, and **7**, having 6-phenyl and *N*-CH_2CONH−Ar substituents (Figure 2).[8b] The atropisomers

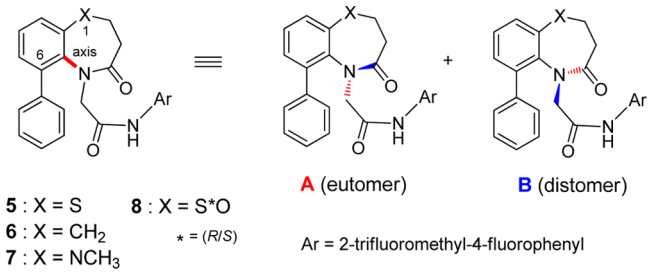


Figure 2. Seven-membered-ring benzolactams (**5**−**7**) as potent ACAT inhibitors, the sulfoxide analogue (**8**), and atropisomers **A** and **B**.

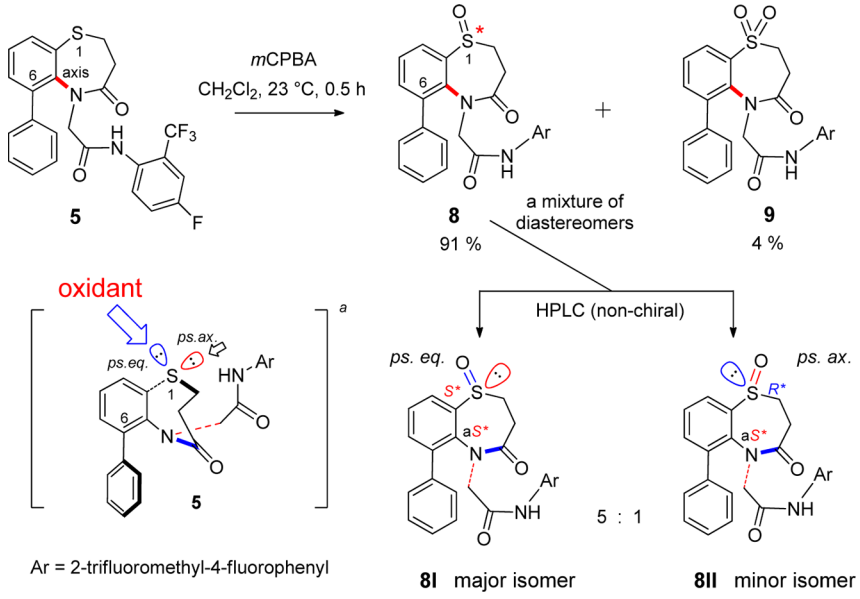
(enantiomers **A** and **B**) of **5**−**7** were separated, and the axial chirality of type **A** was revealed to be recognized by the ACAT enzyme. Interesting information was also obtained in the 1,5-benzodiazepin-2-one nucleus (for **7**-**A**/**B**, X = NCH_3), in which the axial chirality induces a latent chiral center at amine *N*-5 exhibiting chiroptical properties different from those of **5**-**A**/**B** and **6**-**A**/**B**.

In this context, we next focused on the *S*-oxide derivative of 1,5-benzothiazepin-4-one (for **4**/**8**, X = S*O), which possesses a configurational stereogenic center at the sulfur atom in addition to the chirality due to the axis at Ar−N(C═O). There have been many reports on *S*-oxidation of 1,5-benzothiazepin-4-ones with a substituent(s) (chiral center) in the lactam ring and separation of the diastereomeric mixtures.[3−6,10] However, few reports have described the exact (relative and absolute) stereochemistry, and even less attention has been paid to another chirality based on the axis at Ar−N(C═O).[11] This is because the axis of the 1,5-benzothiazepin-4-one *S*-oxide, without a substituent at the 6-position (i.e., compound **4**), is too labile to examine the properties. In this paper, using the 1,5-benzothiazepin-4-one (**5**),[8b] in which the axis is sterically frozen by a phenyl group at the

Received: May 9, 2013

   dx.doi.org/10.1021/jo401020y | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Scheme 1. *S*-Oxidation of 1,5-Benzothiazepin-4-one (5) with *m*CPBA and Separation of the Sulfoxide (8) into the Diastereomers (8I and 8II)[a]



[a]The preferred approach of the oxidant from the pseudoequatorial side is shown in brackets.

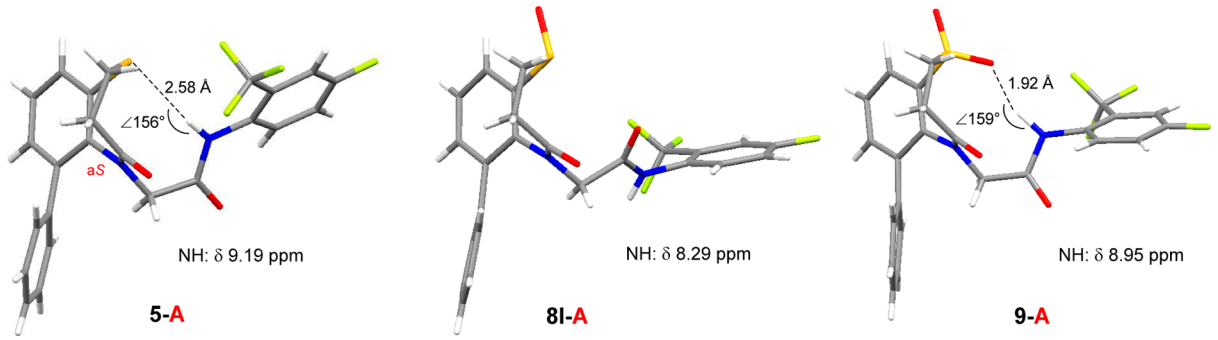
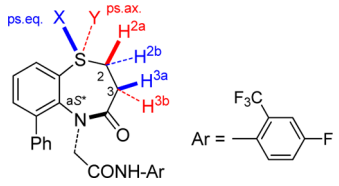


Figure 3. X-ray crystal structures of the sulfide **5-A**,[8b] the major sulfoxide **8I-A**, and sulfone **9-A**. The structure of the (a*S*) atropisomeric form (**A**) of **8I** and **9** is extracted from the CIF data of the X-ray analysis of the racemate.

