

# Absolute Configuration of Atropisomeric Polychlorinated Biphenyl 183 Enantiomerically Enriched in Human Samples

Mitsunobu Toda,<sup>†</sup> Chisato Matsumura,<sup>‡</sup> Masahiro Tsurukawa,<sup>‡</sup> Toshihiro Okuno,<sup>‡</sup> Takeshi Nakano,<sup>\*,§</sup> Yoshihisa Inoue,<sup>†</sup> and Tadashi Mori<sup>\*,†</sup>

<sup>†</sup>Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamada-oka, Suita, Osaka 565-0871, Japan

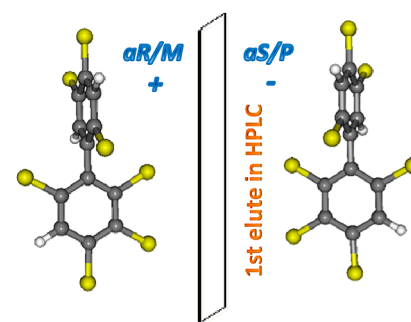
<sup>‡</sup>Hyogo Prefecture Institute of Environmental Science, 3-1-27, Yukihiro, Suma-ku, Kobe, Hyogo 654-0037, Japan

<sup>§</sup>Research Center for Environmental Preservation, Osaka University, 2-4, Yamada-oka, Suita, Osaka 565-0871, Japan

## S Supporting Information

**ABSTRACT:** Polychlorinated biphenyls (PCBs) are still of serious concern as a potential health hazard due to their persistency and bioaccumulation. Of 209 possible PCB congeners, with varying number and position of chlorine atom(s), 19 are chiral. These are mostly highly chlorinated and tend to remain longer against the biological decompositions, suffering biological deracemization in the environment. In this work, we have unequivocally determined the absolute configurations of important chiral PCBs 183 and 171, as well as 132, through the combined theoretical and experimental investigations of the chiroptical properties (circular dichroism and optical rotation), which will be valuable in elucidating the mechanism of biological enantiomer enrichment of PCBs in the environment.

## Absolute Configuration of PCB 183



Atropisomers are stereoisomers resulting from hindered rotation around a single bond, where the rotational barrier is high enough to allow isolation of each conformer.<sup>1</sup> The atropisomeric behavior was first recognized by Cristie for 6,6'-dinitro-2,2'-diphenic acid in 1922,<sup>2</sup> but the term “atropisomerism” was coined by Kuhn in 1933.<sup>3,4</sup> Atropisomeric compounds are often found in natural products, such as vancomycin, knipholone, gossypol, mastigophorene A, or murrastifoline F, and the atropisomerism has been extensively utilized in asymmetric synthesis as well.<sup>5</sup> Although the steric hindrance to cause atropisomerism is rather arbitrary, the existence of atropisomer may be noticed when the half-life of the interconversion is longer than 1000 s at ambient temperatures.<sup>3,4</sup> Thus, the size (and number) of substituents introduced to the ortho positions of biaryl critically influences the atropisomers equilibrium, accelerating the rate with decreasing bulkiness of the substituent: I > Br ≫ CH<sub>3</sub> > Cl > NO<sub>2</sub> > CO<sub>2</sub>H ≫ OCH<sub>3</sub> > F > H. Hence, unsymmetrically polychlorinated biphenyls (PCBs) exhibit the atropisomerism, when three or four chlorine atoms are introduced to the ortho positions. Among the 209 PCB congeners, 19 PCBs are known to be chiral at ambient temperatures.<sup>6</sup>

PCBs are legacy pollutants and now ubiquitous in the environment. Commercial PCBs and environmental extracts contain a variety of PCB congeners,<sup>7</sup> and hence congener-specific analysis of PCBs in environmental extracts is of growing importance in ecological risk assessment.<sup>8</sup> Structure-toxicity correlation studies revealed that, among the congeners,

dioxin-like and coplanar PCBs generally show higher toxic equivalency factors for human and other mammals.<sup>9</sup> However, recent investigation underlined that nondioxin PCBs are also toxic, showing the endocrine-disrupting and neurotoxic effects.<sup>10</sup> This demonstrates that more precise and comprehensive assessment of the overall activity of persistent organic pollutants is absolutely necessary.<sup>11</sup> Over a decade, the PCBs metabolism has been debated in broadly defined biological samples.<sup>12–18</sup>

