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Stereocontrolled Photodimerization with Congested 1,8-Bis(4′-anilino)naphthalene Templates

Marwan W. Ghosn and Christian Wolf*

Department of Chemistry, Georgetown University, Washington, D.C. 20057

cw27@georgetown.edu

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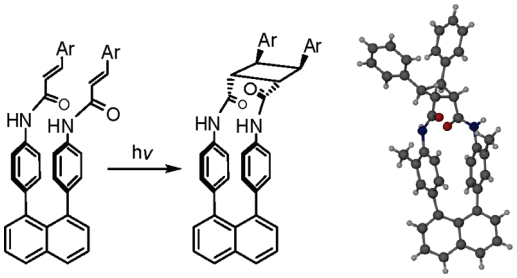

Suzuki cross-coupling of a 1,8-dihalonaphthalene with 4-methoxy-3-methylphenylboronic acid or 4-acetamidophenylboronic acid and subsequent functional group transformation gave 1,8-bis(3′-methyl-4′-anilino)naphthalene, **16**, and 1,8-bis(4′-anilino)naphthalene, **21**, in 65% and 90% overall yield, respectively. These congested compounds exhibit two cofacial aniline rings that favor a proximate, parallel arrangement of covalently attached cinnamoyl units suitable for stereoselective photodimerization. The [2 + 2]cycloaddition was found to proceed with high yield and exclusive formation of *cis*,*trans*,*cis*-cyclobutane-1,2-dicarboxylic acids. Amide formation with cinnamoyl chloride and template **21** followed by photochemical dimerization and acidic hydrolysis gave β-truxinic acid, **10**, in 69% overall yield. Coupling of **21** and (*E*)-3-(3,4-dimethylphenyl)acrylic acid in the presence of EDC, UV irradiation, and cleavage gave *cis*,*trans*,*cis*-3,4-bis(3,4-dimethylphenyl)cyclobutane-1,2-dicarboxylic acid, **26**, in 60% yield. In both cases, the template was quantitatively recovered.

Introduction

The photodimerization of olefinic compounds has attracted considerable interest in recent years.[1] Several strategies to control the regio- and stereochemical outcome of the [2+2]-cycloaddition of fumaric acid, cinnamic acid, and a few other substrates have been developed. This reaction provides access to polysubstituted cyclobutanecarboxylic acids, a common structural motif in natural products and an important component in many pharmaceuticals.[2] Despite the biomedical significance and natural abundance of analogues of truxillic and truxinic acids, which are obtained via photodimerization of cinnamic acid, the stereoselective photoaddition of unsaturated carboxylic acids and amides remains challenging.[3]

Many efforts have been directed toward solid-state synthesis with molecular templates, hosts, and large frameworks to control the reaction topology.[4] A parallel substrate alignment and a centroid−centroid separation of up to 4.2 Å are generally accepted requirements for the photodimerization of unsaturated compounds.[5] The advance of supramolecular chemistry has fueled the development of intriguing templates that utilize noncovalent interactions such as hydrogen bonding, halogen bonding, $\pi-\pi$ interactions, cation$-\pi$ interactions,

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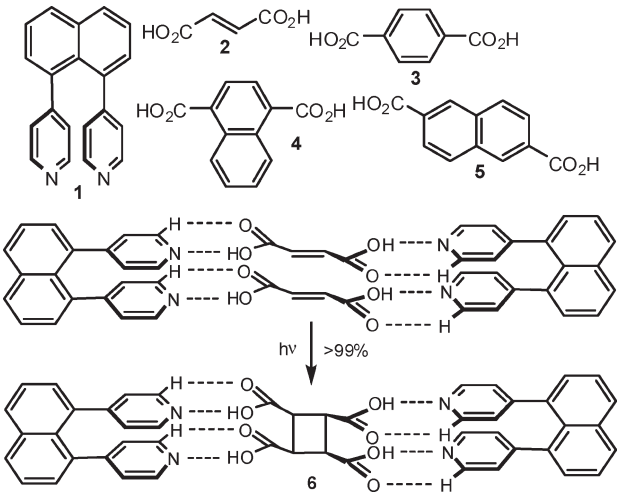
and transition metal coordination to affect the relative orientation of α,β-unsaturated compounds.[6] This approach generally exploits the distinguished regularity and molecular orientation provided by a crystal lattice to control the stereo- and regiochemical selectivity during reaction in a solvent-free environment.[7] For example, solid-state photodimerization of ammonium salts of *trans*-cinnamic acid or cocrystals of *trans*-cinnamamide and phthalic acid have been reported to produce truxinic acids and truxinamides with high stereoselectivity.[8] Several cases of photochemical and γ-radiation-induced topochemical polymerization of unsaturated ammonium carboxylates are also known.[9]

