

Template-Directed Selective Photodimerization Reactions of 5-Arylpenta-2,4-dienoic Acids

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Cite This: *J. Org. Chem.* 2024, 89, 10409–10418



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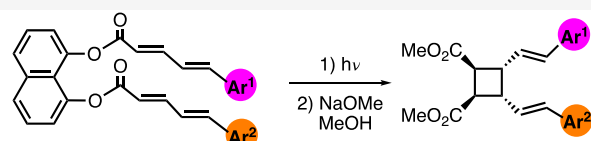
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ABSTRACT: We developed an efficient method that enables selective photodimerization of 5-arylpenta-2,4-dienoic acids (i.e., vinylogous cinnamic acids). The use of 1,8-dihydroxynaphthalene as a template ensures proximity of the two reacting olefins so that irradiation of template-bound dienoic acids gives mono [2 + 2] cycloaddition products in good to excellent yields (up to 99%), as single regioisomers, and with high diastereoselectivities (dr = 3:1 to 13:1). The geometrical and stereochemical features of compounds **12a**, **16a**, and **22a** were analyzed by X-ray crystallography.

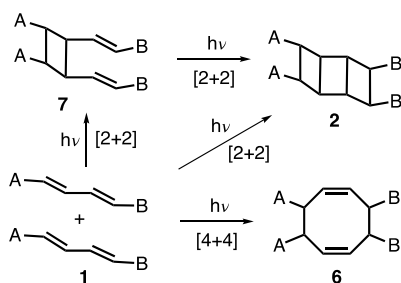


- selective photodimerization of vinylogous cinnamic acids
- works successfully both in solid state and solution phase

- up to 99% cycloaddition yields
- single regioisomers; high diastereoselectivities (dr = 3:1 to 13:1)

Photochemical [2 + 2] cycloadditions of olefins provide direct access to multisubstituted cyclobutanes.¹ Although remarkable advances have been witnessed since the early studies of Ciamician,² analogous reactions of dienes and higher polyenes are surprisingly underdeveloped despite their synthetic potential.³ In one pathway, photodimerization of diene **1** may provide [3]-ladderane product **2** via double [2 + 2] cycloaddition reactions (Scheme 1). [n]-Ladderanes⁴ are a

Scheme 1. Possible Photodimerization Pathways of 1



class of structurally intriguing polycyclobutanes, which are also present in naturally occurring phospholipids in anammox bacteria.^{5,6} Pioneering work of Hopf and co-workers demonstrated that [2,2]-paracyclophane core could be used to suitably orient two polyenes for the synthesis of [3]- and [5]-ladderanes (Scheme 2a).⁷ In an elegant design reported in 2004, MacGillivray and co-workers used 5-methoxyresorcinol (3) as a hydrogen bonding template to build supramolecular assemblies with bis(4-pyridyl)polyenes **4**, the irradiation of which afforded quantitatively [3]- and [5]-ladderanes **5a** and **5b** (Scheme 2b).⁸

Alternatively, irradiation of **1** may give cyclooctadiene **6** either via a direct [4 + 4] cycloaddition or an initial [2 + 2] cycloaddition followed by a thermal Cope rearrangement of

divinylcyclobutane **7** (Scheme 1).⁹ As a third possibility, due to certain electronic and/or geometrical factors, photodimerization of **1** may proceed via a single [2 + 2] cycloaddition affording divinylcyclobutane **7** (Scheme 1).¹⁰ In their elegant studies, Weiss and co-workers showed that intermolecular [2 + 2] cycloadditions can be photocatalyzed using quantum dots via triplet–triplet energy transfer.¹¹ In particular, subjecting dienes **8** to photocatalysis by CdSe quantum dots or nanoplatelets gave divinylcyclobutanes **9** with high diastereoselectivities (Scheme 2c).^{11b}

We recently developed a general solution for the selective photodimerization of cinnamic acids using 1,8-dihydroxynaphthalene (1,8-DHN) as a covalent template.¹² In this design, irradiation of template-bound cinnamic acids **10** followed by hydrolysis gave symmetrical and unsymmetrical β -truxinic acids **11** in high yields and as single diastereomers (Scheme 2d). Despite the rich background^{1b} and recent advances^{12,13} in the photodimerization of cinnamic acid derivatives, the analogous reactions of vinylogous cinnamic acids, namely 5-arylpenta-2,4-dienoic acids, are scarce. Indeed, besides the work of Hopf mentioned above,⁷ and an early report from 1913,¹⁴ to our knowledge, there are only a few studies which involve photodimerization of 5-arylpenta-2,4-dienoic acids. In 1971, Schmidt and co-workers reported the formation of a complex mixture of four- and eight-membered products (seven spots on TLC other than the reactant) upon solid-state irradiation of 5-phenylpenta-2,4-dienoic acid.^{9a} In a second

Received: May 31, 2024

Revised: June 24, 2024

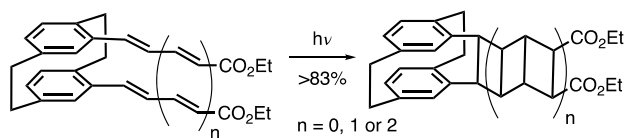
Accepted: July 1, 2024

Published: July 10, 2024

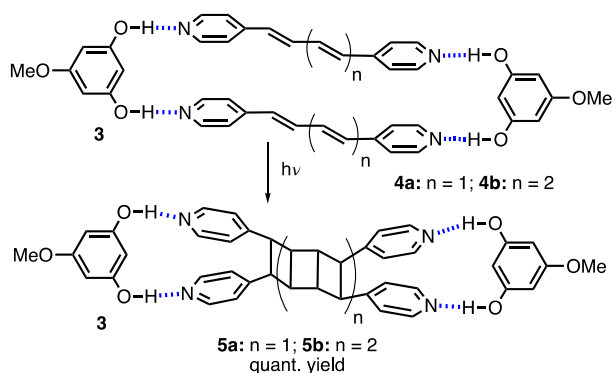


Scheme 2. Examples of [2 + 2] Cycloadditions of Alkenes and Dienes

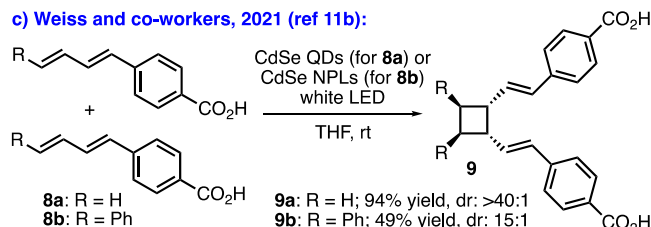
a) Hopf and co-workers, 1995 (ref 7a):



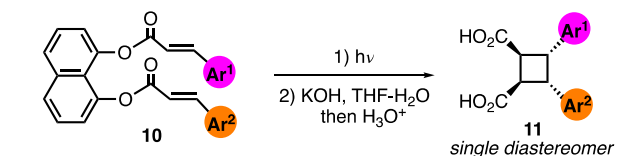
b) MacGillivray and co-workers, 2004 (ref 8a):



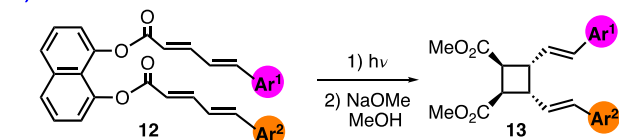
c) Weiss and co-workers, 2021 (ref 11b):



d) Our previous work, 2021 and 2023 (ref 12a and 12b):



e) This work:



study, irradiation of 5-(3-methoxyphenyl)penta-2,4-dienoic acid in solid state was reported by Mascitti and Corey to proceed with a head-to-tail [2 + 2] cycloaddition between the two different olefins of the reactants.^{6b} Recently, Yoon and co-workers reported a single example of an *anti*-head-to-head [2 + 2] cycloaddition of a vinylous cinnamamide derivative for the synthesis of nigramide R.^{13b} The lack of success in selective photodimerization of vinylous cinnamic acids is not surprising given the challenges associated with the presence of two types of olefins that can react with one another, and due to the cycloaddition possibilities in *syn* and *anti* head-to-head and head-to-tail orientations resulting in 12 possible mono [2 + 2] cycloadducts without considering enantiomers (Figure S1). In this work, we applied our template-directed strategy to develop a general solution for the first time to the selective homo- and heterodimerization of 5-arylpenta-2,4-dienoic acids (Scheme 2e). This way, out of the 12 possible cycloaddition products, the *syn*-head-to-head cycloadducts 13 were obtained selectively.

The synthesis of [2 + 2] cycloaddition precursors is described in Scheme 3. The Horner-Wadsworth-Emmons reaction between cinnamaldehydes 14 and triethyl phosphonoacetate gave esters 15 with (*E,E*) configuration in 78–98% yields, and their subsequent hydrolysis afforded 5-arylpenta-2,4-dienoic acids 16 in uniformly high yields (89–98%). The synthesis of symmetrical diesters 12a-c was accomplished via the reaction of 1,8-DHN (17) with excess dienoic acids using DCC (dicyclohexylcarbodiimide) in 66–72% yields. For the synthesis of unsymmetrical diesters 12d and 21, monoester 19 was prepared first by reacting 1,8-DHN (17) with acyl chloride 18 under basic conditions (71%). A subsequent coupling of 19 with dienoic acid 16d afforded 12d in moderate yield (48%). Finally, treatment of a 1:1 mixture of 19 and *trans*-cinnamoyl chloride (20) with one equivalent of NaH afforded diester 21 in 70% yield.