Naturally, a pair of PCB atropisomers show significantly different biological and toxicological behavior,<sup>19,20</sup> and therefore the analytical separation of PCB atropisomers have been extensively investigated by means of chiral GC–MS, (multi-dimensional) GC, HPLC, and capillary electrophoresis,<sup>21,22</sup> to reveal indeed the enantiomer enrichment of some chiral PCBs in environmental samples.<sup>10</sup> The enantiomerically enriched PCB-183 (2,2',3,4,4',5',6-heptachlorobiphenyl) and PCB-171 (2,2',3,3',4,4',6-heptachlorobiphenyl) found in human samples were ascribed to the uptake of nonracemic PCBs through the diet.<sup>8,23,24</sup> The diversity of the enantiomeric excess (ee) of PCBs retrieved from various species supports this view.<sup>25</sup> The absolute configurations of methylsulfonylated metabolites of some PCBs have recently been elucidated by using vibrational circular dichroism.<sup>26,27</sup> Nonetheless, the absolute configurations

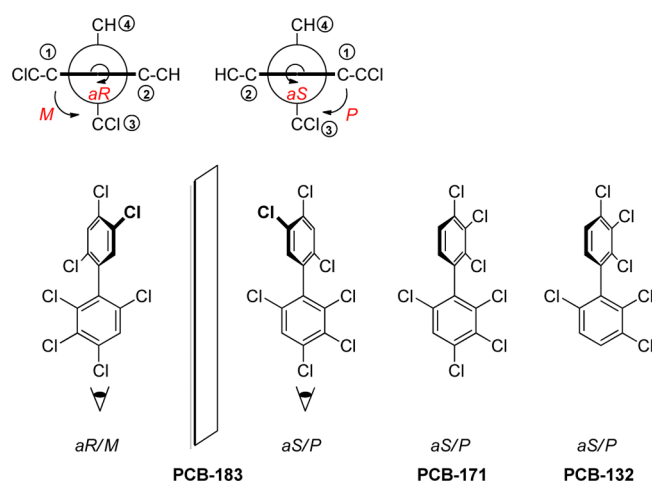
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of the parent PCBs have never been determined,<sup>28</sup> probably due to the limited availability and the relatively difficult optical resolution.<sup>29</sup>

In this combined theoretical and experimental study to determine the absolute configuration of chiral PCB, we chose PCB-183, PCB-171, and PCB-132 (2,2',3,3',4,6'-hexachlorobiphenyl), shown in Chart 1, because PCB-183 and -171 are

**Chart 1. (aR)- or (M)- and (aS)- or (P)-Enantiomers of Atropisomeric PCB-183 and (aS/P)-Enantiomers of PCB-171 and PCB-132**



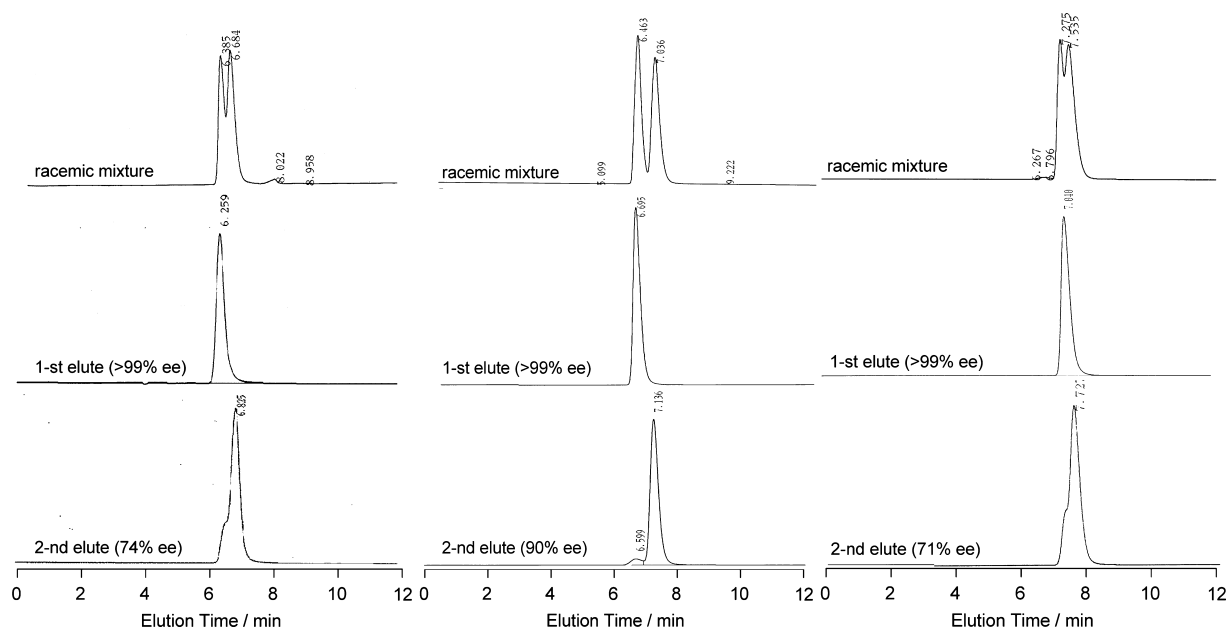
highly chlorinated and tend to remain longer against the biological decompositions, suffering deracemization in the environment, whereas PCB-132 was chosen as a less-chlorinated reference.<sup>8,30</sup>