The use of 1,8-bis(4′-pyridyl)naphthalene, **1**, for template-directed solid-state alignment of unsaturated dicarboxylic acids has recently been reported from our laboratories.[10] Through careful selection of cocrystallization parameters, we obtained a series of four-component assemblies in which two dipyridylnaphthalene molecules undergo OH···N and CH···O hydrogen bonding with two bridging molecules of **2**−**5**, Scheme 1. The cocrystal obtained with fumaric acid, **2**, places two dicarboxylic acid molecules in close proximity with a separation between the superimposed olefinic bonds of less than 4.0 Å. As expected, photochemical irradiation gave quantitative amounts of *cis*,*trans*,*cis*-cyclobutanetetracarboxylic acid, **6**, and the template was fully recovered by extraction with dichloromethane. Unfortunately, numerous attempts to produce a cocrystal with *trans*-cinnamic acid that would afford a similar double bond arrangement suitable for stereoselective photoaddition were unsuccessful. When a cocrystal was obtained by slow evaporation of an ethanol solution containing equimolar amounts of template **1** and the acid, we found that only one pyridyl ring of **1** would participate in hydrogen bonding, resulting in an offset head-to-tail packing arrangement of the cinammic acid molecules with essentially no double bond overlap, Figure 1.

SCHEME 1. Template-Directed Solid-State Photodimerization of Fumaric Acid



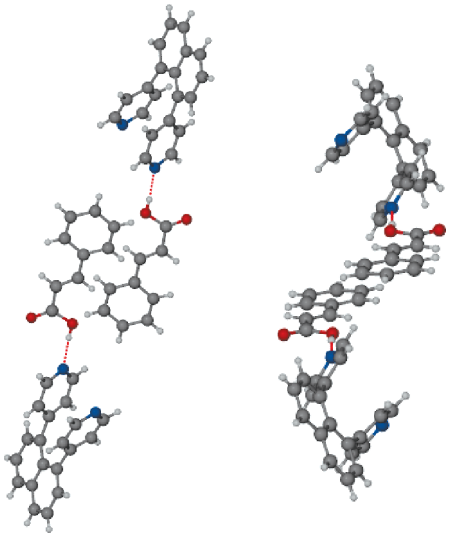


FIGURE 1. Structure of the cocrystal of **1** and *trans*-cinnamic acid.

The cocrystallization experiment with **1** and *trans*-cinnamic acid clearly revealed an important limitation of this solid state approach. Despite the overall success with solid-state photodimerizations, the packing motif and the relative orientation of

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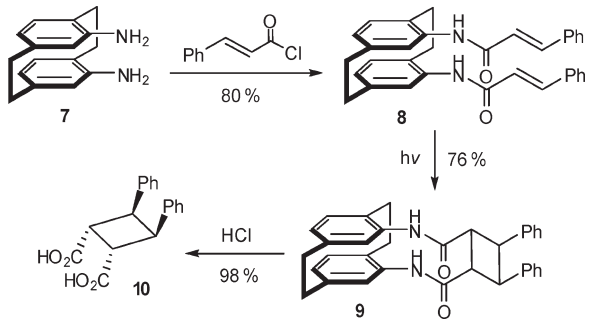
olefinic substrates in the presence of **1** or other templates remain difficult to control. As a result, the application spectrum of template-assisted solid-state photodimerization is often rather narrow and may not be extended to a wide range of substrates. In most cases, a reaction does not occur if the crystallization efforts do not provide a perfect cofacial orientation of proximate substrates unless this can be manipulated by heating of the crystal or by other means.[11]

