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Atropisomeric Properties of 7-, 8-, and 9-Membered-Ring Dibenzolactams: Conformation, Thermal Stability, and Chemical Reactivity

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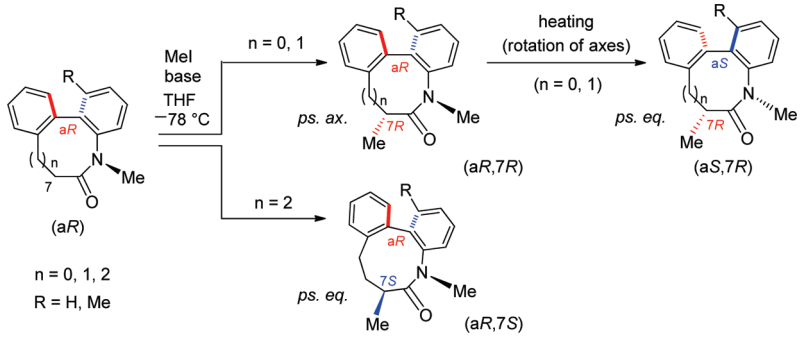

The atropisomeric enantiomers of 7-, 8-, and 9-membered-ring dibenzolactams were separated by using chiral HPLC, and their stereochemistries were clarified by using X-ray crystallographic analysis. The atropisomers showed high stereochemical stability with the 8-membered ring being the most stable. In 7- and 8-membered dibenzolactams, highly stereoselective C7-methylation proceeded from the lower side of the ring to provide the products with a C7-methyl group in the pseudoaxial orientation, which converted to thermodynamically more stable isomers with the pseudoequatorial C7-methyl group. In 9-membered dibenzolactam, C7-methylation occurred from the opposite (upper) side of the ring to provide a thermodynamically stable product with the pseudoequatorial C7-methyl group.

Introduction

Recently, conformational analysis of medium-sized heterocycles, which are found as the scaffolds of many biologically active molecules, has received considerable attention.[1] In the course of our research aimed at developing new γ-secretase inhibitors, we have been interested in LY-411575,[2] which has a 7-membered-ring dibenzolactam, a dibenzo[*b*,*d*]azepin-6-one moiety (**1**) (Figure 1). The stereochemistry of **1** is of interest because, in addition to the one asymmetric center at C7, the moiety has chirality based on the sp^2-sp^2 axis arising from a biphenyl.[3] Our thorough investigation of the stereochemical and physicochemical properties of **1** revealed that it is a racemic compound that can be separated by chiral HPLC into the a*R*- and a*S*-atropisomers with high stereochemical stability.[4] Interestingly, methylation at C7 of **1** stereoselectively gave the

(1) For examples, see: (a) Hassner, A.; Amit, B.; Marks, V.; Gottlieb, H. E. *J. Org. Chem.* **2003**, *68*, 6853–6858. (b) Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1545–1551. (c) Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1552–1557.

(2) (a) Lanz, T. A.; Hosly, J. D.; Adams, W. J.; Merchant, K. M. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 49–55. (b) Lanz, T. A.; Fici, G. J.; Merchant, K. M. *J. Pharmacol. Exp. Ther.* **2005**, *312*, 399–406. (c) Best, J. D.; Jay, M. T.; Out, F.; Ma, J.; Nadin, A.; Ellis, S.; Lewis, H. D.; Pattison, C.; Reilly, M.; Harrison, T.; Shearman, M. S.; Williamson, T. L.; Atack, R. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 902–908. (d) Wong, G. T.; Manfra, D.; Poulet, F. M.; Zhang, Q.; Losien, H.; Bara, T.; Engstrom, L.; Pinzon-Ortiz, M.; Fine, J. S.; Lee, H. J.; Zhang, L.; Higgins, G. A.; Parker, E. M. *J. Biol. Chem.* **2004**, *279*, 12876–12882. (e) Cole, K. P.; Mitchell, D.; Carr, M. A.; Stout, J. R.; Belvo, M. D. *Tetrahedron: Asymmetry* **2009**, *20*, 1262–1266.

(3) For review articles on axial chirality and atropisomerism, see: (a) Clayden, J. *Tetrahedron* **2004**, *60*, 4335 in Tetrahedron Symposia-in-Print on Atropisomerism (Clayden, J., Ed.) and other papers in the issue. (b) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398–6401.

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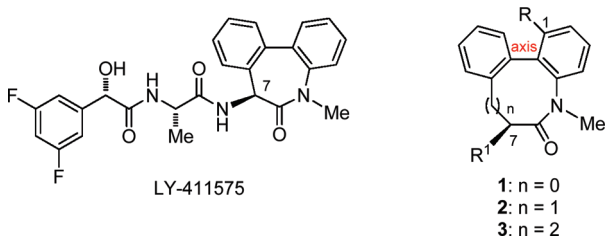
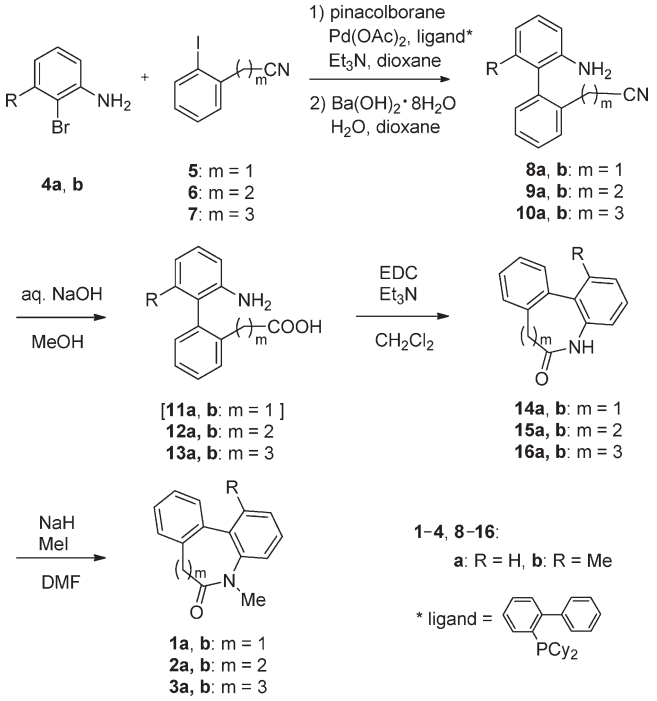


FIGURE 1. Structures of LY-411575 and 7-, 8-, and 9-membered-ring dibenzolactams **1**−**3**.

SCHEME 1. Synthesis of 7-, 8-, and 9-Membered-Ring Dibenzolactams 1−3



(a*R**,7*R**)-isomer (**1**: R^1 = Me), which converted to the thermodynamically stable (a*S**,7*R**)-atropisomer after heating.[4] Such absorbing stereochemical properties of a 7-membered-ring dibenzolactam prompted us to examine the 8- and 9-membered-ring dibenzolactams more closely. In this paper, we deal with 7-, 8-, and 9-membered-ring dibenzolactams (**1**−**3**) by comparison of the separation of the atropisomers and chemical reactivity toward stereoselective C7-methylation to elucidate the conformational properties inherent in each ring system.

Results and Discussion

Synthesis of 7-, 8-, and 9-Membered-Ring Dibenzolactams. The 7-, 8-, and 9-membered-ring dibenzolactams (**1**−**3**) were prepared following the procedure used for the synthesis of dibenzo[*b*,*d*]azepin-6-one derivatives **1** described in our previous papers[4,5] (Scheme 1). Compounds **1b**, **2b**, and **3b** have a

(4) Tabata, H.; Akiba, K.; Lee, S.; Takahashi, H.; Natsugari, H. *Org. Lett.* **2008**, *10*, 4871–4874.

(5) Fuwa, H.; Okamura, Y.; Morohashi, Y.; Tomita, T.; Iwatsubo, T.; Kan, T.; Fukuyama, T.; Natsugari, H. *Tetrahedron Lett.* **2004**, *45*, 2323–2326.

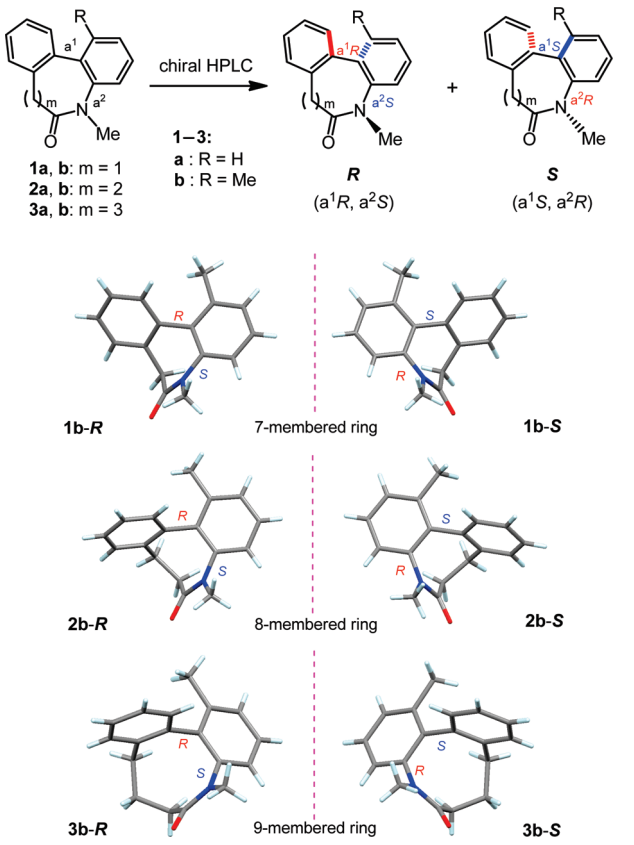
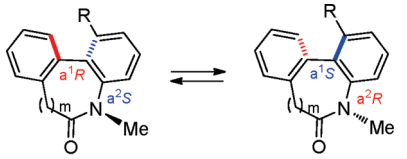


FIGURE 2. Separation of enantiomers of 7-, 8-, and 9-membered-ring dibenzolactams **l**(**a**,**b**), **2**(**a**,**b**), and **3**(**a**,**b**), and X-ray crystal structures of enantiomers **1b**-*R*/**1b**-*S* (top), **2b**-*R*/**2b**-*S* (middle), and **3b**-*R*/**3b**-*S* (bottom).

methyl group at the ortho position on the benzene ring (R = Me), which makes the molecule more rigid by introducing steric hindrance around the biphenyl moiety. Starting from biaryl coupling, three successive steps (i.e., hydrolysis, lactam formation, and *N*-methylation) provided compounds **1**, **2**, and **3** efficiently. It is interesting to note that in the hydrolysis, the nitrile **8**(**a**,**b**) afforded the corresponding lactam **14**(**a**,**b**) directly via the carboxylic acid **11**(**a**,**b**) under hydrolysis conditions, whereas the nitriles **9**(**a**,**b**) and **10**(**a**,**b**) provided the corresponding carboxylic acids **12**(**a**,**b**) and **13**(**a**,**b**), respectively. Thus, lactam formation with *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) was necessary for the 8- and 9-membered-ring compounds **15**(**a**,**b**) and **16**(**a**,**b**).

