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Template-Directed Photochemical Homodimerization and Heterodimerization Reactions of Cinnamic Acids

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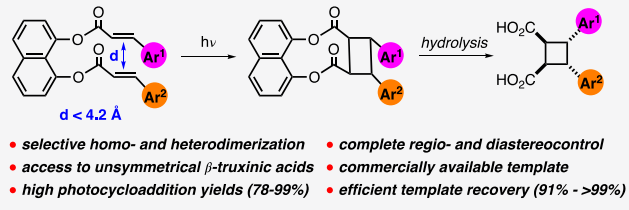
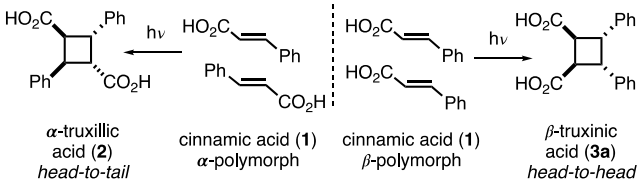
ABSTRACT: We developed a general method for the selective photochemical homo- and heterodimerization of cinnamic acid derivatives with the use of commercially available 1,8-dihydroxynaphthalene as a covalent template. A variety of symmetrical and unsymmetrical β-truxinic acids were obtained in high yields and as single diastereomers. The use of a template not only provides the alignment of the two olefins with suitable proximity (<4.2 Å) but also allows the heterodimerization of two different cinnamic acids, leading to unsymmetrical β-truxinic acid products.



Photochemical [2 + 2] cycloaddition reactions constitute one of the most direct and effective methods for the construction of four-membered rings.[1] One particular type of [2 + 2] cycloadditions that attracted significant attention is the photodimerization of cinnamic acid derivatives due to the challenges associated with this transformation in terms of regio- and stereoselectivity as well as reactivity.[2] In addition, [2 + 2] cycloadducts of cinnamic acids are attractive synthetic targets because of their diverse and promising biological activity profiles and their presence in various natural products.[3] Irradiation of cinnamic acid derivatives in solution leads predominantly to *E*/*Z* photoisomerization, and therefore, efforts to achieve these transformations were focused primarily on solid-state photochemistry.[4] Early studies led to the topochemical reaction principles described by Schmidt for photochemical [2 + 2] cycloadditions in solid state.[4c,5] According to these criteria, for such a photochemical reaction to take place, alkenes must be aligned parallel to each other with a distance of 3.5−4.2 Å between the reactive olefin centers. The crystal structures of certain olefins fulfill these criteria so that irradiation of such compounds in solid state directly affords the corresponding cycloaddition products. For instance, irradiation of the α-polymorph of *trans*-cinnamic acid (**1**) with UV light gives selectively the head-to-tail homodimerization product α-truxillic acid (**2**), whereas the photocycloaddition of the metastable β-polymorph leads to the formation of the head-to-head dimer β-truxinic acid (**3a**) (Scheme 1).[5b,6] On the other hand, the γ-polymorph does not undergo a [2 + 2] cycloaddition upon irradiation since the distance between the olefin centers is greater than 4.2 Å.[4a,5c]

The geometrical requirements described by the Schmidt criteria for alkenes to undergo photochemical cycloadditions make such reactions highly difficult to predict, design, and control, which eventually limit the broad applicability of this methodology. In order to circumvent this problem, the use of covalent and noncovalent templates was developed so that the relative positioning of alkenes could be controlled with the help of such templates.[7] Interactions such as hydrogen bonding, halogen bonding, and metal coordination have been elegantly utilized in the design of many noncovalent templates for photochemical [2 + 2] reactions in solid state.[8−10] Whereas the use of noncovalent interactions obviates the covalent linking of the substrates to the template and the removal of the product from it, the requirement of cocrystallization of substrates with the template limits the scope of this strategy.

Scheme 1. Photodimerization Reactions of Cinnamic Acid



Surprisingly, covalent template-directed photochemical [2 + 2] cycloadditions are much less common.[11−15] After the successful demonstration by Hopf, Jones, and Desvergne that the topochemical principles could be applied to solution chemistry,[16] König and co-workers investigated three diols as covalent templates in the photochemical homodimerization of unsubstituted *trans*-cinnamic acid (**1**) in solution (Scheme 2a).[12] In 2002, Hopf and co-workers reported the use of 4,15-

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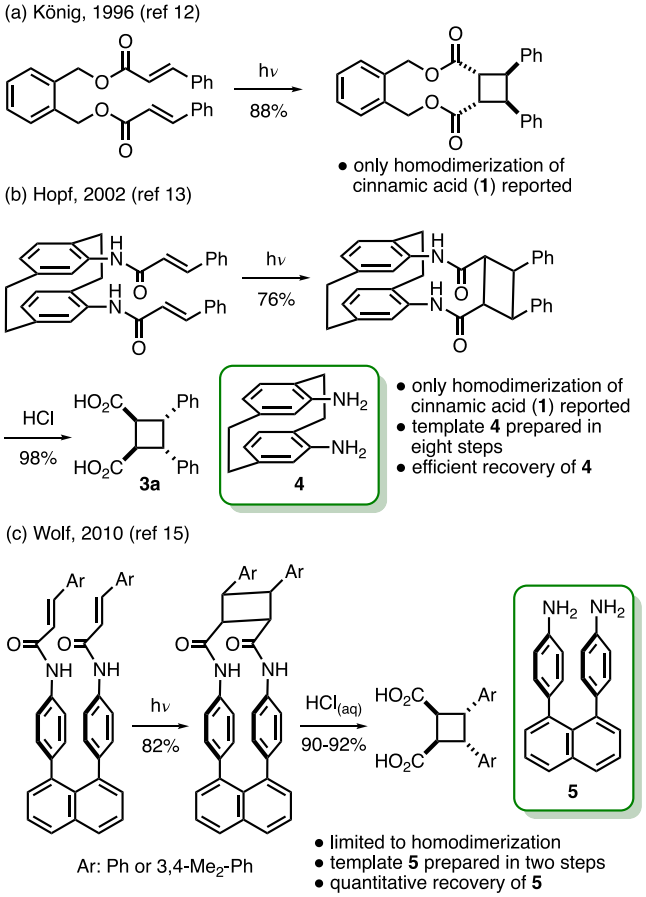
Scheme 2. Previous Examples of Covalent Template-Directed Photochemical [2 + 2] Cycloadditions

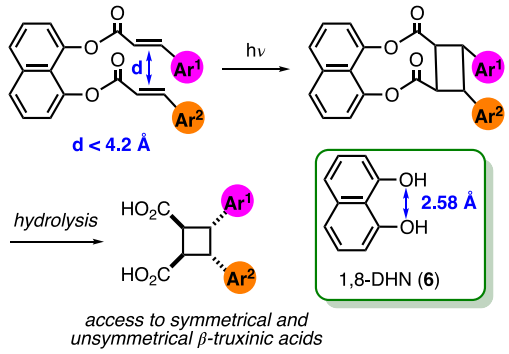


diamino[2.2]paracyclophane (**4**) as an effective covalent template for the homodimerization of cinnamic acid (**1**) in solution (Scheme 2b).[13] Whereas template **4** was shown to be reusable, its eight-step preparation decreases the synthetic utility of this approach. In another study reported by Wolf and co-workers in 2010, template **5** was utilized in the photochemical homodimerization of two cinnamic acid derivatives (Scheme 2c).[15]

The [2 + 2] cycloadditions of cinnamic acid derivatives mentioned so far are predominantly homodimerizations, in which reactions of two identical olefins afford symmetrical cyclobutanes. Indeed, a very high degree of homoselectivity was observed by Nguyen and co-workers even when a suspension of several cinnamic acids in cyclohexane was irradiated.[17] Moreover, visible-light photocatalytic [2 + 2] cycloadditions of cinnamic acid derivatives were shown to furnish symmetrical δ-truxinic acid-based products arising from the *anti*-head-to-head homodimerization process.[18,19] On the other hand, photochemical heterodimerization reactions, where two different cinnamic acids react selectively to give unsymmetrical cyclobutanes, are very rare. The few known examples of such heterodimerizations require either solid solutions or cocrystals of two cinnamic acid derivatives.[20,21] The requirement of two different cinnamic acids to form a cocrystal or solid solution imposes a serious limitation on the scope of this type of heterodimerization reaction. In this context, a general method for the selective and controlled photochemical heterodimerization of cinnamic acids remains elusive. Against this background, we now report a simple and general solution to this long-standing problem.