Results and Discussion

In comparison with the numerous reports of stereoselective photoaddition of olefinic compounds in the solid state, there are relatively few examples that have been accomplished in solution. In these cases, substrate alignment has been controlled by inclusion in cucurbiturils, cyclodextrins, and organometallic hosts,[12] association with biomolecules,[13] in micellar environments,[14] self-assembly of substrates designed for complementary cation−π-interactions and rotaxane formation,[15] or with small molecular templates.[16] A prime example of the use of a template for stereoselective photodimerization in solution has been presented by Hopf and co-workers.[17] They prepared 4,15-diamino[2.2]paracyclophane, **7**, from [2.2]paracyclophane in 8 steps with 14% overall yield. Diamide formation with cinnamoyl chloride then allowed photochemical cycloaddition to the corresponding cyclobutane **9** with 76% yield. Acidic cleavage gave β-truxinic acid, **10**, and the free template in almost quantitative amounts, Scheme 2.

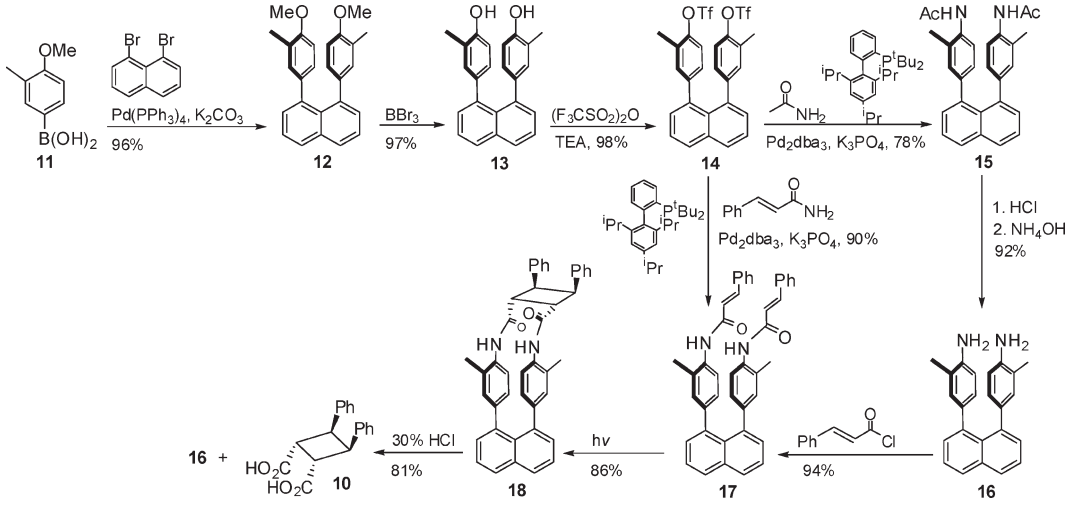
SCHEME 2. Hopf's Synthesis of β-Truxinic Acid with Template 7



