CHEMISTRY
A EUROPEAN JOURNAL

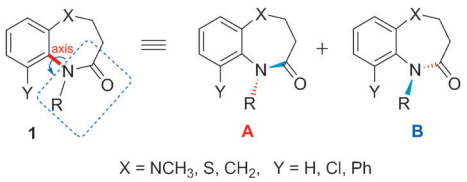
DOI: 10.1002/chem.201103264

Active Conformation of Seven-Membered-Ring Benzolactams as New ACAT Inhibitors: Latent Chirality at *N*5 in the 1,5-Benzodiazepin-2-one Nucleus**

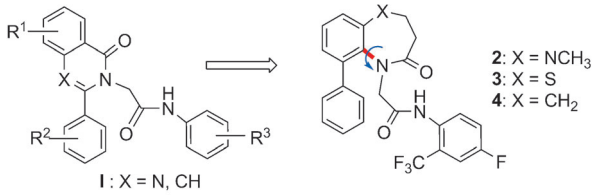
Hidetsugu Tabata,[a] Naoya Wada,[a] Yuko Takada,[a] Jun Nakagomi,[a] Tomohiro Miike,[b] Hiroaki Shirahase,[b] Tetsuta Oshitari,[a] Hideyo Takahashi,[a] and Hideaki Natsugari*[a]

The seven-membered-ring benzolactams (**1**: 1,5-benzodiazepin-2-one (X = NCH_3), 1,5-benzothiazepin-4-one (X = S) and 1-benzazepin-2-one (X = CH_2); Scheme 1) have been used as the core structures of various biologically active molecules: lofendazam,[1] diltiazem[2] and benazepril[3] are the typical therapeutic agents developed using these structures. In our preceding paper,[4] atropisomerism in the heterocycles **1** between **A** and **B** (Scheme 1) was investigated to reveal that the axial chirality[5] at the aryl–N(C=O) (sp^2–sp^2 axis) plays a key role in the entire conformational change of the lactam ring. With various types of information on these heterocycles in hand, we began research to discover acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors. Herein, we report that the enzyme clearly recognizes the active conformation (axial chirality)[6] of the newly found inhibitors (**2**–**4**; Scheme 2), and that the axial chirality of the 1,5-benzodiazepin-2-one nucleus (**2**) induces a latent chiral center at amine *N*5.

The ACAT enzyme, which consists of the two isomeric forms ACAT-1 and -2, plays an important role in intracellular cholesterol esterification (in the intestine, liver, and macrophages, and so on). Many potent ACAT inhibitors have been synthesized in the expectation of their clinical utility in preventing both hypercholesterolemia and atherosclerosis by blocking cholesterol esterification. Some, for example, pactimibe[7] and avasimibe,[8] which are nonselective inhibitors of ACAT-1 and -2, entered clinical trials, but their development was halted because of insufficient efficacy in patients. The search continues for potent ACAT inhibitors, and recent studies[9] have suggested that ACAT-2 inhibition may be more beneficial than ACAT-1 inhibition in reducing plasma lipoprotein cholesterol levels. In our preceding study, potent ACAT inhibitors with isoquinolone and quinazolone nuclei (**I** in Scheme 2) were prepared.[10] The structure–activity relationship study indicated that the important moieties for their activity are a biaryl moiety and an *N*-(phenyl)acetamide group in the proper spatial arrangement.



Scheme 1. Atropisomers (**A** and **B**) of seven-membered-ring benzolactams (**1**).



Scheme 2. New ACAT inhibitors: benzolactam-anilides (**2**–**4**) and the lead compounds (**I**).