Table 1. Selected ^{1}H NMR Data of the Sulfide (5), Diastereomeric Sulfoxides (8I and 8II), and Sulfone (9)[a]



compound	X (ps.eq.)	Y (ps.ax.)	H^{2a} (ppm)	^3J (Hz) (H^{2a},H^{3a})	(H^{2a},H^{3b})	H^{2b} (ppm)	^3J (Hz) (H^{2b},H^{3a})	(H^{2b},H^{3b})
5[a]			3.48	5.9	2.9	3.37	11.1	8.1
8I	O		2.93	8.9	1.4	4. 14	10.8	7.2
8II		O	3.47	6.0	2.9	3.65	10.5	7.4
9	O	O	3.60	6.8	2.2	3.90	12.2	7.2

[a]For reference, see 8b.

6-position, we elucidate the stereochemistry of the sulfoxide **8** from the viewpoint of the relation between two stereogenic elements at the sulfur atom and axis and demonstrate the importance of the axial chirality in controlling the stereochemistry of the lactam ring.

RESULTS AND DISCUSSION

***S*-Oxidation of 1,5-Benzothiazepin-4-one (5) with *m*CPBA.** *S*-Oxidation of the 1,5-benzothiazepin-4-one (**5**)[8b] was performed with *meta*-chloroperoxybenzoic acid (*m*CPBA) (1.05 equiv) at 23 °C for 0.5 h in CH_2Cl_2 to afford a mixture of sulfoxide (**8**) (91%) and sulfone (**9**) (4%). HPLC analysis of the sulfoxide (**8**) using a nonchiral column revealed that **8** is a mixture of diastereomers (**8I** and **8II**) with a ratio of ≈5:1 (Scheme 1), which was separated by preparative HPLC. The oxidation at −78 °C gave similar results, affording **8I** as the major

dx.doi.org/10.1021/jo401020y | J. Org. Chem. XXXX, XXX, XXX−XXX

product, although the reaction proceeded slowly and took approximately 3 h to complete.

The major sulfoxide (**8I**) and sulfone (**9**) were successfully analyzed by X-ray crystallography, and both exhibited a similar boat-like conformation of the seven-membered lactam ring, which the starting sulfide (**5**) also adopts in the crystal structure (Figure 3).[8b] The sulfoxide **8I** was revealed to have a relative stereochemistry of (a*S**,1*S**),[12] with the *S*-oxygen in a stable pseudoequatorial orientation. Attempts to obtain single crystals of the minor sulfoxide (**8II**) for X-ray analysis failed, but ^{1}H NMR analysis (vide infra) implied that **8II** also takes a boat-like conformation of the lactam ring with the pseudoaxial *S*-oxygen and hence has the relative stereochemistry of (a*S**,1*R**).

The ^{1}H NMR spectral data[13] of **8I**, **8II**, and **9** for the methylene protons of the lactam ring are shown in Table 1, which revealed that structures similar to those demonstrated by X-ray crystal analysis exist in solution, as well. For determination of the stereochemistry of **8I**, **8II**, and **9**, the vicinal coupling (^3J) between H^2 and H^3 was diagnostic: a smaller ^3J value for (H^{2a},H^{3b}) (1.4−2.9 Hz) and a larger one for (H^{2b},H^{3a}) (10.5−12.2 Hz) correspond well with the values estimated from the torsion angles obtained from the X-ray crystal structure (vide supra).[14] As seen in Table 1, characteristic shifts of the protons (H^{2a} and H^{2b}) are found for the sulfoxide diastereomers (**8I** and **8II**) when compared with the parent sulfide (**5**). Thus, for the major isomer **8I**, a strong upfield shift of H^{2a} and a marked downfield shift of H^{2b} are observed, whereas the minor isomer **8II** shows a smaller downfield shift of H^{2b}. Also characteristic are moderate downfield shifts of both protons (H^{2a} and H^{2b}) for the sulfone (**9**). Furthermore, the chemical shifts of the amide-NH are noteworthy. The NH proton of **8I** and **9** was observed at δ 8.29 and 8.95 ppm, respectively, while that of **8II** was at a markedly lower field (δ 10.19 ppm). The relatively lower shift of the NH of **9** at 8.95 ppm may be ascribed to the hydrogen bond,[15] which was supported by the distance between S=O^{ax}···HN (1.92 Å) and the O^{ax}···H−N angle (159°) as determined by the X-ray structure of **9** (Figure 3). In addition, the markedly lower field shift of the NH of **8II** (δ 10.19 ppm) implies that the oxygen at the *S*-oxide takes a pseudoaxial orientation to form a very strong hydrogen bond between the amide-NH.

The stereoselective oxidation of **5** to **8I** is of interest. It should be emphasized that the stereocontrolled *S*-oxidation was affected by the remote stereogenic axis at Ar−N(C=O), which indicates that the axial chirality controls the conformation of the entire lactam ring. From the X-ray crystal analysis of the chiral 1,5-benzothiazepin-4-one (**5-A**) (Figure 3),[8b] the pseudoaxial side of the *S*-atom is shown to form a hydrogen bond with the amide-NH and is covered by the substituent at the lactam nitrogen, whereas the pseudoequatorial side is open, as illustrated in Scheme 1 (in brackets). Thus, the reagent preferably approaches from the sterically less-hindered equatorial lone-pair side to form **8I** with the *S*-oxygen disposed in a pseudoequatorial orientation as the major product and **8II** with a pseudoaxial *S*-oxygen as the minor product.

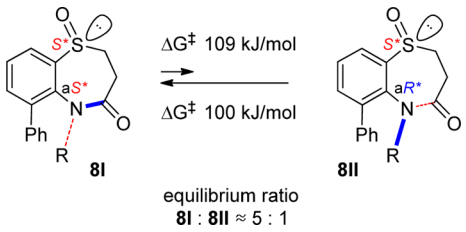


Figure 4. Interconversion between the diastereomeric sulfoxides (**8I** and **8II**) in $CHCl_3$.