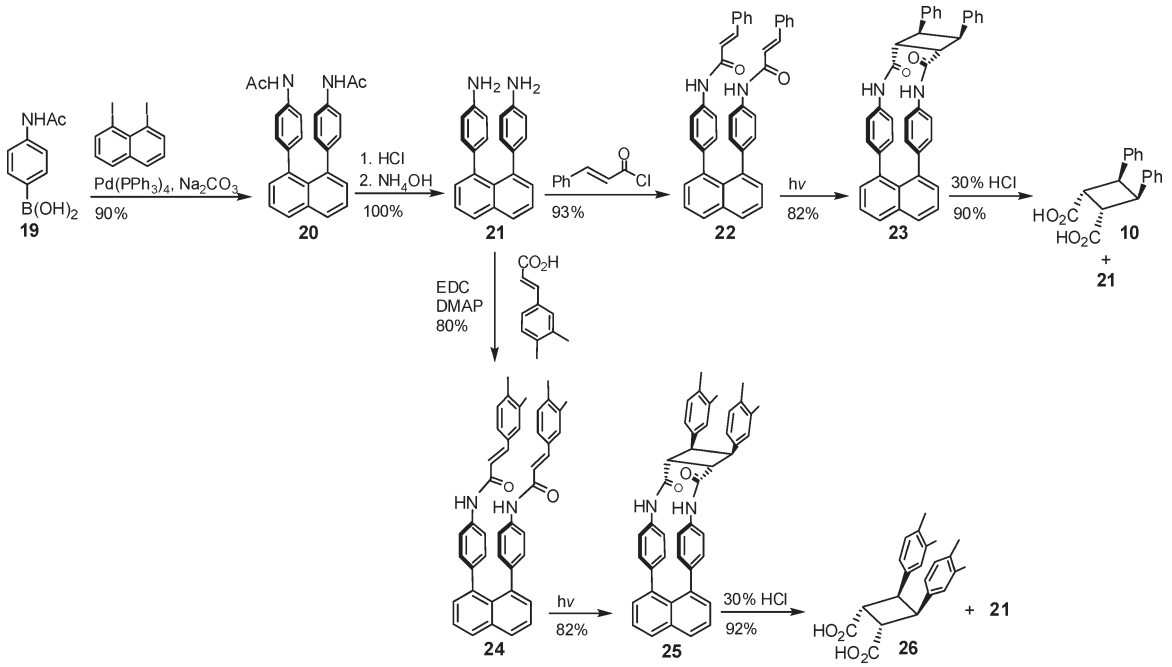
This result encouraged us to develop a rigid template for in-solution photoaddition of covalently attached substrates that would overcome the limitations of **1** and provide synthetic access to polysubstituted cyclobutanes other than **6**. Initially, we rationalized that a template should exhibit two parallel functionalities within less than 4.0 Å combined with a certain degree of rigidity. On the basis of our experience with the structure and conformational flexibility of 1,8-diarylnaphthalenes,[18] we began our study with the synthesis of 1,8-bis(3′-methyl-4′-anilino)-naphthalene, **16**, Scheme 3. Suzuki coupling of boronic acid **11** and 1,8-dibromonaphthalene gave 1,8-bis(3′-methyl-4′-methoxyphenyl)naphthalene, **12**, in 96% yield. Deprotection with boron tribromide and treatment of **13** with trifluoromethanesulfonic anhydride provided **14** in almost quantitative amounts. We first used **14** to make template **16** via palladium-catalyzed amidation and subsequent hydrolysis of 1,8-bis(3′-methyl-4′-acetamidophenyl)naphthalene, **15**. As a result, **16** was prepared in 5 steps from **11** with an overall yield of 65%. Attachment of two cinnamoyl units followed by photodimerization of 1,8-bis-(3′-methyl-4′-cinnamamidophenyl)naphthalene, **17**, and cleavage of the cycloadduct from the template gave β-truxinic acid, **10**, in high yields while **16** was quantitatively recovered. The [2 + 2]-photodimerization apparently proceeds with excellent stereocontrol, and the formation of configurational isomers of **10** was not observed. We then realized that *trans*-cinnamamide can be used to prepare **17** directly from **14** in 90% yield, which eliminates two steps and further enhances the efficiency of the template-assisted stereoselective synthesis of **10**.