In the present study, the heterocycles **1** were incorporated into the structure (Scheme 2). An exploratory study using 1,5-benzodiazepin-2-one (**1**: X = NCH_3, Y = Ph) showed that a derivative with *N*-(4-fluoro-2-(trifluoromethyl)phenyl)-acetamide moiety (**2**), which was prepared from the benzolactam **5a** by direct N-alkylation or amidation through the *N*-acetic acid derivative (**6a**; Scheme 3), is a good inhibitor of ACAT with an IC_{50} value of 3.5 μM (Table 1).[11] Following this, 1,5-benzothiazepin-4-one (**1**: X = S, Y = Ph) and 1-benzazepin-2-one (**1**: X = CH_2, Y = Ph) were used to yield highly potent inhibitors **3** (IC_{50} = 0.43 μM) and **4** (IC_{50} = 0.068 μM), respectively (Scheme 3, Table 1). Compound **4**, which showed excellent activity, warrants further biological studies.[11]

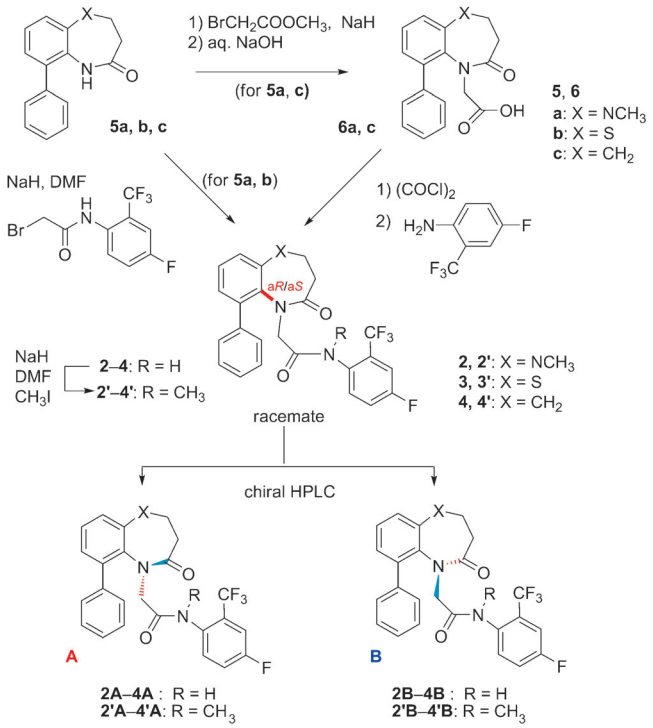
The benzolactams (**2**–**4**) thus obtained were expected to exist as racemates of the atropisomers due to the axial chirality at aryl–N(C=O).[4] Since the compounds have a pendant phenyl adjacent to the lactam moiety, the rotation around the axis is restricted to form relatively stable atro-

[a] H. Tabata, N. Wada, Y. Takada, J. Nakagomi, Dr. T. Oshitari, Prof. Dr. H. Takahashi, Prof. Dr. H. Natsugari
School of Pharmaceutical Sciences, Teikyo University
1091-1 Midori-ku, Sagamihara, Kanagawa 252-5195 (Japan)
Fax: (+81) 426-85-3728
E-mail: natsu@pharm.teikyo-u.ac.jp

[b] T. Miike, Dr. H. Shirahase
Kyoto Pharmaceutical Industries, Ltd.
38 Nishinokyo Tsukinowa-cho, Nakakyo-ku, Kyoto 604-8444 (Japan)

[**] ACAT = acyl-coenzyme A: cholesterol acyltransferase

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201103264.



Scheme 3. Synthesis of racemic benzolactam-anilide derivatives (**2**–**4**/**2′**–**4′**) and their separation using chiral HPLC into the atropisomers (**A** and **B**).

Table 1. Properties of **2**–**4** (racemates and atropisomers): ACAT inhibitory activity, chiroptical properties and thermal stability of the enantiomers.

Compound (axial chirality)	IC_{50} [μM] ACAT[a]	$[\alpha]_D$[b] (CH_3OH)	CD[c]	$\Delta G^{\neq}$[d] [kJ mol^{-1}]	Racemization t[e] [h]
2: racemate	3.5				
A (a*S*)	2.0	+51.0[f]	++	103[g]	5[g]
B (a*R*)	11	−58.2[h]	−−	103[i]	5[i]
3: racemate	0.43				
A (a*S*)	0.19	−16.3	−−−	105[j]	7[j]
B (a*R*)	2.1	+19.7	+++		
4: racemate	0.068				
A (a*R*)[k]	0.038	−34.3	−−−	102[j]	2[l]
B (a*S*)[k]	0.26	+36.1	+++		