Our studies on the targeted photocycloaddition commenced by investigating the irradiation of diester 12a (Tables S1 and S2). Initially, when a powder sample of 12a was irradiated with UV light (365 nm) for 16 h, cycloadduct 22a was isolated in 30% yield and with a diastereomeric ratio (dr) of 8:1 (Table S1, entry 1). Increasing the irradiation time to 48 h had a limited effect on the yield (52%, entry 2). The crystal structure of 12a revealed that the two alkenes neighboring the carbonyl groups have criss-crossed geometry with a distance of 4.00 Å between their centroids (Figure 1a). However, *syn*-head-to-head photocycloaddition process was confirmed by the crystal structure of 22a (Figure 1b). Pedal motion¹⁵ in solid state was previously proposed to account for the reactivity of such criss-crossed alkenes in [2 + 2] cycloadditions.^{12a,16} The distance of 4.00 Å between the reacting alkene centroids fulfills Schmidt criteria (<4.2 Å),¹⁷ and provides a rationale for the success of this reaction. Conversely, the distance between the second set of alkenes is 5.06 Å (Figure 1a). Even though this distance may be shorter after pedal motion, it is anticipated that it will still be greater than 4.2 Å rendering these olefins photoresistant.

Since grinding was proposed to facilitate pedal motion in solid state,^{16d} we opted to check its effect on the reaction performance. However, when ground powder samples of 12a were irradiated for 16 and 48 h, almost no improvement was observed (Table S1, entries 3 and 4). The powder XRD patterns of the powder and ground powder forms match the simulated pattern generated from its single-crystal XRD data meaning that structure of 12a is retained in the bulk powder and ground powder forms (Figure S2). To our delight, running the cycloaddition in CHCl₃ appeared to be superior providing 22a in 88% yield (dr: 8:1, entry 5). When this reaction was performed on 1.0 mmol scale, 22a was isolated in 61% yield (71% yield based on recovered starting material, entry 6). Finally, irradiation of a powder sample of untemplated 16a gave a complex mixture of products, in agreement with Schmidt's observation.^{9a} Our X-ray crystallographic analysis of 16a shows a dimeric structure governed by hydrogen bonds, and matches the structure reported in 1980 (Figure S6).¹⁸ Its crystal packing reveals several olefin orientations which can potentially give [2 + 2] cycloadditions, providing an explanation for the formation of multiple products.

Next, we focused on the photochemical [2 + 2] reactions of other substrates (Scheme 4), which were tested both in solid state and solution (CHCl₃), and subsequently, all cycloadducts were converted to their dimethyl esters via transesterification. For instance, cyclobutane dimethyl ester 13a was obtained in 89% yield when 22a was treated with NaOMe in MeOH. The

Scheme 3. Synthesis of Template-Bound Cycloaddition Precursors

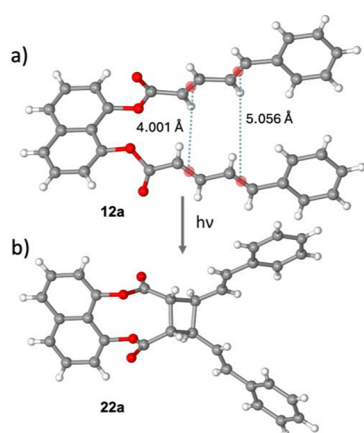
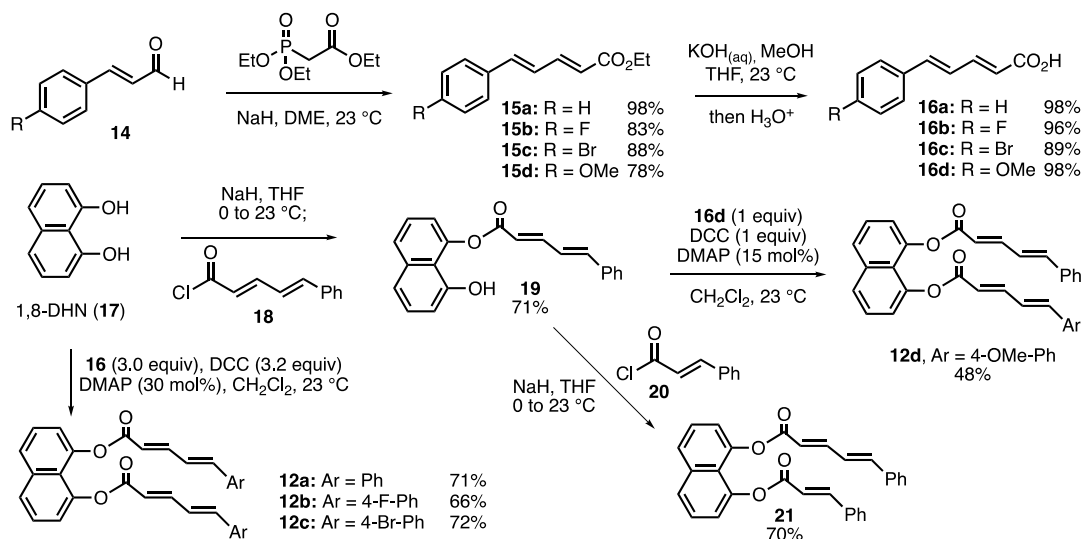


Figure 1. Crystal structures of 12a and 22a.

[2 + 2] cycloaddition of 4-fluorophenyl-substituted diester **12b** proceeded with excellent yields in both solid state and solution (99 and 96%, respectively). However, reaction of the analogous 4-bromophenyl-substituted diester **12c** was inefficient in solid state affording cycloadduct **22c** in only 17% yield, possibly due to an unsuitable olefin orientation in crystal structure. Pleasingly, the same product was isolated in 63% yield and with high dr (11:1) when the reaction was performed in solution. Gratifyingly, reaction of the unsymmetrical diester **12d** proceeded successfully both in solid state and solution to provide the heterodimerization product **22d** in 53 and 84% yields, respectively. To our knowledge, this is the first example of a photochemical heterodimerization between two different 5-arylpenta-2,3-dienoic acids. Finally, the reaction of **21**, which possesses a dienoic acid and cinnamic acid units, gave [2 + 2] cycloadduct **23** in moderate yields of 47 and 42%, respectively, in solid state and solution. All cycloadducts were detached from the template by the aforementioned transesterification reaction affording cyclobutane dimethyl esters in 65–89% yields.

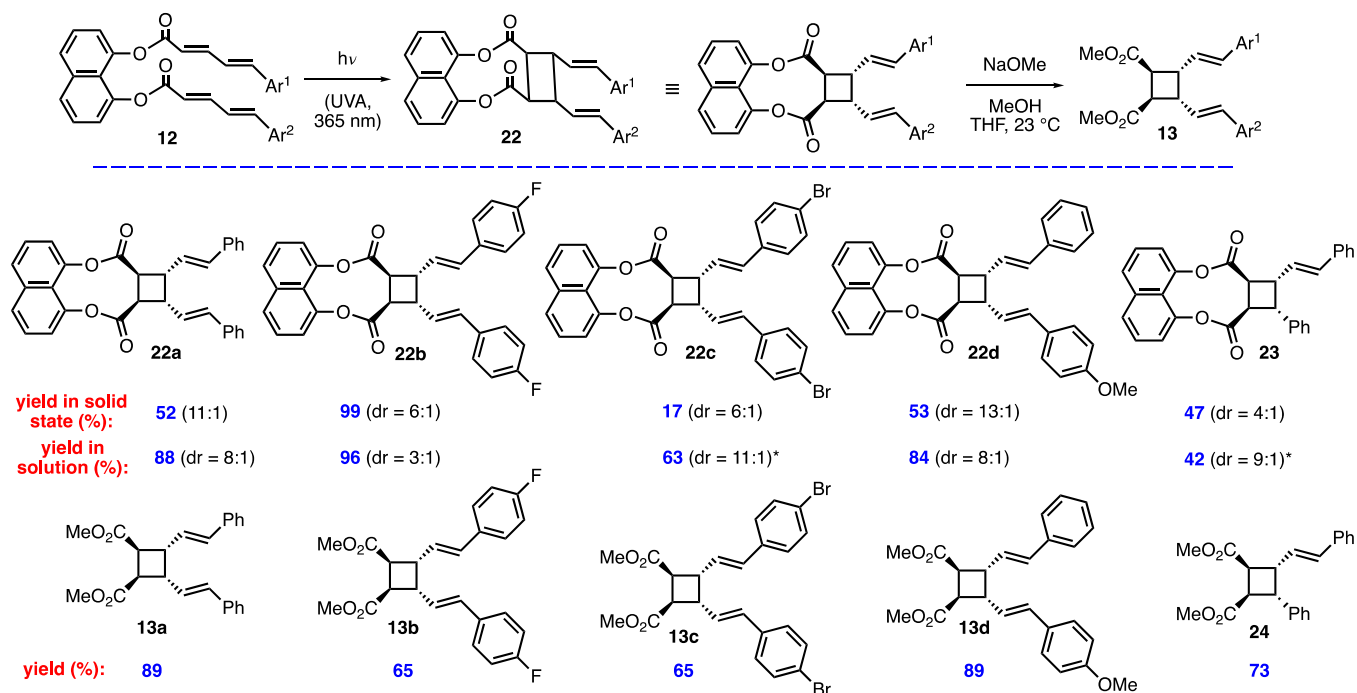
In addition to the transesterification reactions, detachment from the template could also be achieved by other transformations. In this respect, hydrolysis of **22a** afforded dicarboxylic acid **25** in 69% yield (Scheme 5). Moreover, diol **26** was isolated in 65% yield upon reduction of the two

ester groups of **22a**. In control experiments, when toluene solutions of diesters **12a** and **21** were heated at 100 °C under dark, no reaction was observed (Scheme S1). Finally, Cope rearrangement of **22a** and **13a** to access 1,5-cyclooctadiene products was attempted under thermal conditions (Tables S3 and S4). Disappointingly, none of the screened conditions gave the desired cyclooctadienes, possibly due to the steric clash of the two bulky phenyl rings in the transition states.