Stereochemical Stability of the Sulfoxides (8I and 8II). During the separation and isolation of the diastereomeric isomers (**8I** and **8II**), we noted that the minor isomer **8II** is labile and easily transformed into the isomer **8I**. The transformation process is of interest because two stereogenic elements are present in the molecule. Because the chiral center of the *S*-oxide is relatively stable against thermal pyramidal inversion (racemization),[16] the isomerization was assumed to be caused by the rotation around the axis at Ar−N(C=O). Thus, the conversion is presumably triggered by the conformational change in the *S*-oxide of **8II** from the

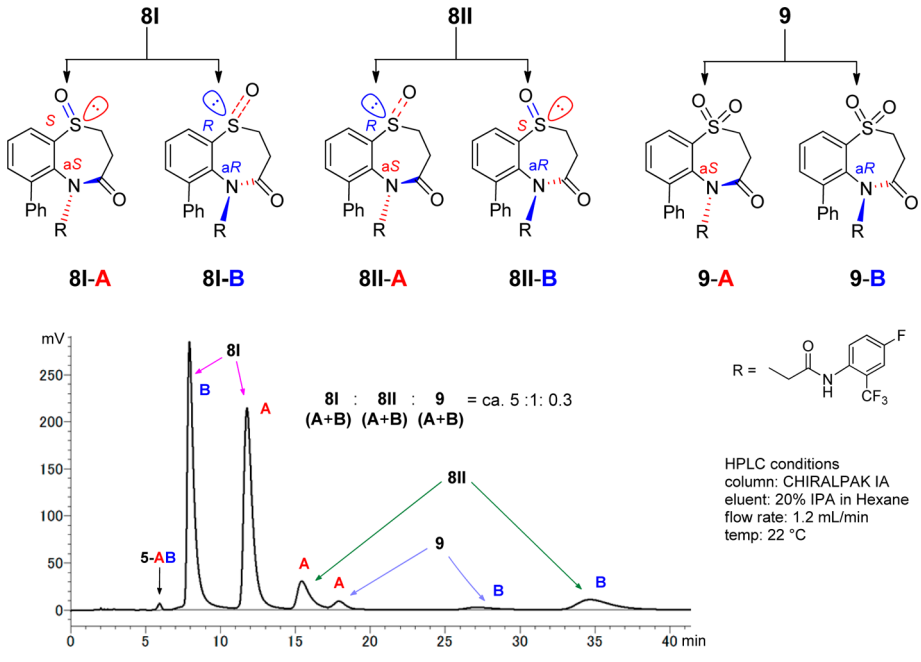


Figure 5. Separation of the sulfoxide (**8I** and **8II**) and sulfone (**9**) into the enantiomers (**A** and **B**) on a chiral column and the chiral HPLC chromatogram of the oxidation of **5** with *m*CPBA at 23 °C for 30 min. The enantiomers of **5** were not separated under those conditions.

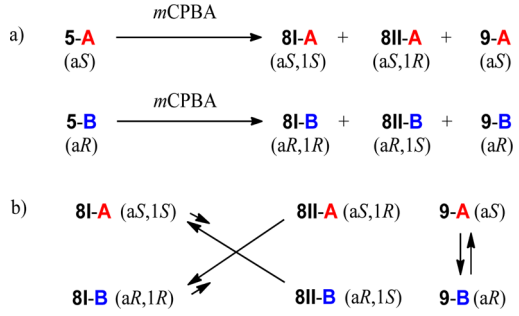
dx.doi.org/10.1021/jo401020y | J. Org. Chem. XXXX, XXX, XXX−XXX

pseudoaxial orientation to the stable pseudoequatorial one, accompanied by the rotation around the axis to form the isomer **8I**. The stereochemical stability of **8I** and **8II** was examined at 37 °C in $CHCl_3$. The isomerization profile is shown in Figure 4, which shows that upon heating both isomers reach an equilibrium state in a ratio of **8I**/**8II** ≈5:1. The activation free-energy barriers to rotation ($\Delta G^{\ddagger}$)[17] calculated from these data are 100 kJ/mol (from **8II** to **8I**) and 109 kJ/mol (from **8I** to **8II**), which reflects the equilibrium ratio of ≈5:1. These results indicate that the isomer **8I** (with pseudoequatorial oxygen) is preferable to **8II** (vide supra) both kinetically and thermodynamically.

Separation of Sulfoxides (8I and 8II) and Sulfone (9) into the Enantiomers (A and B). After obtaining general information on the oxidation products (**8I**, **8II**, and **9**) in the racemic form, the separation into the enantiomers was next attempted using chiral HPLC. Fortunately, all the oxidative products were successfully separated into the respective enantiomers (**A** and **B**) by HPLC on a chiral stationary phase and isolated using preparative HPLC. The chromatogram of chiral HPLC of the enantiomers is shown in Figure 5. The absolute configuration (conformation) of enantiomers (**A** and **B**) was determined by comparison of the HPLC data with those of the oxidation products (**8I-A**, **8II-A**, **9-A**, and the **B**-series enantiomers) of the enantiomerically pure (a*S*)- and (a*R*)-1,5-benzothiazepin-4-one (**5-A** and **5-B**)[8b] (Scheme 2a). In the oxidation, no isomeric products were detected, indicating that the reaction proceeded without rotation around the axis. The circular dichroism (CD) spectra and optical rotation ($[\alpha]_D$) data of the separated enantiomers are shown in Figure 6. It is interesting to note that the chiroptical properties of **8II-A/B** differed from those of **5-A/B**,[8b] **8I-A/B**, and **9-A/B**; for example, the $[\alpha]_D$ value of **8II-A** (a*S*,1*R*) was positive (+42), and that of **5-A** (a*S*), **8I-A** (a*S*,1*S*), and **9-A** (a*S*) was negative (−16, −61, and −37, respectively) (Figure 6). The CD spectral pattern of **8II-A** also differed from those of **5-A**, **8I-A**, and **9-A** as shown in Figure 6. The unique chiroptical properties of **8II-A**, compared with those of **5-A**, **8I-A**, and **9**, indicate that the absolute stereochemistry at the 1*S* affects the chiroptical properties as observed in the 1,5-benzodiazepin-2-one nucleus (**7-A**).[8b,18]

