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Synthesis, structure, and chirality of hydroxyl- and carboxyl-functionalized cubane-like photodimers of 2-naphthalene

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Abstract—Two novel hydroxyl- and carboxyl-functionalized cubane-like photodimers from methyl 2-naphthoate have been successfully achieved under mild conditions. X-ray crystal structures confirm that the cubane-like structure is well retained in these two derivatives and the intermolecular O−H···O hydrogen bonding plays an important role in crystal packing. It is of significance that the isolated racemic mixture can be subsequently resolved into two optically pure enantiomers by high-performance liquid chromatography.

1. Introduction

Since Kagan and Dang declared the first C_2 chiral ligand of diop in 1970s,[1] an explosive growth in this field has been documented and a large number of chiral ligands with C_2 axis appear.[2] The design of new chiral ligand has been known to be of great importance with the development of both asymmetric synthesis and self-assembly.[2,3]

Very recently, we reported a new type of C_2-symmetric chiral compound—photodimer **1** of methyl 2-naphthoate,[4] which was synthesized simply by photoirradiation of methyl 2-naphthoate in degassed cyclohexane solution with a light of wavelength longer than 280 nm. Crystal analysis confirms that the methyl carboxylate functionality is in an *anti*-head-to-head conformation and the cubane-like structure is highly rigid. Particularly, the isolated racemic mixture of **1** can be resolved into its optically pure enantiomers by HPLC.

To expand the scope of this C_2 chiral compound, functional groups are expected to introduce into the skeleton. In this regard, there are two approaches generally involved: (1) direct irradiation of the corresponding functional group-substituted naphthalene; (2) derivation of the cubane-like photodimer **1** of methyl 2-naphthoate by thermo-chemical approach. It has been known that irradiation of alkyl 2-naphthoate results in a 'cubane-like' *anti*-head-to-head photodimer, while other functional group-substituted naphthalene may not give the unique ring system by direct photoirradiation approach.[4–11] Though the first photodimer in naphthalene series was discovered 40 years ago,[12] only a few examples related to the cubane-like skeleton have been reported so far.[4–11] Alternatively, the functionalization of the cubane-like photodimers from alkyl 2-naphthoate derivatives obtained has never been reported. The reason may be due to the fact that the cubane-like photodimer is very sensitive toward heat or acid. Despite this, interest in chirality of the functional group-substituted cubane-like photodimers prompts us to carry out such a kind of derivation. It is anticipated that the photodimer of methyl 2-naphthoate (**1**) could be subsequently reduced or hydrolyzed to its corresponding hydroxyl- or carboxyl-substituted derivatives, respectively.

In the present work, we report that we are able to functionalize the cubane-like photodimer **1** to **2** and **3** in high yield under mild conditions (Scheme 1). Crystal structures demonstrate that the cubane-like skeleton is well retained. Similar to compound **1**, both the compounds **2** and **3** have the C_2 axis and their mirror images cannot overlap with each other. The intermolecular O−H···O hydrogen bonding directs the two enantiomers packing in one-dimensional assemblies. More importantly, the optically pure enantiomers of **2** and **3**, were achieved by HPLC resolution. Compared with photodimer **1** of methyl 2-naphthoate, hydroxyl- and carboxyl-functionalized cubane-like photodimers **2** and **3** are ready to be linked to an active species for the further studies in the area of asymmetric catalysis or chiral assembly.

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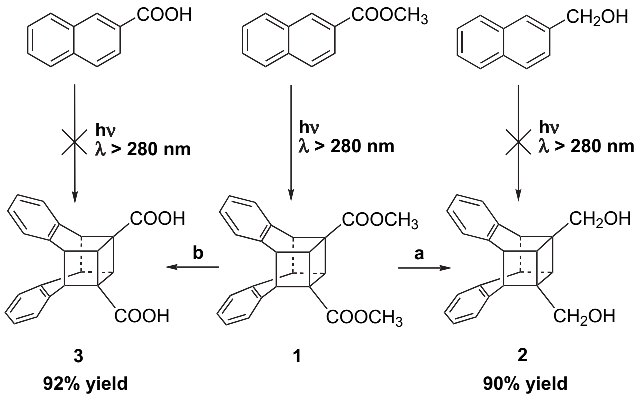

Scheme 1. The synthetic routes of compounds **2** and **3**. Reagents and conditions: (a) $LiAlH_4$ (4 equiv), dry Et_2O, reflux 12 h; (b) 6.25 mol/L KOH in the mixed solution of methanol and water (v/v: 3/1), reflux 3 h.

