Chirality induction by *E*-*Z* Photoisomerization in [2,2]paracyclophane-bridged Azobenzene Dimer

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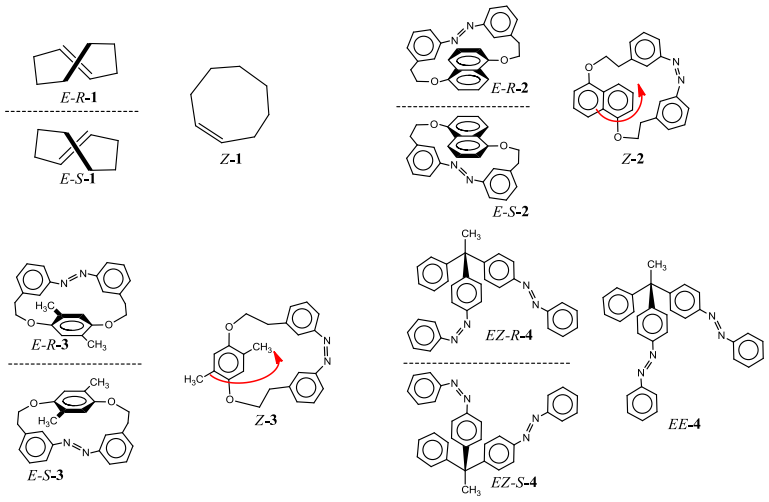
Abstract: We designed and synthesized a new prochiral molecule in which two azobenzene moieties were embedded in [2,2]paracyclophane and showed the chirality induction by *E*-*Z* photoisomerization. We also demonstrated the on/off switching of asymmetry by irradiation and reflux respectively.

Keywords: [2,2]paracyclophane, Azocompounds, Circular dichroism, Planar chirality.

Geometric (*E* and *Z*) and stereo (*R* and *S*) isomerisms are usually independent elements of molecular structures, but sometimes they are related to each other. In 1963 Cope et al. showed that *E*-cyclo-octene **1** giving an 8-shaped three-dimensional structure exhibits *R* and *S* enantiomers, while does not *Z*-cyclo-octene due to its planar ring structure (Scheme 1).[1] This means the geometric isomerization affect to the presence of

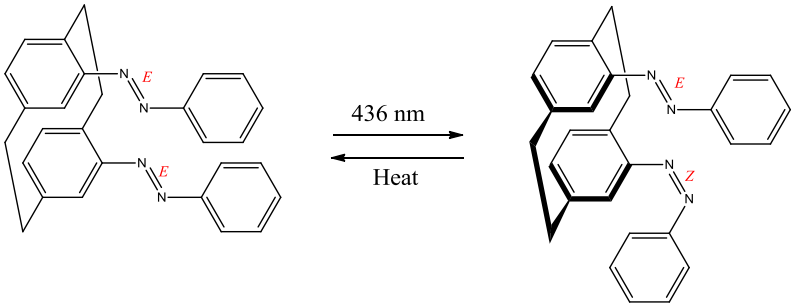
asymmetry. We have also introduced new molecules showing a different stereo isomerism depending on the geometric isomerism of the azobenzene unit in the molecules. Compounds **2**[2] and **3**[3] with the *E*-state of azobenzene shows stable and resolvable enantiomers due to their planar chiral nature of the molecules, while fast racemization originated from the rotation of the included naphthalene or dimethyl benzene rotors at room temperature disturb the isolation of enantiomers in *Z*-state. In 2011 we succeeded in the optical resolution of enantiomers of the *EZ*-isomer of **4** which is non-chiral in *EE*- and *ZZ*-states.[4] In our design the two azobenzene moieties were connected to a common SP3 carbon atom substituted with phenyl and methyl groups. The conformational difference caused by the *E*-*Z* photoisomerization of one of the azobenzene moieties was successfully utilized for the chirality induction in a point chiral molecule. With these new molecular designs the presence of stereo isomers is



Scheme 1: Chemical structures of ever known compounds showing distinct relationship between geometrical and stereo isomerisms.