During our recent studies on the use of 1,8-dihydroxynaphthalene (1,8-DHN, **6**) as a hydrogen bonding catalyst, we observed that the two −OH groups of 1,8-DHN could be methylated in a sequential and selective manner due to the intramolecular HB present in its structure.[22] The proximity of the two oxygens,[23] parallel orientation of the two C−O bonds, the ability to selectively functionalize the two −OHs, and its commercial availability led us to the hypothesis that 1,8-DHN (**6**) would be an ideal covalent template for the photochemical [2 + 2] homo- and heterodimerization reactions of cinnamic acids (Scheme 3). Moreover, covalent attachment of the

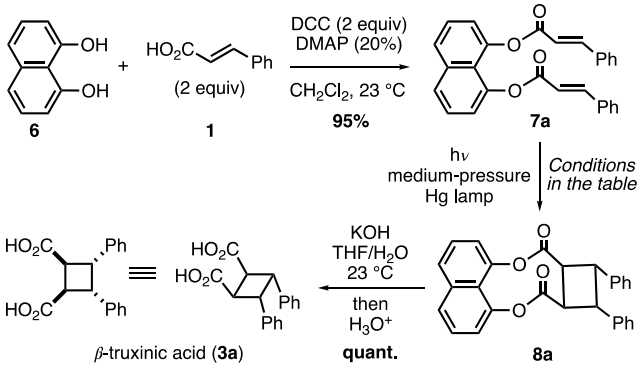
Scheme 3. Our Strategy for Selective Heterodimerization of Cinnamic Acids



substrates to the template and detachment of the product were expected to be facile based on well-established esterification and saponification reactions under mild conditions.

In order to test our hypothesis, we first checked the feasibility of using 1,8-DHN (**6**) as a template in the photodimerization of *trans*-cinnamic acid (**1**) (Table 1). Covalent attachment of two cinnamic acid units to the

Table 1. Template-Directed Photochemical *syn*-Head-to-Head Homodimerization of *trans*-Cinnamic Acid (1)



entry	time (h)	conversion of **7a** to **8a** (%)[a]	yield of **8a** (%)
1	2	17	nd[b]
2	8	44	nd
3[c]	8	>99	95
4[c]	4	>99	92
5[d]	2	90	nd

[a]Determined by ^{1}H NMR spectroscopy. [b]nd = not determined. [c]The solid reaction mixture was mixed every 2 h. [d]The solid reaction mixture was mixed after 1 h.

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template was achieved by double esterification of **6** in the presence of DCC and DMAP, resulting in the isolation of diester **7a** in a 95% yield. Irradiation of **7a** in solid state was examined with the use of a 400 W medium-pressure Hg lamp. When **7a** was irradiated continuously for 2 and 8 h, the [2 + 2] cycloaddition product **8a** was observed to form with 17% and 44% conversion, respectively, as determined by ^{1}H NMR spectroscopy (entries 1 and 2). Mixing the solid mixture at certain intervals was found to have a substantial positive effect on the progress of the reaction. We were pleased to obtain diester **8a** with quantitative conversion and an almost quantitative yield when the sample was irradiated for 8 or 4 h in total with mixing the solid reaction mixture every 2 h (entries 3 and 4). However, irradiation of **7a** for 2 h with a mixing of the sample after 1 h resulted in 90% conversion (entry 5). It should be noted that all these photochemical reactions are very clean transformations with no side products and no decomposition of **7a** or **8a**. In order to check the possibility of utilizing a different irradiation source, we tested the photoreaction of **7a** to **8a** using a commercial gel nail dryer equipped with four 9 W UVA fluorescent bulbs (365 nm).[24] Pleasingly, **7a** was observed to form cycloadduct **8a** with 95% conversion and 92% isolated product yield upon 8 h of irradiation.[25] This preliminary result shows that our strategy can be successfully applied with other irradiation sources. Finally, hydrolysis of diester **8a** was accomplished under basic conditions to afford *β*-truxinic acid (**3a**) as a single diastereomer in a quantitative yield along with complete recovery of template **6**. Control experiments, in which **7a** was heated at 90 °C under dark either as a solid or as a solution in toluene for 6 h, indicated the absence of any reaction under thermal conditions.[26]

The results obtained with the photodimerization of **7a** demonstrated that 1,8-DHN (**6**) could indeed act as a suitable template for such [2 + 2] reactions. We then sought to gain information on the geometries of the substrate-template conjugate before and after the cycloaddition. To this end, the structures of **7a** and **8a** were determined by single-crystal X-ray crystallography (Figure 1). The X-ray structure of **7a**

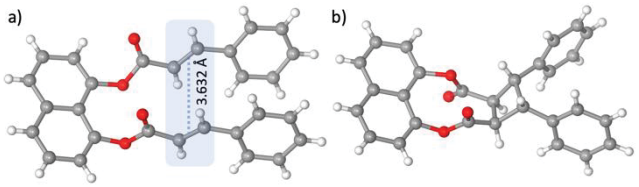
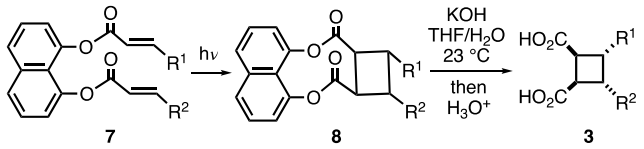


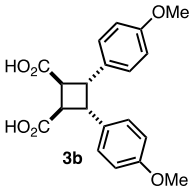
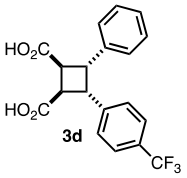
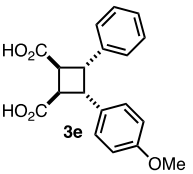
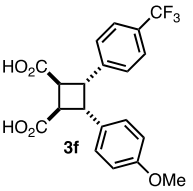
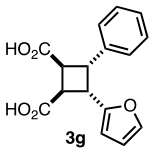
Figure 1. X-ray crystal structures of (a) diester **7a** and (b) [2 + 2] cycloaddition product **8a**.

revealed the ideal parallel alignment of the two cinnamic acid units with a distance of 3.632 Å between the olefin centers, which is in perfect agreement with the Schmidt criteria (Figure 1a).[4c] Moreover, the crystal structure of **8a** confirmed its relative stereochemistry and the stereocontrolled nature of the photoreaction as *syn*-head-to-head dimerization (Figure 1b). The perfect agreement of the NMR data of the hydrolysis product **3a** with those of *β*-truxinic acid reported in the literature[6] provided further confirmation of our structural assignment.

Encouraged by these results, we next sought to investigate homo- and heterodimerization reactions of other cinnamic acid derivatives (Table 2). Irradiation of **7b** bearing 4-methoxyphenyl substituents for 12 h afforded cycloadduct **8b** in 78%

Table 2. Template-Directed Photochemical Homo- and Heterodimerization of *α,β*-Unsaturated Carboxylic Acids



entry	R^1/R^2	yield of **8** (%)	yield of **3** (%)	final product
1	4-MeO-Ph / 4-MeO-Ph (**7b**)	78 (**8b**)	84 (**3b**)	
2	Me / Me (**7c**)	nr[a]	-	-
3	Ph / 4-CF_3-Ph (**7d**)	88 (**8d**)	79 (**3d**)	
4	Ph / 4-MeO-Ph (**7e**)	99 (**8e**)	91 (**3e**)	
5	4-CF_3-Ph / 4-MeO-Ph (**7f**)	93 (**8f**)	92 (**3f**)	
6	Ph / 2-furyl (**7g**)	88 (**8g**)	84 (**3g**)	

[a]nr = no reaction.

yield, which was subsequently hydrolyzed to the *β*-truxinic acid derivative **3b** in high yield (84%, entry 1). The effect of having an aliphatic group at the *β*-position of the acrylate moiety was examined through the use of diester **7c**, which was prepared via the double esterification of 1,8-DHN (**6**) with crotonic acid. Unfortunately, irradiation of **7c** did not provide any cycloadduct, and the reactant was observed to remain intact (entry 2). Next, we turned our attention to the photochemical heterodimerizations of unsymmetrical substrates. For this purpose, diester **7d** that bears phenyl and 4-trifluoromethylphenyl substituents was synthesized selectively and in high yield via sequential esterification reactions (see the Exper-

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imental Section). To our delight, irradiation of **7d** for 6.5 h afforded the [2 + 2] heterodimerization product **8d** in 88% yield (entry 3). Its hydrolysis gave the unsymmetrical cyclobutanedicarboxylic acid **3d** as a single diastereomer (79% yield). Another unsymmetrical substrate tested was diester **7e** with phenyl and 4-methoxyphenyl substituents. Gratifyingly, **7e** underwent the photochemical [2 + 2] reaction successfully with 8 h of irradiation and gave cycloadduct **8e** in 99% yield (entry 4). Diastereomerically pure, unsymmetrical dicarboxylic acid product **3e** was isolated in 91% yield upon hydrolysis of **8e**. We next investigated the reactivity of diester **7f**, which possesses electron-donating 4-OMe and electron-withdrawing 4-CF_3 groups on each of its phenyl rings. This compound was also observed to be a competent substrate with the newly developed methodology, and cyclobutane **8f** was obtained in 93% yield upon irradiation for 8 h (entry 5). Its subsequent hydrolysis gave dicarboxylic acid **3f** in 92% yield. Finally, we opted to investigate the heterodimerization of a substrate containing a heteroaromatic cinnamic acid derivative. In order to achieve this goal, diester **7g** with phenyl and 2-furyl substituents was synthesized by sequential esterification. Irradiation of **7g** for 8 h furnished the cyclobutane product **8g** in 88% yield as a single diastereomer (entry 6). Hydrolysis of **8g** afforded furan-containing cyclobutanedicarboxylic acid **3g** in high yield (84%). This result indicates that the newly developed methodology can be extended to reactions of acrylic acids with heteroaromatic substituents at the β-position.