2. Results and discussion

2.1. Synthesis

Irradiation of 2-naphthylmethanol or 2-naphthalenecarboxylic acid in degassed cyclohexane solution with a light of wavelength longer than 280 nm for 8 h failed to give any photoproducts that may isolate (Scheme 1). This indicates that hydroxyl- and carboxyl-functionalized cubane-like photodimers of **2** and **3** cannot be prepared in a similar way as that of methyl 2-naphthoate (**1**).[4] Therefore we are interested in the functionalization of **1**, which can be prepared in high yield upon irradiation, in terms of thermo-chemical approaches.

Successfully, we can reduce compound **1** to its corresponding hydroxyl-functionalized cubane-like **2** using $LiAlH_4$, AlH_3, $LiBH_4$, and $Al(BH_4)_3$, in which $LiAlH_4$ gave the best performance. Typically, a solution of $LiAlH_4$ and **1** in dry diethyl ether was refluxed for 12 h and then quenched with ethyl acetate and NH_4Cl aqueous solution at 0 °C. Crystallization of the crude product from dichloromethane–methanol solution gave a cubane-like photodimer **2** in colorless block with 90% yield, mp 185–190 °C (decomp.). The synthetic routes in detail are shown in Scheme 1.

At the same time, hydrolysis reaction was used to explore the route of derivation of **1**. It was noted that compound **3** could be obtained in a reasonable yield by using Claisen base (6.25 mol/L KOH in the mixed solution of methanol and water (v/v: 3/1)). Generally, after refluxing solution at 90 °C for 3 h, the reaction was quenched with 1 N HCl at 0 °C to afford a white precipitate. Recrystallization of the precipitate from ethanol gave a cubane-like **3** in colorless block with 92% yield, mp >210 °C (decomp.). Characterization of **3** showed that the framework of cubane-like structure decomposed in a hot aqueous solution of hydrochloride acid, even in dilute solution, while it is quite stable under base condition.

The maxima of absorption wavelength of **2** and **3** (λ_{max}=268 nm, ε=590 $dm^3\,mol^{-1}\,cm^{-1}$ for **2**; λ_{max}=266 nm, ε=553 $dm^3\,mol^{-1}\,cm^{-1}$ for **3**) in acetonitrile solution are comparable with that of photodimer **1** of methyl 2-naphthoate.[4] Their MS spectrometry also establishes the dimeric nature, in which the parent ion peak occurs at 316 ($[M]^+$) for compound **2** and 343 ($[M-1]^+$) for compound **3**. Examination of non-aromatic protons of **2** and **3** in the NMR spectra revealed that the cubane-like structure remained unchanged after derivation. The coupling constants of 11.6 and 7.8 Hz, 11.6 and 8.0 Hz for skeleton in **2** and **3** are entirely consistent with the cubane-like structure presented in **1**.[4]

2.2. Crystal structural analysis

The X-ray crystal structural analysis further confirmed the rigid 'cubane-like' structure of **2** and **3**. Single crystal of $\mathbf{2}\cdot CH_3OH$ was obtained by recrystallization of **2** from dichloromethane–methanol solution. A colorless single crystal with dimensions 0.50×0.35×0.20 mm was used for data collection at 293 K on a Bruker Smart 1000 X-ray diffractometer. The crystal belongs to the triclinic crystal system of $P\text{-}\bar{1}$ space group with unit cell parameters of a=7.6315(15) Å, b=8.4911(17) Å, c=15.130(3) Å; α=87.89(3)°, β=88.28(3)°, γ=73.09(3)°. The bonding of C_1, C_4, C_5, and C_8 to C_2, C_3, C_6, and C_7, respectively, forms the cubane-like structure (Fig. 1a). The dihedral angle formed by the aromatic rings is 109.5°, and torsion angles $C_{21}-C_1-C_2-C_3$ and $C_{22}-C_3-C_4-C_1$ are opened out to