Separation and X-ray Crystallographic Analysis of Atropisomers of 7-, 8-, and 9-Membered-Ring Dibenzolactams. In our previous communication,[4] the 7-membered-ring dibenzolactams **1**(**a**,**b**) were shown to be racemic compounds, which can be separated into atropisomeric enantiomers by using HPLC on a chiral column (CHIRALPAK AD-H) (Figure 2). The structures of the enantiomers have been confirmed to be as shown in Figure 2 (top) by using X-ray crystallographic analysis. The X-ray analysis of **1b**-atropisomers revealed that, in addition to the chirality based on the axis of the biphenyl moiety (a^1), **1b** has another axial chirality arising from the sp^2−sp^2 axis of the benzene−amide bond (a^2).[6] Although latent in the molecule and generally less represented, the latter axial chirality (a^2) actually exists.[7]

TABLE 1. Stability of the Separated Enantiomers of 7-, 8-, and 9-Membered-Ring Dibenzolactams 1−3



R **(a^1*R*, a^2*S*)** ⇌ ***S*** **(a^1*S*, a^2*R*)**

			$[\alpha]_D$[a]			
compd	*m*	R	*R*	*S*	$\Delta G^{\ddagger}$, kJ/mol	conditions required for racemization
1a	1	H	−137.1	+131.2	98	37 °C, 2 h[b]
1b	1	Me	−92.0	+93.7	122	110 °C, 2 h[b]
2a	2	H	−166.1	+165.7	112	80 °C, 3 h[b]
2b	2	Me	−163.6	+170.0		−[c]
3a	3	H	−249.5	+231.7	102	50 °C, 2 h[b]
3b	3	Me	−213.7	+206.1		−[c]

[a]In MeOH. [b]In toluene. [c]No change at 150 °C for 3 h in DMF.

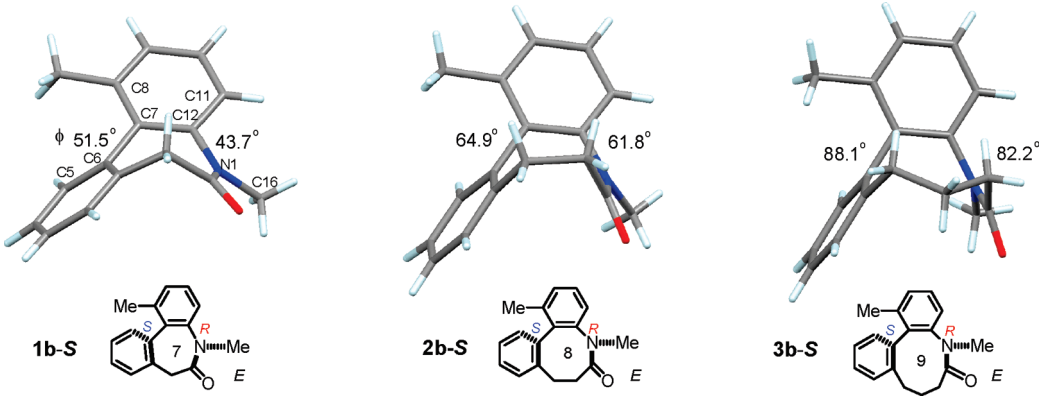


FIGURE 3. Molecular shapes and dihedral angles (ϕ) of 7-, 8-, and 9-membered-ring dibenzolactams **1b**-*S*, **2b**-*S*, and **3b**-*S* determined by X-ray crystallographic analysis.[11]

The configuration of the enantiomers **1b**-*R* and **1b**-*S* was shown to be (a^1*R*,a^2*S*) and (a^1*S*,a^2*R*), respectively.[8,9] Taking into consideration the fact that no diastereomers of **1**(**a**,**b**) are observed with NMR and HPLC, the latter axis (a^2) is assumed to move together like a gear, with the axis at the biphenyl (a^1) forming the stable relative configuration of (a^1*R**,a^2*S**) in the dibenzolactam nucleus. This assumption is also supported by the molecular modeling of **1**(**a**,**b**), in which the relative configuration of (a^1*R**,a^2*S**) is readily built up, while that of (a^1*R**,a^2*R**) is not built up because of the large strain.

Thus, the 8- and 9-membered-ring dibenzolactams, **2**(**a**,**b**) and **3**(**a**,**b**), are also anticipated to occur in the racemic form of the corresponding enantiomers *R* and *S*. By using HPLC on a chiral column (CHIRALPAK AD-H and IA), the compounds **2**(**a**,**b**) and **3**(**a**,**b**) were separated into the respective enantiomers (*R* and *S*), and these enantiomers were successfully isolated by using preparative HPLC. The configuration of each enantiomer was unambiguously determined with X-ray crystallographic analysis as shown in Figure 2 (middle) for **2b** and Figure 2 (bottom) for **3b**, which show the same relative configuration between the two axes (a^1 and a^2) [i.e., (a^1*R*,a^2*S*) or (a^1*S*,a^2*R*)] as that of the enantiomers of **1**.[9] It was revealed that the angle of optical rotation α (in MeOH) of the *R*-series of enantiomers is negative (−), and that of the *S*-series of enantiomers is positive (+) (Table 1).

Figure 3 shows the molecular shapes of **1b**-*S*, **2b**-*S*, and **3b**-*S* viewed from the chain-side of the ring. As shown in the figure, all the molecules have *E*-configuration[10] around the amide bond regardless of the ring size, and each 7-, 8-, and

(6) For the axial chirality arising from the sp^2−sp^2 axis of the benzene−amide bond, see: (a) Ikeura, Y.; Ishichi, Y.; Tanaka, T.; Fujishima, A.; Murabayashi, M.; Kawada, M.; Ishimaru, T.; Kamo, I.; Doi, T.; Natsugari, H. *J. Med. Chem.* **1998**, *41*, 4232–4239. (b) 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. (c) 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. (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) Welch, C. J.; Biba, M.; Pye, P.; Angelaud, R.; Egbertson, M. *J. Chromatogr. B* **2008**, *875*, 118–121. (f) 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.

(7) Atropisomeric properties of the 7-membered-ring benzolactams without biphenyl moiety will be reported in due course.

(8) In this paper, to denote the compound number (suffix), the axial chirality at a^1 is used for clarity; i.e., suffix *R* (and *R*′) is used for (a^1*R*,a^2*S*), and *S* is used for (a^1*S*,a^2*R*).

(9) The absolute stereochemistry was determined based on the Flack parameter.

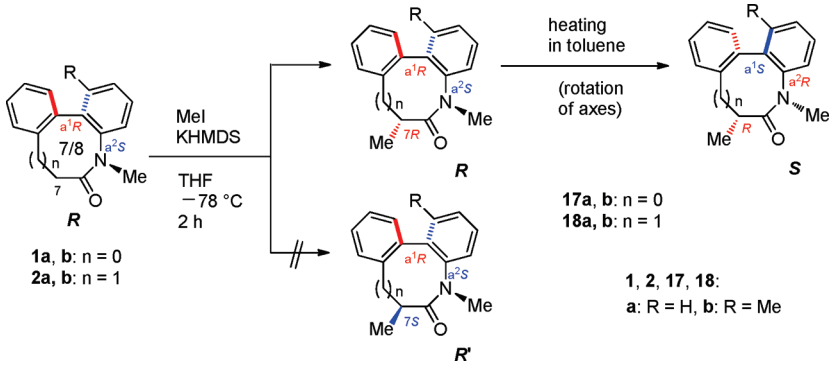
(10) *E* and Z are designated according to the IUPAC recommended rule.

TABLE 2. C7-Methylation and Isomerization of 7-, 8-, and 9-Membered-Ring Dibenzolactams 1−3

		methylation at C7			
entry	substrate[a]	product (stereochemistry at a^1 and C7)	yield, %	isomerization of the C7-methylated product after heating in solvent	$\Delta G^{\ddagger}$, kJ/mol
1	**1a**-*R*	**17a**-*S* (a^1S,7*R*)[b]	96	—[c]	
2	**1b**-*R*	**17b**-*R* (a^1R,7*R*)	99	**17b**-*R* → **17b**-*R*:**17b**-*S* (3:97)[d,e]	113
3	**2a**-*R*	**18a**-*R* (a^1R,7*R*)	79	**18a**-*R* → **18a**-*R*:**18a**-*S* (10:90)[f,e]	108
4	**2b**-*R*	**18b**-*R* (a^1R,7*R*)	78	**18b**-*R* → no isomerization[g]	—
5	**3a**-*R*	**19a**-*R*′ (a^1R,7*S*)	80	—[h]	
6	**3b**-*R*	**19b**-*R*′ (a^1R,7*S*)	90	—[h]	

[a]All the substrates have a^1R-stereochemistry. [b]Intermediary formation of **17a**-*R* (a^1R,7*R*) was observed in the reaction (see main text). [c]**17a**-*S* is the thermodynamically stable product and it did not isomerize at 100 °C for ca. 2 h in toluene. [d]Reached equilibrium state at 80 °C for ca. 7 h in toluene. [e]Equilibrium ratio. [f]Reached equilibrium state at 80 °C for ca. 4 h in toluene. [g]**18b**-*R* did not isomerize at 150 °C for 3 h in DMF. [h]**19a**-*R*′ and **19b**-*R*′ are the thermodynamically stable products and they did not isomerize at 150 °C for 3 h in DMF.

SCHEME 2. Stereoselective Methylation at the C7-Position of 7- and 8-Membered-Ring Dibenzolactams (1 and 2) and Isomerization of *R* to *S*[a]



[a]No isomerization from **18b**-*R* to **18b**-*S* occurred at 150 °C in DMF.