A closer look at the cycloaddition product by NMR analysis revealed the presence of two diastereomers that apparently vary by the orientation of the methyl groups in the template. We were able to separate the *syn*- and *anti*-isomers of **18** by chromatography and found that both form the desired product upon UV irradiation. Slow evaporation of a solution of **18** in chloroform gave single crystals of the *anti*-isomer suitable for X-ray diffraction. Crystallographic analysis proved that **18** has a *cis*,*trans*,*cis*-cyclobutane ring and opposite orientation of the carbonyl groups of the neighboring amide functionalities, Figure 2. Both NMR and X-ray analysis suggest that the bridging of the cofacial 2-methylaniline rings in **18** by the cyclobutane moiety generates a congested framework that does not show rotation about the aryl−aryl bonds, thus

SCHEME 3. Synthesis of β-Truxinic Acid via Template 16



SCHEME 4. Synthesis of 10 and 26 with Template 21



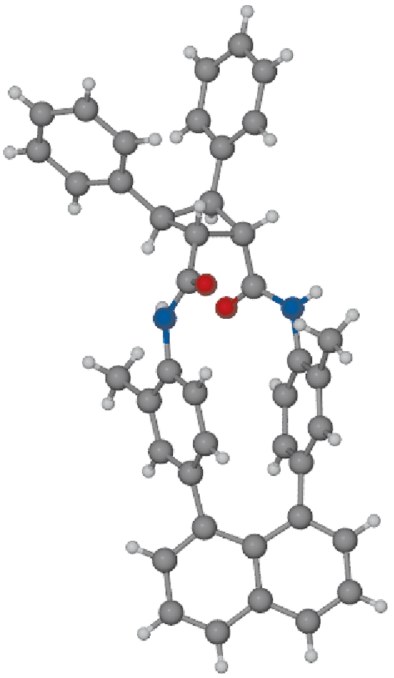


FIGURE 2. Crystal structure of *anti*-**18**.

giving rise to *syn*/*anti*-atropisomers that can be separated at room temperature (see the Supporting Information).

Originally, we assumed that template **16** and its diamide analogue **17** would favorably populate the *anti*-conformation and thus generate the C_2-symmetric δ-truxinic acid. However, crystallographic analysis of **18** and the exclusive formation of β-truxinic **10** after hydrolysis of the photodimer suggested that the presence of the methyl groups in the template does not affect the stereochemical outcome of the cycloaddition. We therefore decided to prepare 1,8-bis(4′-anilino)naphthalene, **21**, in two high-yielding steps from 4-acetamidophenylboronic acid, **19**, Scheme 4. This readily available template then gave access to cyclobutane **10** in just 3 steps with an overall yield of 69%. We then applied our template-assisted cycloaddition strategy in the stereoselective synthesis of *cis*,*trans*,*cis*-3,4-bis(3,4-dimethylphenyl)cyclobutane-1,2-dicarboxylic acid, **26**. Coupling of **21** and (*E*)-3-(3,4-dimethylphenyl)acrylic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) gave 1,8-bis(4′-(3,4-dimethylcinnamido)phenyl)naphthalene, **24**,

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in 80% yield. As expected, photochemical cycloaddition and hydrolysis with concentrated HCl gave cyclobutane-1,2-dicarboxylic acid **26** in excellent yields.

Conclusion

We have introduced 1,8-bis(4′-anilino)naphthalene templates for stereoselective photodimerization of α,β-unsaturated carboxylic acids. The template design affords two cofacial aniline rings that favor a proximate, parallel arrangement of covalently attached cinnamoyl units. The [2 + 2]cycloaddition proceeds with high yield and excellent stereoselectivity and the *cis*,*trans*, *cis*-cyclobutane-1,2-dicarboxylic acid formed is easily cleaved by acidic hydrolysis, which also allows quantitative recovery of the template. This approach overcomes limitations experienced with 1,8-bis(4′-pyridyl)naphthalene which proved useful for the template-directed solid-state dimerization of fumaric acid while cocrystals obtained with cinnamic acid were not suitable for [2+2]cycloaddition toward β-truxinic acid.

Experimental Section

1. General Synthetic Procedures. All reagents and solvents were used without further purification. Reactions were carried out under nitrogen atmosphere and under anhydrous conditions. Products were purified by flash chromatography on SiO_2 (particle size 0.032−0.063 mm). NMR spectra were obtained at 400 (^{1}H NMR) and 100 MHz (^{13}C NMR), using $CDCl_3$ as solvent unless otherwise specified. Chemical shifts are reported in ppm relative to TMS. UV irradiation experiments were conducted with a 400 W Mercury lamp positioned 1 cm away form the quartz reaction vessel. A fan was used to keep the solution at room temperature.