Isomerization of Enantiomeric Sulfoxides (8I-A/B and 8II-A/B) and Sulfone (9A/B). Using the enantiomerically pure lactams (**8I-B** and **8II-B**), the mechanism of the interconversion between **8I** and **8II** was investigated by chiral HPLC analysis (Scheme 2b). Thus, when heated at 50 °C in $CHCl_3$, the enantiomerically pure **8I-B** was converted into the atropisomer **8II-A** with the $\Delta G^{\ddagger}$ values of 109 kJ/mol (the equillibrium state of **8I-B**/**8II-A** ≈5:1), whereas **8II-B** was converted to **8I-A** at 37 °C with the $\Delta G^{\ddagger}$ values of 100 kJ/mol (the equillibrium state of **8II-B**/**8I-A** ≈1:5), which clearly indicates the rotation around the axis (without isomerization of the chiral center at the *S*-oxide) during the conversion process. The stereochemical stability of the atropisomeric sulfone (**9-A/B**) was also examined at 37 °C in toluene. The $\Delta G^{\ddagger}$ value was shown to be 100 kJ/mol (conversion from **9-A** to **9-B**), and the time required for racemization was approximately 7 h. The lower stability of **9-A/B** compared with that of **5-A/B** (105 kJ/mol, 7 h at 50 °C in toluene for racemization)[8b] may be ascribed to the presence of the axial *S*-oxygen in **9-A/B**, which may cause instability of the lactam ring.

Scheme 2. (a) *S*-Oxidation of (a*S*)- and (a*R*)-1,5-Benzothiazepin-4-ones (5-A and 5-B) with *m*CPBA and (b) Interconversion between the Enantiomers of Sulfoxide (8I-A, 8I−B, 8II-A, and 8II−B) and Sulfone (9-A and 9-B)



CONCLUSION

In summary, the stereochemistry of 1,5-benzothiazepin-4-one sulfoxide (**4**/**8**) was first elucidated from the viewpoint of the

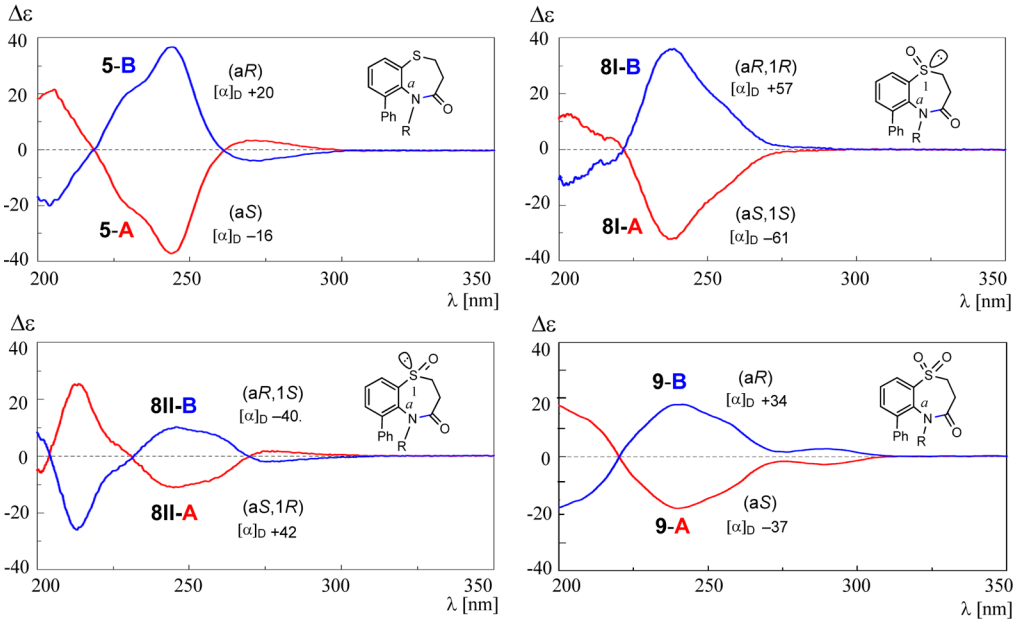


Figure 6. CD spectra and $[\alpha]_D$ data of the enantiomers (**A** and **B**) of **5**, **8I**, **8II**, and **9** measured in MeOH.

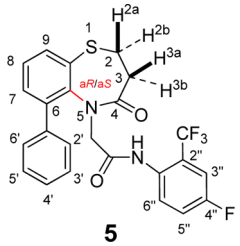
dx.doi.org/10.1021/jo401020y | J. Org. Chem. XXXX, XXX, XXX−XXX

relation between two stereogenic elements at the sulfur atom and axis. The sterically controlled reaction observed in the *S*-oxidation of 1,5-benzothiazepin-4-one (**5**) was shown to be caused by the remote stereogenic axis. Furthermore, using the enantiomerically pure lactams, interconversion between the diastereomers was unequivocally clarified to originate from rotation around the axis. These results indicate that axial chirality plays an important role in controlling the stereochemistry and chemical reactivity of the 1,5-benzothiazepin-4-one nucleus. The stereochemistry of *S*-oxides revealed in this study is also important for understanding the metabolism of the biologically active sulfide derivatives. We hope that this study will contribute to drug design of pharmaceutically important 1,5-benzothiazepin-4-one molecules.

EXPERIMENTAL SECTION[19]

2-Bromo-*N*-(4-fluoro-2-trifluoromethylphenyl)acetamide. To a solution of bromoacetic acid (695 mg, 5.0 mmol) and 4-fluoro-2-trifluoromethylaniline (690 mg, 3.85 mmol) in THF (25 mL) at 23 °C under argon was added *N*,*N*′-dicyclohexylcarbodiimide (DCC) (1.34 g, 6.5 mmol) portionwise with stirring. After being stirred at 23 °C for 24 h, the mixture was filtrated to remove *N*,*N*′-dicyclohexylurea. The filtrate was concentrated, and ethyl acetate was added to the concentrate. The mixture was washed successively with dilute HCl, H_2O, saturated $NaHCO_3$, and H_2O and dried. The solvent was evaporated, and the residue was treated with diisopropyl ether to afford 2-bromo-*N*-(4-fluoro-2-trifluoromethylphenyl)acetamide as colorless crystals (465 mg, 1.55 mmol, 40%): mp 105−107 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.06 (s, 2H, CH_2), 7.30 (1H, dt, J = 8.4, 2.8 Hz, H5), 7.37 (1H, dd, J = 8.4, 2.8 Hz, H3), 8.12 (1H, dd, J = 8.4, 4.8 Hz, H6), 8.51 (1H, br, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.1 (Br−C), 113.7 (dq, C3), 119.7 (d, C5), 122.9 (dq, C2), 122.9 (q, CF_3), 126.7 (d, C6), 130.5 (C1), 159.2 (d, C4), 163.9 (C=O); IR (KBr) 3275, 1670, 1315, 1176, 1122 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_9H_6NOF_4Br$ 297.9496, found 297.9502.