[a] Hepatic ACAT (rabbit liver microsomes). IC_{50} of pactimibe[7] (as a control compound): 1.4 μM. See the Supporting Information for details. [b] See the Supporting Information for each concentration (c = 0.11–0.27 g mL^{-1}). [c] Signs and intensities of Cotton Effect around 230–240 nm measured in CH_3OH. See Figure 1 and Table S2 (the Supporting Information) for detail. [d] Activation free-energy barrier to rotation around the Ar–N(C=O) bond.[12] [e] Time required for racemization at 50 °C in toluene or DMF. See the Supporting Information for details. [f] In $CHCl_3$, +49.8 (c = 0.30). [g] Conversion from **A** to **B** in DMF. [h] In $CHCl_3$, −49.9 (c = 0.30). [i] Conversion from **B** to **A** in DMF. [j] Conversion from **A** to **B** in toluene. [k] For the definition of the axial chirality (a*S* and a*R*), see ref. [16]. [l] Racemization occurred for 7 h when heated at 37 °C in toluene.

pisomers, whose absolute stereochemistry would be recognized by the ACAT enzyme. The inhibitors (**2**–**4**) were successfully separated into the respective enantiomers (**A** and **B**) by preparative HPLC on a chiral stationary phase (Scheme 3, Table 1). The chiral axis of the atropisomers (**A** and **B**) is not fully frozen but rotates slowly with $\Delta G^{\neq}$ (the activation free-energy barrier to rotation) values[12] of 105 kJ mol^{-1} for **3A** (X = S), 103 kJ mol^{-1} for **2A** (X = NCH_3), and 102 kJ mol^{-1} for **4A** (X = CH_2) (Table 1).

Next, the atropisomers (**A** and **B**) of **2**–**4** were evaluated for ACAT inhibitory activity to reveal approximately a 6- to 11-fold difference in potency between the enantiomers (active eutomer **A** and less active distomer **B**),[13] with the median potency in the racemate (Table 1). The results clearly indicate that axial chirality plays an important role in exerting the activity.[6] It is reasonable to assume that the enzyme preferentially binds to the eutomer (**A**) with the same configuration. To confirm this, the chiroptical properties (optical rotation ($[\alpha]_D$) and circular dichroism (CD)) were measured.[14] The angle of $[\alpha]_D$ of **2A** was (+), and that of **3A** and **4A** (−) (Table 1). Compounds **3A** and **4A** exhibited similar CD spectra with negative bands around 230–240 nm (corresponding to absorption maxima of acetanilide (241 nm) and aniline (230 nm)), whereas **2A** showed a markedly different spectrum with a positive band around 230–240 nm (Figure 1 (red lines) and Table 1). These chiroptical data suggest that, contrary to our expectation, the absolute configuration of the eutomer **2A** may be opposite to that of **3A** and **4A**. This confusing situation was finally resolved by X-ray structure analysis of eutomers **2A** and **3A**, which revealed that, as was expected from the activity data, both compounds possess the same stereochemistry with the (a*S*)-configuration.[15] The configuration of eutomer **4A**, which showed chiroptical properties similar to those of **3A**, was thus deduced to be (a*R*).[16]

The X-ray structures of the eutomers **2A**–**4A** are shown in Figure 2. In a unit cell of compound **2A**, two independent molecules (Mol. **I** and **II**) are present which have similar structures. The structure of **4A** in Figure 2 is that with the (a*R*)-form[16] extracted from the X-ray CIF data of the racemate **4**. The conformations of the three (four) structures are similar in that the lactam ring exists in a twisted-boat form and the pendant phenyl is in a perpendicular alignment relative to the benzene ring. On the other hand, the benzanilide moiety in the side chain adopts a different conformation in the position and orientation among the three compounds, which may cause the activity difference.