9-membered ring has a cage structure, in which the dihedral angle (ϕ) of $C^5-C^6-C^7-C^8$ was shown to be 51.5°, 64.9°, and 88.1°, respectively, and that of $C^{11}-C^{12}-N^1-C^{16}$ to be 43.7°, 61.8°, and 82.2°, respectively.[11] It is clear that the deeper cage is formed in proportion to the number of the ring system. The geometry should represent the more significantly populated conformer of **1**, **2**, and **3** in solution.

Stereochemical Stability of Atropisomers of 7-, 8-, and 9-Membered-Ring Dibenzolactams. Next, we examined the stereochemical stability of these separated enantiomers of **1**(**a**,**b**), **2**(**a**,**b**), and **3**(**a**,**b**). It was revealed that all enantiomers are relatively stable toward racemization. Table 1 shows the activation free-energy barrier to rotation ($\Delta G^{\ddagger}$)[12] and the conditions (temperature, time) required for racemization of the enantiomers in solvent. The enantiomers of **1a** (R = H) have stereochemical stability toward racemization with a $\Delta G^{\ddagger}$ value of 98 kJ/mol, whereas, reflecting the steric hindrance around the biphenyl moiety, the enantiomers of **1b** (R = Me) showed higher stereochemical stability with a $\Delta G^{\ddagger}$ value of 122 kJ/mol. Similarly, the enantiomers of **2b** and **3b**, which have a methyl group on the benzene ring (R = Me), are so stable that they did not interconvert at all at 150 °C in DMF even after 3 h. It should be noted that the enantiomoer of **2a** (n = 2: 8-membered-ring lactam) has extreme stability toward racemization ($\Delta G^{\ddagger}$ = 112 kJ/mol) compared with those of **1a** ($\Delta G^{\ddagger}$ = 98 kJ/mol) and **3a** ($\Delta G^{\ddagger}$ = 102 kJ/mol). Although the reason for this difference is not apparent, X-ray crystallographic analysis affords a clue to elucidate the stereochemical properties of each ring system. In the course of racemization, the cage structure should be inverted. It seems reasonable that the deeper and more rigid cage in **2** has greater resistance to the inversion of the ring system than **1**, which is confirmed by the higher $\Delta G^{\ddagger}$ value of 112 kJ/mol observed in **2a**. Meanwhile, **3a**, which has the deepest cage, showed less stability ($\Delta G^{\ddagger}$ = 102 kJ/mol) than **2a**. Although definitive information on this is lacking, the consecutive methylene chain in the 9-membered-ring system may provide sufficient flexibility to decrease the energy barrier for the conversion of the entire molecule.

Stereoselective C7-Methylation of Atropisomers of 7-, 8-, and 9-Membered-Ring Dibenzolactams. In view of the structure of LY-411575, we next focused on the substituent effect at the C7-position of the dibenzolactam ring on the stereochemistry of the entire molecule. Thus, compounds **1**−**3** were methylated (MeI/base in THF at −78 °C) to introduce an asymmetric center at the C7-position (Table 2, Schemes 2 and 3). The results of 7- and 8-membered-ring compounds are shown in Scheme 2 and Table 2 (entries 1−4).

From the 7-membered lactam **1b**-*R* (R = Me: a^1R), two diastereoisomers [**17b**-*R* (=7*R*) and **17b**-*R*′ (=7*S*)] were expected to be produced by this methylation. However, only

(11) The numbering system in Figure 3 is that used for the X-ray crystallographic analysis (CIF files in the Supporting Information).

(12) The $\Delta G^{\ddagger}$ value was determined based on the time-dependent conversion rate (% ee) estimated from chiral HPLC analysis of a solution of the enantiomers after being allowed to stand at designated temperatures; see: Petit, M.; Lapierre, A. J. B.; Curran, D. P. *J. Am. Chem. Soc.* **2005**, *127*, 14994–14995.

17b-*R* (a^1R,7*R*) was obtained in 99% yield (Table 2/entry 2).[13] This result indicates that the conformation defined by the axial chiralities controlled the stereochemistry of the methylation. Compound **17b**-*R* was stable in solution at room temperature but at elevated temperatures gradually converted to the atropisomeric diastereomer **17b**-*S* (a^1S,7*R*) (= the enantiomeric form of **17b**-*R*′). The conversion was temperature dependent. After standing in toluene at 37 °C for 2 h, pure **17b**-*R* was converted to a mixture of the diastereomers (**17b**-*R*:**17b**-*S* = ca. 96:4). Similarly, after standing at 80 °C for 2 h, the ratio was changed to ca. 42:58, and for ca. 7 h the conversion reached equilibrium in a ratio of 3:97. The interconversion barrier ($\Delta G^{\ddagger}$) between **17b**-*R* and **17b**-*S* was calculated to be 113 kJ/mol. It is interesting that the methylation of the less restricted **1a**-*R* (R = H: a^1R) provided the thermodynamically stable isomer **17a**-*S* directly in 96% yield (Table 2/entry 1).[13] However, detailed investigation of the intermediate step with TLC and ^{1}H NMR revealed that the unstable isomer **17a**-*R* was initially formed, which readily isomerized to give **17a**-*S* during workup even at low temperature (ca. 10 °C).

C7-Methylation of the 8-membered-ring lactam **2a**-*R* (R = H: a^1R) also proceeded highly stereoselectively to provide **18a**-*R* (a^1R,7*R*) in 79% yield (Table 2/entry 3). Compound **18a**-*R* was shown to be more stable than the corresponding 7-membered-ring lactam **17a**-*R*. Conversion of **18a**-*R* into the (a^1S)-isomer **18a**-*S* (a^1S,7*R*) occurred at elevated temperature; e.g., slight isomerization occurred at 37 °C in toluene after 4 h (**18a**-*R*:**18a**-*S* = ca. 94:6), and at 80 °C after ca. 4 h the conversion reached equilibrium (**18a**-*R*:**18a**-*S* = ca. 10:90). The interconversion barrier ($\Delta G^{\ddagger}$) between **18a**-*R* and **18a**-*S* was calculated to be 108 kJ/mol. In the more restricted 8-membered-ring lactam **2b**-*R* (R = Me: a^1R), methylation also occurred highly stereoselectively to provide **18b**-*R* (Table 2/entry 4). It should be noted that **18b**-*R* is so stable that no isomerization of **18b**-*R* to **18b**-*S* was observed even at 150 °C in DMF. Taking these results together, it is concluded that the 8-membered-ring lactam has a more stable conformation than the corresponding 7-membered-ring lactam.

The stereochemistry of **17b**-*R* and -*S* and **18a**-*R* and -*S* was determined with NOE analysis (Figure 4). In **17b**-*R*, NOEs were observed between two methyl groups and between two protons, where C7-methyl is in the pseudoaxial orientation. On the other hand, in **17b**-*S*, the NOEs observed were between the C7-methyl and benzene-H and between the C7-H and benzene-methyl, where the C7-methyl is in the pseudoequatorial orientation. Similar NOEs were observed in **18a**-*R* and **18a**-*S*. Thus, the stereochemistry of **17b**-*R* and -*S*, **18a**-*R* and -*S* was determined to be as shown in Figure 4. It is worthy to note that the C7-methylation products (**17b**-*R*, **18a**-*R*, and **18b**-*R*) have (−)-angle of optical rotation α, whereas the isomerized compounds (**17a**-*S*, **17b**-*S*, **18a**-*S*, and **18b**-*S*) have (+)-rotation (Table 3). These findings would support that, by comparison with the (−)/(+)-angle of the enantiomers of the parent dibenzolactams (Table 1), the structures of the products are correctly assigned.

The highly stereoselective methylation observed in compounds **1** and **2** is explained by a kinetically controlled

(13) In our previous work,[4] C7-alkylation and isomerization of the alkylated product were examined by using the racemate of **1**(**a**,**b**), and the same stereochemical results as described in this paper (Table 2/entries 1 and 2) were observed in the racemic form.

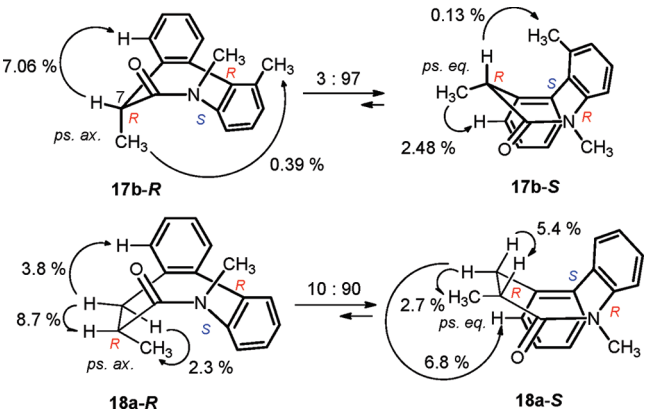
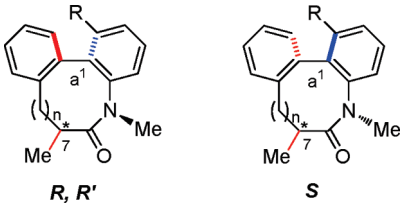


FIGURE 4. NOE analysis of **17b**-*R*/**17b**-*S* and **18a**-*R*/**18a**-*S*.