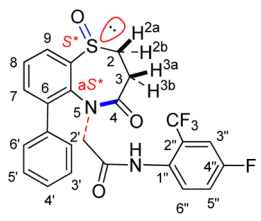
***N*-(4-Fluoro-2-trifluoromethylphenyl)-2-(4-oxo-6-phenyl-3,4-dihydro-2*H*-1,5-benzothiazepin-5-yl)acetamide (5).[8b]**



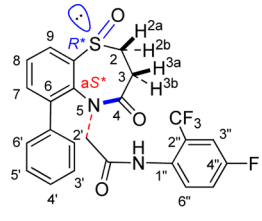
5

To a solution of 2,3-dihydro-6-phenyl-1,5-benzothiazepin-4(5*H*)-one[8a] (120 mg, 0.47 mmol) in DMF (1.0 mL) at 0 °C under argon was added sodium hydride (60% in oil) (20 mg, 0.5 mmol). The mixture was stirred at 23 °C for 30 min, cooled to 0 °C, and treated with 2-bromo-*N*-(4-fluoro-2-trifluoromethylphenyl)acetamide (120 mg, 0.4 mmol). After being stirred at 23 °C for 20 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 (silica gel, ethyl acetate/hexane = 1/2) to afford **5** as colorless crystals (87 mg, 39%): mp 113−115 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.85−2.90 (2H, m, H3a, H3b), 3.30 (1H, d, J = 16.3 Hz, −CH_2CO−), 3.37 (1H, ddd, J = 11.7, 11.1, 8.1 Hz, H2b), 3.48 (1H, ddd, J = 11.7, 5.9, 2.9 Hz, H2a), 4.25 (1H, d, J = 16.3 Hz, −CH_2CO−), 7.20 (1H, dt, J = 8.4, 2.8 Hz, H5″), 7.32 (1H, dd, J = 8.4, 2.8 Hz, H3″), 7.35 (2H, d, J = 7.6 Hz, H2′, H6′), 7.41 (1H, dt, J = 7.6, 1.4 Hz, H4′), 7.42 (1H, t, J = 7.6 Hz, H8), 7.46 (2H, t, J = 7.6 Hz, H3′, H5′), 7.51 (1H, dd, J = 7.6, 1.4 Hz, H7), 7.58 (1H, dd, J = 8.4, 4.8 Hz, H6″), 7.69 (1H, dd, J = 7.6, 1.4 Hz, H9), 9.19 (1H, br, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 33.5, 33.9, 53.3, 113.6 (d), 119.4 (d), 122.6 (q), 125.8 (dd), 128.1 (2 × C), 128.6, 128.8, 129.1, 129.4 (2 × C), 130.4 (d), 130.5, 133.4, 135.0, 137.8, 138.0, 142.8, 159.7 (d), 167.3, 173.0; IR (KBr) 3277, 1681 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{18}N_2O_2F_4SNa$ 497.0917, found 497.0920.

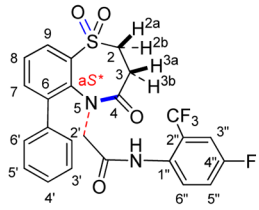
Oxidation Products of *N*-(4-Fluoro-2-trifluoromethylphenyl)-2-(4-oxo-6-phenyl-3,4-dihydro-2*H*-1,5-benzothiazepin-5-yl)-acetamide (5): The Sulfoxide Isomers (8I, 8II) and Sulfone (9).



8I major isomer



8II minor isomer



9

To a solution of **5** (15.4 mg, 0.032 mmol) in CH_2Cl_2 (0.3 mL) at 23 °C under argon was added dropwise a solution of *meta*-chloroperoxybenzoic acid (*m*CPBA) (9.0 mg, 0.034 mmol) in CH_2Cl_2 (0.24 mL). After being stirred at 23 °C for 0.5 h, the mixture was treated with saturated aq $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with brine, dried, and concentrated. The concentrate was purified by column chromatography (silica gel, ethyl acetate/hexane = 1:4) to afford sulfoxide (**8**) (14.4 mg, 91%) and sulfone (**9**) (6.8 mg, 4%). The sulfoxide (**8**) was separated by preparative HPLC using a nonchiral column (YMC SIL-06) to give the diastereomers **8I** and **8II** in a ratio of ≈5:1. See the Supporting Information for the HPLC chromatogram. The oxidation at −78 °C gave similar results, affording **8** (89%) (**8I**/**8II** ≈ 5:1) and **9** (4%), although the reaction proceeded slowly, taking approximately 3 h to complete. The product ratio of the oxidation reaction was also confirmed by HPLC analysis using an aliquot of the reaction mixture before work up.

Major Sulfoxide (8I): Colorless crystals; mp 220−221 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.76 (1H, ddd, J = 12.0, 7.2, 1.4 Hz, H3b), 2.93 (1H, ddd, J = 11.5, 8.9, 1.4 Hz, H2a), 2.98 (1H, ddd, J = 12.0, 10.8, 8.9 Hz, H3a), 4.14 (1H, ddd, J = 11.5, 10.8, 7.2 Hz, H2b), 3.22 (1H, d, J = 14.9 Hz, −CH_2CO−), 4.28 (1H, d, J = 14.9 Hz, −CH_2CO−), 7.21 (1H, dt, J = 8.4, 2.7 Hz, H5″), 7.3 (1H, m, H3″), 7.30 (2H, d, J = 7.6 Hz, H2′, H6′), 7.42 (1H, t, J = 7.6 Hz, H4′), 7.46 (2H, t, J = 7.6 Hz, H3′, H5′), 7.62 (1H, dd, J = 7.6, 1.4 Hz, H7), 7.71 (1H, t, J = 7.6 Hz, H8), 7.90 (1H, dd, J = 8.4, 4.8 Hz, H6″), 7.92 (1H, dd, J = 7.6, 1.4 Hz, H9), 8.26 (1H, br, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.8, 52.9, 54.7, 113.5 (d), 119.6 (d), 123.8, 127.2 (d), 128.2 (2 × C), 128.9, 129.5 (2 × C), 129.7, 134.4, 134.6, 136.7, 137.1, 138.9, 158.9 (d), 165.5, 171.0 (signals due to C$^{2″}$−CF_3 were not determined); IR (KBr) 3161, 1686, 1321, 1175, 1132, 1049, 1036 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{18}N_2O_3F_4SNa$ 513.0866, found 513.0868.