In conclusion, we developed the first general method for the selective photodimerization of vinylogous cinnamic acids. Attachment of two dienoic acids to 1,8-DHN (**17**) brings the two reactants spatially close to each other enabling an efficient [2 + 2] cycloaddition. Irradiation of diesters **12a–d** proceeded effectively both in solid state and solution affording the homo- and heterodimerization products **22a–d** in up to 99% yields, with full regiocontrol and high diastereoselectivities. Cycloadducts were demonstrated to be easily convertible to cyclobutane dicarboxylic ester, dicarboxylic acid and diol products. X-ray crystallographic analysis of diester **12a** provided a rationale for the observed regioselectivity, whereas the X-ray structure of cycloadduct **22a** confirmed its stereochemistry.

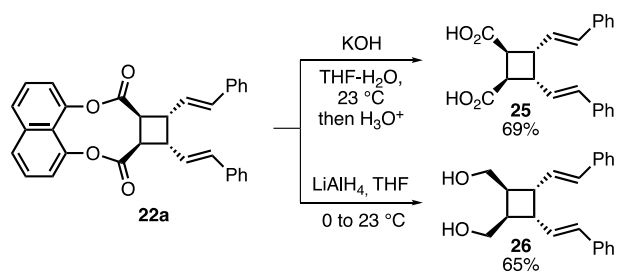
EXPERIMENTAL SECTION

General Information. All air or water sensitive reactions were performed using oven-dried glassware under nitrogen. Reactions were monitored by thin-layer chromatography (TLC) using aluminum-backed plates precoated with silica gel (Silicycle, 60 Å, F₂₅₄). UV light (254 nm) and KMnO₄ staining solution were used for TLC visualization. Flash column chromatography was carried out using Silicycle 40–63 μm (200–400 mesh) flash silica gel. NMR spectra were recorded using a Bruker spectrometer at 400 MHz for ¹H NMR spectra and 100 MHz for ¹³C{¹H} spectra, and calibrated from internal standard (TMS, 0 ppm) or residual solvent signals (chloroform at 7.26, DMSO at 2.50, and methanol at 3.31 ppm for ¹H NMR spectra; chloroform at 77.16, DMSO at 39.52, and methanol at 49.00 ppm for ¹³C{¹H}-NMR spectra). For ¹⁹F{¹H}-NMR experiments, trifluoroacetic acid (CF₃CO₂H) was used as external reference (−76.55 ppm). ¹H NMR data are reported as follows: chemical shift (ppm, parts per million), integration, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, m = multiplet, br s = broad signal, app = apparent), coupling constant (Hz). Infrared (FTIR-ATR) spectra were recorded using a Bruker Alpha-Platinum-ATR spectrometer, and selected peaks are reported.

Scheme 4. Synthesis of Cyclobutane Diesters 13 and 24^a

^aDiastereomeric ratio (dr) values were determined by ¹H-NMR analysis of crude reaction mixtures. *These dr values belong to purified products.

Scheme 5. Hydrolysis and Reduction Reactions of 22a



HRMS (high resolution mass spectrometry) analyses were carried out at UNAM-National Nanotechnology Research Center and Institute of Materials Science and Nanotechnology, Bilkent University, using Agilent Technologies 6224 TOF LC/MS instrument. Single-crystal XRD analysis was performed at Gebze Technical University, Türkiye. Melting points are uncorrected. Photochemical reactions were performed using a commercial UV gel nail dryer (Elle by Beurer, MPES8) equipped with four 9W UV-A (365 nm) fluorescent lamps (Philips PL-S).¹² Anhydrous CH₂Cl₂ and THF were purchased from Acros Organics (AcroSeal). 1,8-Dihydroxynaphthalene was purchased from abcr and used as received. All commercially available reagents were used without further purification, unless stated otherwise. **Caution!** Reactions which require oxalyl chloride, and its subsequent evaporation using a rotary evaporator should be conducted inside a well-ventilated fume hood. Also, caution should be taken when working with ultraviolet radiation.

Ethyl (2*E*,4*E*)-5-Phenylpenta-2,4-dienoate (15a). Triethylphosphonoacetate (2.21 g, 9.84 mmol) was dissolved in 11 mL of DME (1,2-dimethoxyethane) in an oven-dried 50 mL round-bottom flask under nitrogen at 23 °C. NaH (453 mg, 11.36 mmol, 60% dispersion in mineral oil) was added slowly to this solution cooled in an ice bath. Upon the addition of NaH, gas evolution was observed. The reaction mixture was allowed to stir for 25 min in ice bath. Then, *trans*-cinnamaldehyde (1.00 g, 7.57 mmol) was added to the reaction mixture, and the walls of the flask were rinsed with 2 mL of DME. The reaction mixture was stirred at 23 °C for 2 h, and the progress of

the reaction was monitored using TLC (EtOAc/hexanes = 1:19). The reaction mixture was then quenched with a saturated aqueous solution of NH₄Cl (15 mL). The aqueous phase was extracted thrice with CH₂Cl₂. The organic phases were combined, dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. Purification by flash column chromatography (EtOAc/hexanes = 1:19) gave pure product 15a (1.50 g, 98%) as a pale yellow oil. *R*_f = 0.53 (EtOAc/hexanes = 1:19). ¹H NMR (400 MHz, CDCl₃) δ: 7.44–7.36 (3H, m), 7.30–7.21 (3H, m), 6.82–6.74 (2H, m), 5.96 (1H, d, *J* = 15.3 Hz), 4.21 (2H, q, *J* = 7.1 Hz), 1.28 (3H, t, *J* = 7.1 Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ: 167.2, 144.6, 140.5, 136.2, 129.1, 128.9, 127.3, 126.4, 121.5, 60.5, 14.5. The NMR data are in agreement with the values reported in the literature.¹⁹

Ethyl (2*E*,4*E*)-5-(4-Fluorophenyl)penta-2,4-dienoate (15b). Compound 15b was prepared from (*E*)-3-(4-fluorophenyl)acrylaldehyde (500 mg, 435 μL, 3.33 mmol), triethylphosphonoacetate (1.12 g, 5.00 mmol), NaH (200 mg, 5.00 mmol, 60% dispersion in mineral oil) and DME (5 mL) following the same procedure as used for compound 15a. The crude product was purified using flash column chromatography (EtOAc/hexanes = 1:19) to afford 15b (612 mg, 83%) as a white solid. *R*_f = 0.42 (EtOAc/hexanes = 1:19) ¹H NMR (400 MHz, CDCl₃) δ: 7.41–7.35 (3H, m), 6.99 (2H, t, *J* = 8.6 Hz), 6.81–6.69 (2H, m), 5.94 (1H, d, *J* = 15.2 Hz), 4.19 (2H, q, *J* = 7.2 Hz), 1.27 (3H, t, *J* = 7.1 Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ: 166.9, 163.0 (d, *J* = 249.7 Hz), 144.3, 138.9, 132.3 (d, *J* = 3.4 Hz), 128.9 (d, *J* = 8.2 Hz), 126.0 (d, *J* = 2.4 Hz), 121.4, 115.8 (d, *J* = 21.9 Hz), 60.3, 14.3. ¹⁹F{¹H}-NMR (376 MHz, CDCl₃) δ: −110.4. The NMR data are in agreement with the values reported in the literature.²⁰

Ethyl (2*E*,4*E*)-5-(4-Bromophenyl)penta-2,4-dienoate (15c). Compound 15c was prepared from (*E*)-3-(4-bromophenyl)acrylaldehyde (450 mg, 2.13 mmol), triethylphosphonoacetate (621 mg, 2.77 mmol), NaH (128 mg, 3.19 mmol, 60% dispersion in mineral oil) and DME (7 mL) using the same procedure as used for compound 15a. The crude product was purified using flash column chromatography (EtOAc/hexanes = 1:19) to afford 15c (523 mg, 88%) as a white solid. *R*_f = 0.42 (EtOAc/hexanes = 1:9) ¹H NMR (400 MHz, CDCl₃) δ: 7.46 (2H, d, *J* = 8.4 Hz), 7.41 (1H, ddd, *J* = 15.4, 8.7, 1.4 Hz), 7.30 (2H, d, *J* = 8.5 Hz), 6.89–6.75 (2H, m), 5.99

(1H, d, $J = 15.3$ Hz), 4.22 (2H, q, $J = 7.1$ Hz), 1.30 (2H, t, $J = 7.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 167.0, 144.2, 138.9, 135.1, 132.1, 128.7, 127.1, 123.1, 122.1, 60.5, 14.4. The NMR data are in agreement with the values reported in the literature.¹⁹