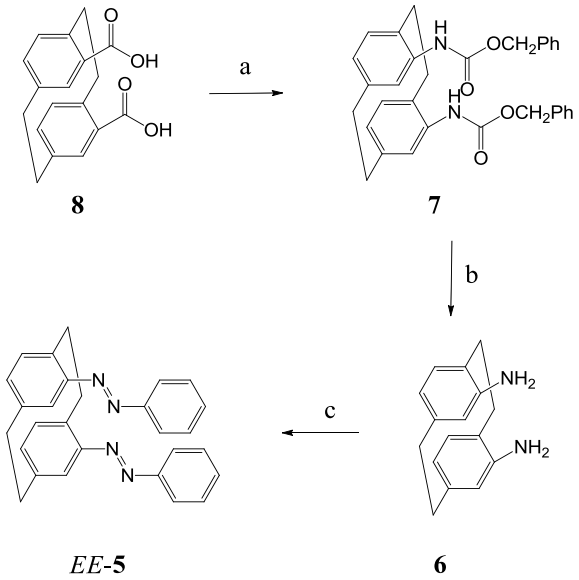
again determined by the geometric isomer states of azobenzene unit(s). One important feature in these works using azobenzene derivatives is that the photo-reversible nature of azobenzene using near UV and blue light irradiation enable us to switch reversibly the stereo isomeric property of the molecules between chiral and non-chiral just by wavelength-selective irradiations.

In this letter we introduce another design using a planar chirality of the substituted [2.2]paracyclophane for switching chirality of molecules by *E-Z* isomerization of azobenzene. We showed the synthesis and photo-stimulated chirality induction in the new prochiral molecule where on light irradiation chirality induction by *E-Z* isomerization generated planar chirality in the molecule and the corresponding enantiomers were well separated in HPLC with distinguished, opposite cotton effects. Moreover, on refluxing the irradiated sample initial symmetric structure was reproduced (Scheme 2).



Scheme 2: Schematic representation showing asymmetry introduction by *E-Z* photoisomerization.

The [2,2]paracyclophane-4,15-diamine **6** synthesized from [2,2]paracyclophane via [2,2]paracyclophane-4,15-dicarboxylic acid **8** by a reported procedure with a slight modification[5] was reacted with nitrosobenzene to obtain the compound *EE*-**5** (Scheme3). Experimental details and spectroscopic data (^{1}H NMR, ^{13}C NMR) are shown in supporting information.



Scheme 3: The preparation of ***EE*-5**; a) DPPA, Et_3N, PhCH2OH, Toluene, heat, 80^{o} C,

25 h.; b) EtOH, KOH, refl., 47 h.; c) PhNO, CH_3COOH, 48 h.

To investigate the photochemical isomerization of azobenzene part in the compound UV/Vis spectroscopy were carried out at room temperature. Figure 1 shows the absorption spectra of **5** in acetonitrile upon irradiation with light of wavelengths 366 and 436 nm. The irradiation at 366 nm caused a gradual decrease in the intensity of the π-π∗ transition band at 324 nm, with a notable increase in the n-π∗ transition band at 420-550 nm due to photochemical *E-Z* isomerization of the azobenzene moieties. The reversal spectral changes were observed upon irradiation with 436 nm. The seeming

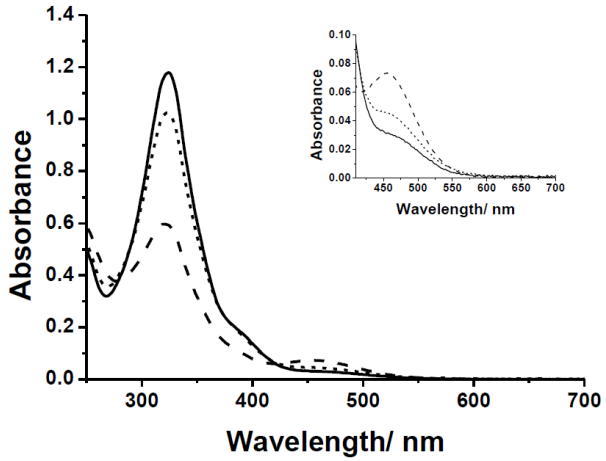


Figure 1: Absorption spectra of **5** in acetonitrile solvent; before irradiation (solid line), at 366nm (dashed line) and at 436 nm (dotted line) photostationary states at room temperature. An enlarged view of n-π∗ band is shown in the inset. The concentration of solution was 6.02 x 10^{-5} mol L^{-1}.