TABLE 3. Optical Rotation of C7-Methylated 7-, 8-, and 9-Membered-Ring Dibenzolactams 17−19



			configuration		
compd	*n*	R	a^1	C7	$[\alpha]_D$ (MeOH)
17a-*S*	0	H	*S*	*R*	+189.3
17b-*R*	0	Me	*R*	*R*	−79.3
17b-*S*	0	Me	*S*	*R*	+116.1
18a-*R*	1	H	*R*	*R*	−164.8
18a-*S*	1	H	*S*	*R*	+112.7
18b-*R*	1	Me	*R*	*R*	−158.9
19a-*R*′	2	H	*R*	*S*	−165.5
19b-*R*′	2	Me	*R*	*S*	−146.1

reaction. A plausible mechanism of the methylation of **1b**-*R* is illustrated in Figure 5. In the enolate form of **1b**-*R*, the benzene ring (A) covers the upper side of the enolate so that the electrophile should come only from the lower side to form **17b**-*R*. This shows that the conformation based on the axial chiralities completely controlled the stereochemistry at the C7-position in methylation. More noteworthy in this figure is that the product **17b**-*R* has a methyl group in the pseudoaxial orientation, which is thermodynamically unstable. This unstable orientation resulted in the thermal atropisomerization from **17b**-*R* to the thermodynamically more stable **17b**-*S*, which has a pseudoequatorial methyl group. Stereoselective methylation of the 8-membered lactams (**2a**-*R* to **18a**-*R* and **2b**-*R* to **18b**-*R*) and isomerization from **18a**-*R* to **18a**-*S* can be similarly explained. It is interesting that the introduction of the methyl group at the C7-position of the ring clearly lowered the $\Delta G^{\ddagger}$ value [i.e., 122 kJ/mol (from **1b**-*R* to **1b**-*S*) (Table 1) vs 113 kJ/mol (from **17b**-*R* to **17b**-*S*) (Table 2)]. A similar phenomenon is observed in the 8-membered-ring lactam [112 kJ/mol (from **2a**-*R* to **2a**-*S*) (Table 1) vs 108 kJ/mol (from **18a**-*R* to **18a**-*S*) (Table 2)]. These imply that atropisomerism is markedly affected by the stereochemical stability of the entire molecule, i.e., the C7-methyl reduces the barrier by raising the ground state of the pseudoaxial conformer.

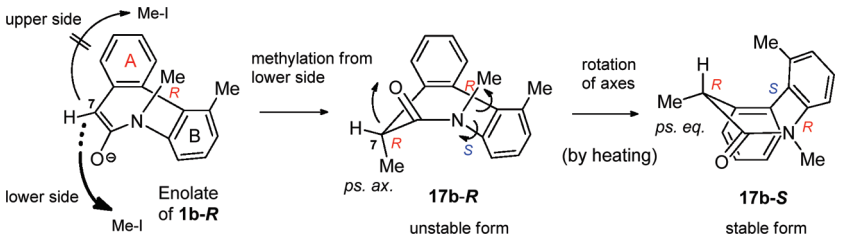
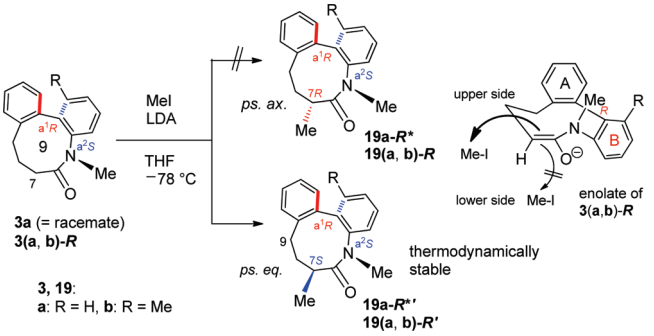


FIGURE 5. A plausible mechanism of stereoselective methylation of **1b**-*R* to **17b**-*R*.

SCHEME 3. Stereoselective C7-Methylation of 9-Membered-Ring Dibenzolactam (3) to 19-*R*′ and a Plausible Mechanism



In the case of **18b**-*R*, since the 8-membered-ring system is highly rigid and stable, the conformational change provided by the C7-methyl group does not promote atropisomerization even at elevated temperature (e.g., at 150 °C in DMF).

Interestingly, in the 9-membered-ring lactam **3(a,b)**, methylation proceeded on a different stereochemical course from that of the 7- and 8-membered-ring lactams (Scheme 3). Methylation was first examined with use of racemate **3a** (R = H: a^1*R**), in which the sole product was obtained in 89% yield. Contrary to our expectation, however, the product did not isomerize after heating even at 150 °C in DMF. The structure was presumed to be (a^1*R**,7*S**) (**19a**-*R**′) by using NOE analysis (Figure 6), in which the NOEs observed between C7-H and C9-H^a (3.4%) and C7-CH$_3$ and C8-H^c (1.9%), and no NOE between C7-H and C8-H^d were diagnostic to determine the C7-methyl in the pseudoequatorial orientation with (7*S**)-configuration. From the optically active lactam **3a**-*R* (R = H: a^1*R*), **19a**-*R*′ with a (7*S*)-methyl was obtained in 80% yield (Table 2/entry 5). Similarly, the compound **3b**-*R* (R = Me: a^1*R*) provided **19b**-*R*′ in 90% yield (Table 2/entry 6). Both compounds **19a**-*R*′ and **19b**-*R*′ did not isomerize at elevated temperature (at 150 °C in DMF). The angle of optical rotation α of **19a**-*R*′ and **19b**-*R*′ was negative (−) (Table 3), which suggests that the axial chirality of the parent compounds (**3a**-*R* and **3b**-*R*: (−)-rotation) is preserved. The stereochemistry of **19b**-*R*′ was unambiguously determined by using X-ray crystallographic analysis as shown in Figure 6 to be (a^1*R*,a^2*S*,7*S*).[10] These results indicate that methylation occurred not from the lower side but from the upper side of the 9-membered ring. It is intriguing that in the 9-membered-ring lactams C7-methylation occurred differently from that in 7- and 8-membered-ring systems. A plausible mechanism of this methylation is illustrated in Scheme 3 (right side). As shown here, steric hindrance of the benzene ring (B) of the 9-membered-ring

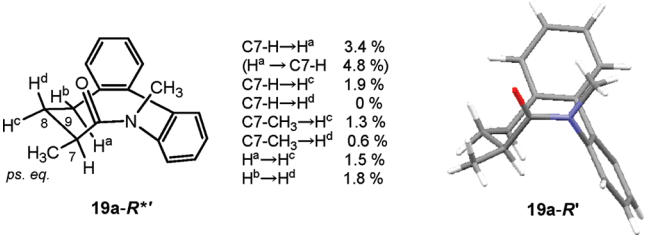


FIGURE 6. Structure of the C7-methylation product of 9-membered-ring dibenzolactam (**3**): NOE analysis (for **19a**-*R**′) and X-ray crystallographic analysis (for **19a**-*R*′).

dibenzolactam covers the lower side of the enolate so that the electrophile should come only from the upper side to form **19a**-*R*′ and **19b**-*R*′, stereoselectively. In addition, it is likely that the additional flexibility in the 9-membered ring permits immediate access to the low-energy conformation, without a kinetic trap. The lack of thermal atropisomerization from the products can be explained by the fact that the C7-methyl group of **19a**-*R*′ and **19b**-*R*′ exists in the pseudoequatorial orientation and thus the compounds are thermodynamically stable.

Conclusion

The atropisomeric enantiomers of 7-, 8-, and 9-membered-ring dibenzolactams (**1**−**3**) were separated and isolated by using chiral HPLC, and their stereochemistries were clarified in X-ray crystallographic analysis. The atropisomers showed generally high stereochemical stability, and among them the 8-membered-ring lactam is the most stable due to the deep, rigid cage-like ring form, which creates a high barrier to inversion of the ring system. Owing to such axial chiralities, C7-methylation of 7-, 8-, and 9-membered-ring benzolactams (**1**−**3**) proceeded highly stereoselectively in all cases. In 7- and 8-membered-ring systems, the methylation first occurred from the lower side of the ring to provide the products with the C7-methyl group in the pseudoaxial orientation, which then isomerized at the axes by heating to form thermodynamically more stable diastereomers with the pseudoequatorial C7-methyl group. It is interesting that the conformational change at the C7-methyl group from pseudoaxial to pseudoequatorial affects the rate of atropisomerism to lower the rotational barrier. On the other hand, in the 9-membered-ring system, C7-methylation occurred from the upper side of the ring to provide the product with the opposite configuration from that in 7- and 8-membered-ring systems. Thus, 9-membered-ring dibenzolactam was shown to possess partly different stereochemical properties from 7- and 8-membered-ring lactams. These findings may prove to be useful for understanding the chemical behavior of the

related medium-sized ring systems and for future drug design of biologically active compounds.

Experimental Section

2-(2′-Aminobiphenyl-2-yl)acetonitrile (8a): To a stirred mixture of 2-bromoaniline (**4a**) (1.79 g, 10.4 mmol), triethylamine (5.8 mL, 41.6 mmol), $Pd(OAc)_2$ (117 mg, 0.52 mmol), 2-(dicyclohexylphosphine)biphenyl (729 mg, 2.1 mmol), and dioxane (21 mL) was added pinacolborane (3.8 mL, 26 mmol) dropwise at 25 °C under argon. The mixture was stirred for 1 h at 80 °C, cooled to room temperature, and treated successively with H_2O (7.0 mL), 2-iodophenylacetonitrile (**5**) (1.70 g, 7.0 mmol) in dioxane (7.0 mL), and $Ba(OH)_2 \cdot 8H_2O$ (9.8 g, 31 mmol). The mixture was heated at 100 °C for 1 h, cooled to room temperature, and filtered through Celite. To the filtrate was added brine (20 mL), and the mixture was extracted with dichloromethane. The extract was dried and concentrated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 8/1) to afford **8a** as a pale yellow oil (1.44 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (br, 2H), 3.54 (d, J = 18.8 Hz, 1H), 3.73 (d, J = 18.8 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.84 (dd, J = 7.3, 7.6 Hz, 1H), 7.01 (d, J = 6.4 Hz, 1H), 7.14−7.30 (m, 2H), 7.40−7.46 (m, 2H), 7.60−7.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 115.3, 118.2, 118.7, 124.9, 128.5, 128.5, 129.2, 129.4, 129.9, 130.6, 138.1, 143.3; IR (neat) 3366, 2249, 1618, 1483 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{12}N_2$ 208.1000 (M^+), found 208.0991.

2-(2′-Amino-6′-methylbiphenyl-2-yl)acetonitrile (8b): Compound **5** (1.64 g, 6.75 mmol) was treated according to a similar procedure as described for the preparation of **8a** with use of 2-bromo-3-methylaniline (**4b**) (1.88 g, 10.1 mmol) in place of **4a** to afford **8b** as brown crystals (1.44 g, 96%): mp 62−64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 3.33 (br, 2H), 3.43 (d, J = 18.8 Hz, 1H), 3.56 (d, J = 18.8 Hz, 1H), 6.63 (dd, J = 0.6, 7.81 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 7.20−7.22 (m, 1H), 7.43−7.46 (m, 2H), 7.63−7.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.1, 112.7, 117.8, 120.1, 124.3, 128.4, 128.6, 128.8, 128.9, 129.4, 130.5, 136.6, 136.9, 143.4; IR (KBr) 3383, 2251, 1614, 1464 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{14}N_2$ 222.1157 (M^+), found 222.1149.