Ethyl (2E,4E)-5-(4-Methoxyphenyl)penta-2,4-dienoate (15d). Compound **15d** was prepared from (*E*)-3-(4-methoxyphenyl)acrylaldehyde (500 mg, 3.08 mmol), triethylphosphonoacetate (1.04 g, 917 μL , 4.62 mmol), NaH (111 mg, 4.62 mmol, 60% dispersion in mineral oil) and DME (10 mL) using the same procedure as used for compound **15a**. The crude product was purified using flash column chromatography (EtOAc/hexanes = 1:19) to afford **15d** (557 mg, 78%) as a white solid. $R_f = 0.30$ (EtOAc/hexanes = 1:19). ^1H NMR (400 MHz, CDCl_3) δ : 7.49–7.36 (3H, m), 6.93–6.82 (3H, m), 6.75 (1H, dd, $J = 15.5$, 10.8 Hz), 5.94 (1H, d, $J = 15.3$ Hz), 4.22 (2H, q, $J = 7.1$ Hz), 3.83 (3H, s), 1.31 (3H, t, $J = 7.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 167.4, 160.6, 145.1, 140.2, 129.1, 128.8, 124.4, 120.2, 114.4, 60.4, 55.5, 14.5. The NMR data are in agreement with the values reported in the literature.¹⁹

(2E,4E)-5-Phenylpenta-2,4-dienoic Acid (16a). To a solution of compound **15a** (1.00 g, 4.94 mmol) in 1:2 mixture of MeOH and THF (15 mL) at 23 °C in a 100 mL round-bottom flask, 5 M aqueous solution of KOH (5 mL) was added, and the reaction mixture was allowed to stir at 23 °C. Progress of the reaction was monitored using TLC (EtOAc/hexanes = 1:1). Full consumption of **15a** was observed after 1 h. The solvents were removed directly under reduced pressure, and a white slurry was obtained. This white slurry was dissolved in fresh CHCl_3 , and then, conc. HCl was added dropwise until the pH of the solution turned 1–2. The organic phase was washed once with distilled water, and then the aqueous phase was extracted thrice with EtOAc. Organic phases were combined, dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum to give pure product **16a** (841 mg, 98%) as a shiny white solid. $R_f = 0.69$ (EtOAc/hexanes = 1:1). ^1H NMR (400 MHz, CDCl_3) δ : 7.55 (1H, dd, $J = 15.1$, 9.7 Hz), 7.49 (2H, app d, $J = 6.9$ Hz), 7.39–7.31 (m, 3H), 6.99–6.87 (m, 2H), 6.01 (1H, d, $J = 15.3$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 172.5, 147.1, 141.8, 136.0, 129.5, 129.0, 127.5, 126.1, 120.5. The NMR data are in agreement with the values reported in the literature.²¹

(2E,4E)-5-(4-Fluorophenyl)penta-2,4-dienoic Acid (16b). Compound **16b** was prepared using **15b** (620 mg, 2.82 mmol), 5 M KOH aqueous solution (10 mL), MeOH (5 mL) and THF (10 mL) using the same procedure as used for compound **16a**. After workup, **16b** (520 mg, 96%) was obtained as a white solid. $R_f = 0.55$ (EtOAc/hexanes = 1:1). ^1H NMR (400 MHz, CDCl_3) δ : 7.55–7.44 (3H, m), 7.06 (2H, t, $J = 8.2$ Hz), 6.91 (1H, d, $J = 15.7$ Hz), 6.82 (1H, dd, $J = 15.7$, 10.7 Hz), 5.99 (1H, d, $J = 15.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 167.6, 162.3 (d, $J = 247.0$ Hz), 143.9, 138.3, 132.7 (d, $J = 3.1$ Hz), 129.2 (d, $J = 8.4$ Hz), 126.6 (d, $J = 2.4$ Hz), 122.6, 115.7 (d, $J = 21.6$ Hz). $^{19}\text{F}\{^1\text{H}\}$ -NMR (376 MHz, CDCl_3) δ : –109.9. The NMR data are in agreement with the values reported in the literature.^{20,21}

(2E,4E)-5-(4-Bromophenyl)penta-2,4-dienoic Acid (16c). Compound **16c** was prepared using **15c** (520 mg, 1.86 mmol), 5 M KOH aqueous solution (6 mL), MeOH (3 mL) and THF (6 mL) using the same procedure as used for compound **16a**. After workup, **16c** (416 mg, 89%) was obtained as a white solid. $R_f = 0.38$ (EtOAc/hexanes = 1:1). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 7.59 (2H, d, $J = 8.5$ Hz), 7.52 (2H, d, $J = 8.5$ Hz), 7.33 (1H, dd, $J = 15.1$, 10.7 Hz), 7.15 (1H, dd, $J = 15.5$, 10.7 Hz), 7.03 (1H, d, $J = 15.6$ Hz), 6.03 (1H, d, $J = 15.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 167.4, 144.0, 138.4, 135.3, 131.8, 129.0, 127.5, 122.8, 122.0. The NMR data are in agreement with the values reported in the literature.²²

(2E,4E)-5-(4-Methoxyphenyl)penta-2,4-dienoic Acid (16d). Compound **16d** was prepared using **15d** (495 mg, 2.13 mmol), 5 M KOH aqueous solution (20 mL), MeOH (10 mL) and THF (20 mL) using the same procedure as used for compound **16a**. After workup, **16d** (425 mg, 98%) was obtained as a pale yellow solid. $R_f = 0.42$ (EtOAc/hexanes = 1:1). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 12.15 (1H, s), 7.51 (2H, d, $J = 8.8$ Hz), 7.32 (1H, ddd, $J = 15.2$, 9.0, 1.2 Hz), 7.02–6.92 (4H, m), 5.93 (1H, d, $J = 15.2$ Hz), 3.78 (3H, s).

$^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, $\text{DMSO}-d_6$) δ : 167.6, 160.0, 144.8, 139.7, 128.7, 124.3, 120.8, 114.3, 56.2. The NMR data are in agreement with the values reported in the literature.²³

Naphthalene-1,8-diyl (2E,2'E,4E,4'E)-Bis-5-phenylpenta-2,4-dienoate (12a). Carboxylic acid **16a** (530 mg, 3.04 mmol) was dissolved in 8 mL of anhydrous CH_2Cl_2 under nitrogen at 23 °C. To this solution, 1,8-DHN (**17**) (162 mg, 1.01 mmol), DCC (667 mg, 3.23 mmol), and DMAP (37 mg, 0.30 mmol) were added sequentially. The reaction mixture was stirred at 23 °C for 24 h. The reaction mixture was filtered through Celite (CH_2Cl_2 was used to aid filtration). The organic phase was washed once with distilled water, and the aqueous phase was extracted thrice with CH_2Cl_2 . Organic phases were combined, dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. Purification by column chromatography (CH_2Cl_2 /hexanes = 1:1) gave pure product **12a** (335 mg, 71%) as a white solid. **Note:** The compound is light-sensitive so it should be kept in the dark or wrapped with Al foil. Mp: 207–209 °C. $R_f = 0.22$ (DCM/hexanes = 1:1). ^1H NMR (400 MHz, CDCl_3) δ : 7.80 (2H, d, $J = 8.3$ Hz), 7.62 (2H, dd, $J = 15.3$ Hz, 10.3 Hz), 7.48 (2H, t, $J = 7.0$ Hz), 7.27–7.21 (6H, m), 7.19–7.14 (6H, m), 6.92–6.80 (4H, m), 6.15 (2H, d, $J = 15.3$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 166.0, 146.9, 145.4, 142.0, 137.0, 135.7, 129.3, 128.9, 127.4, 127.0, 126.2, 126.0, 121.6, 120.8. FTIR ν_{max} (ATR, film)/ cm^{-1} : 3055, 3024, 1728, 1621, 1448, 1345, 1312, 1225, 1167. HRMS (ESI+) calcd for $\text{C}_{32}\text{H}_{24}\text{NaO}_4$ [$\text{M} + \text{Na}$] $^+$: 495.1567, found 495.1543.

Naphthalene-1,8-diyl (2E,2'E,4E,4'E)-Bis(5-(4-fluorophenyl)penta-2,4-dienoate) (12b). Compound **12b** was prepared using **16b** (179 mg, 0.93 mmol), 1,8-DHN (**17**) (50 mg, 0.31 mmol), DCC (204 mg, 0.99 mmol), DMAP (11 mg, 0.09 mmol) and anhydrous CH_2Cl_2 (10 mL) was the same procedure as used for compound **12a**. Purification by flash column chromatography (CH_2Cl_2 /hexanes = 1:1) afforded **12b** (103 mg, 66%) as a white solid. **Note:** The compound is light-sensitive so it should be kept in the dark or wrapped with Al foil. Mp: 274–276 °C. $R_f = 0.63$ (DCM/hexanes = 1:1). ^1H NMR (400 MHz, CDCl_3) δ : 7.82 (2H, d, $J = 8.3$ Hz), 7.58 (2H, dd, $J = 15.3$, 10.7 Hz), 7.49 (2H, t, $J = 7.9$ Hz), 7.23–7.16 (6H, m), 6.88–6.81 (6H, m), 6.72 (2H, dd, $J = 15.6$, 10.7 Hz), 6.14 (2H, d, $J = 15.3$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 165.9, 163.4 (d, $J = 250.7$ Hz), 146.6, 145.4, 140.4, 137.0, 131.9 (d, $J = 2.9$ Hz), 129.0 (d, $J = 8.2$ Hz), 127.0, 126.2, 125.80, 125.78, 121.0, 120.8, 116.0 (d, $J = 2.1$ Hz). $^{19}\text{F}\{^1\text{H}\}$ -NMR (376 MHz, CDCl_3) δ : –109.9. FTIR ν_{max} (ATR, film)/ cm^{-1} : 2957, 2920, 2851, 1744, 1723, 1625, 1597, 1508, 1234, 1156. HRMS (ESI+) calcd for $\text{C}_{32}\text{H}_{22}\text{NaO}_4\text{F}_2$ [$\text{M} + \text{Na}$] $^+$: 531.1378, found 531.1380.