X-ray analysis of the 1,5-benzodiazepin-2-one **2A** revealed particularly interesting structural features. The nitrogen at the 5-position takes a slightly twisted pyramidal form,[17] and the *N*5 methyl exists in a pseudo-equatorial (pseudo-eq) position with the lone pair in a pseudo-axial (pseudo-ax) position (i.e., the *N*5-*S* configuration) in the crystal state, which should be a stable conformation. At first glance at the planar structure of **2A**, a hydrogen bond[18] between the amide-NH and lactam-oxygen (NH···O) may be envisioned. However, the X-ray structure of **2A** had a hydrogen bond between the amide-NH and *N*5-nitrogen (NH···N) (Table 2): bond distance (NH···N), 2.18 Å for Mol. **I**, and 2.43 Å for Mol. **II**. The hydrogen bond NH···S

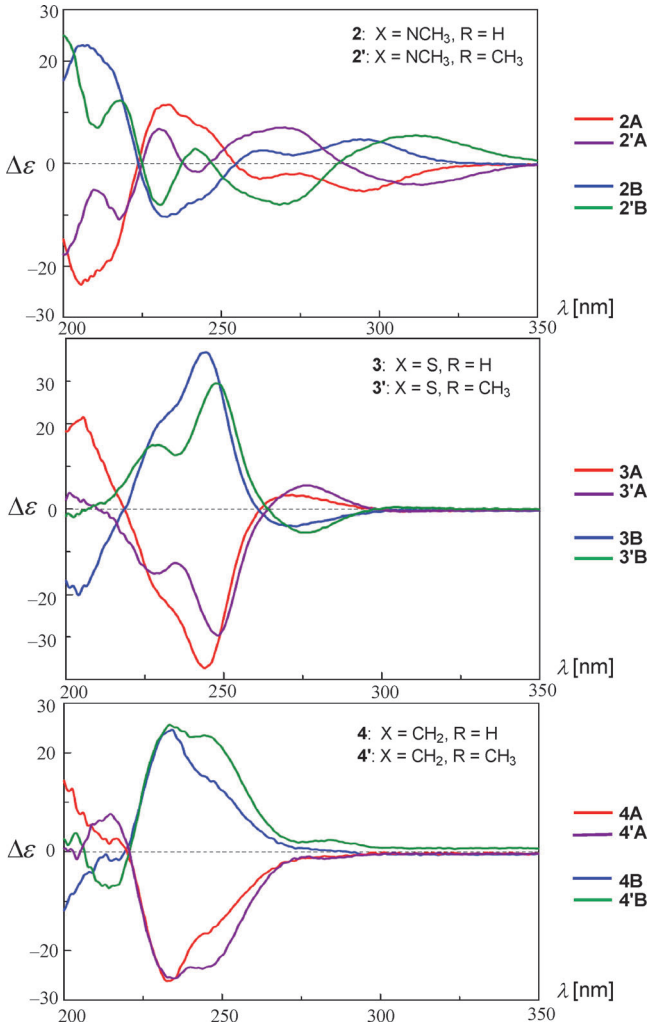


Figure 1. CD spectra of the atropisomers (A and B) of the benzolactam-anilide derivatives (**2**–**4**) and their N-CH_3 derivatives (**2′**–**4′**).

(2.58 Å) was also observed in **3A**. In contrast, **4A** had the hydrogen bond NH···O (2.07 Å). The presence of these hydrogen bonds is also supported by the bond angles of N-H-X/N-H-O (Table 2). The hydrogen bond in **2A** (NH···N) may further constrain the stable conformation described above. Since the chemical shift of the amide-NH of **2A** is observed at quite a low field ($\delta = 9.87$ ppm) in the ^{1}H NMR spectrum, the same structure is assumed to exist in solution as well. These results mean that, due to the rigid conformation, the *N*5-nitrogen in **2A** may exist as a chiral center (with the *S*-configuration) not only in the crystal state but also in solution. The difference in chiroptical properties between **2A** and **3A**/**4A** may be explained by this additional chirality in **2A** in solution. In terms of biological activity, the hydrogen bond NH···O in **4A** may cause the preferred conformation of the side chain by controlling the spatial position and orientation of the benzene ring to exhibit excellent activity. At this point, the conformation in **2A** with the hydrogen bond NH···N may not be favored.