The enantiomers of PCB-183, -171, and -132 were resolved by semipreparative chiral HPLC on a Chiralcel OJ-H column (Figure 1). The optical resolution of other chiral congeners, such as PCB-174 (2,2',3,3',4,5,6'-heptachlorobiphenyl), was not

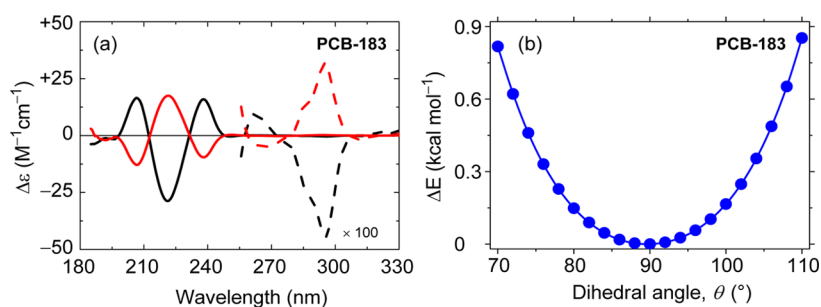
successful under the same conditions; Figure S1 in the Supporting Information. Because the resolution factors ( $R_s$ )<sup>31,32</sup> were moderate for the enantiomeric PCBs (Table S1, Supporting Information), we were unable to perfectly resolve the enantiomers. Accordingly, the optically pure first fractions (>99% ee) and the optically enriched second fractions (74%, 90%, and 71% ee for PCB-183, 171, and 132, respectively) were used in the spectral investigations. The electronic circular dichroism (CD) spectra of the second fractions numerically corrected for the optical purities determined by chiral HPLC were almost identical in shape and intensity to those of the corresponding first fractions, indicating that our resolved samples were optically (for the first fractions) and chemically pure (for PCB-183, see Figure S2a in the Supporting Information).

The experimental CD spectra of the enantiomeric PCB-183 pair, obtained in hexane at 25 °C (Figure 2a), were exactly mirror-imaged but slightly different in intensity. The first fraction exhibits fairly strong positive-negative-positive ("trisignate") Cotton effects (CEs) (from longer  $\lambda$ ) at 200–250 nm and additional much weaker negative-positive CEs at 250–310 nm. The characteristic trisignate pattern is shared by relevant chiral biaryl systems, such as polyhalogenated bipyridine atropisomers<sup>33</sup> and the chiral metabolites of PCB.<sup>27</sup> Furthermore, the spectra of dynamically chiral (nonhalogenated) biaryls also show very similar CD patterns with much reduced intensities.<sup>34</sup> However, a close inspection of the theoretical results revealed that the apparently trisignate CE pattern is actually a more complicated ensemble of multiple overlapping transitions (vide infra).