Naphthalene-1,8-diyl (2E,2'E,4E,4'E)-Bis(5-(4-bromophenyl)penta-2,4-dienoate) (12c). Compound **12c** was prepared using **16c** (50 mg, 0.21 mmol), 1,8-DHN (**17**) (11.2 mg, 0.069 mmol), DCC (43.3 mg, 0.21 mmol), DMAP (2.8 mg, 0.02 mmol) and anhydrous CH_2Cl_2 (5 mL) was the same procedure as used for compound **12a**. Purification by flash column chromatography (CH_2Cl_2 :hexanes = 1:1) afforded **12c** (31.6 mg, 72%) as a white solid. **Note:** The compound is light-sensitive so it should be kept in the dark or wrapped with Al foil. Mp: 248–249 °C. $R_f = 0.45$ (DCM/hexanes = 1:1). ^1H NMR (400 MHz, CDCl_3) δ : 7.82 (2H, d, $J = 9.1$ Hz), 7.57 (2H, ddd, $J = 15.3$, 7.1, 3.2 Hz), 7.51–7.47 (2H, m), 7.28 (4H, d, $J = 8.5$ Hz), 7.17 (2H, d, $J = 8.3$ Hz), 7.05 (4H, d, $J = 8.5$ Hz), 6.78–6.77 (4H, m), 6.15 (2H, d, $J = 15.3$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 165.8, 146.4, 145.3, 145.1, 140.3, 137.0, 134.4, 132.1, 128.6, 127.0, 126.6, 126.2, 123.7, 121.5, 120.8. FTIR ν_{max} (ATR, film)/ cm^{-1} : 1726, 1620, 1599, 1581, 1484, 1313, 1264, 1122. HRMS (APCI+) calcd for $\text{C}_{32}\text{H}_{23}\text{O}_4^{79}\text{Br}_2$ [$\text{M} + \text{H}$] $^+$: 628.9958, found 628.9960; calcd for $\text{C}_{32}\text{H}_{23}\text{O}_4^{79}\text{Br}^{81}\text{Br}$ [$\text{M} + \text{H}$] $^+$: 630.9938, found 630.9942; calcd for $\text{C}_{32}\text{H}_{23}\text{O}_4^{81}\text{Br}_2$ [$\text{M} + \text{H}$] $^+$: 632.9917, found 632.9917.

8-Hydroxynaphthalen-1-yl-(2E,4E)-5-phenylpenta-2,4-dienoate (19). In a 25 mL round-bottom flask, **16a** (250 mg, 1.44 mmol) was dissolved in 3 mL of oxalyl chloride at 23 °C under nitrogen atmosphere. This solution was stirred in a preheated oil bath at 60 °C for 2 h. Afterward, the reaction mixture was cooled to room

temperature, and all volatiles were removed by a rotary evaporator to give acyl chloride **18** (271 mg, 98%) as a yellow solid. In another 50 mL round-bottom flask, 1,8-DHN (**17**) (226 mg, 1.41 mmol) was dissolved in 5 mL of anhydrous THF under an inert atmosphere of nitrogen. This solution was cooled to 0 °C in an ice bath, and NaH (62 mg, 1.55 mmol, 60% dispersion in mineral oil) was added portionwise. The reaction mixture was then stirred at this temperature for 20 min. Acyl chloride **18** (271 mg, 1.41 mmol), which was prepared as described above, was dissolved in 5 mL of anhydrous THF, and this solution was added slowly to the reaction mixture. Then, the reaction mixture was stirred at 23 °C for 3 h. After full consumption of 1,8-DHN (**17**), the reaction mixture was quenched with 10 mL of saturated aqueous NH₄Cl solution. The aqueous phase was extracted thrice with EtOAc. Combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. Purification by flash column chromatography (EtOAc/hexanes = 1:5) afforded pure product **19** (316 mg, 71%) as an orange solid. $R_f = 0.66$ (EtOAc/hexanes = 1:5). ¹H NMR (400 MHz, CDCl₃) δ : 7.75–7.68 (2H, m), 7.51–7.48 (3H, m), 7.45–7.31 (6H, m), 7.24 (1H, d, $J = 7.5$ Hz), 7.04–6.93 (2H, m), 6.87 (1H, d, $J = 6.9$ Hz), 6.28 (1H, d, $J = 15.2$ Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ : 164.7, 152.2, 148.1, 146.2, 142.9, 137.0, 135.8, 129.7, 129.0, 127.6, 127.3, 126.5, 125.9, 125.5, 120.3, 119.2, 118.5, 117.1, 111.5. FTIR ν_{\max} (ATR, film)/cm⁻¹: 3385, 3057, 1702, 1621, 1600, 1580, 1393, 1278, 1263, 1174. HRMS (APCI+) calcd for C₂₁H₁₇O₃ [M + H]⁺: 317.1172, found 317.1175.

8-(((2E,4E)-5-(4-Methoxyphenyl)penta-2,4-dienoyl)oxy)naphthalen-1-yl (2E,4E)-(5-Phenylpenta-2,4-dienoate) (12d).

In an oven-dried 50 mL round-bottom flask, **16d** was dissolved in anhydrous CH₂Cl₂ (8 mL) under a nitrogen atmosphere at 23 °C. Monoester **19** (234 mg, 0.74 mmol), DCC (153 mg, 0.74 mmol), and DMAP (13.4 mg, 0.11 mmol) were added sequentially. The reaction mixture was stirred at 23 °C for 21 h. Then, the reaction mixture was quenched with saturated aqueous NH₄Cl solution, and the aqueous phase was extracted thrice with CH₂Cl₂. The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded pure product **12d** (178 mg, 48%) as a white solid. **Note:** The compound is light-sensitive so it should be kept in the dark or wrapped with Al foil. Mp: 177–179 °C. $R_f = 0.39$ (CH₂Cl₂/hexanes = 1:1) ¹H NMR (400 MHz, CDCl₃) δ : 7.80 (2H, d, $J = 8.3$ Hz), 7.61 (2H, ddd, $J = 14.9, 10.6, 4.1$ Hz), 7.48 (2H, t, $J = 7.9$ Hz), 7.25–7.22 (3H, m), 7.21–7.16 (6H, m), 6.91–6.79 (3H, m), 6.74–6.65 (3H, m), 6.16 (1H, d, $J = 15.2$ Hz), 6.10 (1H, d, $J = 15.3$ Hz), 3.78 (3H, s). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ : 166.1, 166.0, 160.7, 147.4, 146.8, 145.5, 141.8, 137.0, 135.8, 131.0, 129.2, 128.9, 128.8, 128.6, 127.4, 126.91, 126.85, 126.2, 126.13, 126.08, 123.9, 121.7, 120.9, 120.8, 120.7, 119.5, 114.4, 55.4. FTIR ν_{\max} (ATR, film)/cm⁻¹: 3058, 2837, 1725, 1624, 1597, 1509, 1448, 1348, 1250, 1228, 1175. HRMS (APCI+) calcd for C₃₃H₂₇O₅ [M + H]⁺: 503.1853, found 503.1859.

8-(Cinnamoyloxy)naphthalen-1-yl (2E,4E)-5-Phenylpenta-2,4-dienoate (21). In a round-bottom flask, *trans*-cinnamic acid (50 mg, 0.34 mmol) was dissolved in 2 mL of oxalyl chloride at 23 °C under nitrogen atmosphere. This solution was stirred in a preheated oil bath at 60 °C for 1.5 h. Afterward, the reaction mixture was cooled to room temperature, and all volatiles were removed by a rotary evaporator to give cinnamoyl chloride (**21**) (51 mg, 90%). In another 50 mL round-bottom flask, monoester **19** (92 mg, 0.29 mmol) was dissolved in 3 mL of anhydrous THF under an inert atmosphere of nitrogen. To this solution, which was cooled to 0 °C in an ice bath, was added a solution of the cinnamoyl chloride (**21**) in 2 mL of anhydrous THF. Afterward, to the reaction mixture, NaH (13 mg, 0.32 mmol, 60% dispersion in mineral oil) was added portionwise at 0 °C. The reaction mixture was then stirred at this temperature for 20 min, and at 23 °C for 3 h. At the end of this time, the reaction mixture was quenched with 10 mL of saturated aqueous NH₄Cl solution. The aqueous phase was extracted thrice with EtOAc. The combined organic phases were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. Purification by flash column chromatog-

raphy (CH₂Cl₂/hexanes = 1:2) afforded pure product **21** (90 mg, 70%) as a white solid. Mp: 156–158 °C. $R_f = 0.34$ (CH₂Cl₂/hexanes = 1:1). ¹H NMR (400 MHz, CDCl₃) δ : 7.89 (1H, d, $J = 16.1$ Hz), 7.83 (2H, dt, $J = 8.4, 1.3$ Hz), 7.64 (1H, ddd, $J = 15.3, 11.1, 0.4$ Hz), 7.54–7.49 (4H, m), 7.36–7.33 (3H, m), 7.27–7.17 (7H, m), 6.84 (1H, d, $J = 15.6$ Hz), 6.68 (1H, d, $J = 16.1$ Hz), 6.57 (1H, dd, $J = 15.7, 11.4$ Hz), 6.15 (1H, d, $J = 15.3$ Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ : 165.9, 146.85, 146.79, 145.35, 145.33, 141.7, 137.0, 135.8, 134.1, 130.7, 129.4, 129.1, 128.8, 128.4, 127.5, 127.0, 126.9, 126.18, 126.15, 126.0, 121.5, 120.8, 120.73, 120.72, 117.7. FTIR ν_{\max} (ATR, film)/cm⁻¹: 3059, 3026, 1729, 1623, 1603, 1576, 1448, 1344, 1328, 1229, 1174. HRMS (APCI+) calcd for C₃₀H₂₃O₄ [M + H]⁺: 447.1591, found 447.1570.