To examine the effect of the hydrogen bond on the conformation, the amide-NCH_3 derivatives of **2**–**4** (**2′**–**4′**) were prepared (Scheme 3)[19] and separated into the respective enantiomers (**A** and **B**), and the CD spectra were measured (Figure 1, purple and green lines). Compound **2′A**, which lacks the hydrogen bond, caused a large change in the spectral pattern compared with **2A**, whereas the spectra of **3′A**/**4′A** remained similar to those of **3A**/**4A**. Taking into consideration the markedly different spectral pattern of **2′A** from those of **3′A**/**4′A**, it is reasonable to assume that the chirality at the *N*5-nitrogen in **2A** remains. This may be further supported by the ^{1}H NMR spectra of **2A** and **2′A**, in which the coupling patterns of the methylene protons in the lactam ring remain similar, suggesting that the conformation of the seven-membered ring itself remains unchanged in **2A** and **2′A** regardless of the hydrogen bond.[20] Thus, the (a*S*)-atropisomer is assumed to take a predominantly stable isomeric form with the *N*5-CH_3 disposed in the pseudo-equatorial conformation (i.e., the amine at *N*5 is a chiral center with the *S*-configuration), as shown in Scheme 4 (upper): that is, the axial chirality (a*S*) controls the stereochemistry of the entire lactam ring. In other words, both chiralities may move together like a gear. It should be noted that the preferred isomer has stereochemistry lacking steric repulsion between *N*5-CH_3 and the substituent (Z) at the lactam nitrogen, as shown in Scheme 4.

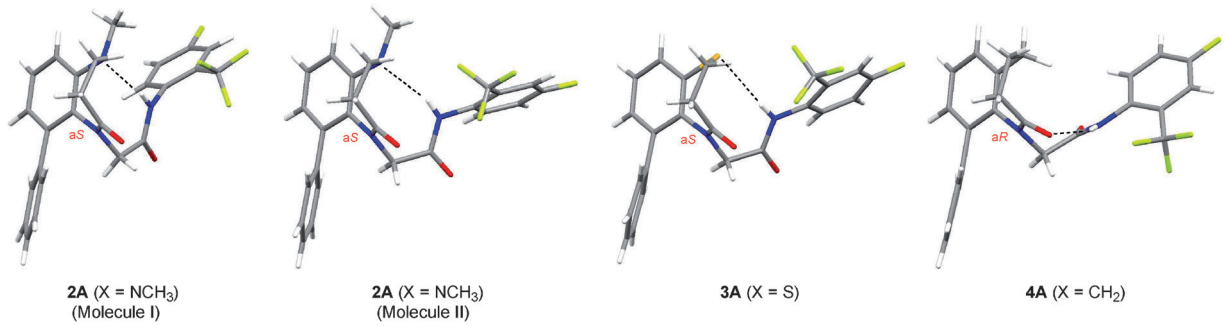
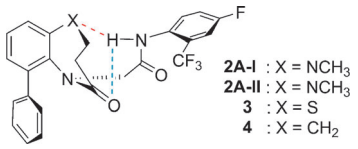


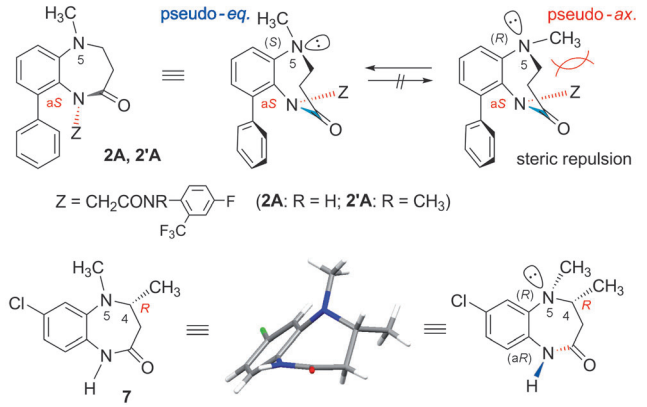
Figure 2. X-ray structures of atropisomers (eutomers: **2A**, **3A** and **4A**) generated from the CIF data. In a unit cell of compound **2A**, two independent molecules (Molecules **I** and **II**) are present. The structure of **4A** is extracted from the CIF data of the X-ray analysis of the racemate of **4**.[16] Hydrogen bonds are indicated with dotted lines.