The crystal structure of the unsymmetrical diester **7f** was elucidated by single crystal XRD analysis (Figure 2). Whereas

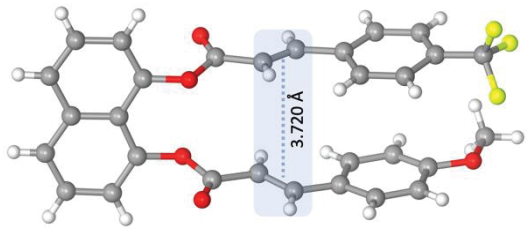
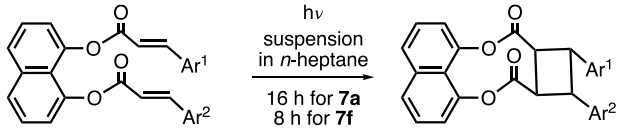


Figure 2. X-ray crystal structure of diester **7f**.

the distance between the olefin centers was found to be 3.72 Å, the two carbonyls of **7f**, in contrast to **7a**, were observed to have opposite orientations resulting in a criss-crossed geometry for the reacting olefins.[26] A [2 + 2] cycloaddition with this type of arrangement of olefins is not only expected to be unfavorable geometrically[27] but also would give a δ-truxinic acid via an *anti*-head-to-head dimerization. However, extensive NMR spectroscopic studies on the structure of cyclobutane **3f** including NOESY and *J* coupling constant analysis confirmed its β-truxinic acid nature, which points to a *syn*-head-to-head dimerization of **7f**.[26] This sort of *syn*-head-to-head photodimerization was observed by others,[8k,28] and it was proposed to be caused by the pedal motion of olefins prior to photocycloaddition so that the two olefins adopt a parallel alignment suitable for the cycloaddition.[27,29] In our case, we propose that a similar pedal motion might be responsible for the high efficiency of the [2 + 2] photocycloaddition of **7f**.

Having shown the successful application of the newly developed methodology to a variety of photochemical homo- and heterodimerization reactions, we next examined its scalability. To this end, a suspension of **7a** (1.2 mmol) in *n*-heptane was irradiated for 16 h, and cycloadduct **8a** was isolated in 72% yield as a single diastereomer (Scheme 4). Importantly, unreacted **7a** could be reisolated efficiently (27%)

Scheme 4. Scalability of the Photodimerization Reactions



7a (1.2 mmol) or 7f (1.0 mmol)

8a: Ar^1=Ar^2=Ph, 72% (99% brsm) *single diastereomer;*
8f: Ar^1: 4-CF_3-Ph, Ar^2: 4-OMe-Ph 83%, *single diastereomer*

at the end of the reaction, which makes the overall reaction yield 99% based on recovered starting material (brsm). A similar experiment was performed with the unsymmetrical diester **7f**. The irradiation of a suspension of **7f** (1.0 mmol) in *n*-heptane for 8 h afforded diastereomerically pure [2 + 2] heterodimerization product **8f** in 83% yield (Scheme 4). These results clearly demonstrate the suitability of the present method for scale up.

In summary, we present a general solution for the selective photochemical homo- and heterodimerization of cinnamic acids. The commercially available 1,8-DHN (**6**) is used as a template to enable the preorganization of the two cinnamic acid units for an efficient photocycloaddition. The ability to attach sequentially two different cinnamic acids to the template paved the way for a highly selective photochemical heterodimerization. The photochemical [2 + 2] reaction proceeds in high yields (78−99%) and with complete regio- and diastereocontrol, affording a variety of symmetrical and unsymmetrical β-truxinic acids. The template was found to be recoverable in high yields during the detachment step of the β-truxinic acid products from the template. Importantly, the cycloaddition step was found to be scalable when the photochemical reactions were carried out in heptane as suspension. Our current efforts are focused on the extent of the utility of this strategy to the synthesis of other unsymmetrical cyclobutane scaffolds.

EXPERIMENTAL SECTION

General Information. All solution-phase reactions were performed using oven-dried glassware under an inert atmosphere of nitrogen. Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed plates precoated with silica gel (Silicycle, Silica Gel 60 F_{254}). UV light and/or $KMnO_4$ staining solution were used for TLC visualization. Flash column chromatography was performed on Silicycle 40−63 μm (230−400 mesh) flash silica gel. ^{1}H NMR (400 MHz), $^{13}C\{^1H\}$ NMR (100 MHz), and $^{19}F\{^1H\}$ NMR (376 MHz) spectra were recorded using a Bruker Avance 400 spectrometer in $CDCl_3$ and DMSO-d_6. Internal standard signal (TMS, 0 ppm) or residual solvent signals (chloroform at 7.26 ppm, and DMSO at 2.50 ppm for ^{1}H NMR; chloroform at 77.16 ppm and DMSO at 39.52 ppm for $^{13}C\{^1H\}$ NMR spectra) were used for the calibration of ^{1}H and $^{13}C\{^1H\}$ NMR spectra. Trifluoroacetic acid (CF_3CO_2H) was used as an external reference (−76.55 ppm) for $^{19}F\{^1H\}$ NMR experiments. ^{1}H NMR data are reported as follows: chemical shift (parts per million, ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br = broad, app = apparent), coupling constant (Hz). Infrared (FTIR) spectra were recorded on a Bruker Alpha-Platinum-ATR spectrometer with only selected peaks reported. High-resolution mass spectral analyses (HRMS) were performed on Agilent Technologies 6530 QTOF-LC/MS at DAYTAM-East Anatolia

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High Technology Application and Research Center, Atatürk University, and on Agilent Technologies 6224 TOF LC/MS at UNAM-National Nanotechnology Research Center and Institute of Materials Science and Nanotechnology, Bilkent University. Single-crystal X-ray diffraction analysis was performed at Gebze Technical University, Turkey. Photochemical reactions were performed using a reactor obtained from Photochemical Reactors Ltd., composed of a 400 W medium-pressure mercury lamp (3040/PX0686) and a quartz double-walled immersion well with water cooling. Regular microscope slides made of soda-lime glass were used without any additional filters for the photochemical reactions in solid state. The slides were kept at ca. 4 cm away from the lamp during the irradiation. All photochemical reactions were performed inside a fully closed safety cabinet. 1,8-Dihydroxynaphthalene (1,8-DHN) was purchased from abcr Co. and used as received. Anhydrous CH_2Cl_2 was purchased from Acros Organics (AcroSeal). All other commercially available reagents were used as received unless stated otherwise.

Naphthalene-1,8-diyl(2*E*,2′*E*)-bis(3-phenyl acrylate) (7a). 1,8-DHN (**6**) (100 mg, 0.62 mmol) was dissolved in 15 mL of anhydrous CH_2Cl_2 in a 100 mL, round-bottomed flask at 23 °C under nitrogen. *trans*-Cinnamic acid (**1**) (185 mg, 1.25 mmol), DCC (258 mg, 1.25 mmol), and DMAP (15.3 mg, 0.125 mmol) were added sequentially. The resulting cloudy, heterogeneous mixture was stirred at 23 °C for 24 h. TLC analysis indicated full consumption of 1,8-DHN (**6**). The reaction mixture was quenched with a 10% (w/v) aqueous solution of citric acid (30 mL) and H_2O (10 mL). The two phases were partitioned. The organic phase was washed once with brine. It was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 1:1) afforded pure **7a** (248 mg, 95%) as a pale yellow solid.

*Synthesis of Diester **7a** on a 6.2 mmol Scale.* 1,8-DHN (**6**) (1.00 g, 6.24 mmol) was dissolved in 20 mL of anhydrous CH_2Cl_2 in a 100 mL, round-bottomed flask at 23 °C under nitrogen. *trans*-Cinnamic acid (**1**) (1.85 g, 12.5 mmol), DCC (2.58 g, 12.5 mmol), and DMAP (153 mg, 1.25 mmol) were added sequentially. The resulting cloudy, heterogeneous mixture was stirred at 23 °C for 40 h. The reaction mixture was quenched with a 10% (w/v) aqueous solution of citric acid and H_2O. The two phases were partitioned. The organic phase was washed once with brine. It was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 1:1) afforded pure **7a** (2.29 g, 87%) as a pale yellow solid. Mp: 222−223 °C ($CHCl_3$). R_f = 0.56 (CH_2Cl_2/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.86 (2H, d, J = 16.0 Hz), 7.82 (2H, d, J = 8.3 Hz), 7.50 (2H, t, J = 7.9 Hz), 7.31−7.25 (6H, m), 7.21 (2H, d, J = 7.3 Hz), 7.13 (4H, t, J = 7.6 Hz), 6.63 (2H, d, J = 16.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ 166.0, 147.1, 145.3, 136.9, 133.9, 130.7, 128.9, 128.3, 127.0, 126.2, 121.5, 120.7, 117.4. FTIR: ν_{max} (ATR, film)/cm^{-1}3061, 2924, 2853, 1718, 1633, 1601, 1576, 1497, 1450. HRMS (ESI+): calcd for $C_{28}H_{20}O_4Na$ $[M + Na]^+$, 443.1254; found, 443.1255.