2. Synthesis of β-Truxinic Acid 10 with Template 16. 1,8-Bis(3′-methyl-4′-methoxyphenyl)naphthalene (12). A solution of 1,8-dibromonaphthalene, (1.20 g, 4.2 mmol), 3-methyl-4-methoxyphenylboronic acid (**11**) (2.10 g, 12.7 mmol), $Pd(PPh_3)_4$ (0.74 g, 0.64 mmol), and K_3PO_4, (4.05 g, 19.1 mmol) in 40 mL of toluene was stirred at reflux for 24 h. The resulting mixture was allowed to come to room temperature, quenched with water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes:CH_2Cl_2 3:1) afforded 1.50 g (4.1 mmol, 96%) of **12** as off-white crystals.

^{1}H NMR δ 1.91 (s, 3H), 2.02 (s, 3H), 3.73 (s, 6H), 6.30−6.90 (m, 6H), 7.38 (dd, J = 1.2, 7.0 Hz, 2H), 7.48 (dd, J = 7.3, 7.9 Hz, 2H), 7.89 (dd, J = 1.0, 8.0 Hz, 2H). ^{13}C NMR δ 15.9, 55.3, 108.6, 108.9, 124.8, 124.9, 127.6, 127.9, 128.2, 130.3, 130.5, 132.4, 132.8, 135.4, 135.4, 135.4, 135.5, 140.4, 155.7. Anal. Calcd for $C_{26}H_{24}O_2$: C, 84.75; H, 6.57. Found: C, 84.74; H, 6.61.

1,8-Bis(3′-methyl-4′-hydroxyphenyl)naphthalene (13). To a solution of 1,8-bis(3′-methyl-4′-methoxyphenyl)naphthalene (**12**) (1.50 g, 4.1 mmol) in 40 mL of anhydrous CH_2Cl_2 at 0 °C was added BBr_3 (24.4 mL, 24.4 mmol) dropwise and the mixture was stirred for 6 h. The reaction was carefully quenched with isopropyl alcohol followed by addition of water and extraction with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH_2Cl_2:EtOAc 7:1) afforded 1.33 g of **13** (3.92 mmol, 97%) as a white solid.

^{1}H NMR δ 1.98 (s, 3H), 2.10 (s, 3H), 4.95 (s, 2H), 6.35−6.90 (m, 6H), 7.39 (dd, J = 1.3, 7.0 Hz, 2H), 7.51 (dd, J = 7.1, 8.1 Hz, 2H), 7.91 (dd, J = 1.3, 8.2 Hz, 2H). ^{13}C NMR δ 15.44, 15.61, 113.3, 113.9, 121.8, 122.0, 125.0, 127.8, 128.3, 129.7, 130.4, 132.6, 132.8, 135.4, 136.1, 140.1, 151.6. Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.69; H, 5.92.

1,8-Bis(3′-methyl-4′-trifluoromethanesulfonatophenyl)naphthalene (14). To a solution of 1,8-bis(3′-methyl-4′-hydroxyphenyl)-naphthalene (**13**) (1.33 g, 3.9 mmol) and triethylamine (2.2 mL, 15.7 mmol) in 25 mL of toluene was added trifluoromethanesulfonic anhydride (6.6 mL, 39.2 mmol) at 0 °C. The temperature was gradually increased to 95 °C over a period of 1 h, and the reaction mixture was then allowed to stir for 14 h. The mixture was cooled to room temperature, quenched with water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes:CH_2Cl_2 4:1) afforded 2.30 g of **14** (3.8 mmol, 98%) as a yellow oil.