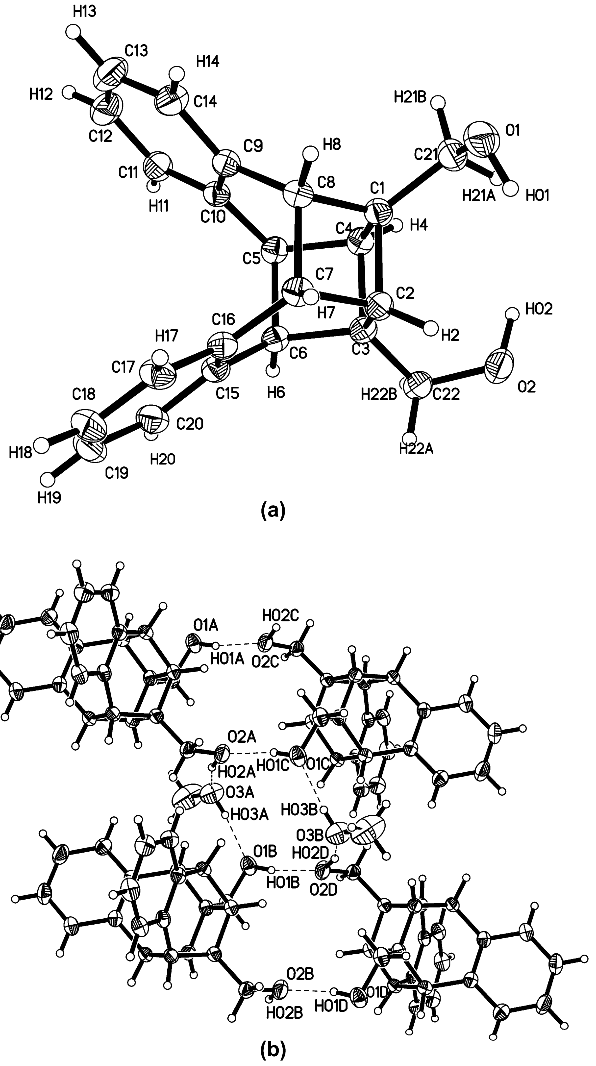

Figure 1. (a) Perspective drawing of compound **2** with atomic numbering. (b) Packing diagram of compound **2**.

about 120°. All of the features imply the C_2 axis presented in compound **2**.

Interestingly, the strong intermolecular O—H⋯O hydrogen bonding was found to direct the molecular packing. Two enantiomers of **2** interact with each other in a 'head-to-head' manner via O—H⋯O hydrogen bonding (Fig. 1b). The H⋯O distance of 1.82(3) Å in O(1A)—HO(1A)⋯O(2C) and O(1C)—HO(1C)⋯O(2A) hydrogen bonding observed is appreciably shorter than the sum of the van der Waals' radii for H (1.20 Å) and O (1.52 Å), respectively. Methanol molecules link the two molecules via hydrogen bonds of O(2A)—HO(2A)⋯O(3A)=2.724(2) Å, O(3A)—HO(3A)⋯O(1B)=2.730(3) Å and O(3B)—HO(3B)⋯O(1C)=2.730(3) Å, O(2D)—HO(2D)⋯O(3B)=2.724(2) Å, respectively, leading to infinite extending in the *a*-axis in the crystal lattice.