General Procedure A for the Photochemical [2 + 2] Cycloaddition in Solid State. Cycloaddition precursor (ca. 20 mg) was placed between two quartz microscopic glass slides as a solid powder (for ground samples, grinding was done in mortar and pestle for 5 min), and irradiated inside a UV gel nail dryer having four 9-W UV-A (365 nm) fluorescent lamps. For the irradiation experiments for 8, 16, and 24 h, the reaction powder was mixed with a spatula every 4 h, and for the irradiation experiments which required 48 h, the reaction powder was mixed every 8 h. At the end of the reaction, the solid mixture was transferred into a clean vial using CHCl₃. The diastereomeric ratio was determined via the ¹H NMR analysis of the crude mixture. Purification was performed by flash column chromatography.

General Procedure B for the Photochemical [2 + 2] Cycloaddition in Solution Phase. Cycloaddition precursor (ca. 20 mg) was dissolved in 2 mL of CHCl₃ in a quartz test tube, and irradiated inside a UV gel nail dryer having four 9-W UV-A (365 nm) fluorescent lamps. Progress of the reaction was monitored using TLC. After the reaction is over, the solvent was removed under reduced pressure, and the diastereomeric ratio was determined via the ¹H NMR analysis of the crude mixture. Purification was performed by flash column chromatography.

(8aR,9S,10R,10aS)-9,10-Di((E)-styryl)-8a,9,10,10a-tetrahydrocyclobuta[g]naphtho[1,8-bc][1,5]dioxonine-8,11-dione (22a). Cycloadduct **22a** was synthesized using diester **12a** (20.3 mg, 0.043 mmol) following General Procedure A with an irradiation time of 48 h (crude dr = 11:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22a** (10.5 mg, 52%, dr = 25:1) as an orange-yellow solid.

In a second experiment, cycloadduct **22a** was synthesized using diester **12a** (24.6 mg, 0.052 mmol) following General Procedure B with an irradiation time of 4 h (crude dr = 8:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22a** (21.7 mg, 88%, dr = 97:3) as an orange-yellow solid.

In a third experiment, diester **12a** (500 mg, 1.06 mmol) was dissolved in 15 mL of CHCl₃ in a beaker and irradiated inside a UV gel nail dryer having four 9-W UV-A (365 nm) fluorescent lamps. Progress of the reaction was monitored using TLC (CH₂Cl₂/hexanes = 1:1). After 7 h, the solvent was removed under reduced pressure, and the diastereomeric ratio was determined via the ¹H NMR analysis of the crude mixture (dr = 13:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22a** (304 mg, 61%) as a yellow solid, along with recovered starting material **12a** (53 mg). $R_f = 0.48$ (CH₂Cl₂/hexanes = 1:1). ¹H NMR (400 MHz, CDCl₃) δ : 7.81 (2H, d, $J = 8.4$ Hz), 7.52 (2H, t, $J = 7.9$ Hz), 7.39 (4H, d, $J = 7.2$ Hz), 7.34–7.28 (6H, m), 7.27–7.23 (2H, m), 6.59 (2H, d, $J = 15.9$ Hz), 6.39 (2H, ddd, $J = 15.9, 5.2, 2.4$ Hz), 4.15–4.11 (2H, m), 3.87 (2H, app d, $J = 5.1$ Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ : 170.1, 145.5, 137.1, 136.8, 132.6, 128.8, 127.9, 127.6, 127.1, 126.53, 126.51, 121.1, 119.6, 45.0, 42.1. FTIR ν_{\max} (ATR, film)/cm⁻¹: 3058, 3026, 2925, 1764, 1607, 1577, 1494, 1448, 1364, 1217, 1176. HRMS (APCI+) calcd. for C₃₂H₂₅O₄ [M + H]⁺: 473.1747, found 473.1758.

(8aR,9S,10R,10aS)-9,10-Bis((E)-4-fluorostyryl)-8a,9,10,10a-tetrahydrocyclobuta[g]naphtho[1,8-bc][1,5]dioxonine-8,11-dione (22b). Cycloadduct **22b** was synthesized using diester **12b** (20.4 mg, 0.040 mmol) following General Procedure A with an

irradiation time of 24 h (crude dr = 6:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22b** (20.2 mg, 99%, dr = 6:1) as an orange-yellow solid.

In a second experiment, cycloadduct **22b** was synthesized using diester **12b** (20.1 mg, 0.039 mmol) following General Procedure B with an irradiation time of 2 h (crude dr = 3:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22b** (19.3 mg, 96%) as an orange-yellow solid. *R*_f = 0.43 (1:5 EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ: 7.81 (2H, d, *J* = 8.2 Hz), 7.51 (2H, t, *J* = 7.9 Hz), 7.34 (4H, dd, *J* = 8.4, 5.5 Hz), 7.29 (2H, d, *J* = 7.4 Hz), 7.01 (4H, t, *J* = 8.6 Hz), 6.54 (2H, d, *J* = 15.9 Hz), 6.28 (2H, ddd, *J* = 15.8, 5.1, 2.2 Hz), 4.11 (2H, br s), 3.85 (2H, app d, *J* = 4.9 Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ: 170.0, 162.6 (d, *J* = 247.3 Hz), 145.4, 132.9 (d, *J* = 3.4 Hz), 131.5, 128.0 (d, *J* = 8.0 Hz), 127.2 (d, *J* = 2.0 Hz), 127.1, 126.5, 121.1, 115.9, 115.6, 114.9 (d, *J* = 21.2 Hz), 45.0, 42.1. ¹⁹F{¹H}-NMR (376 MHz, CDCl₃) δ: -112.4. FTIR *ν*_{max} (ATR, film)/cm⁻¹: 3041, 2956, 2927, 1759, 1605, 1507, 1363, 1213, 1175. HRMS (APCI+): calcd for C₃₂H₂₃O₄F₂ [M + H]⁺: 509.1559, found 509.1556.

(8aR,9S,10R,10aS)-9,10-Bis((E)-4-bromostyryl)-8a,9,10,10a-tetrahydrocyclobuta[g]naphtho[1,8-bc][1,5]dioxine-8,11-dione (22c). Cycloadduct **22c** was synthesized using diester **12c** (18.2 mg, 0.029 mmol) following General Procedure A with an irradiation time of 24 h (crude dr = 6:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22c** (3.1 mg, 17%, dr = 5:1) as a yellow solid.

In a second experiment, cycloadduct **22c** was synthesized using diester **12c** (15.0 mg, 0.024 mmol) following General Procedure B with an irradiation time of 1.5 h. Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22c** (9.4 mg, 63%, dr = 11:1) as a yellow solid. *R*_f = 0.56 (CH₂Cl₂/hexanes = 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.81 (2H, d, *J* = 8.0 Hz), 7.51 (2H, t, *J* = 7.8 Hz), 7.44 (4H, d, *J* = 8.4 Hz), 7.28 (2H, d, *J* = 7.5 Hz), 7.23 (4H, d, *J* = 8.5 Hz), 6.52 (2H, d, *J* = 15.9 Hz), 6.34 (2H, ddd, *J* = 15.8, 5.2, 2.4 Hz), 4.10 (2H, br s), 3.85 (2H, app d, *J* = 5.1 Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ: 169.9, 145.4, 137.1, 135.6, 132.0, 131.6, 130.6, 128.2, 128.0, 127.1, 126.5, 121.8, 121.1, 44.9, 42.0. FTIR *ν*_{max} (ATR, film)/cm⁻¹: 2953, 2923, 2852, 1764, 1607, 1487, 1460, 1364, 1214, 1176. HRMS (APCI+) calcd for C₃₂H₂₃O₄⁷⁹Br₂ [M + H]⁺: 628.9958, found 628.9944; calcd for C₃₂H₂₃O₄⁷⁹Br⁸¹Br [M + H]⁺: 630.9938, found 630.9921; calcd for C₃₂H₂₃O₄⁸¹Br₂ [M + H]⁺: 632.9917, found 632.9915.

(8aR,9S,10R,10aS)-9((E)-4-Methoxystyryl)-10((E)-styryl)-8a,9,10,10a-tetrahydrocyclobuta[g]naphtho[1,8-bc][1,5]dioxine-8,11-dione (22d). Cycloadduct **22d** was synthesized using diester **12d** (20.6 mg, 0.041 mmol) following General Procedure A with an irradiation time of 24 h (crude dr = 13:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22d** (11.0 mg, 53%, dr = 20:1) as a yellow solid.