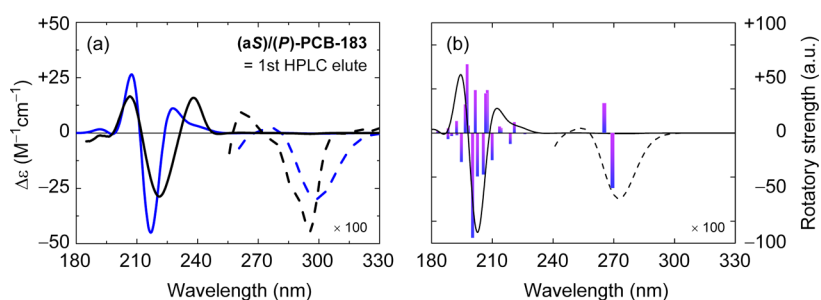
Recent combined theoretical and experimental studies<sup>35–37</sup> have successfully simulated the chiroptical properties and determined the absolute configurations of a number of natural and synthetic chiral molecules.<sup>38–41</sup> An approach similar to that for conformationally flexible chiral PCBs requires some prior considerations for the potential energy change associated with



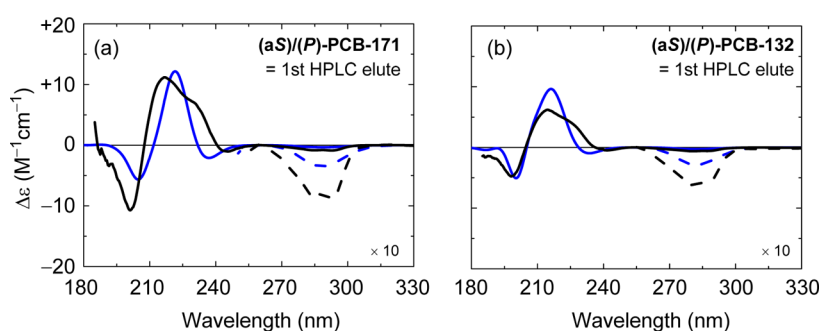
**Figure 1.** Chiral HPLC chromatograms (monitored by a UV detector at 291 nm) of racemic mixture (top), first- (middle), and second-eluted enantiomer (bottom) of PCB-183 (left), 171 (middle), and 132 (right) on a Daicel Chiralcel OJ-H column (4.6 mm i.d. × 15 cm) at 38 °C, eluted by *n*-hexane at a flow rate of 0.5 mL min<sup>-1</sup>.



**Figure 2.** (a) Experimental CD spectra of first (black) and second (red) fractions of PCB-183 in hexane at 25 °C. Note that the enantiomeric excess (ee) of the second fraction was 74%. (b) Potential energy curve calculated for PCB-183 in the gas phase as a function of dihedral angle  $\theta$  at the DFT-D3-B-LYP/def2-TZVP level.



**Figure 3.** (a) Comparison of experimental (black) and theoretical (blue) CD spectra of PCB-183. The theoretical spectrum was calculated for (aS/*P*)-enantiomer at the RI-CC2/aug-def2-TZVPP level and 0.4 eV red-shifted, whereas the rotational strengths were not scaled. (b) Bar presentation of the rotational strengths calculated for PCB-183 with the corresponding Gaussian-expanded theoretical spectrum. The excitation energies and rotational strengths were not shifted or scaled.



**Figure 4.** Comparison of experimental (black) and theoretical (blue) CD spectra of (a) PCB-171 and (b) PCB-132. The experimental spectra were obtained in *n*-hexane at 25 °C for the first fractions on chiral HPLC on a Daicel Chiralcel OJ-H column. The theoretical spectrum was obtained for (aS/*P*)-enantiomer at the RI-CC2/aug-def2-TZVPP level. The theoretical spectra were scaled to 1/3 and 0.3 eV red-shifted.