^{1}H NMR δ 2.09 (s, 3H), 2.18 (s, 3H), 6.70−7.00 (m, 6H), 7.34 (dd, J = 1.1, 7.1 Hz, 2H), 7.52 (dd, J = 7.2, 8.1 Hz, 2H), 7.98 (dd, J = 1.1, 8.2 Hz, 2H). ^{13}C NMR δ 15.8, 16.0, 118.5 (q, J_{C-F} = 320.0 Hz), 120.0, 123.3, 125.3, 127.8, 128.5, 128.8, 129.2, 129.3, 129.5, 131.1, 133.1, 133.5, 135.3, 137.9, 143.0, 146.5. Anal. Calcd for $C_{26}H_{18}F_6O_6S_2$: C, 51.66; H, 3.00. Found: C, 51.51; H, 2.98.

1,8-Bis(3′-methyl-4′-acetamidophenyl)naphthalene (15). To acetamide (0.26 g, 4.4 mmol), tris(dibenzylideneacetone)dipalladium (0.20 g, 0.22 mmol), potassium phosphate (0.69 g, 3.3 mmol), and 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (0.46 mg, 1.1 mmol) was added a solution of **14** (0.65 g, 1.1 mmol) in 15 mL of nitrogen-purged isopropyl alcohol, and the mixture was stirred at 90 °C for 19 h. The resulting mixture was allowed to come to room temperature, quenched with water, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtAOc to EtOAc:EtOH 90:10) afforded 0.35 g (0.84 mmol, 78%) of **15** as a yellow paste. This material was used in the following step without further purification.

^{1}H NMR δ 1.87 (s, 3H), 1.97 (s, 3H), 2.15 (s, 6H), 6.40 (s, 1H), 6.66−6.84 (m, 2H), 7.04−7.11 (m, 2H), 7.38 (d, J = 7.0 Hz, 2H), 7.50 (dd, J = 7.3, 7.9 Hz, 2H), 7.70 (s, 1H), 7.86 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H). ^{13}C NMR δ 17.5, 17.9, 23.6, 23.7, 124.6, 125.1, 125.4, 126.6, 127.5, 128.7, 129.4, 129.5, 130.4, 131.1, 132.2, 132.4, 132.6, 133.0, 133.0, 135.3, 135.4, 139.7, 141.0, 141.4, 169.3.

1,8-Bis(3′-methyl-4′-anilino)naphthalene (16). To a solution of 1,8-bis(3′-methyl-4′-acetamidophenyl)naphthalene (**15**) (0.27 g, 0.64 mmol) in 8 mL of ethanol was added 3 M HCl (4.3 mL, 12.7 mmol) and the mixture was stirred at 95 °C for 24 h. The resulting mixture was allowed to come to room temperature, basified with a stoichiometric amount of 28% NH_4OH, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:EtOH 97.5:2.5) afforded 0.20 g (0.59 mmol, 92%) of **16** as a yellow powder.

^{1}H NMR δ 1.85 (s, 3H), 1.98 (s, 3H), 3.18 (s, 4H), 6.20−6.90 (m, 6H), 7.39 (dd, J = 1.2, 7.0 Hz, 2H), 7.49 (dd, J = 7.2, 8.0 Hz, 2H), 7.87 (dd, J = 1.2, 8.1 Hz, 2H). ^{13}C NMR δ 17.1, 17.7, 113.4, 114.1, 120.8, 124.9, 126.5, 127.9, 129.7, 130.3, 132.1, 134.2, 135.5, 140.8, 142.0. Anal. Calcd for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.08; H, 7.13; N, 7.87.

1,8-Bis(3′-methyl-4′-cinnamamidophenyl)naphthalene (17): (A) From 14: To *trans*-cinnamamide (0.75 g, 5.1 mmol), tris-(dibenzylideneacetone)dipalladium (0.22 g, 0.24 mmol), potassium phosphate (0.81 g, 3.82 mmol), and 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (0.54 mg, 1.3 mmol) was added a solution of **14** (0.77 g, 1.3 mmol) in 35 mL of nitrogen-purged isopropyl alcohol, and the mixture was stirred at 90 °C for 19 h. The resulting mixture was allowed to come to room temperature, quenched with water, and extracted with THF. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The material was suspended in 10 mL of CH_2Cl_2 and filtered to isolate the precipitate (0.39 g, 0.65 mmol). The filtrate was subjected to flash chromatography on silica gel (CH_2Cl_2:EtOAc 15:1) to

afford another 0.30 g (0.50 mmol, 40%) of **17** as a white powder, which was combined with the precipitate to give a total of 0.69 g (1.15 mmol, 90%).