9,10-Diphenyl-8a,9,10,10a-tetrahydrocyclobuta[*g*]-naphtho[1,8-*bc*][1,5]dioxonine-8,11-dione (8a). Diester **7a** (25.6 mg, 0.061 mmol) was placed between two glass microscope slides as a solid powder. The sample was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp for 4 h (Figure S1). The solid powder was mixed with a spatula to ensure homogeneity after two h. At the end of 4 h in total, the sample was transferred to a vial by washing with $CDCl_3$. ^{1}H NMR spectroscopic analysis indicated full conversion of diester **7a** to the cyclobutane product **8a**. The presence of diester **7a** or any other side product was not observed in this spectrum. Cyclobutane **8a** was obtained as a light brown solid upon removal of the solvent (23.3 mg, 92%).

In another experiment, diester **7a** (26.3 mg, 0.063 mmol) was irradiated using the same experimental setup for 8 h. The solid powder was mixed with a spatula to ensure homogeneity every 2 h. At the end of 8 h in total, the sample was transferred to a vial by washing with $CDCl_3$. ^{1}H NMR spectroscopic analysis indicated full conversion of diester **7a** to the cyclobutane product **8a**. The presence of diester **7a** or any other side product was not observed. Cyclobutane **8a** was obtained as a light brown solid upon removal of the solvent (24.9 mg, 95%). Mp: 228−229 °C ($CHCl_3$). R_f = 0.62 (CH_2Cl_2/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.82 (2H, d, J = 8.3 Hz), 7.51 (2H, t, J = 7.9 Hz), 7.28 (2H, d, J = 7.5 Hz), 7.17 (4H, t, J = 7.3 Hz), 7.10 (2H, t, J = 7.2 Hz), 7.03 (4H, d, J = 7.2 Hz), 4.77 (2H, app d, J = 6.0 Hz), 4.24 (2H, app d, J = 6.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz; $CDCl_3$): δ 170.1, 145.5, 138.2, 137.1, 128.3, 127.9, 127.1, 126.8, 126.5, 121.1, 119.6, 44.9, 44.3. FTIR: ν_{max} (ATR, film)/cm^{-1} 2924, 2853, 1762, 1607, 1497, 1452, 1366. HRMS (ESI+): calcd for $C_{28}H_{21}O_4$ $[M + H]^+$, 421.1434; found, 421.1436.

*Photochemical Reaction of **7a** using the UV Gel Nail Dryer.* Diester **7a** (20.3 mg, 0.048 mmol) was placed between two glass microscope slides as a solid powder. The sample was irradiated inside a UV gel nail dryer, equipped with four 9 W UVA fluorescent bulbs, for 8 h (Figure S3). The solid powder was mixed with a spatula to ensure homogeneity every hour. At the end of 8 h in total, ^{1}H NMR spectroscopic analysis indicated 95% conversion of diester **7a** to the cyclobutane product **8a**. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 1:1, then only CH_2Cl_2) afforded pure **8a** (18.7 mg, 92%) as a white solid.

*Photochemical Reaction of **7a** in Heptane on a 1.2 mmol Scale.* Heptane (250 mL) was degassed by purging with nitrogen and was transferred to an immersion well reactor flask containing solid diester **7a** (505 mg, 1.20 mmol). The resulting suspension was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp while stirring under a balloon of argon for 16 h (Figure S2). During the irradiation, the suspension was cooled continuously with a flow of cold water to prevent heating of the reaction mixture. The color turned from white to orange during the reaction. At the end of 16 h, the sample was transferred to a round-bottomed flask by washing with CH_2Cl_2. ^{1}H NMR analysis of the crude mixture indicated 74% conversion to the cycloaddition product. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 1:1) afforded pure **8a** (361 mg, 72%) as a pale yellow solid and pure starting material diester **7a** (138 mg, 27% recovery) as an orange solid.

(1*R*,2*S*,3*R*,4*S*)-3,4-Diphenylcyclobutane-1,2-dicarboxylic Acid (*meso*-3a). In a 20 mL scintillation vial, diester **8a** (25 mg, 0.059 mmol) was dissolved in 2.0 mL of THF. Afterward, distilled water (1.0 mL) and KOH (65 mg, 1.13 mmol) were added. The resulting mixture was stirred at 23 °C for 2 h. It was then quenched with 1.0 M HCl solution until the pH was adjusted to 1−2. The aqueous phase was extracted three times with EtOAc. The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) afforded pure **3a** (18 mg, 100%) as a yellow solid and pure 1,8-DHN (**6**) (10 mg, 100% recovery) as a black solid.

In another experiment, diester **8a** (200 mg, 0.48 mmol) was dissolved in 6.0 mL of THF in a 20 mL scintillation vial. Afterward, distilled water (3.0 mL) and KOH (507 mg, 9.04 mmol) were added. The resulting mixture was stirred at 23 °C for 3 h. It was then quenched with 1.0 M HCl solution until the pH was adjusted to 1−2. The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; first EtOAc/hexanes = 1:1, then 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) afforded pure **3a** (140 mg, 98%) as a black solid, and pure 1,8-DHN (**6**) (70 mg, 91% recovery) as a black solid. Mp: 206−208 °C. (lit.[6] Mp: 207.6−208.6 °C). R_f = 0.20 (0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) ^{1}H NMR (400 MHz; DMSO-d_6): δ 12.42 (2H, br s), 7.09−6.97 (10H, m), 4.22 (2H, app d, J = 4.2 Hz), 3.81 (2H, app d, J = 4.3 Hz). $^{13}C\{^1H\}$ NMR (100 MHz; DMSO-d_6): δ 174.0, 139.3, 127.9, 127.7, 125.9, 44.5, 42.6. FTIR: ν_{max} (ATR, film)/cm^{-1}3031, 2931 (br s), 1696, 1497, 1450, 1414. HRMS (ESI−): calcd for $C_{18}H_{15}O_4$ $[M - H]^-$, 295.0976; found, 295.0984. The ^{1}H and $^{13}C\{^1H\}$ NMR spectral data are in accordance with the values reported in the literature.[6]

Naphthalene-1,8-diyl(2*E*,2′*E*)-bis(3-(4-methoxphenyl)-acrylate) (7b). 1,8-DHN (**6**) (100 mg, 0.62 mmol) was dissolved in 15 mL of anhydrous CH_2Cl_2 in a 100 mL, round-bottomed flask at 23

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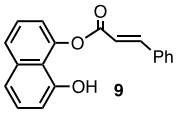
°C under nitrogen. *trans*-4-Methoxycinnamic acid (223 mg, 1.25 mmol), DCC (258 mg, 1.25 mmol) and DMAP (15.3 mg, 0.125 mmol) were added sequentially. The resulting cloudy, heterogeneous mixture was stirred at 23 °C for 24 h. The reaction mixture was quenched with a 10% (w/v) aqueous solution of citric acid (30 mL) and H_2O (10 mL). The two phases were partitioned. The organic phase was washed once with brine. It was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; only CH_2Cl_2) afforded pure **7b** (250 mg, 87%) as a pale yellow solid. Mp: 231−232 °C ($CHCl_3$). R_f = 0.50 (only CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.81 (2H, d, J = 7.7 Hz), 7.79 (2H, d, J = 15.9 Hz), 7.49 (2H, t, J = 7.9 Hz), 7.23 (4H, d, J = 8.7 Hz), 7.19 (2H, d, J = 7.5 Hz), 6.64 (4H, d, J = 8.7 Hz), 6.48 (2H, d, J = 16.0 Hz), 3.79 (6H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 166.4, 161.6, 146.6, 145.5, 136.9, 130.0, 126.9, 126.8, 126.2, 121.7, 120.8, 114.9, 114.3, 55.3. FTIR: ν_{max} (ATR, film)/cm^{-1}2923, 2842, 1718, 1633, 1601, 1572, 1513. HRMS (ESI+): calcd for $C_{30}H_{24}O_6Na$ [M + Na]$^+$, 503.1465; found, 503.1467.

9,10-Bis(4-methoxyphenyl)-8a,9,10,10a-tetrahydrocyclobuta[*g*]naphtho[1,8-*bc*][1,5]dioxonine-8,11-dione (8b). Diester **7b** (16.1 mg, 0.034 mmol) was placed between two glass microscope slides as a solid powder. The sample was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp for 12 h. The solid powder was mixed with a spatula to ensure homogeneity every 2 h. The reaction was stopped at the end of 12 h in total. Purification by column chromatography (SiO_2; only CH_2Cl_2) afforded pure **8b** (12.5 mg, 78%) as a yellow solid. Mp: 204−205 °C. R_f = 0.66 (only CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.80 (2H, d, J = 8.2 Hz), 7.50 (2H, t, J = 7.9 Hz), 7.27 (2H, d, J = 7.7 Hz), 6.93 (4H, d, J = 8.6 Hz), 6.71 (4H, d, J = 8.6 Hz), 4.66 (2H, app d, J = 6.0 Hz), 4.16 (2H, app d, J = 5.9 Hz), 3.71 (6H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 170.2, 158.4, 145.5, 137.1, 130.4, 129.0, 127.0, 126.5, 121.1, 119.7, 113.8, 55.3, 45.2, 43.7. FTIR: ν_{max} (ATR, film)/cm^{-1}2923, 2842, 1718, 1633, 1601, 1513. HRMS (ESI+): calcd for $C_{30}H_{24}O_6Na$ [M + Na]$^+$, 503.1465; found, 503.1475.