Table 2. Hydrogen bond in **2A**, **3A**, and **4A**: in crystal state (distance and bond angle) and in solution (chemical shift).



	NH···X (distance)[a] [Å]	N-H-X (angle)[b] [°]	NH···O (distance)[a] [Å]	N-H-O (angle)[b] [°]	NH[c] δ [ppm]
2A-I[d]	2.18	154	3.57	116	9.87
2A-II[d]	2.43	161	3.28	99	
3A	2.58	156	3.08	110	9.19
4A[e]	3.85	88	2.07	151	8.22

[a] Distance estimated from the X-ray crystal data. [b] Angle estimated from the X-ray crystal data. [c] Chemical shift of amide-NH (in $CDCl_3$) in ^{1}H NMR spectrum. [d] Two independent molecules exist in a unit cell of crystal **2A** (Mol. **I** and **II**). [e] The data obtained from the X-ray analysis of the racemate **4**.



Scheme 4. Stereochemistry of 1,5-benzodiazepin-2-ones: **2A**/**2′A** and **7**.

Any atom that is tetrahedral with four different groups has the potential to be stereogenic, and pyramidal atoms with an unshared electron pair can be stereocenters. If the atoms do not invert, these molecules will be chiral. Thus, small amines have the potential to be stereogenic, although they usually exhibit rapid inversion rates ($\Delta G^{\neq} \approx 30\,kJ\,mol^{-1}$) and the pyramidal nitrogen will not be a chiral center. In the present study, the *N*5-nitrogen in the 1,5-benzodiazepin-2-one ring was first shown to be chiral because the ring system is rigidly held, as in chiral bicyclic amines (e.g., Tröger's base[21] and sparteine[22]).

The CD spectra of 1,5-benzodiazepin-2-ones with a chiral *C*4-methyl were previously reported,[1] and X-ray analysis of 4*R*-7-chloro-4-methyl-1,5-benzodiazepin-2-one (**7**) followed.[1d] Although the report only describes the determination of the absolute configuration at the *C*4 chiral center, X-ray analysis of **7** (Scheme 4, lower) gave us very important information on the molecular chirality. Inspection of the CIF data deposited, compound **7** was found to have (a*R*, *N*5-*R*)-stereochemistry in the crystal state[17] (corresponding to the stereochemistry of **2B**/**2′B**); this means that the entire conformation of the ring is rigidly held so as to adopt the *C*4-*R*-methyl in the most stable conformation. The reported CD spectra of **7**[1] and **2′B** showed a similar pattern,[23] suggesting that the two molecules have a similar molecular chirality also in solution.

In conclusion, the potent new ACAT inhibitors **2**–**4** with the seven-membered-ring benzolactams as the core structures were first prepared, and the axial chirality recognized by the enzyme was clarified. The unique structural feature of the 1,5-benzodiazepin-2-one nucleus (**2A**) was revealed by CD, ^{1}H NMR spectroscopy and X-ray structural analyses; that is, the chirality at the axis (a*S*) controls the conformation of the entire lactam ring, causing *N*5-CH_3 to arrange in the pseudo-equatorial orientation (=*N*5-*S* configuration). We hope that these stereochemical findings in seven-membered-ring benzolactams will assist in future drug design in which heterocyclic systems are utilized as the core structure for biologically active molecules.

Acknowledgements

We are grateful to Sagami Chemical Research Center for X-ray analysis. 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.