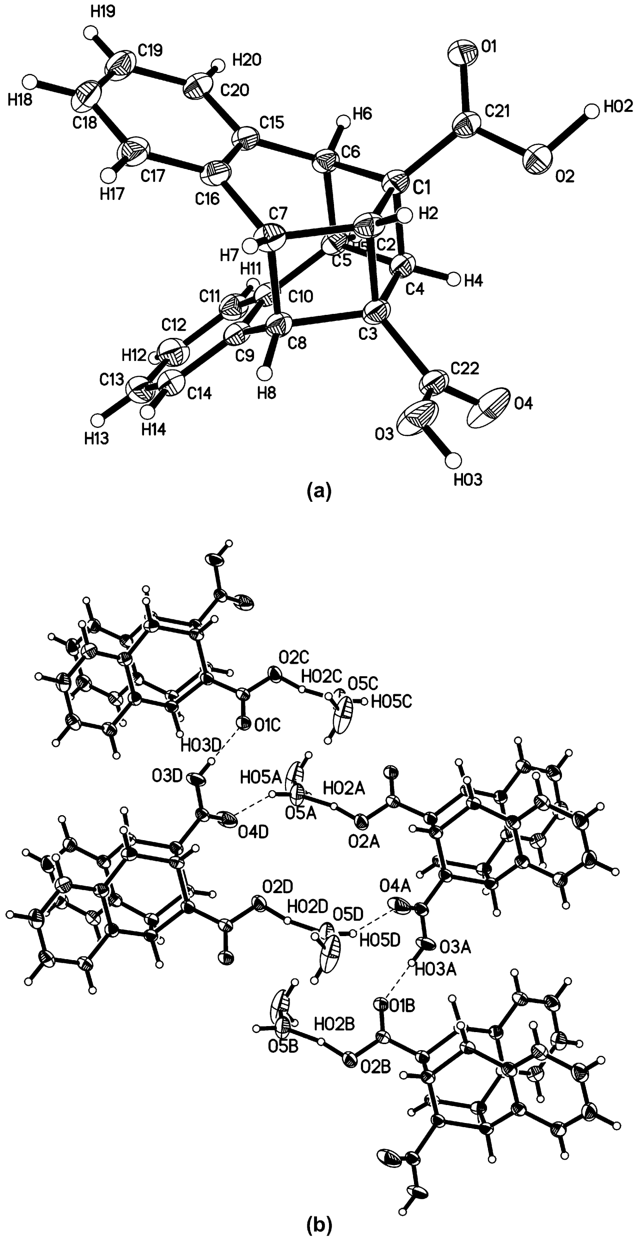

Figure 2. (a) Perspective drawing of compound **3** with atomic numbering. (b) Packing diagram of compound **3**.

Single crystal of compound $\mathbf{3}\cdot CH_3CH_2OH$ suitable for X-ray diffraction analysis was also obtained by recrystallization from ethanol solution. A colorless single crystal with dimensions 0.55×0.40×0.25 mm was used for data collection at 293 K. The crystal belongs to the triclinic crystal system of *P*-1 space group with unit cell parameters of a=8.4163(17) Å, b=9.7021(19) Å, c=13.143(3) Å; α=110.25(3)°, β=101.76(3)°, γ=98.81(3)°. The bonding of C_1, C_2, C_7, and C_6 to C_4, C_3, C_8, and C_5, respectively, forms the cubane-like structure of **3** (Fig. 2a). The dihedral angle formed by the aromatic rings is 65.5°, and torsion angles $C_{21}—C_1—C_2—C_3$ and $C_{22}—C_3—C_4—C_1$ are opened out to about 120°, indicating the C_2-symmetry of **3**.

Unlike the packing diagram of compound **2**, two enantiomers of **3** are stacking with each other mediated by two ethanol molecules. The H⋯O distance of 1.43(4) Å in O(2A)—HO(2A)⋯O(5A) and O(2D)—HO(2D)⋯O(5D) hydrogen bonding is much shorter than the other one of 1.88(6) Å in O(5D)—HO(5D)⋯O(4A) and O(5A)—HO(5A)⋯O(4D). As sketched in Figure 2b, each molecule of **3** is stacking with adjacent molecules in a 'head-to-head' manner via hydrogen bonds. The intermolecular contact of 2.705(3) Å at O(3A)—HO(3A)⋯O(1B) and O(3D)—HO(3D)⋯O(1C) with angle of 176(3)° forms one-dimensional assemblies along the *a*-axis.

2.3. Chirality

As observed in crystals of **2** and **3**, two respective enantiomers are combined in one unit cell of the single crystals. The intermolecular hydrogen bonding shows considerable strength and directionality for the control of their self-assemblies. In order to obtain these two enantiomers, the separation by high-performance liquid chromatography was carried out with a Shimadzu-LC-20 apparatus on a Chiralcel OJ-RH column (Daicel Chemical Industries, Ltd., 4.6×150 mm).

It is noteworthy that the isolated racemic mixtures of **2** and **3** can be subsequently resolved into their enantiomers. As shown in Figures 3a and 4a, the chromatograms show two product peaks, respectively, monitored by UV detector.

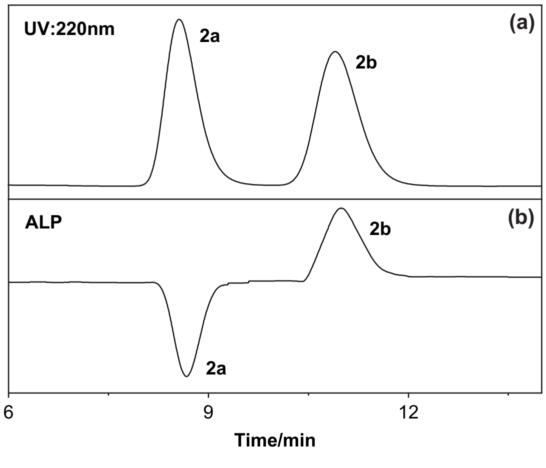

Figure 3. Typical HPLC chromatogram of **2** with OJ-RH column: (a) UV detector at 220 nm and (b) polarimeter detector at 220 nm (eluent: water/methanol=20/80, 25 °C, flow rate 0.4 mL/min).