(1*R*,2*S*,3*R*,4*S*)-3,4-Bis(4-methoxyphenyl)cyclobutane-1,2-dicarboxylic Acid (*meso*-3b). In a 20 mL scintillation vial, diester **8b** (21.7 mg, 0.045 mmol) was dissolved in 2.0 mL of THF. Afterward, distilled water (1.0 mL) and KOH (50 mg, 0.89 mmol) were added. The resulting mixture was stirred at 23 °C for 2 h. It was then quenched with 1.0 M HCl solution until the pH was adjusted to 1−2. The aqueous phase was extracted three times with EtOAc. The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) afforded pure **3b** (13.4 mg, 84%) as an orange oil, and pure 1,8-DHN (**6**) (6.8 mg, 94% recovery) as a black solid. R_f = 0.18 (0.5% (v/v) AcOH in EtOAc/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.09 (2H, br s), 6.84 (4H, d, J = 8.6 Hz), 6.67 (4H, d, J = 8.7 Hz), 4.35 (2H, d, J = 5.8 Hz), 3.85 (2H, d, J = 5.9 Hz), 3.71 (6H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 179.9, 158.3, 130.5, 129.0, 113.7, 55.3, 44.3, 44.2. FTIR: ν_{max} (ATR, film)/cm^{-1}2929 (br s), 2837, 1704, 1611, 1513, 1424, 1248. HRMS (ESI−): calcd for $C_{20}H_{19}O_6$ [M − H]$^-$, 355.1187; found, 355.1187. The 1H-NMR spectral data are in accordance with the values reported in the literature.[10a]

Naphthalene-1,8-diyl (2*E*,2′*E*)-bis(but-2-enoate) (7c). 1,8-DHN (**6**) (100 mg, 0.62 mmol) was dissolved in 15 mL of anhydrous CH_2Cl_2 in a 100 mL, round-bottomed flask at 23 °C under nitrogen. Crotonic acid (108 mg, 1.25 mmol), DCC (258 mg, 1.25 mmol) and DMAP (15.3 mg, 0.125 mmol) were added sequentially. The resulting cloudy, heterogeneous mixture was stirred at 23 °C for 24 h. The reaction mixture was quenched with a 10% (w/v) aqueous solution of citric acid (30 mL) and H_2O (10 mL). The two phases were partitioned. The organic phase was washed once with brine. It was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 1:1) afforded pure **7c** (158 mg, 85%) as a white solid with >96% purity. A portion of this product was further purified via recrystallization from heptane to give an analytically pure sample of **7c**. Mp: 153−154 °C (heptane). R_f = 0.42 (CH_2Cl_2/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.77 (2H, d, J = 8.2 Hz), 7.45 (2H, t, J = 7.9 Hz), 7.22−7.15 (2H, m), 7.12 (2H, d, J = 7.7 Hz), 6.04 (2H, app dd, J = 15.6, 1.6 Hz), 1.96 (6H, dd, J = 6.9, 1.5 Hz). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 165.3, 147.0, 145.3, 136.9, 126.9, 126.1, 122.6, 121.6, 120.6, 18.3. FTIR: ν_{max} (ATR, film)/cm^{-1}3057, 2922, 2850, 1742, 1659, 1603, 1442, 1377, 1312. HRMS (ESI+): calcd for $C_{18}H_{16}O_4Na$ [M + Na]$^+$, 319.0941; found, 319.0940.

*Irradiation of Diester **7c**.* Diester **7c** (23 mg, 0.078 mmol) was placed between two glass microscope slides as a solid powder. The sample was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp for 4 h. The solid powder was mixed with a spatula to ensure homogeneity after 2 h. At the end of 4 h in total, the sample was transferred to a vial by washing with $CDCl_3$. ^{1}H NMR spectroscopic analysis indicated no formation of the desired cyclobutane product, and the reactant **7c** was observed to remain intact. The same result was obtained when quartz microscope slides were used.



9

8-Hydroxynaphthalen-1-yl Cinnamate (9). In a 100 mL round-bottomed flask, *trans*-cinnamic acid (520 mg, 3.51 mmol) was dissolved in 2 mL of oxalyl chloride at 23 °C under an inert atmosphere of nitrogen. The clear solution was heated in an oil bath at 60 °C for 2 h. Afterward, it was cooled back to an ambient temperature, and the volatiles were removed by the use of a rotary evaporator to give *trans*-cinnamoyl chloride (575 mg, 99%) as a yellow solid. In another 100 mL round-bottomed flask, 1,8-DHN (**6**, 500 mg, 3.12 mmol) was dissolved in 10 mL of anhydrous THF under an inert atmosphere of nitrogen. The clear solution was cooled to 0 °C in an ice bath, and NaH (137 mg, 3.43 mmol, 60% dispersion in mineral oil) was added carefully in portions. The reaction mixture was stirred at this temperature for 20 min. *trans*-Cinnamoyl chloride (520 mg, 3.12 mmol), which was prepared as described above, was dissolved in 5 mL of anhydrous THF, and this solution was added slowly via syringe to the reaction mixture at 0 °C. Afterward, the reaction mixture was stirred at 23 °C for 75 min. TLC analysis indicated full consumption of 1,8-DHN (**6**). The reaction mixture was quenched with 50 mL of saturated aqueous NH_4Cl solution. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; EtOAc/hexanes = 1:5) afforded pure **9** (740 mg, 82%) as an orange solid. Mp: 119−120 °C ($CHCl_3$). R_f = 0.27 (EtOAc/hexanes = 1:5). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.91 (1H, d, J = 16.0 Hz), 7.67 (1H, t, J = 8.3 Hz), 7.56−7.54 (2H, m), 7.41−7.37 (5H, m), 7.30−7.28 (2H, m), 7.20 (1H, d, J = 7.3 Hz), 6.82 (1H, d, J = 7.6 Hz), 6.68 (1H, d, J = 15.9 Hz). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 164.7, 152.1, 148.2, 146.2, 137.0, 133.9, 131.3, 129.2, 128.6, 127.2, 126.6, 125.6, 120.4, 118.6, 117.2, 116.5, 111.5. FTIR: ν_{max} (ATR, film)/cm^{-1}3388 (br s), 3058, 2924, 2853, 1704, 1633, 1601, 1579, 1449. HRMS (ESI+): calcd for $C_{19}H_{14}O_3Na$ [M + Na]$^+$, 313.0835; found, 313.0839.

8-(Cinnamoyloxy)naphthalen-1-yl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate (7d). Monoester **9** (100 mg, 0.35 mmol) was dissolved in 10 mL of anhydrous CH_2Cl_2 in a 100 mL, round-bottomed flask at 23 °C under nitrogen. 4-Trifluoromethylcinnamic acid (75 mg, 0.35 mmol), DCC (72 mg, 0.35 mmol) and DMAP (4.2 mg, 0.035 mmol) were added sequentially. The resulting orange, heterogeneous mixture was stirred at 23 °C for 24 h. The reaction mixture was quenched with a 10% (w/v) aqueous solution of citric acid (30 mL). The aqueous phase was extracted with CH_2Cl_2(3 × 30 mL). The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; hexanes: $CHCl_3$ = 1:5) afforded pure **7d** (127 mg, 76%) as a white solid. Mp: 172−173

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°C. R_f = 0.36 (hexanes:$CHCl_3$ = 1:5). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.85−7.79 (4H, m), 7.51−7.46 (2H, m), 7.56−7.54 (2H, m), 7.30−7.27 (4H, m), 7.25−7.19 (5H, m), 7.07 (2H, t, J = 7.7 Hz), 6.67 (1H, d, J = 16.1 Hz), 6.59 (1H, d, J = 16.1 Hz). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 165.9, 165.4, 147.0, 145.3, 145.1, 144.9, 137.1 (q, $^4J_{C-F}$ = 1.4 Hz), 137.0, 133.7, 131.9 (q, $^2J_{C-F}$ = 33.9 Hz), 131.0, 128.9, 128.3, 128.2, 127.2, 127.1, 126.3, 126.2, 125.8 (q, $^3J_{C-F}$ = 3.7 Hz), 123.8 (q, $^1J_{C-F}$ = 272 Hz), 121.4, 120.9, 120.7, 120.1, 117.4. FTIR: ν_{max} (ATR, film)/cm^{-1}3064, 2925, 1731, 1716, 1642, 1332. HRMS (ESI+): calcd for $C_{29}H_{19}O_4F_3Na$ [M + Na]$^+$, 511.1128; found, 511.1129.