the dihedral angle ( $\theta$ ) between the two benzene rings.<sup>42–44</sup> Hence, the potential energy curve for PCB-183 was calculated by optimizing the geometries of rotamers with varying  $\theta$  from 70° to 110° at every 2° by the cost-effective, yet accurate, dispersion-corrected DFT-D3-B-LYP/def2-TZVP method (Figure 2b).<sup>45,46</sup> The optimization of PCB-183 without fixing  $\theta$  at the same level led to a perpendicular geometry ( $\theta = 89.9^\circ$ ), and the same was true for PCB-171 and 132 ( $\theta = 90.1–90.2^\circ$ ). Molecular mechanics calculation also predicted a perpendicular structure ( $\theta = 90^\circ$ ) for triply ortho-chlorinated PCB-84 (2,2',3,3',6-pentachlorobiphenyl).<sup>47</sup> On the other hand, X-ray crystallographic studies revealed less-twisted structures for PCB-84 ( $\theta = 81.5^\circ$ )<sup>47</sup> and PCB-95 (2,2',3,5',6-pentachlorobiphenyl) ( $\theta = 75.3^\circ$ ),<sup>48</sup> suggesting considerable rotational tolerance or shallow potential well for PCBs. Nevertheless, it is a reasonable approximation to employ the perpendicular geometries of these PCBs as local minima (and not to reflect the dynamic behavior)<sup>42–44</sup> in the theoretical prediction of CD

spectra. The kinetic energy at room temperature ( $k_B T \approx 0.6$  kcal mol<sup>-1</sup>) allows these PCBs to populate in a  $\theta$  range of 72–108°, which is, however, much narrower than those reported for less-chlorinated PCBs (ca. 50–130°)<sup>49</sup> and 2,2'-dimethoxybinaphthyl (ca. 60–120°),<sup>42</sup> rationalizing the approximation.

Theoretical CD calculations were run at the resolution-of-identity, linear response, approximate coupled cluster method (RI-CC2)<sup>50–53</sup> with augmented def2-TZVPP basis-sets on the DFT-D3-B-LYP/def2-TZVP optimized structures (Figure 3a). An excellent reproduction of the experimental CD spectrum of PCB-183, in both excitation energy and rotational strength, was achieved by this state-of-the-art theoretical method, allowing us to directly assign the absolute configuration of the first elute from the chiral HPLC column as aS or *P*, which turned out to elute as the first fraction also in the chiral GC/MS analyses (Figures S1 and S4 in the Supporting Information). Although the calculated CD spectrum nicely reproduced the trisignate CEs observed at the main band, a closer inspection of the

theoretical result (see the bar spectrum in Figure 3b) revealed that the observed CD spectrum is a consequence of overlapping (more than 10) same/oppositely signed transitions, which are not readily assignable. The theoretical calculation also reproduced correctly the bisignate CE at longer wavelengths, which is composed of only two transitions, but the configuration analysis revealed that the nature of the transitions is quite intricate.

Direct comparison of the experimental and theoretical CD spectra of PCB-171 and -132, shown in Figure 4 (and Figure S3 in the Supporting Information), allows us to unambiguously assign the absolute configurations of the first-eluted enantiomers of these two PCBs as *aS* or *P*. It should be noted that first elutes from our HPLC became the second elutes in the GC–HRMS/MS analysis for PCB-171 and -132 (Figure S1, Supporting Information). It is interesting to note that enantiomeric PCB-171 and -132 also exhibit strong trisignate CEs at the main band but inverted in sign (negative-positive-negative) despite the same *aS/P* configuration. This is presumably due to the biphenyl's electric/magnetic dipole moments altered by the substitution pattern. The second CEs at longer  $\lambda$  tend to be split to a pair of transitions in experiment. The negative CEs at longer  $\lambda$  were the same in sign with that of PCB-183, which was nevertheless very well reproduced by theory. The apparently broad CE at this band was actually composed of two negative rotational contributions, as judged from the configurational analyses.

Specific rotation ( $[\alpha]_D$ ) sometimes plays a supplementary role in determining absolute configuration of chiral molecule.<sup>54,55</sup> Hence, the experimental  $[\alpha]_D$  of enantiomeric PCB-183, -171, and -132 measured in hexane were compared with the corresponding values calculated by the TD-DFT method.<sup>56</sup> As shown in Table 1, the signs of  $[\alpha]_D$  were correctly

**Table 1. Experimental and Theoretical Specific Rotations ( $[\alpha]_D$ ) of (*aS/P*)-enantiomers of PCB-183, -171, and -132<sup>a</sup>**

PCB	Experimental ( <i>c</i> ) <sup>b</sup>	theoretical		
		BH-LYP/ augT	BH-LYP/ augD	B3-LYP/ augD
183	$-15 \pm 3$ (0.013) <sup>c</sup>	-4.9	-4.7	-6.2
171	$+44 \pm 6$ (0.0052) <sup>d</sup>	+38	+38	+46
132	$+39 \pm 15$ (0.0020) <sup>e</sup>	+52	+51	+62