Minor Sulfoxide (8II): Colorless crystals; mp 224−225 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.85−2.90 (2H, m, H3a, H3b), 3.47 (1H, ddd, J = 14.8, 6.0, 2.9 Hz, H2a), 3.65 (1H, ddd, J = 14.8, 10.5, 7.4 Hz, H2b), 3.36 (1H, d, J = 16.6 Hz, −CH_2CO−), 4.25 (1H, d, J = 16.6 Hz, −CH_2CO−), 7.16 (1H, dt, J = 8.4, 2.8 Hz, H5″), 7.27 (1H, dd, J = 8.4, 2.8 Hz, H3″), 7.3 (1H, m, H6″), 7.32 (2H, d, J = 7.6 Hz, H2′, H6′), 7.44 (1H, t, J = 7.6 Hz, H4′), 7.49 (2H, t, J = 7.6 Hz, H3′, H5′), 7.55 (1H, t, J = 7.6 Hz, H8), 7.63 (1H, dd, J = 7.6, 1.4 Hz, H7), 7.71 (1H, dd, J = 7.6, 1.4 Hz, H9), 10.20 (1H, br, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 31.0, 52.9, 53.6, 113.7 (d), 119.3 (d), 128.1 (2 × C), 128.2, 129,0 129.1, 129.7 (2 × C), 132.1 (d), 134.4, 134.6, 137.3, 137.4, 139.6, 139.8, 160.3 (d), 167.7, 173.0 (signals due to C$^{2″}$−CF_3 were not determined); IR (KBr) 3127, 1679, 1319, 1167, 1137, 1048, 1023 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{18}N_2O_3F_4SNa$ 513.0866, found 513.0863.

dx.doi.org/10.1021/jo401020y | J. Org. Chem. XXXX, XXX, XXX−XXX

Sulfone (9): Colorless crystals; mp 219−220 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.95 (1H, ddd, J = 12.2, 12.0, 6.8 Hz, H3a), 3.00 (1H, ddd, J = 12.0, 7.2, 2.2 Hz, H3b), 3.60 (1H, ddd, J = 13.8, 6.8, 2.2 Hz, H2a), 3.90 (1H, ddd, J = 13.8, 12.2, 7.2 Hz, H2b), 3.54 (1H, d, J = 15.4 Hz, $-CH_2CO-$), 4.15 (1H, d, J = 15.4 Hz, $-CH_2CO-$), 7.17 (1H, dt, J = 8.4, 2.8 Hz, H5″), 7.28 (1H, dd, J = 8.4, 2.8 Hz, H3″), 7.33 (2H, d, J = 7.6 Hz, H2′, H6′), 7.40 (1H, t, J = 7.6 Hz, H4′), 7.45 (2H, t, J = 7.6 Hz, H3′, H5′), 7.68 (1H, t, J = 7.6 Hz, H8), 7.69 (1H, dd, J = 8.4, 5.5 Hz, H6″), 7.79 (1H, dd, J = 7.6, 1.4 Hz, H7), 8.14 (1H, dd, J = 7.6, 1.4 Hz, H9), 8.94 (1H, br, NH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 30.7, 54.6, 56.5, 113.3 (d), 119.3 (d), 122.7 (q), 124.8 (dd), 128.3 (2 × C), 128.6, 128.8, 129.2, 129.6 (2 × C), 129.3 (d), 130.8, 133.3, 136.7, 138.5, 138.6, 139.3, 159.4 (d), 165.8, 170.8; IR (KBr) 3313, 1685, 1320, 1163, 1122 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{24}H_{18}N_2O_4F_4S$ 505.0851, found 505.0858.

Separation of the Oxidation Products of 5 (a*S*/a*R*) into the Enantiomers (8I-A, 8I-B, 8II-A, 8II-B, 9-A, and 9-B) by Chiral HPLC. The oxidation of **5**[8b] with *m*CPBA was performed by the procedure described above (at 23 °C for 0.5 h), and the products were analyzed by a chiral column (CHIRALPAK IA). All the enantiomers (**8I-A**, **8I-B**, **8II-A**, **8II-B**, **9-A**, and **9-B**) were separated as shown in Figure 5.

Oxidation of 5-A (a*S*) with *m*CPBA. Oxidation of **5-A** (a*S*)[8b] with *m*CPBA by the procedure described above (at 23 °C for 0.5 h) afforded the sulfoxide (**8I-A**, **8II-A**) and sulfone (**9-A**) with the (a*S*)-form. The chiral HPLC chromatogram of the reaction is shown in the Supporting Information.

Oxidation of 5-B (a*R*) with *m*CPBA. Oxidation of **5-B** (a*R*)[8b] with *m*CPBA by the procedure described above (at 23 °C for 0.5 h) afforded the sulfoxide (**8I-B**, **8II-B**) and sulfone (**9-B**) with the (a*R*)-form. The chiral HPLC chromatogram of the reaction is shown in the Supporting Information.

Single-Crystal X-ray Analysis. All measurements were made on an imaging plate area detector 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 3.8 crystallographic software package. Typical crystal data of **5-A**, **8I**, and **9** are as follows.

Crystal Data for 5-A.[8b] $C_{24}H_{18}O_2N_2F_4S$: mp 113−115 °C, M_r = 474.47; Cu Kα (λ = 1.54187 Å); orthorhombic, $P2_12_12_1$, colorless prism 0.30 × 0.25 × 0.20 mm; crystal dimensions, a = 8.25733(15) Å, b = 14.0039(3) Å, c = 18.1857(3) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1565.41(12) Å^3, D_{calcd} = 1.499 g·cm^{-3}, μCu Kα = 19.188 cm^{-1}, F_{000} = 976.00, GOF = 1.003, R_{int} = 0.025, R_1 = 0.0263, wR_2 = 0.0578, Flack parameter = 0.001(13), CCDC-831104.