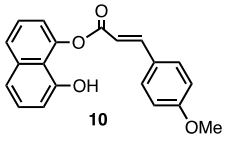
9-Phenyl-10-(4-(trifluoromethyl)phenyl)-8a,9,10,10a-tetrahydrocyclobuta[*g*]naphtho[1,8-*bc*][1,5]dioxonine-8,11-dione (8d). Diester **7d** (25.5 mg, 0.052 mmol) was placed between two glass microscope slides as a solid powder. The sample was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp for 6.5 h. The solid powder was mixed with a spatula to ensure homogeneity every 2 h. At the end of 6.5 h in total, the sample was transferred to a vial by washing with $CDCl_3$. ^{1}H NMR spectroscopic analysis indicated 96% conversion of diester **7d** to the cyclobutane product **8d**. Purification by column chromatography (SiO_2; only CH_2Cl_2) afforded pure **8d** (22.5 mg, 88%) as a white solid. Mp: 86−87 °C ($CHCl_3$). R_f = 0.43 (hexanes:CH_2Cl_2 = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.83 (2H, d, J = 8.3 Hz), 7.52 (2H, t, J = 7.9 Hz), 7.42 (2H, d, J = 8.1 Hz), 7.29 (2H, d, J = 7.4 Hz), 7.21−7.17 (2H, m), 7.15−7.11 (3H, m), 7.02 (2H, d, J = 7.3 Hz), 4.86−4.78 (2H, m), 4.27−4.22 (2H, m). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 169.83, 169.79, 145.4, 142.4, 137.6, 137.1, 128.6, 128.4, 128.3, 128.0, 127.9, 127.22, 127.20, 127.17, 126.6, 126.5, 125.3 (q, $^3J_{C-F}$ = 3.7 Hz), 121.11, 121.06, 44.9, 44.7, 44.2, 44.1 (Since the aromatic region is very crowded, the two quartet signals with ^{13}C−^{19}F couplings could not be identified with certainty). FTIR: ν_{max} (ATR, film)/cm^{-1}3062, 2928, 1761, 1607, 1578, 1365, 1324. HRMS (ESI+): calcd for $C_{29}H_{19}F_3O_4Na$ [M + Na]$^+$, 511.1128; found, 511.1126.

(1*R*,2*S*,3*R*,4*S*)-3-Phenyl-4-(4-(trifluoromethyl)phenyl)-cyclobutane-1,2-dicarboxylic Acid (*rac*-3d). In a 20 mL scintillation vial, diester **8d** (38.5 mg, 0.079 mmol) was dissolved in 2.0 mL of THF. Afterward, distilled water (1.0 mL) and KOH (84 mg, 1.50 mmol) were added. The resulting mixture was stirred at 23 °C for 2 h. It was then quenched with 1.0 M HCl solution until the pH was adjusted to 1−2. The aqueous phase was extracted three times with EtOAc. The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; first EtOAc/hexanes = 1:1; then 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) afforded pure **3d** (22.8 mg, 79%) as a white solid with a brown tinge. Mp: 123−126 °C ($CHCl_3$). R_f = 0.23 (0.5% (v/v) AcOH in EtOAc/hexanes = 1:1). ^{1}H NMR (400 MHz; DMSO-d_6): δ 12.54 (2H, br s), 7.42 (2H, d, J = 8.0 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.11−6.99 (5H, m), 4.35 (1H, app t, J = 8.8 Hz), 4.22 (1H, dd, J = 10.1, 6.5 Hz), 3.92 (1H, app t, J = 8.7 Hz), 3.78 (1H, dd, J = 9.8, 6.6 Hz). ^{13}C{^{1}H} NMR (100 MHz; DMSO-d_6): δ 173.9, 173.7, 144.3, 138.9, 128.6, 127.9, 127.8, 126.5 (q, $^2J_{C-F}$ = 31.8 Hz), 126.1, 124.4 (app d, $^3J_{C-F}$ = 3.6 Hz), 124.2 (q, $^1J_{C-F}$ = 271.8 Hz), 44.5, 44.2, 42.7, 42.1. ^{19}F{^{1}H} NMR (376 MHz; DMSO-d_6): δ −59.0 (s). FTIR: ν_{max} (ATR, film)/cm^{-1}3030, 2926, 1707, 1619, 1423, 1326. HRMS (ESI−): calcd for $C_{19}H_{14}F_3O_4$ [M − H]$^-$, 363.0850; found, 363.0847.

8-(Cinnamoyloxy)naphthalen-1-yl-(*E*)-3-(4-methoxyphenyl)acrylate (7e). Monoester **9** (100 mg, 0.35 mmol) was dissolved in 10 mL of anhydrous CH_2Cl_2 in a 100 mL, round-bottomed flask at 23 °C under nitrogen. 4-Methoxycinnamic acid (61 mg, 0.35 mmol), DCC (72 mg, 0.35 mmol) and DMAP (4.2 mg, 0.035 mmol) were added sequentially. The resulting orange, heterogeneous mixture was stirred at 23 °C for 24 h. The reaction mixture was quenched with a 10% (w/v) aqueous solution of citric acid (30 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; hexanes: $CHCl_3$ = 1:2) afforded pure **7e** (110 mg, 66%) as a pale yellow solid. Mp: 130−131 °C. R_f = 0.53 (hexanes:$CHCl_3$ = 1:2). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.87−7.79 (4H, m), 7.49 (2H, app t, J = 7.9 Hz), 7.31−7.28 (3H, m), 7.24 (2H, d, J = 7.9 Hz), 7.21−7.19 (2H, m), 7.15 (2H, t, J = 7.6 Hz), 6.64−6.60 (3H, m), 6.48 (1H, d, J = 16.0 Hz), 3.78 (3H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 166.3, 166.0, 161.7, 146.9, 146.8, 145.40, 145.36, 136.9, 134.0, 130.5, 130.0, 128.9, 128.3, 127.0, 126.9, 126.7, 126.2, 126.1, 121.6, 120.8, 120.7, 117.5, 114.8, 114.4, 55.4. FTIR: ν_{max} (ATR, film)/cm^{-1}2926, 1732, 1634, 1602, 1512. HRMS (ESI+): calcd for $C_{29}H_{22}O_5Na$ [M + Na]$^+$, 473.1359; found, 473.1360.

9-(4-Methoxyphenyl)-10-phenyl-8a,9,10,10a-tetrahydrocyclobuta[*g*]naphtho[1,8-*bc*][1,5]dioxonine-8,11-dione (8e). Diester **7e** (19.6 mg, 0.044 mmol) was placed between two glass microscope slides as a solid powder. The sample was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp for 8 h. The solid powder was mixed with a spatula to ensure homogeneity every 2 h. At the end of 8 h in total, the sample was transferred to a vial by washing with $CDCl_3$. ^{1}H NMR spectroscopic analysis indicated full conversion of diester **7e** to the cyclobutane product **8e**. Cyclobutane **8e** was obtained as an orange solid upon removal of the solvent (19.4 mg, 99%). Mp: 177−178 °C. R_f = 0.62 (EtOAc/hexanes = 1:2). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.81 (2H, d, J = 8.3 Hz), 7.50 (2H, t, J = 7.8 Hz), 7.27 (2H, d, J = 7.4 Hz), 7.18 (2H, t, J = 7.1 Hz), 7.11 (1H, t, J = 7.3 Hz), 7.02 (2H, d, J = 7.4 Hz), 6.93 (2H, d, J = 8.3 Hz), 6.70 (2H, d, J = 8.4 Hz), 4.76−4.68 (2H, m), 4.24 (1H, dd, J = 10.3, 5.4 Hz), 4.16 (1H, dd, J = 10.6, 5.4 Hz), 3.72 (3H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 170.2, 158.4, 145.5, 138.3, 137.1, 129.1, 128.4, 128.0, 127.0, 126.8, 126.5, 121.1, 119.7, 113.8, 55.3, 45.4, 44.7, 44.3, 43.7. FTIR: ν_{max} (ATR, film)/cm^{-1}2930, 1764, 1608, 1514, 1365. HRMS (ESI+): calcd for $C_{29}H_{22}O_5Na$ [M + Na]$^+$, 473.1359; found, 473.1373.

(1*S*,2*R*,3*S*,4*R*)-3-(4-Methoxyphenyl)-4-phenylcyclobutane-1,2-dicarboxylic Acid (*rac*-3e). In a 20 mL scintillation vial, diester **8e** (18.4 mg, 0.041 mmol) was dissolved in 2.0 mL of THF. Afterward, distilled water (1.0 mL) and KOH (44 mg, 0.78 mmol) were added. The resulting mixture was stirred at 23 °C for 2 h. It was then quenched with 1.0 M HCl solution until the pH was adjusted to 1−2. The aqueous phase was extracted three times with EtOAc. The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) afforded pure **3e** (12.2 mg, 91%) as a brown oil, and pure 1,8-DHN (**6**) (5.9 mg, 91% recovery) as a black solid.R_f = 0.21 (0.5% (v/v) AcOH in EtOAc/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 11.31 (2H, br s), 7.15 (2H, t, J = 7.2 Hz), 7.08 (1H, t, J = 7.2 Hz), 6.94 (2H, d, J = 7.2 Hz), 6.85 (2H, d, J = 8.5 Hz), 6.66 (2H, d, J = 8.6 Hz), 4.45−4.38 (2H, m), 3.94 (1H, dd, J = 9.8, 5.4 Hz), 3.86 (1H, dd, J = 9.8, 5.4 Hz), 3.70 (3H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 179.9, 179.8, 158.3, 138.3, 130.4, 129.0, 128.3, 127.9, 126.7, 113.7, 55.3, 44.8, 44.34, 44.29, 43.7. FTIR: ν_{max} (ATR, film)/cm^{-1}3030, 2923 (br s), 2851, 1704, 1611, 1514, 1424, 1248. HRMS (ESI−): calcd for $C_{19}H_{17}O_5$ [M − H]$^-$, 325.1081; found, 325.1071.