3-(2″-Aminobiphenyl-2-yl)propanenitrile (9a): According to a similar procedure as described for the preparation of **8a**, 2-bromoaniline **4a** (1.41 g, 8.2 mmol) and 2-iodophenylpropanenitrile **6** (1.42 g, 5.58 mmol) were treated to afford **9a** as brown crystals (1.19 g, 97%): mp 46−48 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 2.48−2.47 (m, 2H), 2.79−2.85 (m, 2H), 3.48 (br, 2H), 6.75−6.83 (m, 2H), 6.99 (d, J = 7.3 Hz, 1H), 7.17−7.25 (m, 2H), 7.35−7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 29.2, 115.2, 118.3, 119.3, 125.8, 127.7, 128.3, 128.8, 129.6, 129.9, 130.6, 137.0, 138.3, 143.5; IR (KBr) 3371, 2361, 1616, 1483 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{14}N_2$ 223.1230 $(M + H)^+$, found 223.1217.

3-(2′-Amino-6′-methylbiphenyl-2-yl)propanenitrile (9b): According to a similar procedure as described for the preparation of **8a**, 2-bromo-3-methylaniline **4b** (721 mg, 3.9 mmol) and 2-iodophenylpropanenitrile **6** (669 mg, 2.6 mmol) were treated to afford **9b** as brown crystals (545 mg, 89%): mp 76−78 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.42−2.53 (m, 2H), 2.66−2.80 (m, 2H), 3.36 (br, 2H), 6.62 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 7.3 Hz, 1H), 7.07−7.17 (m, 2H), 7.36−7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 20.3, 29.2, 112.7, 119.4, 120.0, 125.5, 128.2, 1278.3, 129.9, 130.4, 136.5, 137.0, 137.2, 143.7; IR (KBr) 3375, 2243, 1612, 1464 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2$ 237.1386 ($M + H^+$), found 237.1374.

4-(2′-Aminobiphenyl-2-yl)butanenitrile (10a): According to a similar procedure as described for the preparation of **8a**, 2-bromoaniline (1.48 g, 8.6 mmol) and 2-iodophenylbutanenitrile **7** (1.57 g, 5.8 mmol) were treated to afford **10a** as a brown oil (1.1 g, 80%): ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.77 (td, J = 7.3, 7.5 Hz, 2H), 2.16 (t, J = 7.3 Hz, 2H), 2.66−2.80 (m, 2H), 3.47 (br, 2H), 6.76 (d, J = 7.8 Hz, 1H), 6.80 (t, J = 7.5 Hz, 1H), 6.99 (dd, J = 1.4, 7.5 Hz, 1H), 7.16−4.22 (m, 2H), 7.28−7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 26.3, 32.1, 115.1, 118.2, 119.4, 126.3, 127.0, 128.0, 128.6, 129.5, 130.0, 130.5, 138.4, 138.8, 143.5; IR (neat) 3373, 2361, 1616, 1481 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2$ 237.1386 ($M + H^+$), found 237.1400.

4-(2′-Amino-6′-methylbiphenyl-2-yl)butanenitrile (10b): According to a similar procedure as described for the preparation of **8a**, 2-bromo-3-methylaniline (614 mg, 3.3 mmol) and 2-iodophenylbutanenitrile **7** (600 mg, 2.2 mmol) were treated to afford **10b** as a brown oil (482 mg, 87%): ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.75−1.83 (m, 2H), 1.91 (s, 3H), 2.20 (dd, J = 6.8, 7.0 Hz, 2H), 2.46−2.60 (m, 2H), 3.34 (br, 2H), 6.62 (m, 1H), 6.70 (m, 1H), 7.08 (dd, J = 7.5, 7.8 Hz, 1H), 7.11−7.15 (m, 1H), 7.30−7.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 20.4, 25.9, 32.1, 112.6, 119.5, 119.9, 126.0, 127.4, 127.9, 128.1, 129.7, 130.4, 136.6, 137.2, 138.9, 143.7; IR (neat) 3373, 2361, 1612, 1464 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{18}N_2$ 251.1543 ($M + H^+$), found 251.1540.

3-(2′-Aminobiphenyl-2-yl)propanoic acid (12a): A mixture of **9a** (130 mg, 0.59 mmol), sodium hydroxide (234 mg, 5.9 mmol), H_2O (2.0 mL), and EtOH (4.0 mL) was stirred for 8 h at 100 °C. After being cooled to room temperature, the mixture was concentrated. The concentrate was acidified with 1 N HCl and extracted with ethyl acetate. The extract was dried and concentrated to afford **12a** as pale yellow crystals (116 mg, 82%): mp 107−108 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 2.39−2.52 (m, 2H), 2.73−2.789 (m, 2H), 5.21 (br, 2H), 6.75 (d, J = 7.8 Hz, 1H), 6.80 (t, J = 7.3 Hz, 1H), 7.00 (dd, J = 1.4, 7.5 Hz, 1H), 7.15−7.20 (m, 2H), 7.25−7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 34.7, 115.3, 118.3, 126.6, 126.8, 128.0, 128.5, 129.2, 130.0, 130.4, 138.3, 138.9, 143.3, 178.2; IR (KBr) 3378, 1714 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{15}NO_2$ 242.1176 ($M + H^+$), found 242.1172. Similarly, carboxylic acids, **12b**, **13a**, and **13b** were prepared from the corresponding nitriles, **9b**, **10a**, and **10b**, respectively.

3-(2′-Amino-6′-methylbiphenyl-2-yl)propanoic acid (12b): brown crystals (76%), mp 132−134 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.40−2.55 (m, 2H), 2.65−2.75 (m, 2H), 4.28 (br, 2H), 6.62 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 7.3 Hz, 1H), 7.06−7.12 (m, 2H), 7.30−7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 28.1, 34.3, 112.9, 120.2, 126.4, 127.3, 127.9, 128.0, 129.4, 130.3, 136.7, 137.1, 138.9, 143.4, 178.0; IR (KBr) 3372, 1714 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{17}NO_2$ 256.1332 ($M + H^+$), found 256.1314.

4-(2′-Aminobiphenyl-2-yl)butanoic acid (13a): brown oil (76%); ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.71−1.81 (m, 2H), 2.20 (t, J = 7.5 Hz, 2H), 2.45−2.62 (m, 2H), 4.41 (br, 2H), 6.77 (dd, J = 0.7, 8.0 Hz, 1H), 6.81 (dd, J = 1.2, 7.5 Hz, 1H), 7.01 (dd, J = 1.4, 7.5 Hz, 1H), 7.13−7.20 (m, 2H), 7.23−7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 32.2, 33.4, 115.3, 118.4, 126.5, 127.0, 127.8, 128.3, 129.4, 130.2, 130.3, 138.2, 140.1, 143.1, 178.4; IR (neat) 3379, 1706 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{17}NO_2$ 256.1332 ($M + H^+$), found 256.1330.

4-(2′-Amino-6′-methylbiphenyl-2-yl)butanoic acid (13b): pale yellow crystals (98%), mp 67−69 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.80 (m, 2H), 1.92 (s, 3H), 2.24 (t, J = 7.5 Hz, 2H), 2.37−2.49 (m, 2H), 4.80 (br, 2H), 6.62 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 7.3 Hz, 1H), 7.04−7.12 (m, 2H), 7.27−7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 25.1, 32.0, 33.4, 112.6, 120.0, 126.5, 126.9, 127.7, 127.8, 129.4, 130.1, 136.7, 136.9, 140.0, 143.4, 178.3; IR (KBr) 3378, 1707 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{19}NO_2$ 270.1489 ($M + H^+$), found 270.1479.

5*H*,7*H*-Dibenzo[*b*,*d*]azepin-6-one (14a): To a solution of **8a** (339 mg, 1.63 mmol) in methanol (10 mL) was added sodium

hydroxide (652 mg, 16.3 mmol) in H_2O (5 mL), then the mixture was heated at 90 °C for 8 h. After being cooled to room temperature, the mixture was treated with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed successively with 1 N HCl and saturated aqueous NH_4Cl, dried, and concentrated. The concentrate was purified by column chromatography (silica gel, hexane/ethyl acetate = 4/1) to afford **14a** as colorless crystals (223 mg, 65%), mp 114−116 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (d, J = 11.7 Hz, 1H), 3.57 (d, J = 11.7 Hz, 1H), 7.11 (dd, J = 7.8, 8.1 Hz, 1H), 7.29 (td, J = 1.2, 7.8 Hz, 1H), 7.35−7.44 (m, 4H), 7.55−7.59 (m, 1H), 7.65 (dd, J = 7.6, 7.8 Hz, 1H), 8.28 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.8, 121.8, 125.0, 127.7, 128.4, 128.6, 128.7, 130.0, 132.0, 134.1, 135.7, 136.4, 173.1; IR (KBr) 3063, 1695 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{11}ON$ 209.0841 (M^+), found 209.0838.

1-Methyl-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (14b): According to a similar procedure as described for the preparation of **14a**, compound **8b** (274 mg, 1.23 mmol) was treated to afford **14b** as colorless crystals (170 mg, 62%), mp 155−158 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.43 (d, J = 12.5 Hz, 1H), 3.47 (dd, J = 1.7, 12.5 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.25 (dd, J = 7.6, 9.5 Hz, 1H), 7.31−7.45 (m, 4H), 8.05 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 41.5, 119.3, 126.1, 127.5, 127.7, 127.8, 128.2, 130.4, 131.2, 134.2, 135.4, 136.4, 137.0, 173.9; IR (KBr) 3065, 1670 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{13}ON$ 223.0997 (M^+), found 223.1006.