Crystal Data for 8I. $C_{24}H_{18}N_2O_3F_4S$: mp 220−221 °C, M_r = 490.47; Cu Kα (λ = 1.54187 Å); monoclinic, $P2_1/n$, colorless prism 0.20 × 0.15 × 0.10 mm; crystal dimensions, a = 12.8334(2) Å, b = 7.98785(14) Å, c = 20.8843(7) Å, α = 90°, β = 99.1302(9)°, γ = 90°, T = 173 K, Z = 4, V = 2113.75 (7) Å^3, D_{calcd} = 1.541 g·cm^{-3}, μCu Kα = 19.668 cm^{-1}, F_{000} = 1008.00, GOF = 1.585, R_{int} = 0.040, R_1 = 0.0429, wR_2 = 0.1198, CCDC-933115.

Crystal Data for 9. $C_{24}H_{18}N_2O_4F_4S$: mp 219−220 °C; Mr = 506.47; Cu Kα (λ = 1.54187 Å); monoclinic, $P2_1/c$, colorless prism 0.20 × 0.15 × 0.05 mm; crystal dimensions, a = 12.4476(2) Å, b = 25.6010(4) Å, c = 8.0385(1) Å, α = 90°, β = 94.3930°, γ = 90°, T = 173 K, Z = 4, V = 2554.11 (7) Å^3, D_{calcd} = 1.317 g·cm^{-3}, μCu Kα = 16.755 cm^{-1}, F_{000} = 1040.00, GOF = 3.496, R_{int} = 0.0371, R_1 = 01517, wR_2 = 0.3664, CCDC-941996.

Separation of Sulfoxides (8I and 8II) and Sulfone (9) into the Enantiomers (A and B) and Characterization of the Separated Enantiomers. The sulfoxides (**8I** and **8II**) and sulfone (**9**) were obtained by the procedure described above and were separated into the respective atropisomers (**A** and **B**) by preparative HPLC using a chiral column. The separation conditions and the physicochemical data are described below.

Atropisomers (A and B) of Major Sulfoxide (8I). CHIRALPAK IA (1.0 cmϕ × 25 cm): eluent, hexane/EtOH (9/1); flow rate, 4.0 mL/min; temperature, 24 °C; detection, 254 nm; former peak (**8I-A**), white solids; retention time = 41.7 min; $[\alpha]_D^{20}$ −61 (c 0.155, MeOH); latter peak (**8I-B**), white solids; retention time = 57.2 min; $[\alpha]_D^{20}$ +57 (c 0.245, MeOH). The retention time of **8I-A** was 11.7 min and that of **8I-B** was 7.9 min under the following analytical conditions: CHIRALPAK IA (0.46 cm ϕ × 25 cm); eluent, hexane:IPA (9:1); flow rate, 1.2 mL/min; temperature, 23 °C; detection, 254 nm.

Atropisomers (A and B) of Minor Sulfoxide (8II). CHIRALPAK IA (0.46 cmϕ × 15 cm): eluent, hexane/IPA (5/1); flow rate, 1.2 mL/min; temperature, 22 °C; detection, 254 nm; former peak (**8II-A**), white solids; retention time = 15.6 min; $[\alpha]_D^{20}$ +42 (c 0.085, MeOH); latter peak (**9-B**), white solids; retention time = 35.0 min; $[\alpha]_D^{20}$ −40 (c 0.135, MeOH).

Atropisomers (A and B) of Sulfone (9). CHIRALPAK IA (1.0 cmϕ × 25 cm): eluent, hexane/IPA (5/1); flow rate, 4.0 mL/min; temperature, 22 °C; detection, 254 nm; former peak (**9-A**), white solids; retention time = 34.0 min; $[\alpha]_D^{20}$ −37 (c 0.07, MeOH); latter peak (**9-B**), white solids; retention time = 57.3 min; $[\alpha]_D^{20}$ +34 (c 0.04, MeOH).

Stereochemical (Thermodynamic) Stability of Diastereomers (8I and 8II) and Atropisomers (8I-B, 8II-B, and 9-A) (Determination of $\Delta G^{\ddagger}$ Value). To examine the thermal stability of diastereomers and enantiomers, the time-dependent conversion rate (%) was estimated from chiral or nonchiral HPLC analysis of a solution of the diastereomers or enantiomer in toluene (or $CHCl_3$) after it was allowed to stand at designated temperatures. The $\Delta G^{\ddagger}$ value was determined according to a calculation method reported in the literature.[17] The details, including the figures of conversion profiles, are shown in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure, ^{1}H, ^{13}C, and 2D (CH and HH COSY) NMR spectra for new compounds, figures of thermal isomerization rate of diastereomers (**8I** and **8II**) and atropisomers (**8I-B**, **8II-B**, and **9-A**), and X-ray data (CIF) for compounds **8I** and **9**. 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.

■ ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research (C) (21590124) and a Grant-in-Aid for Young Scientists (B) (21790025) from the Japan Society for the Promotion of Sciences.

■ REFERENCES

(1) (a) Kugita, H.; Inoue, H.; Ikezaki, M.; Konda, M.; Takeo, S. *Chem. Pharm. Bull.* **1971**, *19*, 595−602. (b) Bariwal, J. B.; Upadhyay, K. D.; Manvar, A. T.; Trivedi, J. C.; Singh, J. S.; Jain, K. S.; Shah, A. K. *Eur. J. Med. Chem.* **2008**, *43*, 2279−2290.

(2) (a) Krapcho, J.; Spitzmiller, E. R.; Turk, C. F. *J. Med. Chem.* **1963**, *6*, 544−546. (b) Krapcho, J.; Turk, C. F. *J. Med. Chem.* **1966**, *9*, 191−195. (c) Krapcho, J.; Turk, C. F.; Piala, J. J. *J. Med. Chem.* **1968**, *11*, 361−364.

(3) DeVita, R. J.; Schoen, W. R.; Doldouras, G. A.; Fisher, M. H.; Wyvratt, M. J.; Cheng, K.; Chan, W. W.-S.; Butler, B. S.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1281−1286.

(4) (a) Slade, J.; Stanton, J. L.; Ben-David, D.; Mazzenga, G. C. *J. Med. Chem.* **1985**, *28*, 1517−1521. (b) Itoh, K.; Kori, M.; Inada, Y.; Nishikawa, K.; Kawamatsu, Y.; Sugihara, H. *Chem. Pharm. Bull.* **1986**, *34*, 1128−1147.