In a second experiment, cycloadduct **22d** was synthesized using diester **12d** (20.4 mg, 0.041 mmol) following General Procedure B with an irradiation time of 1 h (crude dr = 8:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **22d** (17.1 mg, 84%, dr = 16:1) as a yellow solid. *R*_f = 0.53 (CH₂Cl₂/hexanes = 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.81 (2H, d, *J* = 7.6 Hz), 7.51 (2H, d, *J* = 7.6 Hz), 7.38 (2H, app d, *J* = 7.1 Hz), 7.34–7.28 (7H, m), 6.86 (2H, d, *J* = 8.7 Hz), 6.58 (1H, d, *J* = 15.8 Hz), 6.53 (1H, d, *J* = 15.8 Hz), 6.41–6.36 (1H, m), 6.26–6.21 (1H, m), 4.12–4.09 (2H, m), 3.85 (2H, d, *J* = 4.7 Hz), 3.81 (3H, s). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ: 170.19, 170.17, 159.5, 145.5, 137.1, 136.9, 132.5, 132.0, 129.6, 129.0, 128.8, 128.0, 127.8, 127.72, 127.70, 127.0, 126.52, 126.50, 125.3, 121.0, 120.7, 119.6, 114.2, 113.4, 55.5, 45.2, 45.0, 42.20, 42.16. FTIR *ν*_{max} (ATR, film)/cm⁻¹: 3058, 2954, 2851, 1761, 1606, 1577, 1510, 1364, 1216, 1174. HRMS (APCI+) calcd for C₃₃H₂₆NaO₅ [M + Na]⁺: 525.1672, found 525.1677.

(8aR,9S,10R,10aS)-9-Phenyl-10((E)-styryl)-8a,9,10,10a-tetrahydrocyclobuta[g]naphtho[1,8-bc][1,5]dioxine-8,11-dione (23). Cycloadduct **23** was synthesized using diester **21** (20.0 mg, 0.045 mmol) following General Procedure A with an irradiation

time of 24 h (crude dr = 4:1). Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **23** (9.3 mg, 47%, dr = 14:1) as an orange-yellow solid.

In a second experiment, cycloadduct **23** was synthesized using diester **21** (20.0 mg, 0.045 mmol) following General Procedure B with an irradiation time of 3.5 h. Purification by flash column chromatography (CH₂Cl₂/hexanes = 1:1) afforded product **23** (8.4 mg, 42%; dr = 9:1) as a yellow solid. *R*_f = 0.50 (CH₂Cl₂/hexanes = 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.84 (2H, d, *J* = 8.3 Hz), 7.57–7.52 (2H, m), 7.40 (2H, t, *J* = 7.5 Hz), 7.35–7.28 (7H, m), 7.24–7.18 (3H, m), 6.53 (1H, d, *J* = 15.9 Hz), 5.97 (1H, dd, *J* = 15.8, 8.2 Hz), 4.66 (1H, dd, *J* = 9.2, 8.4 Hz), 4.30–4.21 (2H, m), 3.92 (1H, dd, *J* = 10.4, 5.8 Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ: 170.2, 170.0, 145.52, 145.50, 138.4, 137.1, 137.0, 132.4, 128.8, 128.7, 128.0, 127.9, 127.7, 127.2, 127.06, 127.05, 126.6, 126.5, 126.4, 121.1, 119.7, 45.4, 44.5, 43.7, 42.2. FTIR *ν*_{max} (ATR, film)/cm⁻¹: 3058, 3027, 2925, 1764, 1607, 1495, 1449, 1364, 1213, 1177. HRMS (APCI+) calcd for C₃₀H₂₃O₄ [M + H]⁺: 447.1591, found 447.1587.

Dimethyl (1R,2S,3R,4S)-3,4-Di((E)-styryl)cyclobutane-1,2-dicarboxylate (13a). Cycloadduct **22a** (11.4 mg, 0.024 mmol) was dissolved in a mixture of MeOH (4 mL) and THF (1 mL) in a vial at 23 °C. NaOMe (3.3 mg, 0.068 mmol) was added to this solution. Upon the addition of NaOMe, the color of the solution turned from yellow to orange immediately. The reaction mixture was stirred at 23 °C, and the reaction progress, which was monitored by TLC (EtOAc/hexanes = 1:5), indicated completion of the reaction after 8 h. Afterward, all volatiles were directly evaporated. Purification by flash column chromatography (EtOAc/hexanes = 1:5) gave product **13a** (8.2 mg, 89% yield) as an orange solid. *R*_f = 0.48 (CH₂Cl₂/hexanes = 1:1). ¹H NMR (400 MHz, CDCl₃) δ: 7.35–7.33 (4H, m), 7.29 (4H, t, *J* = 7.5 Hz), 7.21 (2H, app t, *J* = 7.1 Hz), 6.50 (2H, d, *J* = 15.8 Hz), 6.29 (2H, ddd, *J* = 15.8, 5.3, 2.4 Hz), 3.74 (6H, s), 3.73–3.67 (2H, m), 3.45 (2H, app d, *J* = 5.4 Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ: 172.9, 137.0, 132.3, 128.7, 128.1, 127.7, 126.5, 52.2, 44.0, 43.1. FTIR *ν*_{max} (ATR, film)/cm⁻¹: 2952, 2850, 1735, 1602, 1495, 1436, 1365, 1264, 1170. HRMS (ESI+) calcd for C₂₄H₂₅O₄ [M + H]⁺: 377.1747, found 377.1743.

Dimethyl (1R,2S,3R,4S)-3,4-Di((E)-4-fluorostyryl)cyclobutane-1,2-dicarboxylate (13b). Cycloadduct **22b** (20.2 mg, 0.040 mmol) was dissolved in a mixture of MeOH (3 mL) and THF (3 mL) in a vial at 23 °C. NaOMe (5.4 mg, 0.1 mmol) was added to this solution. Upon the addition of NaOMe, the color of the solution turned from yellow to orange immediately. The reaction mixture was stirred at 23 °C, and the reaction progress, which was monitored by TLC (EtOAc/hexanes = 1:5), indicated completion of the reaction after 8 h. Afterward, all volatiles were directly evaporated. Purification by flash column chromatography (EtOAc/hexanes = 1:5) gave product **13b** (10.8 mg, 65% yield, dr = 10:1) as a yellow solid. *R*_f = 0.33 (EtOAc/hexanes = 1:5). ¹H NMR (400 MHz, CDCl₃) δ: 7.32–7.27 (4H, m), 6.97 (4H, t, *J* = 8.7 Hz), 6.45 (2H, d, *J* = 15.8 Hz), 6.18 (2H, ddd, *J* = 15.8, 5.4, 2.5 Hz), 3.73 (6H, s), 3.73–3.71 (2H, m), 3.42 (2H, app d, *J* = 5.4 Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ: 172.9, 162.5 (d, *J* = 246.9 Hz), 131.2, 127.9 (d, *J* = 8.0 Hz), 127.8 (d, *J* = 2.0 Hz), 125.2, 115.6 (d, *J* = 21.6 Hz), 52.2, 44.0, 43.0. ¹⁹F{¹H}-NMR (376 MHz, CDCl₃) δ: -113.4 (s). FTIR *ν*_{max} (ATR, film)/cm⁻¹: 3054, 2953, 1736, 1601, 1508, 1264, 1226, 1158. HRMS (ESI+) calcd for C₂₄H₂₃O₄F₂ [M + H]⁺: 413.1559, found 413.1546.

Dimethyl (1R,2S,3R,4S)-3,4-Di((E)-4-bromostyryl)cyclobutane-1,2-dicarboxylate (13c). Cycloadduct **22c** (9.4 mg, 0.015 mmol) was dissolved in a mixture of MeOH (1.5 mL) and THF (1.5 mL) in a vial at 23 °C. NaOMe (2.0 mg, 0.038 mmol) was added to this solution. Upon the addition of NaOMe, the color of the solution turned from yellow to orange immediately. The reaction mixture was stirred at 23 °C, and the reaction progress, which was monitored by TLC (EtOAc/hexanes = 1:5), indicated completion of the reaction after 3 h. Afterward, all volatiles were directly evaporated. Purification by flash column chromatography (EtOAc/hexanes = 1:5) gave product **13c** (5.1 mg, 65% yield, dr = 10:1) as a yellow solid. *R*_f = 0.38 (EtOAc/hexanes = 1:5). ¹H NMR (400 MHz, CDCl₃) δ: 7.40

(4H, d, $J = 8.5$ Hz), 7.18 (4H, d, $J = 8.5$ Hz), 6.43 (2H, d, $J = 15.9$ Hz), 6.24 (2H, ddd, $J = 15.8, 5.4, 2.2$ Hz), 3.73 (8H, m, overlapping signals), 3.42 (2H, app d, $J = 5.3$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 172.8, 135.9, 131.9, 131.3, 128.9, 128.0, 121.5, 52.3, 43.9, 43.0. FTIR ν_{max} (ATR, film)/ cm^{-1} : 2950, 2924, 1736, 1487, 1434, 1364, 1274, 1167. HRMS (APCI+) calcd for $\text{C}_{24}\text{H}_{23}\text{O}_4$ $^{79}\text{Br}_2$ $[\text{M} + \text{H}]^+$: 532.9958, found 532.9953; calcd for $\text{C}_{24}\text{H}_{23}\text{O}_4$ $^{79}\text{Br}^{81}\text{Br}$ $[\text{M} + \text{H}]^+$: 534.9938, found 534.9944; calcd for $\text{C}_{24}\text{H}_{23}\text{O}_4$ $^{81}\text{Br}_2$ $[\text{M} + \text{H}]^+$: 536.9917, found 536.9914.