Keywords: atropisomerism · chirality · circular dichroism · lactams · medium-ring compounds

[1] a) F. Malik, M. Hasan, K. M. Khan, S. Perveen, G. Snatzke, H. Duddeck, W. Voelter, *Liebigs Ann.* **1995**, 1861–1869; b) K. M. Khan, F. Malik, M. Hasan, S. Perveen, G. Snatzke, W. Voelter, *Z. Naturforsch.* **1995**, *50b*, 1869–1882; c) K. M. Khan, F. Malik, G. Snatzke, W. Voelter, *Z. Naturforsch.* **1996**, *51b*, 588–598; d) M. Hasan, T. A. Nizami, A. Malik, C. Ohlendorf, W. Hiller, W. Voelter, *Z. Naturforsch.* **1998**, *53b*, 485–487.

[2] J. B. Bariwal, K. D. Upadhyay, A. T. Manvar, J. C. Trivedi, J. S. Singh, K. S. Jain, A. K. Shah, *Eur. J. Med. Chem.* **2008**, *43*, 2279–2290.

[3] J. W. H. Watthey, J. L. Stanton, M. Desai, J. E. Babiarz, B. M. Finn, *J. Med. Chem.* **1985**, *28*, 1511–1516.

[4] H. Tabata, N. Wada, Y. Takada, T. Oshitari, H. Takahashi, H. Natsugari, *J. Org. Chem.* **2011**, *76*, 5123–5131.

[5] For recent review articles on axial chirality and atropisomerism, see: a) J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem.* **2009**, *121*, 6516–6520; *Angew. Chem. Int. Ed.* **2009**, *48*, 6398–6401; b) S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller, P. J. Edwards, *J. Med. Chem.* **2011**, *54*, 7005–7022.

[6] For the relation between the axial chirality arising from the sp^2–sp^2 axis of the benzene–amide bond and biological activity, see: a) Y. Ikeura, T. Doi, A. Fujishima, H. Natsugari, *Chem. Commun.* **1998**, 2141–2142; b) Y. Ikeura, Y. Ishichi, T. Tanaka, A. Fujishima, M. Murabayashi, M. Kawada, T. Ishimaru, I. Kamo, T. Doi, H. Natsugari, *J. Med. Chem.* **1998**, *41*, 4232–4239; c) H. Natsugari, Y. Ikeura, I. Kamo, T. Ishimaru, Y. Ishichi, A. Fujishima, T. Tanaka, F. Kasahara, M. Kawada, T. Doi, *J. Med. Chem.* **1999**, *42*, 3982–3993; d) J. S. Albert, D. Aharony, D. Andisik, H. Barthlow, P. R. Bernstein, R. A. Bialecki, R. Dedinas, B. T. Dembofsky, D. Hill, K. Kirkland, G. M. Koether, B. J. Kosmider, C. Ohnmacht, W. Palmer, W. Potts, W. Rumsey, L. Shen, A. Shenvi, S. Sherwood, P. J. Warwick, K. Rus-

sell, *J. Med. Chem.* **2002**, *45*, 3972–3983; e) S. D. Guile, J. R. Bantick, M. E. Cooper, D. K. Donald, C. Eyssade, A. H. Ingall, R. J. Lewis, B. P. Martin, R. T. Mohammed, T. J. Potter, R. H. Reynolds, S. A. St-Gallay, A. D. Wright, *J. Med. Chem.* **2007**, *50*, 254–263; f) J. Porter, A. Payne, I. Whitcombe, B. de Candole, D. Ford, R. Garlish, A. Hold, B. Hutchinson, G. Trevitt, J. Turner, C. Edwards, C. Watkins, J. Davis, C. Stubberfield, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1767–1772; g) H. Takahashi, S. Wakamatsu, H. Tabata, T. Oshitari, A. Harada, K. Inoue, H. Natsugari, *Org. Lett.* **2011**, *13*, 760–763; h) H. Tabata, J. Nakagomi, D. Morizono, T. Oshitari, H. Takahashi, H. Natsugari, *Angew. Chem.* **2011**, *123*, 3131–3135; *Angew. Chem. Int. Ed.* **2011**, *50*, 3075–3079.

[7] K. Takahashi, M. Kasai, M. Ohta, Y. Shoji, K. Kunishiro, M. Kanda, K. Kurahashi, H. Shirahase, *J. Med. Chem.* **2008**, *51*, 4823–4833.