5*H*,7*H*,8*H*-Dibenzo[*b*,*d*]azocin-6-one (15a): To a solution of **12a** (597 mg, 2.47 mmol) in CH_2Cl_2 (80 mL) under argon were added triethylamine (1.0 mL, 7.4 mmol) and EDC (1.42 g, 7.42 mmol). After being stirred for 23 h at 25 °C, the mixture was washed successively with saturated aqueous $NaHCO_3$, 1 N HCl, and saturated aqueous NH_4Cl, dried, and concentrated. The concentrate was purified by column chromatography (silica gel, hexane/ethyl acetate = 3/1) to afford **15a** as colorless crystals (373 mg, 68%), mp 215−217 °C: ^{1}H MMR (400 MHz, $CDCl_3$) δ 2.56−2.64 (m, 1H), 2.90 (m, 3H), 6.99 (br, 1H), 7.13−7.15 (m, 1H), 7.19−7.37 (m, 5H), 7.38−7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6, 34.4, 126.3, 126.8, 127.8, 128.3, 128.5, 129.5, 130.4, 135.5, 138.0, 138.5, 140.8, 174.3; IR (KBr) 3055, 2947, 1653, 1394 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{13}NO$ 224.1070 (M + H$^+$), found 224.1060. Similarly, dibenzolactams, **15b**, **16a**, and **16b** were prepared from the corresponding carboxylic acids, **12b**, **13a**, and **13b**, respectively.

1-Methyl-5*H*,7*H*,8*H*-dibenzo[*b*,*d*]azocin-6-one (15b): colorless crystals (64%), mp 216−218 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.50−2.73 (m, 3H), 2.76−2.86 (m, 1H), 6.70 (br, 1H), 7.05−7.08 (m, 2H), 7.25−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) 20.8, 29.4, 34.4, 124.2, 126.7, 128.0, 128.2, 129.2, 129.8, 135.8, 137.1, 137.5, 138.3, 140.2, 174.5; IR (KBr) 3182, 3055, 1657, 1446 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{15}NO$ 238.1226 (M + H$^+$), found 238.1207.

5*H*,7*H*,8*H*,9*H*-Dibenzo[*b*,*d*]azonin-6-one (16a): colorless crystals (75%), mp 174−177 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.87−2.22 (m, 5H), 2.73 (dd, J = 1.7, 5.8 Hz, 1H), 6.58 (br, 1H), 6.97 (d, J = 7.3 Hz, 1H), 7.19−7.24 (m, 2H), 7.30−7.38 (m, 3H), 7.42−7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 33.8, 34.1, 126.1, 127.8, 128.4, 128.6, 128.7, 128.9, 129.4, 129.9, 136.0, 138.4, 140.1, 176.1; IR (KBr) 3260, 2930, 1630, 1452 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{15}NO$ 260.1046 (M + Na$^+$), found 260.1041.

1-Methyl-5*H*,7*H*,8*H*,9*H*-dibenzo[*b*,*d*]azonin-6-one (16b): colorless crystals (81%), mp 216−219 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.82−2.15 (m, 5H), 2.06 (s, 3H), 2.73 (dd, J = 3.9, 13.1 Hz, 1H), 6.61 (br, 1H), 6.88 (d, J = 7.3 Hz, 1H), 7.14−7.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 28.4, 33.6, 33.8, 126.1, 126.6, 127.5, 128.1, 128.4, 129.7, 130.1, 136.1, 137.4, 137.4, 139.7, 142.5, 176.2; IR (KBr) 3177, 3055, 2932, 1660, 1442 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{17}NO$ 252.1383 (M + H$^+$), found 252.1366.

5-Methyl-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (1a): To a stirred solution of **14a** (104.6 mg, 0.5 mmol) in DMF (5 mL) at 0 °C under argon was added sodium hydride (60% in oil) (30 mg, 0.75 mmol). The mixture was stirred for 30 min at 25 °C, cooled to 0 °C, and treated with MeI (0.16 mL, 2.5 mmol). After the mixture was stirred for 1 h at 25 °C, water and ethyl acetate were added to the mixture. The organic layer was separated, washed with brine, dried, and concentrated. The concentrate was purified by column chromatography (silica gel, hexane/ethyl acetate = 5/1) to afford **1a** as colorless crystals (104.4 mg, 94%), mp 156−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.42 (d, J = 12.7 Hz, 1H), 3.58 (d, J = 12.7 Hz, 1H), 7.28−7.46 (m, 6H), 7.57−7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.1, 42.1, 122.4, 125.1, 127.5, 127.7, 127.9, 128.3, 128.5, 129.9, 133.7, 135.4, 136.2, 141.7, 171.5; IR (KBr) 2995, 1651 cm^{-1}; HRMS (EI) m/z calcd for $C_{15}H_{13}NO$ 223.0997 (M^+), found 223.0998. Similarly, *N*-methylation of dibenzolactams **14b**, **15a**, **15b**, **16a**, and **16b** afforded *N*-methyl derivatives **1b**, **2a**, **2b**, **3a**, and **3b**, respectively.

1,5-Dimethyl-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (1b): colorless crystals (93%), mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.26 (s, 3H), 3.40 (d, J = 12.5 Hz, 1H), 3.47 (d, J = 12.5 Hz, 1H), 7.19 (d, J = 7.8 Hz, 2H), 7.29−7.40 (m, 4H), 7.47 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 36.0, 42.0, 119.9, 125.9, 127.3, 127.6, 127.9, 128.2, 130.0, 132.8, 133.8, 136.6, 136.8, 142.4, 172.3; IR (KBr) 2982, 1668 cm^{-1}; HRMS (EI) m/z calcd for $C_{16}H_{15}ON$ 237.1154 (M^+), found 237.1156.

5-Methyl-5*H*,7*H*,8*H*-dibenzo[*b*,*d*]azocin-6-one (2a): colorless crystals (99%), mp 96−97 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 2.48−2.54 (m, 1H), 2.61−2.69 (m, 1H), 2.81−2.88 (m, 1H), 2.94−3.02 (m, 1H), 2.95 (s, 3H), 7.09−7.11 (m, 1H), 7.21−7.36 (m, 5H), 7.39−7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4, 34.0, 35.9, 125.9, 126.6, 128.0, 128.3, 129.0, 129.5, 130.4, 130.4, 138.0, 138.1, 141.0, 142.8, 172.7; IR (KBr) 3051, 2970, 1655, 1450 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{15}NO$ 238.1226 (M + H$^+$), found 238.1210.

1,5-Dimethyl-5*H*,7*H*,8*H*-dibenzo[*b*,*d*]azocin-6-one (2b): colorless crystals (89%), mp 130−132 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.47−2.56 (m, 2H), 2.60−2.70 (m, 1H), 2.83−2.91 (m, 1H), 2.88 (s, 3H), 7.05−7.06 (m, 1H), 7.13 (d, J = 7.6 Hz, 1H), 7.23−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 29.8, 34.3, 35.7, 123.5, 126.5, 128.1, 128.5, 128.8, 129.7, 130.4, 136.8, 137.6, 138.3, 140.0, 143.1, 172.5; IR (KBr) 2941, 1649, 1466 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{17}NO$ 252.1383 (M + H$^+$), found 252.1380.

5-Methyl-5*H*,7*H*,8*H*,9*H*-dibenzo[*b*,*d*]azonin-6-one (3a): colorless crystals (96%), mp 128−130 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 2.48−2.54 (m, 1H), 2.61−2.69 (m, 1H), 2.81−2.88 (m, 1H), 2.94−3.02 (m, 1H), 2.95 (s, 3H), 7.09−7.11 (m, 1H), 7.21−7.36 (m, 5H), 7.39−7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 34.4, 34.9, 36.8, 125.3, 127.3, 128.0, 128.2, 128.6, 129.1, 129.7, 129.8, 137.5, 140.4, 142.8, 143.1, 172.7; IR (KBr) 2932, 1653, 1446 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{17}NO$ 252.1383 (M + H$^+$), found 252.1381.

1,5-Dimethyl-5*H*,7*H*,8*H*,9*H*-dibenzo[*b*,*d*]azonin-6-one (3b): colorless crystals (93%), mp 160−162 °C; ^{1}H MMR (400 MHz, $CDCl_3$) δ 1.88−1.97 (m, 2H), 2.01−2.09 (m, 3H + 2H), 2.13−2.20 (m, 1H), 2.69−2.74 (m, 1H), 2.83 (s, 3H), 6.95 (d, J = 7.3 Hz, 1H), 7.14−7.21 (m, 2H), 7.25−7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 28.3, 34.1, 34.7, 36.7, 124.5, 125.8, 127.9, 128.5, 128.6, 129.3, 129.9, 136.4, 137.8, 140.1, 141.3, 143.2, 173.6; IR (KBr) 2930, 1651, 1444 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{19}NO$ 266.1539 (M + H$^+$), found 266.1537.

Separation of Enantiomers by Using Chiral HPLC. Atropisomers of 1,5-dimethyl-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (1b-*R* and 1b-*S*): CHIRALPAK AD-H (1.0 cm ϕ × 25 cm); eluent,

hexane:2-propanol (9:1); flow rate, 3.0 mL/min; temperature, 22 °C; detection, 254 nm. Former peak (**1b**-*R*): retention time = 14.4 min; $[\alpha]^{21}_{D}$ −92.0 (*c* 0.3, MeOH). Latter peak (**1b**-*S*): retention time = 21.7 min; $[\alpha]^{21}_{D}$ +93.7 (*c* 0.3, MeOH). The absolute stereochemistry of **1b**-*R* and **1b**-*S* was determined by the single-crystal X-ray analysis as described below. The crystal structures determined by the X-ray analysis are shown in Figure 2 (top). Similarly, atropisomers of **1a**, **2a**, **2b**, **3a**, and **3b** were separated with chiral HPLC.

Atropisomers of 5-methyl-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (1a-*R* and 1a-*S*): Separation of **1a** into its atropisomers was carried out by preparative HPLC with CHIRALPAK AD-H (1.0 cm ϕ × 25 cm) under detection at 254 nm. Elution with a mixture of hexane:2-propanol (9:1) at a flow rate of 2.0 mL/min at 22 °C gave **1a**-*S* and **1a**-*R*. Fomer peak (**1a**-*R*): retention time = 12.9 min; $[\alpha]^{21}_{D}$ −137.1 (*c* 0.3, MeOH). Latter peak (**1a**-*S*): retention time = 16.7 min; $[\alpha]^{21}_{D}$ +131.2 (*c* 0.3, MeOH). The absolute stereochemistry of the separated atropisomers of **1a** was assigned by comparison with the retention time and the (−)/(+)-angle of optical rotation α of **1b**-*R* and **1b**-*S*.