<sup>a</sup>Specific rotation at sodium-D line (589 nm) in deg cm<sup>3</sup> g<sup>-1</sup> dm<sup>-1</sup>. The theoretical values were calculated for (*aS/P*)-enantiomers by the TD-DFT method with B3-LYP or BH-LYP functional by using Dunning's aug-cc-pVDZ (augD) or aug-cc-pVTZ (augT) basis-set. <sup>b</sup>Experimental  $[\alpha]_D$  of the first-eluted enantiomers on chiral HPLC; measured in *n*-hexane at 25 °C. Concentration (*c*) in g/100 mL. <sup>c</sup>Original  $[\alpha]_D$  was obtained for an 88% ee sample and the value was corrected for the enantiomeric excess (ee).  $[\alpha]_D = +(8 \pm 2)$  (*c* 0.021) was obtained for the 84% ee sample of the (*aR/M*)-enantiomer. <sup>d</sup> $[\alpha]_D = -(32 \pm 4)$  (*c* 0.010) was obtained for the 90% ee sample of (*aR/M*)-enantiomer. <sup>e</sup> $[\alpha]_D = -(31 \pm 8)$  (*c* 0.0036) was obtained for the 71% ee sample of (*aR/M*)-enantiomer.

reproduced and the absolute values were in modest agreement with the theoretical ones within the relatively large experimental error (due to the limited availability) in all the examined cases, supporting the above CD spectral assignments.

Atropisomeric PCBs in environmental biota are often nonracemic, indicating the existence of stereoselective biotransformation/accumulation.<sup>10</sup> Hence, the chiral analysis of PCBs provides indispensable insights into biological and

environmental processes for these legacy pollutants. Among the five atropisomeric heptachlorinated biphenyls, PCB-175 and -176 were not contained in the manufactured PCBs and therefore barely found in air or biological samples. In contrast, PCB-174 and -183 are the main components (among heptachlorinated biphenyls) found in air samples, and the latter is the only congener found in biological samples.<sup>23,25</sup> Our study allowed us to assign the absolute configuration of the first elute of PCB 183 from chiral HPLC (Chiralcel OJ-H; based on cellulose tris(4-methylbenzoate)) and GC (BGB Analytik BGB-172; based on *tert*-butyldimethylsilyl  $\beta$ -cyclodextrin) as *aS/P*. This reveals that (*aR/M*)-(*+*)-PCB-183 is enriched indeed (in ca. 40% ee) in adipose tissue (Figure S4, Supporting Information),<sup>57</sup> as a consequence of the combined effect of enantiomeric accumulation through food chain and the enantioselective metabolism of racemic PCBs. The bio/environmental origins of enantiomerically enriched PCBs are remained to be elucidated by further biological and toxicological studies.