[8] G. Llaverías, J. Laguna, M. Alegret, *Cardiovasc. Drug Rev.* **2003**, *21*, 33–50.

[9] a) A. T. Lada, M. Davis, C. Kent, J. Chapman, H. Tomoda, S. Omura, L. L. Rudel, *J. Lipid Res.* **2004**, *45*, 378–386; b) T. Ohshiro, D. Matsuda, K. Sakai, C. Degirolamo, H. Yagyu, L. L. Rudel, S. Omura, S. Ishibashi, H. Tomoda, *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 1108–1115.

[10] H. Natsugari, T. Kamide, *Jpn. Kokai Tokkyo Koho* **2007**, JP2007176809. See Supporting Information for the typical lead compounds (**I**) and their inhibitory activity.

[11] The assay for the ACAT inhibitory activity shown in Table 1 is that using rabbit liver microsomes, which is regarded as the assay for ACAT-2 isoform. By this assay, the intrinsic enzyme inhibitory activity of the compound is well evaluated. Another assay using esterified cholesterol (EC) accumulation in THP-1 cell-derived macrophages, which is regarded as the assay for ACAT-1 isoform, was also performed. In this EC accumulation assay, a similar pattern of the difference in potency between **A** (eutomer) and **B** (distomer) was also observed. See the Supporting Information for details.

[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 allowing them to stand at designated temperatures (see Supporting Information for measurements); see M. Petit, A. J. B. Lapierre, D. P. Curran, *J. Am. Chem. Soc.* **2005**, *127*, 14994–14995.

[13] Since the distomer **B** partly isomerizes to the eutomer **A** (ca. 1–9%) during the assay period (for 25 min at 37 °C), the intrinsic potency of **B** is weaker than the data and the difference in potency between **A** and **B** may be intrinsically larger than the data obtained (also isomerization from **A** to **B** affects the data). See the Supporting Information for the isomerization profiles.

[14] See the Supporting Information for CD and UV data and spectra.

[15] CCDC-831103 (**2A**), CCDC-831104 (**3A**) and CCDC-831105 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The absolute stereochemistry was determined based on the Flack parameter ($Cu_{K\alpha}$ radiation was used for the measurement).

[16] Note that the definition of axial chirality (a*S* and a*R*) leads to reversed stereochemical designations between **2/3** (X = NCH_3/S) and **4** (X = CH_2) according to the priority rule. The terms a*S* and a*R* (chiral axis nomenclature) correspond to *P* and *M* (helix nomenclature), respectively.

[17] See the Supporting Information for the bond angles around the *N*5-nitrogen in **2A** and **7**.

[18] For review articles on the hydrogen bond, see: a) T. Steiner, *Angew. Chem.* **2002**, *114*, 50–80; *Angew. Chem. Int. Ed.* **2002**, *41*, 48–76; b) G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, Oxford, **1997**, pp 11–32.

[19] Compounds **2′–4′** were shown to exist as a mixture of *E*- and *Z*-conformers at the *N*-CH_3 amide moiety in the ^{1}H NMR spectra (ratio: 4.4–5.0:1). See the Supporting Information for details.

[20] See the Supporting Information for detailed ^{1}H NMR data on **2A** and **2′A**, including a magnified view of the methylene region.

[21] D. Didier, B. Tylleman, N. Lambert, C. M. L. V. Velde, F. Blockhuys, A. Collas, S. Sergeyev, *Tetrahedron* **2008**, *64*, 6252–6262.

[22] M. J. Dearden, C. R. Firkin, J.-P. R. Hermet, P. O'Brien, *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871.

[23] The Cotton effects in the CD spectrum [λ_{nm} ($\Delta\varepsilon$)] for **7**,[1] 306 (+1.76), 281 (−1.30), 259 (+1.98) (sh), 241 (+3.68), 231 (−5.21), 212 (+3.80), and those for the de-chloro derivative of **7**,[1] 299 (+1.74), 270 (−2.05), 237 (+5.26), 226 (−3.10), 211 (+1.75).

Received: October 17, 2011
Published online: December 28, 2011