Atropisomers of 1,5-dimethyl-5*H*,7*H*,8*H*-dibenzo[*b*,*d*]azocin-6-one (2b-*R* and 2b-*S*): CHIRALPAK IA (1.0 cm ϕ × 25 cm); eluent, hexane:2-propanol (19:1); flow rate, 1.0 mL/min; temperature, 28 °C; detection, 254 nm. Former peak (**2b**-*R*): retention time = 44.6 min; $[\alpha]^{22}_{D}$ −163.5 (*c* 0.4, MeOH). Latter peak (**2b**-*S*): retention time = 55.3 min; $[\alpha]^{22}_{D}$ +170.0 (*c* 0.4, MeOH). The absolute stereochemistry of **2b**-*R* and **2b**-*S* was determined by the single-crystal X-ray analysis as described below. The crystal structures determined by the X-ray analysis are shown in Figure 2 (middle).

Atropisomers of 5-methyl-5*H*,7*H*,8*H*-dibenzo[*b*,*d*]azocin-6-one (2a-*R* and 2a-*S*): CHIRALPAK IA (1.0 cm ϕ × 25 cm); eluent, hexane:2-propanol (19:1); flow rate, 1.0 mL/min; temperature, 28 °C; detection, 254 nm. Former peak (**2a**-*R*): retention time = 52.5 min; $[\alpha]^{23}_{D}$ −166.1 (*c* 0.37, MeOH). Latter peak (**2a**-*S*): retention time = 64.3 min; $[\alpha]^{23}_{D}$ +165.7 (*c* 0.37, MeOH). The absolute stereochemistry of the separated atropisomers of **2a** was assigned by comparison with the retention time and the (−)/(+)-angle of optical rotation α of **2b**-*R* and **2b**-*S*.

Atropisomers of 1,5-dimethyl-5*H*,7*H*,8*H*,9*H*-dibenzo[*b*,*d*]azonin-6-one (3b-*S* and 3b-*R*): CHIRALPAK IA (1.0 cm ϕ × 25 cm); eluent, hexane:EtOH (97:3); flow rate, 1.5 mL/min; temperature, 27 °C; detection, 254 nm. Fomer peak (**3b**-*S*): retention time = 39.0 min; $[\alpha]^{22}_{D}$ + 206.1 (*c* 0.21, MeOH). Latter peak (**3b**-*R*): retention time = 44.5 min; $[\alpha]_{D}^{22}$ −213.7 (*c* 0.195, MeOH). The absolute stereochemistry of **3b**-*S* and **3b**-*R* was determined by the single-crystal X-ray analysis as described below. The crystal structures determined by the X-ray analysis are shown in Figure 2 (bottom).

Atropisomers of 5-methyl-5*H*,7*H*,8*H*,9*H*-dibenzo[*b*,*d*]azonin-6-one (3a-*S* and 3a-*R*): CHIRALPAK IA (1.0 cm ϕ × 25 cm); eluent, hexane:2-propanol (100:1); flow rate, 2.5 mL/min; temperature, 27 °C; detection, 254 nm. Former peak (**3a**-*S*): retention time = 53.8 min; $[\alpha]^{22}_{D}$ +231.7 (*c* 0.215, MeOH). Latter peak (**3a**-*R*): retention time = 64.9 min; $[\alpha]^{22}_{D}$ −249.5 (*c* 0.215, MeOH). The absolute stereochemistry of the separated atropisomers of **3a** was assigned by comparison with the retention time and the (−)/(+)-angle of optical rotation α of **3b**-*S* and **3b**-*R*.

Thermal stability of the atropisomers of 1a, 1b, 2a, 2b, 3a, and 3b (Table 1): A solution of the enantiomers of 7-, 8-, and 9-membered-ring dibenzolactams (**1a**, **1b**, **2a**, **2b**, **3a**, and **3b**) in toluene (or DMF) was heated at the designated temperature (Table 1), and the time-dependent conversion rate (% ee) was estimated from chiral HPLC analysis. The figures of the conversion rate are included in the Supporting Information. The activation free-energy barrier to rotation ($\Delta G^{\ddagger}$) was determined based on the conversion rate. The calculation was carried out according to the procedure reported by Curran et al.[12]

5,7-Dimethyl-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (17a-*S*): To a solution of **1a**-***R*** (13.4 mg, 0.06 mmol) in THF (0.3 mL) at −78 °C under argon was added KHMDS (0.5 M in toluene) (0.6 mL, 0.3 mmol). The mixture was stirred for 10 min and treated with MeI (19 μL, 0.3 mmol). After being stirred for 1 h at −78 °C, the mixture was gradually warmed to 0 °C, to which was added saturated aqueous NH_4Cl. The mixture was extracted with diethyl ether, the extract was dried, and the solvent was evaporated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 6/1) to afford **17a**-*S* (13.7 mg, 96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (d, *J* = 6.8 Hz, 3H), 3.33 (s, 3H), 3.44 (q, *J* = 6.8 Hz, 1H), 7.29−7.47 (m, 6H), 7.56−7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 36.1, 39.6, 122.2, 123.3, 125.0, 126.9, 127.9 128.3, 128.5, 129.7, 133.9, 136.5, 139.3, 141.5, 172.9; IR (neat) 2980, 1665 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{15}NO$ 238.1232 (M + H^+), found 238.1248. $[\alpha]^{23}_{D}$ +189.3 (*c* 0.29, MeOH). Monitoring of the intermediate step of the reaction with TLC and ^{1}H NMR revealed that the unstable isomer **17a**-*R* was initially formed, which readily isomerized to give **17a**-*S* during workup.

1,5,7-Trimethyl-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (17b-*R*): According to a similar procedure as described for the C7-methylation of **1a**-*R*, compound **1b**-*R* (19.2 mg, 0.081 mmol) was treated to afford **17b**-*R* (20.2 mg, 99%) as colorless crystals, mp 97−102 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 7.6 Hz, 3H), 2.39 (s, 3H), 3.29 (s, 3H), 3.97 (q, *J* = 7.6 Hz, 1H), 7.16 (dd, *J* = 7.3, 8.1 Hz, 2H), 7.26−7.34 (m, 4H), 7.43−7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 22.2, 37.2, 51.0, 119.8, 126.1, 127.7, 127.8, 128.0, 128.6, 131.0, 133.1, 133.2, 136.4, 141.2, 141.4, 175.1; IR (KBr) 2930, 1651 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{17}H_{17}ON$ 251.1310 (M^+), found 251.1306; $[\alpha]^{23}_{D}$ −79.3 (*c* 0.15, MeOH).

Thermal isomerization of 17b-*R* to a*S*-1,5,7-trimethyl-5*H*,7*H*-dibenzo[*b*,*d*]azepin-6-one (17b-*S*): A solution of **17b**-*R* (17.1 mg, 0.068 mmol) in toluene (1.8 mL) under argon was heated at 110 °C for 30 min with stirring. The solvent was evaporated to afford an oily residue of a mixture of **17b**-*R* and **17b**-*S* in a ratio of 3:97, from which **17b**-*S* was obtained as colorless crystals (16.5 mg, 96%), mp 154−156 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, *J* = 6.8 Hz, 3H), 2.41 (s, 3H), 3.26 (s, 3H), 3.46 (q, *J* = 6.8 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.26−7.34 (m, 2H), 7.38−7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 22.0, 36.1, 39.6, 119.7, 123.1, 125.4, 127.7, 127.8, 128.2, 128.9, 129.8, 133.0, 136.4, 140.6, 142.2, 173.7; IR (KBr) 2938, 1668 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}NO$ 252.1383 (M + H^+), found 252.1385; $[\alpha]^{23}_{D}$ +116.1 (*c* 0.15, MeOH).

5,7-Dimethyl-5*H*,7*H*,8*H*-dibenzo[*b*,*d*]azocin-6-one (18a-*R*): According to a similar procedure as described for the C7-methylation of **1a**-*R*, compound **2a**-*R* (27.0 mg, 0.11 mmol) was treated to afford **18a**-*R* (23.0 mg, 79%) as colorless crystals, mp 120−122 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, *J* = 7.3 Hz, 3H), 1.98 (dd, *J* = 10.7, 13.4 Hz, 1H), 2.71 (dd, *J* = 9.5, 13.4 Hz, 1H), 2.93 (s, 3H), 3.09−3.19 (m, 1H), 7.25−7.35 (m, 6H), 7.41 (td, *J* = 1.5, 7.6 Hz, 1H), 7.46 (td, *J* = 1.7, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 38.5, 39.8, 45.3, 126.8, 126.9, 127.5, 127.9, 128.2, 128.5, 128.9, 129.5, 138.4, 138.8, 140.3, 142.0, 174.6; IR (KBr) 2924, 1635, 1444 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}NO$ 252.1383 (M + H^+), found 252.1392; $[\alpha]^{23}_{D}$ −164.8 (*c* 0.15, MeOH).

Thermal isomerization of 18a-*R* to a*S*-1,5-dimethyl-5*H*,7*H*,-8*H*-dibenzo[*b*,*d*]azocin-6-one (18a-*S*): A solution of **18a**-*R* (14.3 mg, 0.057 mmol) in toluene (1.4 mL) under argon was heated at 110 °C for 3 h with stirring. The solvent was evaporated to afford an oily residue of a mixture of **18a**-*R* and **18a**-*S* in a ratio of 10:90, from which **18a**-*S* was obtained as colorless crystals (12.9 mg, 90%), mp 141−142 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, *J* = 6.6 Hz, 3H), 2.52 (dd, *J* = 9.3, 14.9 Hz, 1H), 2.84−2.92 (m, 1H), 2.95 (s, 3H), 3.10 (dd, *J* = 9.0, 14.9 Hz, 1H), 7.06−7.08 (m, 1H), 7.14−7.16 (m, 1H), 7.22−7.52 (m, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 18.7, 35.8, 36.4, 41.7, 126.3, 126.7, 128.1, 128.4, 129.2, 130.4, 130.7, 131.0, 137.9, 138.2, 141.5, 142.7, 175.4; IR (KBr) 2928, 1664, 1442 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{17}NO$ 252.1383 (M + H^+), found 252.1389; $[\alpha]^{22}_D$ +112.7 (c 0.15, MeOH).