isobestic points observed at 278 nm and 423 nm are indicative of almost independent conversion among three isomers i.e. *EE*, *EZ* and *ZZ* with *E-Z* photoisomerizations of azobenzene moieties. The photostationary states (PSS) were attained in less than 100 seconds by irradiation at 366 nm or 436 nm, while the thermal back isomerization from *ZZ* to *EE* was quite slow and found to occur over one week.

The first insight into the chiral nature of the molecule was obtained from the chiral HPLC studies. The HPLC trace for the compound **5** before irradiation showed a single peak at retention time (Rt) = 28.01. The irradiation of **5** at 366 nm generated three new peaks at Rt = 30.52, 34.13 and 78.45 in addition to the initial peak. The irradiations with light of wavelength 436 nm to the solution at 366 nm PSS resulted the increased intensity of first peak with almost diminished fourth peak maintaining second and third peaks (Figure 2). The intensity of second and third peaks changed during irradiations but they remained equal in intensity to each other. Basically, in the normal phase HPLC including chiral HPLC polar *Z* azobenzene derivative elutes slower than corresponding *E* isomer.[4, 6] Since the *E* isomer of azobenzene derivative is thermodynamically stable,[6]

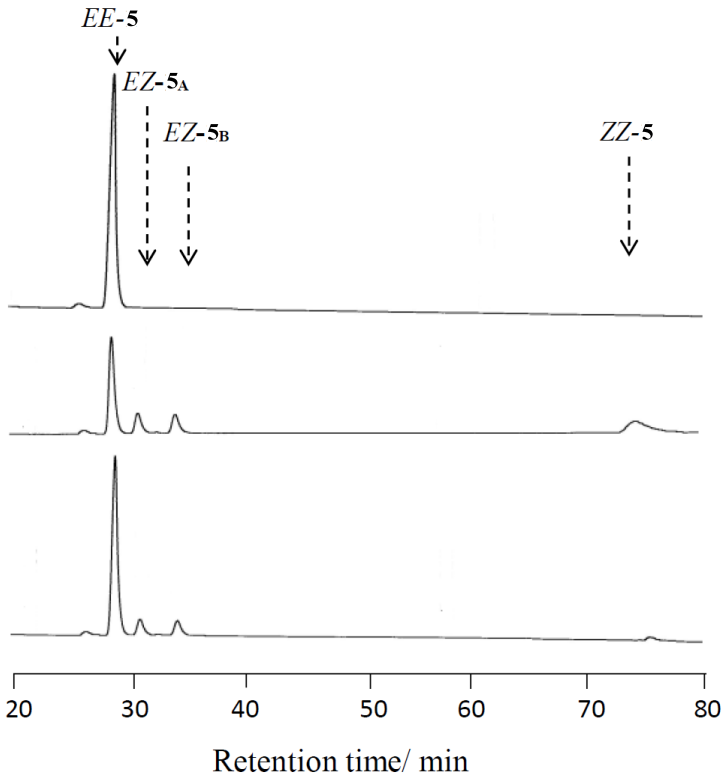


Figure 2: Chromatogram of *EE*-**5** before irradiation (top), the PSS after irradiation at 366 nm (middle) the PSS after irradiation at 436 (bottom) obtained by chiral HPLC with a solvent combination of 10: 90 (Isopropanol: Hexane), flow rate at 1 mL min^{-1}.

before irradiation the compound should exist as *EE* isomer. From the above information and the obtained results the second and third HPLC peaks can be assigned as enantiomers of *EZ*-**5**. Hence from the HPLC studies of the compounds **5**, initial proof for the chiral nature of the compound which resulted from chirality induction after suitable wavelength irradiation was observed.