## EXPERIMENTAL DETAILS

The circular dichroism (CD) spectra were measured in a conventional quartz cell (path = 1 cm) fitted with temperature controller under the following conditions: bandwidth, 2 nm; scan rate, 100 nm min<sup>-1</sup>, response, 4 s; accumulation, 4 times; data interval, 0.5 nm. Aqueous solution of (+)-ammonium camphorsulfonate-*d*<sub>10</sub> (0.06%) was used for a calibration of the spectrometer sensitivity and wavelength ( $\theta = 0.1904^\circ$  at 290.5 nm). The three PCBs were purchased from AccuStandard [Lot #960607LB-AC (PCB-183), #041993 (PCB-171), #081706MT-AC (PCB-132)]. The concentrations of PCB solutions were calculated using  $\epsilon_{209} = 73000$  (for PCB-183),  $\epsilon_{208} = 80800$  (for PCB-171), or  $\epsilon_{205} = 58400$  M<sup>-1</sup> cm<sup>-1</sup> (for PCB-132), respectively. The spectra were combined for data with two different concentrations to adjust detection limit: 0.2  $\mu$ M for main band region (185–255, –260, and –240 nm for PCB-183, -171, and -132, respectively) and 1.0  $\mu$ M for the longer wavelength region. HPLC analyses were performed with Daicel Chiralcel OJ-H (4.6 mm i.d.  $\times$  15 cm) using *n*-hexane as eluent with a flow rate of 0.5 mL min<sup>-1</sup> at 38 °C (Tosoh CO-8020, Shimadzu LC-10AT). The absolute configuration of the first elute was assigned as *aS/P* by comparison with theoretical one (*vide supra*). The adipose tissue sample was obtained after receipt of written informed consent. About 2 g of sample was added to cleanup spike solution (2.5 mL of diethyl ether and 5 mL of ethanol) and was extracted twice with 10 mL of *n*-hexane. The combined extract was purified by passing through double layer column (1 g of florisil and 1 g of silica gel, Supelco), eluted with 15 mL of 15% diethyl ether/*n*-hexane solution. This was concentrated to ca. 0.1 mL under a gentle stream of nitrogen, and syringe spike solution was added into this concentrated sample. The combined sample was then analyzed as follows.<sup>58</sup> The enantiomeric excess of PCB-183 in human sample was determined by chiral GC–HRMS/MS using BGB-172 column (30 m  $\times$  0.25 mm i.d., film thickness = 0.25  $\mu$ m, BGB Analytik AG) using helium as carrier gas (JEOL JMS-800D). The injector and transfer line temperatures were 230 and 245 °C, respectively, and the column temperature was initially kept at 120 °C, which was increased to 180 °C (at a rate of 4 °C min<sup>-1</sup>) and then to 230 °C (1 °C min<sup>-1</sup>), and kept at this temperature for 10 min. The ion source was operated in the electron-impact mode (EI, 38 eV, 250 °C). The first fraction in this GC–HRMS/MS analysis for PCB-183 was

again assigned as aS/P, but the absolute configurations of first fractions for PCBs 171 and 132 in GC–HRMS/MS were determined as aR/M. The first elutes in GC–HRMS/MS always possess negative optical rotations at the sodium-D line.

## THEORETICAL CALCULATIONS

All calculations were performed on Linux-PCs using the TURBOMOLE 6.3 program suite.<sup>59</sup> Geometries of PCBs were optimized at the DFT-D3-B-LYP/def2-TZVP level<sup>45,46</sup> (H, [3s1p]; C, [5s3p2d1f]; Cl, [5s5p2d1f]) with numerical quadrature grid m5. The resolution of identity (RI) approximation was employed in all calculations,<sup>60</sup> and the corresponding auxiliary basis sets were taken from the TURBOMOLE basis-set library. The convergence criterion for the optimization regarding the change of total energy between two subsequent optimization cycles was set to  $10^{-7}$  E<sub>h</sub>. All excited-state calculations were performed with the optimized ground-state geometries of aS/P atropisomers and were calculated by the resolution of the identity, time-dependent approximate coupled cluster (RI-CC2) method<sup>50–52</sup> with the basis sets of aug-def2-TZVPP quality. (H, [4s3p2d]; C, [6s4p3d2f]; Cl, [6s6p4d2f]). A prefix aug denotes adding of the diffuse spd functions taken from the Dunning's correlation consistent aug-cc-pVTZ basis-set to more accurately describe Rydberg and related states.<sup>61</sup> The spectra of PCB-183 were also compared with those calculated at the nonaugmented RI-CC2/def2-TZVPP level. The spectra obtained with the latter basis sets provided a similar pattern in the predicted CD with those obtained using aug-TZVPP basis sets, but with slight shifts in rotational strengths and excitation energies (Figure S2b in the Supporting Information). Thus, the spectra at the RI-CC2/aug-def2-TZVPP level were reported in the main text. The UV and CD spectra were simulated by overlapping Gaussian functions for each transition from the length-gauge representations where the width of the band at 1/e height is fixed at 0.4 eV. Due to the systematic errors of the theoretical transition energies compared to the experimental ones, the spectra were uniformly red-shifted by 0.3 or 0.4 eV.<sup>62–65</sup>

## ASSOCIATED CONTENT

### Supporting Information

Details of experimental CD spectra, enantiomeric analyses, and theoretical calculations for PCBs. This information is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [tmori@chem.eng.osaka-u.ac.jp](mailto:tmori@chem.eng.osaka-u.ac.jp).

### Notes

The authors declare no competing financial interest.

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