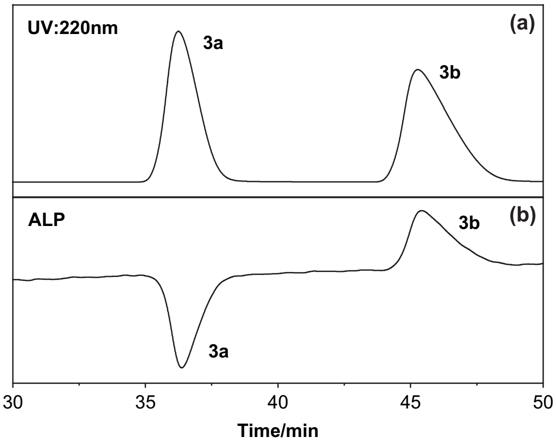

Figure 4. Typical HPLC chromatogram of **3** with OJ-RH column: (a) UV detector at 220 nm and (b) polarimeter detector at 220 nm (eluent: pH 2.0 KH_2PO_4/H_3PO_4 buffer (20 mM KH_2PO_4)/acetonitrile=75/25, 25 °C, flow rate 0.4 mL/min).

Moreover, the two peak areas are identical in magnitude within experimental error. However, in the case of polarimeter detector installed after the UV detector in HPLC system, the two peaks areas were found to be equal but the direction is opposite by measuring both the magnitude and direction of the net optical activity (rotation) of the respective enantiomers (Figures 3b and 4b), indicating that the peaks represent the two enantiomers of **2** and **3**, respectively. Importantly, the optically pure enantiomers of **2** (**2a** $[\alpha]_D^{20}$ −46.0±0.1 (*c* 0.0242, methanol), **2b** $[\alpha]_D^{20}$ +45.9±0.1 (*c* 0.0244, methanol)) and **3** (**3a** $[\alpha]_D^{20}$ −67.6±0.5 (*c* 0.0058, acetonitrile), **3b** $[\alpha]_D^{20}$ +67.5±0.5 (*c* 0.0059, acetonitrile)) can be obtained by HPLC resolution. The two isolated enantiomers show near mirror image behavior in the circular dichroism (CD) spectra, while the absorption spectra are not distinguishable from each other (Fig. 5).

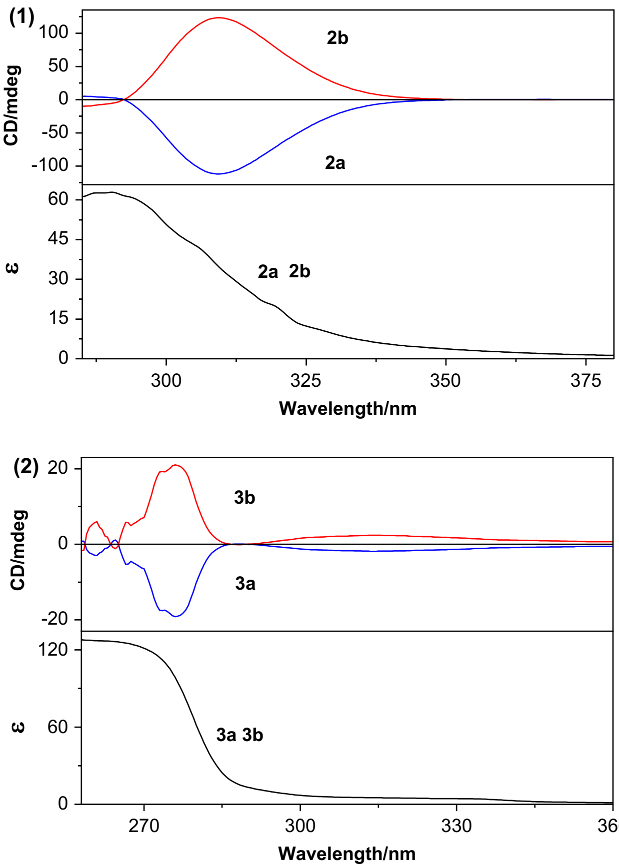

Figure 5. (1) The circular dichroism (top) and absorption (bottom) spectra of enantiomers of **2** in methanol. (2) The circular dichroism (top) and absorption (bottom) spectra of enantiomers of **3** in acetonitrile.