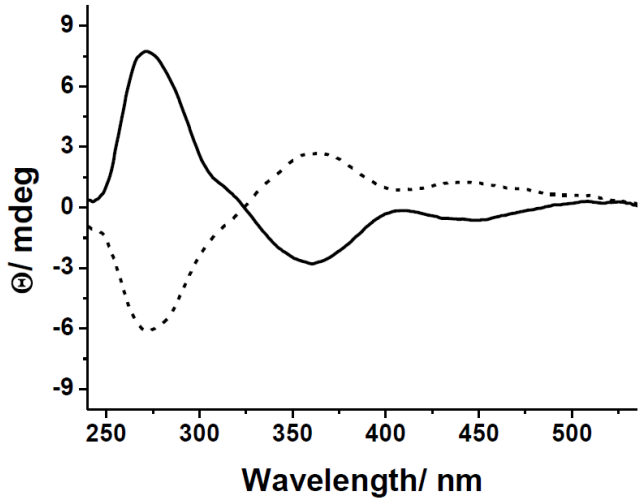


Figure 3: CD Spectra of enantiomers of *EZ*-**5** in isopropanol; first eluted enantiomer, *EZ*-$\mathbf{5_A}$ (dotted line) and second eluted enantiomer *EZ*-$\mathbf{5_B}$ (solid line). The concentration of the solution was 3.90 x 10^{-4} mol L^{-1}.

In order to further assign the HPLC peaks we isolated the second and third portions of HPLC chromatogram preparatively and measured the CD spectra. The CD spectrum of second eluted fraction of **5** in isopropanol solvent shows one nagative (270 nm) and two positive bands (at 360 nm and 450 nm), and the mirror image spectrum was observed in the case of third fraction (Figure 3).

From the results of HPLC and CD, we could unambiguously assign the first peak in HPLC as *EE*-**5**, where both the azobenzene units are in *trans* state, while the second and third peaks as *EZ*-$\mathbf{5_A}$ and *EZ*-$\mathbf{5_B}$ with one azobenzene unit is in *trans* and the other in *cis* state but with opposite stereo-structure. The fourth peak in HPLC

chromatogram can be assigned as *ZZ*-**5**, where both the azobenzene units are in *cis* state. Hence it is clear that the regio-structural difference in the substituents generated by the *E-Z* photoisomerization of one of the azobenzene moieties caused the chirality induction in [2,2]paracyclophane which resulted separable enantiomers with detectable difference in CD spectra.

We investigated switching between symmetric and asymmetric structures of **5**. As we discussed earlier upon irradiation with 366 or 436 nm, chromatograms corresponding to enantiomers of *EZ*-**5** were generated. After refluxing the same sample for 1 hour in isopropanol solvent, the peaks corresponding to *EZ*-**5** were completely disappeared and the peak for *EE*-**5** was regenerated **(**for chromatogram see supporting information**)**. Moreover this ON-OFF switching of asymmetry was entirely reproducible at least for three cycles. In this study the amount of induced asymmetry species (ratio of *EZ* with respect to initial *EE*) was estimated to be 12 % for **5** as calculated for the concentration of *EZ*-**5** isomer obtained after irradiation at 436 nm in the HPLC chromatogram.

In conclusion, we have designed and synthesized a novel prochiral molecule in which two azobenzene moieties were embedded in [2,2]paracyclophane. On 366 or 436 nm wavelength irradiation, *E-Z* photoisomerization of one of the azobenzene moieties

turned to produce a difference in substituents on the [2,2]paracyclophane and thus planar chirality was generated as a result of chirality induction in the compound **5**. Moreover *Z*-*E* thermal isomerization regenerated initial symmetric molecule and this on/off switching of the asymmetry was repeatedly accomplished by light and heat respectively. It is expected that this method could be used as photoswitchable chirality induction by circular polarized lights to enrich one of the enantiomers of **5**.[3] Such a photoisomerization favoring one of the enantiomers as a product at PSS is under investigation.