10

8-Hydroxynaphthalen-1-yl-(*E*)-3-(4-methoxyphenyl)-acrylate (10). In a 50 mL round-bottomed flask, *trans*-4-methoxycinnamic acid (1.00 g, 5.61 mmol) was dissolved in 2 mL of oxalyl chloride at 23 °C under an inert atmosphere of nitrogen. The clear solution was heated in an oil bath at 60 °C for 2 h. Afterward, it was cooled back to ambient temperature, and the volatiles were removed by the use of a rotary evaporator to give *trans*-4-methoxycinnamoyl chloride (1.104 g, 99%) as yellow solid. In another 100 mL round-bottomed flask, 1,8-DHN (**6**, 900 mg, 5.61 mmol) was dissolved in 10 mL of anhydrous THF under an inert atmosphere of nitrogen. The clear solution was cooled to 0 °C in an ice bath, and NaH (247 mg, 6.18 mmol, 60% dispersion in mineral oil) was added carefully in portions. The reaction mixture was stirred at this temperature for 20 min. *trans*-4-Methoxycinnamoyl chloride (1.104 g, 5.61 mmol), which was prepared as described above, was

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dissolved in 10 mL of anhydrous THF, and this solution was added slowly via syringe to the reaction mixture at 0 °C. Afterward, the reaction mixture was stirred at 23 °C for 2 h. The reaction mixture was quenched with 50 mL of saturated aqueous NH_4Cl solution and 10 mL of brine. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 1:1 → CH_2Cl_2/hexanes = 2:1 → only CH_2Cl_2) afforded pure **10** (1.450 g, 81%) as an orange solid. Mp: 151−152 °C. R_f = 0.50 (only CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.90 (1H, d, J = 15.9 Hz), 7.70 (1H, d, J = 8.2 Hz), 7.55−7.52 (3H, m), 7.44−7.40 (2H, m), 7.32 (1H, t, J = 7.9 Hz), 7.23 (1H, d, J = 7.9 Hz), 6.93 (2H, d, J = 8.7 Hz), 6.87 (1H, d, J = 7.5 Hz), 6.57 (1H, d, J = 15.9 Hz), 3.85 (3H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 164.8, 162.3, 152.3, 148.1, 146.2, 137.0, 130.5, 127.3, 126.7, 126.5, 125.6, 120.3, 118.5, 117.1, 114.7, 113.6, 111.5, 55.6. FTIR: ν_{max} (ATR, film)/cm^{-1}3391 (br s), 3057, 2838, 1707, 1633, 1601, 1512. HRMS (ESI−): calcd for $C_{20}H_{15}O_4$ $[M - H]^-$, 319.0976; found, 319.0979.

8-(((*E*)-3-(4-Methoxyphenyl)acryloyl)oxy)naphthalen-1-yl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate (7f). Monoester **10** (100 mg, 0.31 mmol) was dissolved in 15 mL of anhydrous CH_2Cl_2 in a 100 mL, round-bottomed flask at 23 °C under nitrogen. 4-Trifluoromethylcinnamic acid (68 mg, 0.31 mmol), DCC (64 mg, 0.31 mmol) and DMAP (3.8 mg, 0.031 mmol) were added sequentially. The resulting pale yellow, heterogeneous mixture was stirred at 23 °C for 24 h. The reaction mixture was quenched with 10 mL of water and 10 mL of brine. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; hexanes: CH_2Cl_2 = 1:1 to 1:2) afforded pure **7f** (107 mg, 66%) as a white solid. Mp: 207.7−208.3 °C ($CHCl_3$).R_f = 0.45 (hexanes:CH_2Cl_2 = 1:2). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.84−7.78 (4H, m), 7.51 (1H, t, J = 7.9 Hz), 7.50 (1H, t, J = 7.9 Hz), 7.34 (4H, app s), 7.21 (4H, app d, J = 7.2 Hz), 6.70 (1H, d, J = 16.1 Hz), 6.62 (2H, d, J = 8.6 Hz), 6.46 (1H, d, J = 16.0 Hz), 3.77 (3H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 166.2, 165.4, 161.9, 146.7, 145.4, 145.1, 144.8, 137.2, 136.9, 131.8 (q, $^2J_{C-F}$ = 32.3 Hz), 129.9, 128.3, 127.1, 126.9, 126.4, 126.3, 126.1, 125.6 (q, $^3J_{C-F}$ = 3.7 Hz), 123.9 (q, $^1J_{C-F}$ = 272.2 Hz), 121.4, 120.9, 120.6, 120.1, 114.7, 114.3, 55.3.FTIR: ν_{max} (ATR, film)/cm^{-1}3079, 2924, 1724, 1642, 1599, 1575, 1511, 1321, 1251. HRMS (ESI+) Calcd for $C_{30}H_{21}F_3O_5Na$ $[M + Na]^+$, 541.1233; found, 541.1255.

9-(4-Methoxyphenyl)-10-(4-(trifluoromethyl)phenyl)-8a,9,10,10a-tetrahydrocyclobuta[*g*]naphtho[1,8-*bc*][1,5]-dioxonine-8,11-dione (8f). Diester **7f** (25.6 mg, 0.049 mmol) was placed between two glass microscope slides as a solid powder. The sample was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp for 8 h. The solid powder was mixed with a spatula to ensure homogeneity after every 2 h. At the end of 8 h in total, the sample was transferred to a vial by washing with $CHCl_3$. ^{1}H NMR spectroscopic analysis indicated full conversion of diester **7f** to the cyclobutane product **8f**. The presence of diester **7f** or any other side product was not observed in this spectrum. Cyclobutane **8f** was obtained as a light brown amorphous solid upon removal of the solvent (23.9 mg, 93%). Mp: 83−85 °C. R_f = 0.44 (EtOAc/hexanes = 1:5). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.83 (2H, d, J = 8.2 Hz), 7.52 (2H, t, J = 7.8 Hz), 7.43 (2H, d, J = 7.8 Hz), 7.29 (2H, d, J = 7.3 Hz), 7.12 (2H, d, J = 7.8 Hz), 6.93 (2H, d, J = 8.3 Hz), 6.72 (2H, d, J = 8.3 Hz), 4.82−4.78 (1H, m), 4.76−4.72 (1H, m), 4.25 (1H, dd, J = 10.4, 6.6 Hz), 4.17 (1H, dd, J = 10.5, 6.0 Hz), 3.73 (3H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 169.91, 169.88, 158.7, 145.4, 142.5, 137.1, 129.7, 129.1, 129.0 (q, $^2J_{C-F}$ = 32.7 Hz), 128.2, 127.2, 127.1, 126.6, 126.5, 125.3 (q, $^3J_{C-F}$ = 3.5 Hz), 124.2 (q, $^1J_{C-F}$ = 272.1 Hz), 121.10, 121.05, 119.5, 114.0, 55.3, 45.3, 44.6, 44.1, 43.6.FTIR: ν_{max} (ATR, film)/cm^{-1}3060, 2928, 2840, 1763, 1608, 1580, 1514, 1365, 1324. HRMS (ESI+): calcd for $C_{30}H_{21}F_3O_5Na$ $[M + Na]^+$, 541.1233; found, 541.1263.

*Photochemical Reaction of **7f** in Heptane on a 1.0 mmol Scale.* Heptane (250 mL) was degassed via a flow of nitrogen and was transferred to an immersion well reactor flask containing solid diester **7f** (519 mg, 1.00 mmol). The resulting suspension was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp while stirring under a balloon of argon for 8 h. During the irradiation, the suspension was cooled continuously with a flow of cold water to prevent heating of the reaction mixture. The color turned from white to orange during the reaction. At the end of 8 h, the sample was transferred to a round-bottomed flask by washing with CH_2Cl_2. ^{1}H NMR analysis of the crude mixture indicated full conversion to the cycloaddition product. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 2:1) afforded pure **8f** (431 mg, 83%) as an orange solid.

(1*R*,2*S*,3*R*,4*S*)-3-(4-Methoxyphenyl)-4-(4-(trifluoromethyl)-phenyl)cyclobutane-1,2-dicarboxylic Acid (*rac*-3f). In a 20 mL scintillation vial, diester **8f** (23 mg, 0.044 mmol) was dissolved in 2.0 mL of THF. Afterward, distilled water (1.0 mL) and KOH (47 mg, 0.84 mmol) were added. The resulting mixture was stirred at 23 °C for 2.5 h. It was then quenched with 1.0 M HCl solution until the pH was adjusted to 1−2. The aqueous phase was extracted three times with EtOAc. The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; first EtOAc/hexanes = 1:1, then 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) afforded pure **3f** (16 mg, 92%) as a brownish amorphous solid, and pure 1,8-DHN (**6**) (6.8 mg, 97% recovery) as a black solid.