3. Conclusion

Hydroxyl- and carboxyl-functionalized cubane-like photodimers **2** and **3**, which cannot be prepared by direct photoirradiation, have been successfully achieved by reduction and hydrolysis of photodimer **1** of methyl 2-naphthoate under mild conditions. Spectroscopy and X-ray structural analysis provide unambiguous evidences of the cubane-like structure unchanged. The two respective enantiomers of **2** and **3** were found to combine in one unit cell of crystals. The intermolecular O—H···O hydrogen bonding shows considerable strength and directionality for the control of their self-assemblies. It is of significance that the isolated racemic mixture can be subsequently resolved into two optically pure enantiomers by high-performance liquid chromatography, which provides a potential for their further studies in the area of asymmetric catalysis or chiral assembly.

4. Experimental

4.1. General

All reagents for synthesis were of analytical grade and used as received. Compound **1** was prepared according to the literature method.[4] ^1H NMR spectra were obtained with a Brucker Avance DPX 400 MHz instrument using TMS as internal standard. Mass spectra were obtained on Brucker Esquire 3000plus ESI and BIFLEXIII MALDI-TOF spectrometers. The X-ray crystal structural data were collected on a Bruker Smart 1000 X-ray diffractometer. The HPLC was carried out on Shimadzu-LC-20 with the PDR-Chiral Advanced Laser Polarimeter-ALP 2002 and UV as the detector. The values of specific rotation were measured on Perkin–Elmer 341LC polarimeter. Circular dichroism spectrum was carried out on JASCO J-810 spectropolarimeter. UV–visible spectrum was detected on UV–visible spectrophotometer Shimadzu-UV-1601PC.

4.2. Hydroxyl-functionalized cubane-like photodimer 2

Compound **1** (500 mg, 1.34 mmol) was dissolved in dry diethyl ether (Et_2O, approximately 40 mL) and then an excess of $LiAlH_4$ (204.3 mg, 5.38 mmol) was introduced slowly with care. The reaction mixture was refluxed for 12 h and cooled to 0 °C, then quenched with minimum amount of ethyl acetate (10 mL) dropwise, followed by addition of saturated NH_4Cl aqueous solution (2 mL) and stirred at 0 °C for 30 min. After filtration, the filtrate was extracted with diethyl ether, washed with brine, and dried over anhydrous magnesium sulfate. After evaporation of solvent, the resultant residue was purified by recrystallization from dichloromethane–methanol solution to give a cubane-like photodimer **2** with 90% yield. ^{1}H NMR, ^{13}C NMR spectroscopies and MS (TOF) spectrometry confirmed the identity of **2**. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 6.89–6.97 (m, 8H), 4.15–4.20 (dd, 2H, J=11.6 and 7.8 Hz), 3.90–3.93 (d, 2H, J=11.6 Hz), 3.83–3.86 (d, 2H, J=10.9 Hz), 3.65–3.67 (d, 2H, J=10.9 Hz), 3.06–3.08 (d, 2H, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz, δ ppm): 34.6, 42.1, 42.3, 47.1, 67.0, 126.5, 126.6, 128.4, 128.5, 137.0, 137.1; TOF-MS-EI: [M$^+$] 316. Crystallographic data for **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 635464.

4.3. Carboxyl-functionalized cubane-like photodimer 3

Compound **1** (500 mg, 1.34 mmol) was dissolved in 5 mL Claisen base (6.25 mol/L KOH in the mixed solution of CH_3OH and H_2O (v/v: 3/1)) to reflux for 3 h, and then cooled to 0 °C. The reaction mixture was quenched with 1 N HCl to afford white precipitate when the pH value was 1. The precipitate was filtered off and washed with water until the pH value was 7; which was recrystallized from ethanol to give a cubane-like photodimer **3** with 92% yield. ^{1}H NMR, ^{13}C NMR spectroscopies and MS (ESI) spectrometry confirmed the identity of **3**. ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 6.94–7.00 (m, 8H), 4.53–4.56 (d, 2H, J=11.6 Hz), 4.40–4.45 (dd, 2H, J=11.6 and 8.0 Hz), 3.92–3.94 (d, 2H, J=8.0 Hz); ^{13}C NMR (DMSO-d_6, 400 MHz, δ ppm): 39.3, 42.4, 42.7, 47.4, 127.2, 127.1, 128.7, 129.0, 136.6, 136.8, 175.4; ESI-MS: [M−1]$^+$ 343. Crystallographic data for **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 635465.

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