Acknowledgment

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Supplementary data

Supplementary data (Synthetic procedures, NMR and HPLC profile) associated with this article can be found, in the online version,

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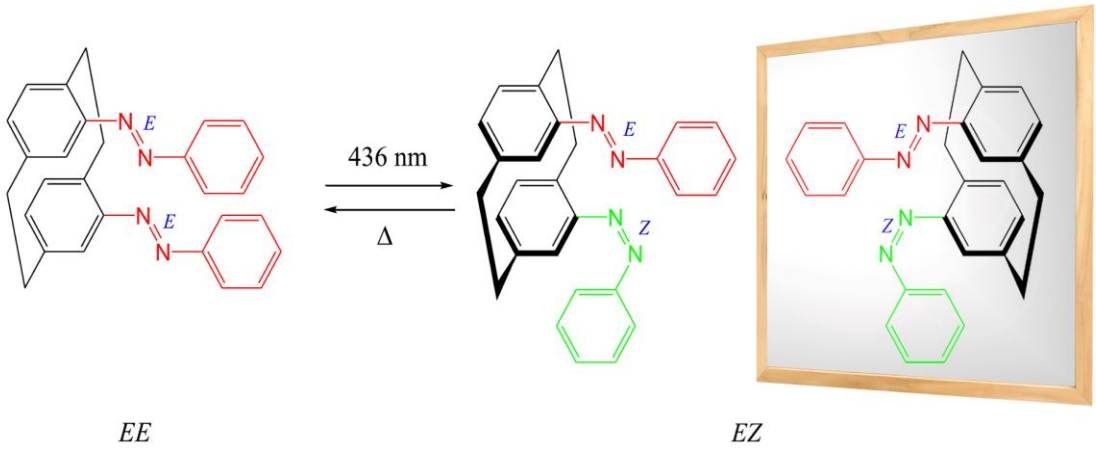
Graphical Abstract



EE *EZ*

Supporting Information

Chirality induction by *E*-*Z* Photoisomerization in [2,2]paracyclophane-bridged Azobenzene Dimer

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General Introduction

Unless otherwise noted, all reagents including solvents were obtained from major commercial suppliers such as TCI, Sigma-Aldrich and Wako used directly without further purification. Thin layer Chromatography and Column chromatography were performed with silica sheet and silica gel (6-21 mm).

^{1}H NMR spectra were recorded on a JEOL ECX 400 spectrometer using tetramethylsilane as an internal standard. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) was performed on an Applied Biosystems Voyager-DE pro instrument. Absorption spectra were recorded on an Agilent 8453 spectrophotometer. CD spectra were recorded on a JASCO J-S720 spectrophotometer. Photoisomerization studies were conducted using radiation from a super-high-pressure mercury lamp (500W, USHIO Inc.) or mercury-Xenon lamp (Hamamatsu photonics K.K 200W) after passage through appropriate filters (366 or 436 nm). High-pressure liquid chromatography (HPLC) was conducted on a Hitachi Elite La Chrome HPLC system using a CHIRALPAK IB (DAICEL Chemical Industries Ltd.) to separate the enantiomers and analyze the *E-Z* and enantiomer ratio. The mixture of isopropanol and hexane with ratio of 10:90 was used as an eluent for the HPLC experiments. *E-Z* isomer ratio at photo stationary states was determined by NMR or

HPLC monitored at common isosbestic point, 278 nm.

Synthesis

[2.2]Paracyclophane-4,15-dicarboxylic Acid (8) was prepared according to the procedure of Psiorz and Schmid.[1] ^{1}H NMR (400 MHz, DMSO-d_6, 25^o C): δ = 7.02 (d, 2H), 6.64−6.71 (dd, 2H), 6.64 (d, 2H), 4.03-4.07 (dd, 2H), 3.04 (s, 4H), 2.91-2.96 (dd, 2H).