(5) Skiles, J. W.; Sorcek, R.; Jacober, S.; Miao, C.; Mui, P. W.; McNeil, D.; Rosenthal, A. S. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 773−778.

(6) Campiani, G.; Nacci, V.; Fiorini, I.; De Filippis, M. P.; Garofalo, A.; Greco, G.; Novellino, E.; Altamura, S.; Di Renzo, L. *J. Med. Chem.* **1996**, *39*, 2672−2680.

(7) For representative reports, including review articles on the relation between axial chirality and biological activity, see the following:

(a) Natsugari, H.; Ikeura, Y.; Kamo, I.; Ishimaru, T.; Ishichi, Y.; Fujishima, A.; Tanaka, T.; Kasahara, F.; Kawada, M.; Doi, T. *J. Med. Chem.* **1999**, *42*, 3982−3993. (b) Albert, J. S.; Aharony, D.; Andisik, D.; Barthlow, H.; Bernstein, P. R.; Bialecki, R. A.; Dedinas, R.; Dembofsky, B. T.; Hill, D.; Kirkland, K.; Koether, G. M.; Kosmider, B. J.; Ohnmacht, C.; Palmer, W.; Potts, W.; Rumsey, W.; Shen, L.; Shenvi, A.; Sherwood, S.; Warwick, P. J.; Russell, K. *J. Med. Chem.* **2002**, *45*, 3972−3983. (c) Clayden, J. *Tetrahedron* **2004**, *60*, 4335. (d) Guile, S. D.; Bantick, J. R.; Cooper, M. E.; Donald, D. K.; Eyssade, C.; Ingall, A. H.; Lewis, R. J.; Martin, B. P.; Mohammed, R. T.; Potter, T. J.; Reynolds, R. H.; St-Gallay, S. A.; Wright, A. D. *J. Med. Chem.* **2007**, *50*, 254−263. (e) Lee, S.; Kamide, T.; Tabata, H.; Takahashi, H.; Shiro, M.; Natsugari, H. *Bioorg. Med. Chem.* **2008**, *16*, 9519−9523. (f) Tabata, H.; Akiba, K.; Lee, S.; Takahashi, H.; Natsugari, H. *Org. Lett.* **2008**, *10*, 4871−4874. (g) Porter, J.; Payne, A.; Whitcombe, I.; de Candole, B.; Ford, D.; Garlish, R.; Hold, A.; Hutchinson, B.; Trevitt, G.; Turner, J.; Edwards, C.; Watkins, C.; Davis, J.; Stubberfield, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1767−1772. (h) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398−6401. (i) LaPlante, S. R.; Edwards, P. J.; Fader, L. D.; Jakalian, A.; Hucke, O. *Chem. Med. Chem* **2011**, *6*, 505−513. (j) Takahashi, H.; Wakamatsu, S.; Tabata, H.; Oshitari, T.; Harada, A.; Inoue, K.; Natsugari, H. *Org. Lett.* **2011**, *13*, 760−763. (k) Tabata, H.; Nakagomi, J.; Morizono, D.; Oshitari, T.; Takahashi, H.; Natsugari, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3075−3079.

(8) (a) Tabata, H.; Wada, N.; Takada, Y.; Oshitari, T.; Takahashi, H.; Natsugari, H. *J. Org. Chem.* **2011**, *76*, 5123−5131. (b) Tabata, H.; Wada, N.; Takada, Y.; Nakagomi, J.; Miike, T.; Shirahase, H.; Oshitari, T.; Takahashi, H.; Natsugari, H. *Chem.—Eur. J.* **2012**, *18*, 1572−1576.

(9) Numbering for 1,5-benzothiazepin-4-ones includes **1**, **4**, **5**, **8**, and **9**. The number 6 corresponds to 9 for compounds with other nuclei (**2**/**6** and **3**/**7**).

(10) Breitschuh, R.; Seebach, D. *Synthesis* **1992**, 1170−1178.

(11) The relative configuration (*cis*−*trans*) of the racemic 1,5-benzothiazepin-4-one *S*-oxide with a substituent at *C*2 has been reported. Patonay, T.; Adam, W.; Jeko, J.; Kövér, K. E.; Lévai, A.; Németh, M.; Peters, K. *Heterocycles* **1999**, *51*, 85−94 Although not mentioned in the report, it should be recognized that the molecule has axial chirality due to the sp^2−sp^2 axis at Ar−N(C═O), which exists in the latent form and is moving together like a gear with the stereochemistry specified by the two chiral centers at 1*S* and 2*C*.

(12) The terms a*S* and a*R* (chiral axis nomenclature) correspond to *P* and *M* (helix nomenclature), respectively.

(13) For a recent paper on the ^{1}H chemical shifts in NMR for sulfoxides and sulfones in general, see: Abraham, R. J.; Byrne, J. J.; Griffiths, L. *Magn. Reson. Chem.* **2008**, *46*, 667−675.

(14) See the Supporting Information for detailed NMR analysis of the methylene protons for **5**, **8I**, **8II**, and **9**, including the torsion angles around the 1*S*−2*C*−3*C* moiety, obtained from the X-ray structures. The values of the vicinal coupling (^3J) correspond well with those estimated from the torsion angles by the Karplus equation. Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870−2871.

(15) For review articles on the hydrogen bond, see: (a) Steiner, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 48−76. (b) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, U.K., 1997.

(16) (a) Axelrod, M.; Bickart, P.; Jacobus, J.; Green, M. M.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4835−4842. (b) Korpiun, O.; Lewis, R. A.; Chickos, J.; Mislow, K.; Rayner, D. R.; Gordon, A. J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4854−4860. (c) Miller, E. G.; Rayner, D. R.; Thomas, H. T.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4861−4868. (d) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869−4876.

(17) For determination of $\Delta G^{\ddagger}$ values, see: Petit, M.; Lapierre, A. J. B.; Curran, D. P. *J. Am. Chem. Soc.* **2005**, *127*, 14994−14995.

(18) For an informative study on the correlation of absolute configuration and the chiroptical properties of alkyl aryl sulfoxides, see: Rosini, C.; Donnoli, M. I.; Superchi, S. *Chem.—Eur. J,* **2001**, *7*, 72−79.

(19) For general experimental methods, see the Supporting Information.

dx.doi.org/10.1021/jo401020y | *J. Org. Chem.* XXXX, XXX, XXX−XXX