Dimethyl (1S,2R,3S,4R)-3-((E)-4-Methoxystyryl)-4-((E)-styryl)cyclobutane-1,2-dicarboxylate (13d). Cycloadduct **22d** (17.1 mg, 0.034 mmol) was dissolved in a mixture of MeOH (2 mL) and THF (2 mL) in a vial at 23 °C. NaOMe (4.6 mg, 0.085 mmol) was added to this solution. Upon the addition of NaOMe, the color of the solution turned from yellow to orange immediately. The reaction mixture was stirred at 23 °C, and the reaction progress, which was monitored by TLC (EtOAc/hexanes = 1:5), indicated completion of the reaction after 6 h. Afterward, all volatiles were directly evaporated. Purification by flash column chromatography (EtOAc/hexanes = 1:5) gave product **13d** (12.3 mg, 89% yield) as a yellow solid. $R_f = 0.38$ (EtOAc/hexanes = 1:3) ^1H NMR (400 MHz, CDCl_3) δ : 7.35–7.28 (5H, m), 7.23–7.17 (2H, m), 6.82 (2H, d, $J = 8.7$ Hz), 6.49 (1H, d, $J = 15.9$ Hz), 6.44 (1H, d, $J = 15.8$ Hz), 6.28 (1H, dd, $J = 15.8, 7.4$ Hz), 6.14 (1H, dd, $J = 15.8, 7.6$ Hz), 3.79 (3H, s), 3.73 (6H, s), 3.73–3.71 (2H, m), 3.43 (2H, d, $J = 5.1$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 173.0, 159.4, 137.1, 132.1, 131.7, 129.9, 128.70, 128.66, 128.3, 127.6, 126.5, 125.9, 114.2, 113.1, 55.4, 52.2, 44.2, 44.0, 43.12, 43.08. FTIR ν_{max} (ATR, film)/ cm^{-1} : 3058, 2926, 1760, 1730, 1602, 1366, 1226, 1174. HRMS (APCI+) calcd for $\text{C}_{25}\text{H}_{27}\text{O}_5$ $[\text{M} + \text{H}]^+$: 407.1853, found 407.1859.

Dimethyl (1S,2R,3S,4R)-3-Phenyl-4-((E)-styryl)cyclobutane-1,2-dicarboxylate (24). Cycloadduct **23** (8.4 mg, 0.019 mmol) was dissolved in a mixture of MeOH (1.5 mL) and THF (1.5 mL) in a vial at 23 °C. NaOMe (2.6 mg, 0.048 mmol) was added to this solution. Upon the addition of NaOMe, the color of the solution turned from yellow to orange immediately. The reaction mixture was stirred at 23 °C, and the reaction progress, which was monitored by TLC (EtOAc/hexanes = 1:5), indicated completion of the reaction after 2.5 h. Afterward, all volatiles were directly evaporated. Purification by flash column chromatography (EtOAc/hexanes = 1:5) gave product **24** (4.8 mg, 73%) as a yellow solid. $R_f = 0.27$ (EtOAc/hexanes = 1:5). ^1H NMR (400 MHz, CDCl_3) δ : 7.33–7.29 (2H, m), 7.23–7.16 (6H, m), 7.13–7.11 (2H, m), 6.41 (1H, d, $J = 15.8$ Hz), 5.84 (1H, dd, $J = 15.8, 8.5$ Hz), 4.32 (1H, t, $J = 8.9$ Hz), 3.85–3.80 (2H, m), 3.76 (3H, s), 3.73 (3H, s), 3.45 (1H, dd, $J = 9.9, 5.4$ Hz). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 173.1, 173.0, 138.9, 137.1, 132.0, 128.7, 128.6, 128.5, 127.7, 127.5, 126.8, 126.4, 52.3, 52.2, 44.4, 44.3, 43.2, 42.9. FTIR ν_{max} (ATR, film)/ cm^{-1} : 2951, 2924, 1733, 1601, 1496, 1449, 1366, 1206, 1167. HRMS (APCI+) calcd for $\text{C}_{22}\text{H}_{23}\text{O}_5$ $[\text{M} + \text{H}]^+$: 351.1591, found 351.1604.

(1R,2S,3R,4S)-3,4-Di((E)-styryl)cyclobutane-1,2-dicarboxylic Acid (25). Cycloadduct **22a** (8.4 mg, 0.018 mmol) was dissolved in 2 mL of THF in a 25 mL round-bottom flask at 23 °C. Then distilled water (1 mL) and KOH (19 mg, 0.34 mmol) were added to the reaction vessel sequentially, and the reaction mixture was stirred at 23 °C. Reaction progress was monitored using TLC (EtOAc/hexanes = 1:1). After 2 h, full consumption of **22a** was observed. The reaction mixture was quenched with 1 M HCl solution in an ice bath until the pH became 1–2. The aqueous phase was extracted thrice with EtOAc. The combined organic phases were dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. Purification by flash column chromatography (EtOAc/hexanes = 1:1, then 0.5% (v/v) AcOH in EtOAc/hexanes = 1:1) gave product **25** (4.3 mg, 69%) as a yellow solid. $R_f = 0.13$ (EtOAc/hexanes = 1:1 + 0.5% (v/v) Acetic acid). ^1H NMR (400 MHz, CD_3OD) δ : 7.36 (4H, d, $J = 7.5$ Hz), 7.26 (4H, t, $J = 7.5$ Hz), 7.17 (2H, t, $J = 7.5$ Hz), 6.51 (2H, d, $J = 15.9$ Hz), 6.41 (2H, ddd, $J = 7.2, 4.8, 1.9$ Hz), 3.66 (2H, br s), 3.48 (2H, app d, $J = 4.7$ Hz) (Signal at 4.88 ppm originates from water and the signal at 5.49 is from CH_2Cl_2). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CD_3OD) δ : 176.5, 138.6, 132.9, 130.0, 129.5, 128.3, 127.3, 45.3, 44.5. FTIR ν_{max} (ATR,

film)/ cm^{-1} : 3028, 2955, 2921, 2851, 1707, 1600, 1449, 1258, 1176. HRMS (ESI-) Calcd for $\text{C}_{22}\text{H}_{19}\text{O}_4$ $[\text{M}-\text{H}]^-$: 347.1288, found 347.1293.

(1R,2S,3R,4S)-3,4-Di((E)-styryl)cyclobutane-1,2-diol-dimethanol (26). Cycloadduct **22a** (11.8 mg, 0.025 mmol) was dissolved in THF (4 mL) in a round-bottom flask under nitrogen. This solution was cooled to 0 °C in an ice bath. LiAlH_4 (9.5 mg, 0.25 mmol) was added to this cooled solution, and the reaction mixture was then stirred at 23 °C for 2 h. After full consumption of **22a**, the reaction was quenched with 10 mL of water, and the aqueous phase was extracted thrice with EtOAc. The organic phases were combined, dried over anhydrous Na_2SO_4 , filtered, and concentrated under vacuum. Purification by flash column chromatography (5% MeOH in CH_2Cl_2) afforded product **26** (5.2 mg, 65%) as a pale yellow solid. $R_f = 0.52$ (5% MeOH in CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ : 7.34–7.28 (8H, m), 7.19 (2H, tt, $J = 7.1, 2.2$ Hz), 6.41 (2H, d, $J = 15.8$ Hz), 6.34 (2H, ddd, $J = 15.9, 4.9, 2.2$ Hz), 3.96 (2H, t, $J = 10.8$ Hz), 3.83 (2H, dd, $J = 10.8, 2.7$ Hz), 3.02–2.99 (2H, m), 2.80–2.76 (4H, m). $^{13}\text{C}\{^1\text{H}\}$ -NMR (100 MHz, CDCl_3) δ : 137.4, 130.9, 130.1, 128.7, 127.4, 126.3, 62.5, 42.0, 41.6. FTIR ν_{max} (ATR, film)/ cm^{-1} : 3313, 3025, 2853, 1665, 1599, 1492, 1450, 1260. HRMS (APCI+) calcd for $\text{C}_{22}\text{H}_{25}\text{O}_2$ $[\text{M} + \text{H}]^+$: 321.1849, found 321.1847.

Crystallization of Compounds 12a, 16a, and 22a for Single-Crystal XRD Analysis. Each compound (**12a**, **16a** and **22a**; ca. 5–10 mg) was dissolved in 1.0 mL of CH_2Cl_2 in a 2 mL vial, which was placed inside a 20 mL scintillation vial containing ca. 5 mL of pentane. The outer vial was sealed with a screw cap, and crystallization was carried out via vapor-diffusion technique under dark inside a cupboard at room temperature.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its [Supporting Information](#).

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.4c01374>.

Tables S1–S5, Figures S1–S7, Scheme S1, NMR spectra for all synthesized compounds, X-ray analysis data of **12a**, **16a** and **22a** (PDF)

FAIR data, including the primary NMR FID files, for compounds **12a-d**, **13a-d**, **15a-d**, **16a-d**, **19**, **21**, **22a-d**, and **23-26** (ZIP)

Accession Codes

CCDC [2354337](#)–[2354338](#) and [2354346](#) 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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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Y.E.T. acknowledges financial support by the GEBIP Award of the Turkish Academy of Sciences.

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