Compound 7; To the compound **8** (500 mg, 1.69 mmol) taken in round bottom flask added diphenylphosphoryl azide (DPPA) (928 mg, 3.37 mmol), triethyl amine (343 mg, 3.37 mmol), benzyl alcohole (365 mg, 3.37 mmol), toluene (10 mL) and stirred for 24 h at 80^o C. Evaporated the solvent and carried out column chromatography and recrystallized from ethanol. ^{1}H NMR (400 MHz, acetone-d_6, 25^o C): δ = 8.15 (br-s, 2H), 7.32-7.38 (m, 10H), 6.58 (d, 2H), 6.56 (d, 2H), 6.45-6.47 (dd, 2H), 5.21 (d, 2H), 5.04 (d, 2H), 3.41-3.46 (m, 2H), 2.97-3.05 (m, 4H), 2.84 (d, 2H).

[2.2]Paracyclophane-4,15-diamine (6): Compound **7** was suspended in 20 mL of ethanol and heated under reflux for 2 h. Aqueous KOH (20%, 2 mL) was added to the reaction mixture and heated under reflux for another 45 h. The cooled reaction mixture was poured into 25 mL of ice-cold KOH solution (20 %) and the light brown colored

precipitate formed was filtered through a glass filter. the filtrate was concentrated in a rotory evaporator yielding additional product. The combined precipitate was washed with water and dried to provide 17 as a colored product (81 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25^{o} C): δ = 6.52-6.51 (d, 2H), 6.33-6.31 (d, 2H), 6.20 (d, 2H), 4.30 (br-s, 4H), 4.19-4.16 (m, 2H), 3.84-3.74 (m, 6H).

Compound *EE*-5: To a solution of **6** (100 mg, 0.42 mmol) in acetic acid (10 mL) nitrosobenzene (179.83 mg, 1.68 mmol) was added and the reaction mixture was stirred for 48 hour at room temperature. The reaction mixture was extracted with dichloromethane, washed with water and brine, dried over Mg_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane/AcOEt as eluent to give ***EE*-5** (4 mg, 3%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$, 25^{o} C): δ = 7.53-7.50 (d, 4H), 7.21-7.11 (m, 6H), 6.81-6.74 (m, 6H), 4.50-4.45 (d, 2H), 3.23-3.16 (m, 6H).

NMR Spectra

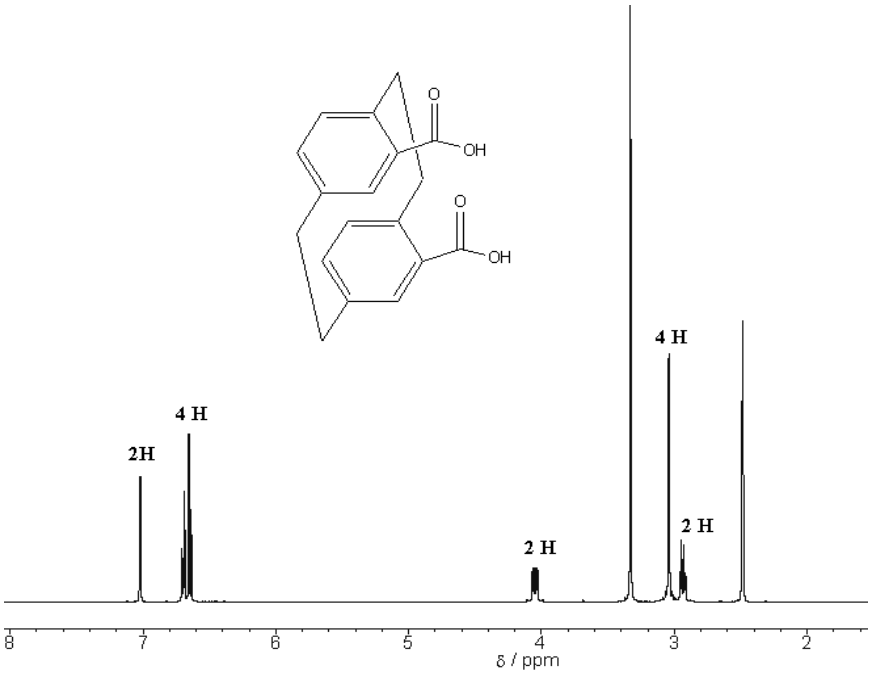

Figure S3: ^{1}H NMR Spectra of compound **8** in DMSO-d_6 at room temperature.