1,5,7-Trimethyl-5*H*,7*H*,8*H*-dibenzo[*b*,*d*]azocin-6-one (18b-*R*): According to a similar procedure as described for the C7-methylation of **2a**-*R*, compound **2b**-*R* (18.6 mg, 0.074 mmol) was treated to afford **18b**-*R* (15.3 mg, 78%) as colorless crystals, mp 142−145 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, J = 7.3 Hz, 3H), 1.88 (dd, J = 10.2, 13.1 Hz, 1H), 2.13 (s, 3H), 2.71 (dd, J = 9.5, 13.1 Hz, 1H), 2.89 (s, 3H), 3.02−3.11 (m, 1H), 7.17 (dd, J = 0.7, 7.5 Hz, 1H), 7.21−7.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4, 20.5, 38.4, 39.2, 45.7, 125.1, 126.4, 127.6, 128.35, 128.37, 128.4, 129.6, 136.6, 136.9, 138.9, 139.2, 142.0, 174.5; IR (KBr) 2966, 1639, 1458 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{19}NO$ 288.1359 (M + Na^+), found 288.1361; $[\alpha]^{23}_D$ −158.9 (c 0.11, MeOH). Compound **18b**-*R* did not isomerize at 150 °C for 3 h in DMF.

5,7-Dimethyl-5*H*,7*H*,8*H*,9*H*-dibenzo[*b*,*d*]azonin-6-one (19a-*R′):** To a solution of diisopropylamine (0.2 mL, 1.51 mmol) in THF (1.5 mL) at −78 °C under argon was added *n*-BuLi (1.58 M in hexane) (0.96 mL, 1.51 mmol). After being stirred for 10 min, the mixture was treated with **3a** (75.9 mg, 0.30 mmol), stirred for 10 min, and treated with MeI (94 μL, 1.51 mmol). After being stirred for 2.5 h at −78 °C, the mixture was treated with saturated aqueous NH_4Cl, then extracted with ethyl acetate. The extract was dried, and the solvent was evaporated. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 3/1) to afford **19a**-*R**′ (71 mg, 89%) as colorless crystals, mp 165−167 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (d, J = 6.6 Hz, 3H), 1.63−1.67 (m, 1H), 1.79−1.88 (m, 1H), 2.28−2.33 (m, 1H), 2.28−2.33 (m, 1H), 2.66 (ddd, J = 1.9, 5.8, 6.1 Hz, 1H), 2.78 (s, 3H), 7.04 (dd, J = 1.2, 1.4 Hz, 1H), 7.15−7.21 (m, 2H), 7.28−7.35 (m, 3H), 7.40−7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 34.0, 36.8, 36.9, 38.2, 125.3, 127.6, 127.9, 128.2, 128.6, 129.1, 129.7, 129.8, 137.5, 140.4, 142.1, 142.9, 176.6; IR (KBr) 2935, 1657, 1477 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{19}NO$ 266.1539 (M + H^+), found 266.1533. Compound **19a**-*R**′ did not isomerize at 150 °C for 3 h in DMF. The NOE experiment of **19a**-*R**′ is described in Figure 6 to reveal that the relative stereochemistry is (a^1*R**, a^2*S**,7*S**). Similarly, C7-methylation of the atropisomer **3a**-*R* (25.7 mg, 0.102 mmol) afforded optically active compound **19a**-*R*′ (a^1*R*,a^2*S*,7*S*) (21.7 mg, 80%), mp 157−159 °C: $[\alpha]^{23}_D$ −165.5 (c 0.15, MeOH); ^{1}H NMR and ^{13}C NMR were identical with those of **19a**-*R**′. The crystal structure of **19a**-*R*′ determined by the X-ray analysis is shown in Figure 6, and the crystal data are described below.

1,5,7-Trimethyl-5*H*,7*H*,8*H*,9*H*-dibenzo[*b*,*d*]azonin-6-one (19b-*R*′): According to a similar procedure as described for the C7-methylation of **3a**-*R*, compound **3b**-*R* (7.4 mg, 0.03 mmol) was treated to afford **19b**-*R*′ (7.0 mg, 90%) as colorless crystals, mp 154−156 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, J = 6.8 Hz, 3H), 1.59−1.64 (m, 1H), 1.77−1.86 (m, 1H), 2.05 (s, 3H), 2.05−2.12 (m, 1H), 2.21−2.28 (m, 1H), 2.66 (ddd, J = 1.9, 5.8, 13.4 Hz, 1H), 2.78 (s, 3H), 6.96 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 7.18 (td, J = 1.4, 7.3 Hz, 1H), 7.22−7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 29.9, 33.8, 36.7, 38.0, 124.8, 125.7, 128.0, 128.6, 129.2, 129.9, 136.4, 137.8, 140.0, 141.2, 143.0, 176.7; IR (KBr) 2934, 1660, 1464 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{21}NO$ 280.1696 (M + H^+), found 280.1682; $[\alpha]^{22}_D$ −146.1 (c 0.11, MeOH). Compound **19b**-*R*′ did not isomerize at 150 °C for 3 h in DMF.

Single-Crystal X-ray Analysis. Crystal data of 1b-*S*: $C_{16}H_{15}ON$, mp 137−139 °C, M_r = 237.30, Cu Kα (λ = 1.54187 Å), orthorhombic, $P2_12_12_1$, colorless prism 0.30 × 0.30 × 0.20 mm^3, crystal dimensions a = 8.04449(15) Å, b = 8.25073(15) Å, c = 18.7160(3) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1242.24(4) $Å^3$, D_{calc} = 1.269 g cm^{-3}, μ(Cu Kα) = 6.206 cm^{-1}, F_{000} = 504.00, GOF = 0.715, R_{int} = 0.045, R_1 = 0.0320, wR_2 = 0.0808, Flack = 0.2(3). The CIF file of the crystal data for **1b**-*S* is available in the Supporting Information of our preceding paper.[4]

Crystal data of 1b-*R*: $C_{16}H_{15}ON$, mp 137−139 °C, M_r = 237.30, Cu Kα (λ = 1.54187 Å), orthorhombic, $P2_12_12_1$, colorless prism 0.50 × 0.50 × 0.40 mm^3, crystal dimensions a = 8.04577(15) Å, b = 8.25270(15) Å, c = 18.7170(3) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1242.80(4) $Å^3$, D_{calc} = 1.268 g cm^{-3}, μ(Cu Kα) = 6.204 cm^{-1}, F_{000} = 504.00, GOF = 1.228, R_{int} = 0.025, R_1 = 0.0290, wR_2 = 0.0683, Flack parameter = −0.3(3). The CIF file of the crystal data for **1b**-*R* is available in the Supporting Information of our preceding paper.[4]

Crystal data of 2b-*S*: $C_{17}H_{17}ON$, mp 130−132 °C, M_r = 251.33, Cu Kα (λ = 1.54187 Å), tetragonal, $P4_1$, colorless prism 0.70 × 0.60 × 0.50 mm^3, crystal dimensions a = 10.00744(18) Å, c = 13.5007(3) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1352.08(4) $Å^3$, D_{calc} = 1.235 g cm^{-3}, μ(Cu Kα) = 5.972 cm^{-1}, F_{000} = 536.00, GOF = 1.278, R_{int} = 0.027, R_1 = 0.0264, wR_2 = 0.0615, Flack parameter = −0.1(2).

Crystal data of 2b-*R*: $C_{17}H_{17}ON$, mp 130−132 °C, M_r = 251.33, Cu Kα (λ = 1.54187 Å), tetragonal, $P4_3$, colorless prism 0.30 × 0.30 × 0.10 mm^3, crystal dimensions a = 10.00645(18) Å, c = 13.4991(3) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1351.65(4) $Å^3$, D_{calc} = 1.235 g cm^{-3}, μ(Cu Kα) = 5.974 cm^{-1}, F_{000} = 536.00, GOF = 1.020, R_{int} = 0.040, R_1 = 0.0404, wR_2 = 0.1002, Flack parameter = 0.3(4).

Crystal data of 3b-*S*: $C_{18}H_{19}ON$, mp 160−162 °C, M_r = 265.35, Cu Kα (λ = 1.54187 Å), orthorhombic, $P2_12_12_1$, colorless prism 0.40 × 0.35 × 0.20 mm^3, crystal dimensions a = 8.85223(16) Å, b = 11.3388(2) Å, c = 14.4403(3) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1449.43(5) $Å^3$, D_{calc} = 1.216 g cm^{-3}, μ(Cu Kα) = 5.823 cm^{-1}, F_{000} = 568.00, GOF = 0.966, R_{int} = 0.025, R_1 = 0.0381, wR_2 = 0.1091, Flack parameter = −0.2(3).

Crystal data of 3b-*R*: $C_{18}H_{19}ON$, mp 160−162 °C, M_r = 265.35, Cu Kα (λ = 1.54187 Å), orthorhombic, $P2_12_12_1$, colorless prism 0.40 × 0.40 × 0.15 mm^3, crystal dimensions a = 8.8513(3) Å, b = 11.3404(3) Å, c = 14.4414(5) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1449.58(8) $Å^3$, D_{calc} = 1.216 g cm^{-3}, μ(Cu Kα) = 5.822 cm^{-1}, F_{000} = 568.00, GOF = 0.862, R_{int} = 0.047, R_1 = 0.0344, wR_2 = 0.0752, Flack parameter = −0.0(3).

Crystal data of 19a-*R*′: $C_{18}H_{19}ON$, mp 157−159 °C, M_r = 265.35, Cu Kα (λ = 1.54187 Å), orthorhombic, $P2_12_12_1$, colorless prism 0.25 × 0.20 × 0.10 mm^3, crystal dimensions a = 8.62372(16) Å, b = 11.6285(2) Å, c = 14.8609(3) Å, α = 90°, β = 90°, γ = 90°, T = 173 K, Z = 4, V = 1490.27(5) $Å^3$, D_{calc} = 1.183 g cm^{-3}, μ(Cu Kα) = 5.663 cm^{-1}, F_{000} = 568.00, GOF = 0.994, R_{int} = 0.037, R_1 = 0.0429, wR_2 = 0.0992, Flack parameter = 0.0(5). The CIF files of the crystal data for **2b**-*S*, **2b**-*R*, **3b**-*S*, **3b**-*R*, and **19a**-*R*′ are available in the Supporting Information.

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Supporting Information Available: General experimental procedure, spectral data for all compounds, figures of thermal isomerization rate of enantiomers of **1a**, **1b**, **2a**, **3a**, **17b**-*R*, and **18a**-*R*, and X-ray crystal data (CIF) for **2b**-*R*, **2b**-*S*, **3b**-*R*, **3b**-*S*, and **19b**-*R*′. This material is available free of charge via the Internet at http://pubs.acs.org.