In another experiment, diester **8f** (300 mg, 0.58 mmol) was dissolved in 4.0 mL of THF in a 20 mL scintillation vial. Afterward, distilled water (2.0 mL) and KOH (618 mg, 11.0 mmol) were added. The resulting mixture was stirred at 23 °C for 2 h. It was then quenched with 1.0 M HCl solution until the pH was adjusted to 1−2. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; first EtOAc/hexanes = 1:1, then 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) afforded pure **3f** (207 mg, 90%) as an amorphous dark brown solid. Mp: 88−89 °C ($CHCl_3$). R_f = 0.14 (0.5% (v/v) AcOH in EtOAc/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 10.27 (2H, s), 7.39 (2H, d, J = 8.1 Hz), 7.03 (2H, d, J = 8.1 Hz), 6.84 (2H, d, J = 8.6 Hz), 6.68 (2H, d, J = 8.6 Hz), 4.53 (1H, app t, J = 8.8 Hz), 4.36 (1H, dd, J = 10.0, 6.1 Hz), 3.95 (1H, app t, J = 8.9 Hz), 3.83 (1H, dd, J = 10.0, 6.1 Hz), 3.71 (3H, s). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 179.7, 179.3, 158.6, 142.5, 129.7, 128.94, 128.92 (q, $^2J_{C-F}$ = 32.6 Hz), 128.1, 125.2 (q, $^3J_{C-F}$ = 3.5 Hz), 124.2 (q, $^1J_{C-F}$ = 272.4 Hz), 114.0, 55.3, 44.6, 44.5, 44.3, 43.4. ^{19}F{^{1}H} NMR (376 MHz; $CDCl_3$): δ −61.3 (s). FTIR: ν_{max} (ATR, film)/cm^{-1} 2925 (br s), 2853, 1705, 1614, 1514, 1421, 1324. HRMS (ESI−): calcd for $C_{20}H_{16}F_3O_5$ $[M - H]^-$, 393.0955; found, 393.0968.

8-(Cinnamoyloxy)naphthalen-1-yl-(*E*)-3-(furan-2-yl)acrylate (7g). In a 50 mL round-bottomed flask, (*E*)-3-(2-furyl)acrylic acid (60 mg, 0.43 mmol) was dissolved in 2 mL of oxalyl chloride at 23 °C under an inert atmosphere of nitrogen. The clear solution was heated in an oil bath at 60 °C for 2 h. Afterward, it was cooled back to ambient temperature, and the volatiles were removed by the use of a rotary evaporator to give (*E*)-3-(2-furyl)acryloyl chloride (64 mg, 94%) as a pale yellow solid. In another 100 mL round-bottomed flask, monoester **9** (100 mg, 0.34 mmol) was dissolved in 10 mL of anhydrous THF under an inert atmosphere of nitrogen. The clear solution was cooled to 0 °C in an ice bath, and NaH (15.2 mg, 0.38 mmol, 60% dispersion in mineral oil) was added carefully. The resulting dark purple mixture was stirred at this temperature for 15 min. (*E*)-3-(2-Furyl)acryloyl chloride (64 mg, 0.41 mmol), which was prepared as described above, was dissolved in 5 mL of anhydrous THF, and this solution was added slowly via syringe to the reaction mixture at 0 °C. Afterward, the reaction mixture was stirred at 23 °C for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. The aqueous phase was extracted three times with CH_2Cl_2. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 1:1) afforded pure **7g** (125 mg, 90%) as a brown solid. Mp: 174−176 °C ($CHCl_3$). R_f =

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0.28 (CH_2Cl_2/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.87 (1H, d, J = 16.1 Hz), 7.82 (2H, d, J = 8.3 Hz), 7.60 (1H, d, J = 15.7 Hz), 7.53−7.48 (2H, m), 7.39−7.37 (2H, m), 7.34−7.31 (1H, m), 7.27−7.20 (4H, m), 7.12 (1H, d, J = 1.4 Hz), 6.64 (1H, d, J = 16.0 Hz), 6.53−6.48 (2H, m), 6.30 (1H, dd, J = 3.4, 1.8 Hz). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 166.02, 165.98, 150.5, 147.0, 145.33, 145.31, 145.26, 136.9, 134.2, 132.9, 130.5, 128.9, 128.3, 126.95, 126.93, 126.2, 121.5, 120.7, 117.5, 115.9, 115.1, 112.4. FTIR: ν_{max} (ATR, film)/cm^{-1} 3141, 3056, 1722, 1631, 1602, 1370. HRMS (ESI+): calcd for $C_{26}H_{18}O_5Na$ $[M + Na]^+$, 433.1046; found, 433.1046.

9-(Furan-2-yl)-10-phenyl-8a,9,10,10a-tetrahydrocyclobuta[*g*]naphtho[1,8-*bc*][1,5]dioxonine-8,11-dione (8g). Diester **7g** (24.7 mg, 0.060 mmol) was placed between two glass microscope slides as a solid powder. The sample was irradiated in a safety box using a 400 W broadband medium-pressure Hg lamp for 8 h. The solid powder was mixed with a spatula to ensure homogeneity every 2 h. At the end of 8 h in total, the sample was transferred to a vial by washing with $CDCl_3$. ^{1}H NMR spectroscopic analysis indicated almost full conversion of diester **7g** to the cyclobutane product **8g**. Purification by column chromatography (SiO_2; CH_2Cl_2/hexanes = 1:1) afforded pure **8g** (21.8 mg, 88%) as a white solid. Mp: 149−150 °C ($CHCl_3$). R_f = 0.27 (CH_2Cl_2/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.80 (2H, d, J = 8.4 Hz), 7.53−7.48 (2H, m), 7.29−7.22 (4H, m), 7.19−7.17 (2H, m), 7.13−7.11 (2H, m), 6.17 (1H, dd, J = 3.2, 1.9 Hz), 6.03 (1H, d, J = 3.2 Hz), 4.74 (1H, t, J = 9.3 Hz), 4.62 (1H, dd, J = 10.1, 4.8 Hz), 4.40 (1H, ddd, J = 10.5, 8.6, 0.8 Hz), 4.20 (1H, ddd, J = 10.6, 4.8, 0.9 Hz). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 170.1, 169.6, 152.1, 145.5, 145.4, 142.2, 138.1, 137.1, 128.3, 127.3, 127.09, 127.06, 126.99, 126.5, 121.2, 121.0, 119.6, 110.4, 108.2, 45.1, 44.3, 43.7, 38.4. FTIR: ν_{max} (ATR, film)/cm^{-1} 3060, 3030, 2924, 1765, 1608, 1500, 1364, 1216. HRMS (ESI+): calcd for $C_{26}H_{18}O_5Na$ $[M + Na]^+$, 433.1046; found, 433.1046.

(1*S*,2*R*,3*S*,4*R*)-3-(Furan-2-yl)-4-phenylcyclobutane-1,2-dicarboxylic Acid (*rac*-3g). In a 20 mL scintillation vial, diester **8g** (19.3 mg, 0.047 mmol) was dissolved in 2.0 mL of THF. Afterward, distilled water (1.0 mL) and KOH (50 mg, 0.89 mmol) were added. The resulting mixture was stirred at 23 °C for 2 h. It was then quenched with 1.0 M HCl solution until the pH was adjusted to 1−2. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was then dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (SiO_2; first EtOAc/hexanes = 1:1, then 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) afforded pure **3g** (11.4 mg, 84%) as a pale yellow oil and pure 1,8-DHN (**6**) (6.8 mg, 91% recovery) as a black solid. R_f = 0.17 (0.5% (v/v) AcOH in EtOAc/hexanes = 1:1). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.20−7.12 (4H, m), 7.03 (2H, d, J = 7.1 Hz), 6.13 (1H, dd, J = 3.0, 1.9 Hz), 5.94 (1H, d, J = 3.1 Hz), 4.48 (1H, t, J = 9.4 Hz), 4.24 (1H, dd, J = 9.7, 4.7 Hz), 4.13 (1H, t, J = 9.6 Hz), 3.84 (1H, dd, J = 10.0, 4.7 Hz). ^{13}C{^{1}H} NMR (100 MHz; $CDCl_3$): δ 179.4, 179.2, 152.2, 142.0, 138.3, 128.2, 127.2, 126.9, 110.3, 108.1, 44.6, 43.6 (two overlapping signals), 38.9. FTIR: ν_{max} (ATR, film)/cm^{-1} 3029, 2924 (br s), 2854, 1706, 1603, 1498, 1423. HRMS (ESI−): calcd for $C_{16}H_{13}O_5$ $[M - H]^-$, 285.0768, found 285.0779.

*Crystallization of **7a**, **8a**, and **7f** for X-ray Crystallographic Analysis.* Each of the compounds (**7a**, **8a**, and **7f**; ca. 10 mg) was dissolved in CH_2Cl_2 (1.0 mL) in a small vial, which was placed in a 20 mL scintillation vial containing pentane (3 mL). The outer vial was sealed with a screw cap and left at an ambient temperature for crystallization.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01534.

Single crystal XRD data of **7a**, **8a**, and **7f**, and NMR spectra for all synthesized compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a**−**3g**, **7a**−**7g**, **8a**−**8g**, **9**, and **10** (ZIP)

Accession Codes

CCDC 2086783−2086785 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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