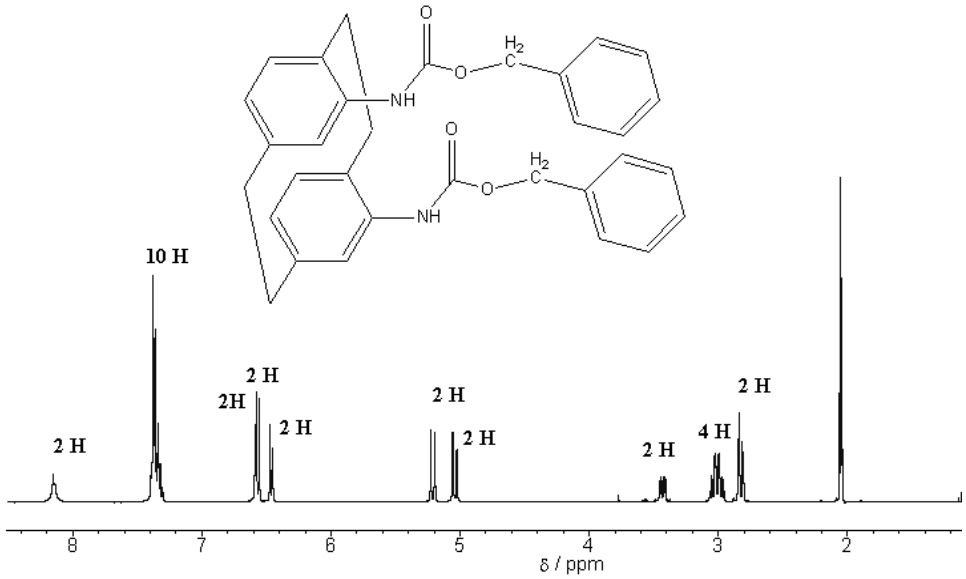

Figure S4: ^{1}H NMR Spectra of compound **7** in acetone-d_6 at room temperature.

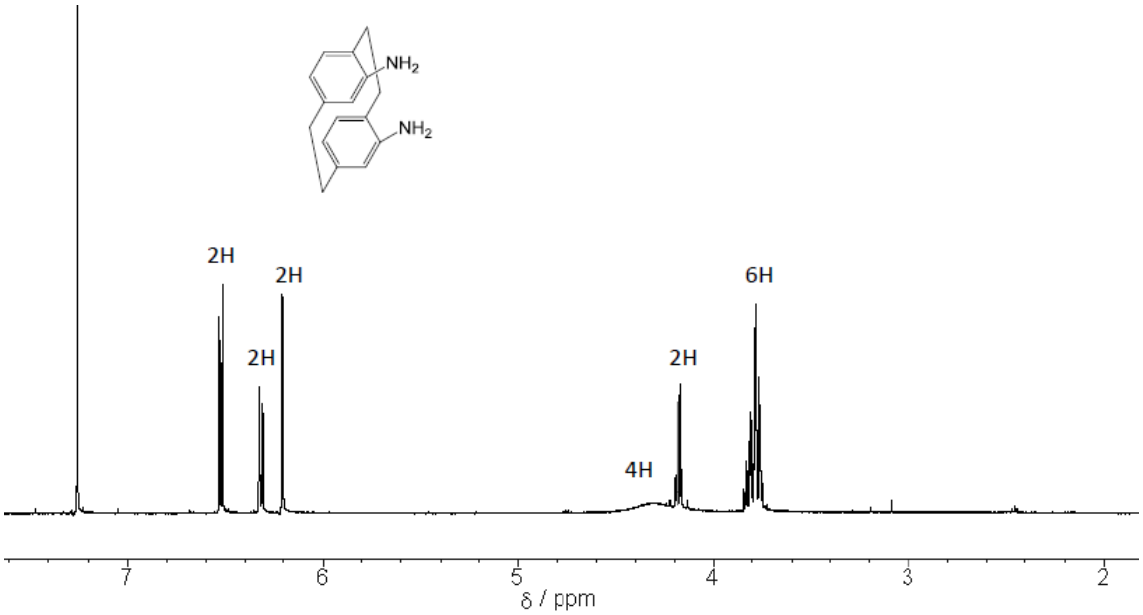

Figure S5: ^{1}H NMR Spectra of compound **6** in $CDCl_3$ at room temperature.

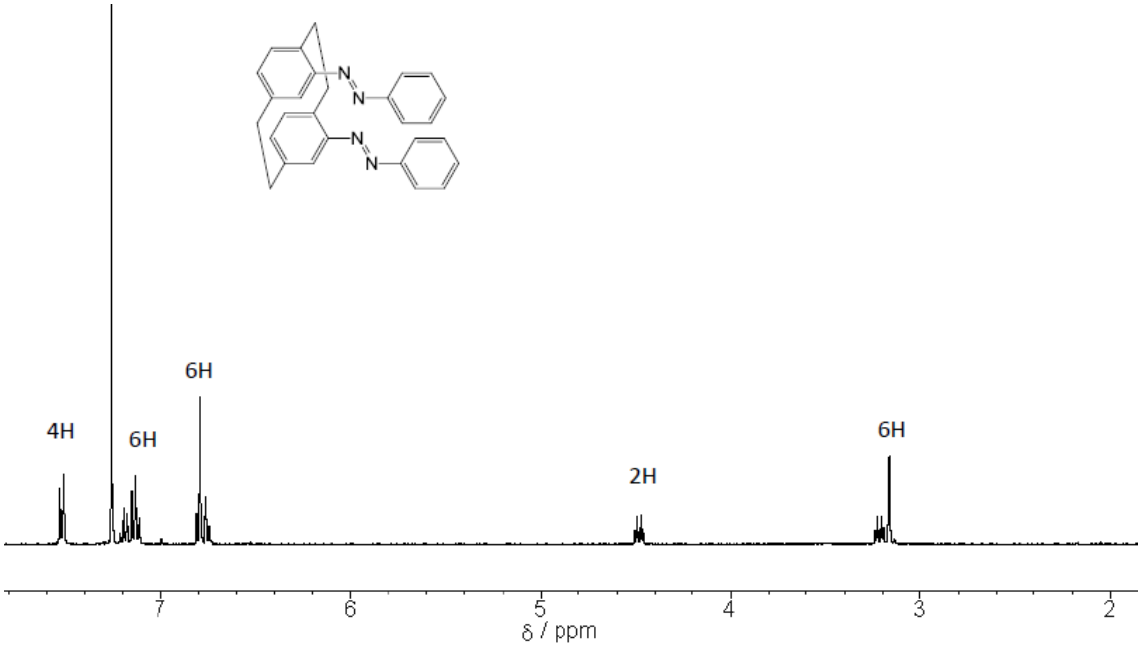

Figure S6: ^{1}H NMR Spectra of compound **5** in $CDCl_3$ at room temperature.

HPLC Chromatogram

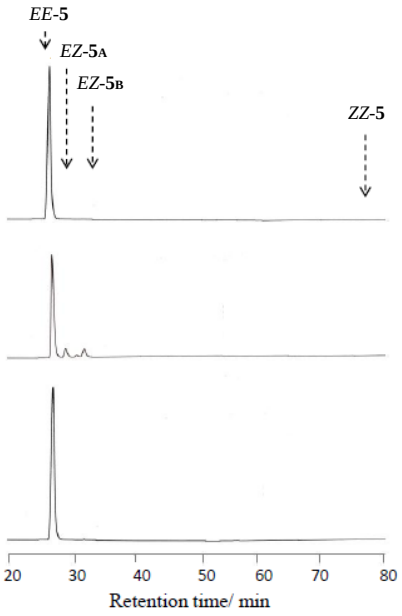

Figure S7: Chromatograms of **5,** before irradiation (top), the PSS after irradiation at 436 nm (middle), reflux in isopropanol solvent (bottom) (asymmetry switching cycle). The ratio of the asymmetric species, *EZ*-$\mathbf{5}_A$ and *EZ*-$\mathbf{5}_B$, formed at the 436 nm PSS was 12 % of the initial *EE*-**5**.

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