(**B**) **From 16:** To **16** (0.20 g, 0.59 mmol) in 18 mL of THF was added a solution of cinnamoyl chloride (0.24 g, 1.4 mmol) in 5 mL of THF at 0 °C, then the solution was allowed to stir for 24 h at room temperature. The resulting mixture was quenched with 1 M NaOH and extracted with THF. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was suspended in 10 mL of CH_2Cl_2 and filtered to isolate the precipitate (0.22 g. 0.38 mmol). The filtrate was then subjected to flash chromatography on silica gel (CH_2Cl_2:EtOAc 95:5) to afford another 0.11 g (0.17 mmol, 29%) of **17** as a white powder, which was combined with the precipitate to give a total of 0.33 g (0.55 mmol, 94%).

^{1}H NMR δ 2.02 (s, 3.7H), 2.16 (s, 2.3H), 6.47 (s, 1H), 6.60−6.85 (m, 4H), 6.95 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.20−7.58 (m, 16H), 7.70 (s, 1H), 7.78 (d, J = 6.6 Hz, 1H), 7.82 (d, J = 6.6 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H). ^{13}C NMR δ 17.7, 18.1, 121.2, 123.9, 125.1, 126.7, 127.6, 127.9, 128.7, 128.8, 128.9, 129.5, 130.3, 130.5, 132.3, 132.7, 132.9, 133.0, 134.7, 134.8, 135.4, 139.8, 140.8, 141.4, 141.8, 164.8. Anal. Calcd for $C_{42}H_{34}N_2O_2$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.43; H, 6.07; N, 4.49.

Cycloadduct (18). A suspension of **17** (0.53 g, 0.88 mmol) in 120 mL of nitrogen-purged acetone was placed in a quartz vessel and subjected to 48 h of irradiation from a 400 W medium pressure wide band mercury lamp placed 1 cm away. A fan was used to maintain the solution at room temperature. The solvent was then removed, and purification by flash chromatography on silica gel (CH_2Cl_2) afforded 0.45 g (0.77 mmol, 86%) of **18** as a white solid (mixture of two isomers that can be isolated).

First eluting isomer (*anti*-**18**): ^{1}H NMR δ 2.09 (s, 3H), 2.16 (s, 3H), 3.75 (dd, J = 2.0, 9.6 Hz, 1H), 4.32−4.48 (m, 2H), 4.60 (dd, J = 2.0, 9.6 Hz, 1H), 6.41 (d, J = 8.1 Hz, 2H), 6.95−7.20 (m, 13H), 7.45−7.58 (m, 5H), 7.94 (d, J = 8.0 Hz, 2H), 8.17 (d, J = 8.3 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H). ^{13}C NMR δ 17.2, 17.4, 43.9, 45.0, 48.4, 49.4, 117.2, 117.4, 124.6, 124.7, 125.0, 126.7, 126.8, 127.3, 128.2, 128.4, 128.5, 128.7, 129.8, 129.9, 130.0, 132.5, 134.5, 135.6, 137.5, 137.7, 138.9, 139.7, 168.5, 169.8.

Second eluting isomer (*syn*-**18**): ^{1}H NMR δ 2.03 (s, 3H), 2.17 (s, 3H), 3.70 (dd, J = 9.2 Hz, 11.1 Hz, 1H), 3.96 (m, 1H), 4.10 (dd, J = 7.8 Hz, 9.9 Hz, 1H), 4.60 (m, 1H), 6.38 (s, 1H), 6.43 (s, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.90 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.27−7.51 (m, 15H), 7.64 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.92 (m, 1H), 8.18 (d, J = 8.4 Hz, 1H). ^{13}C NMR δ 17.3, 17.4, 44.8, 46.4, 49.7, 51.9, 116.6, 118.4, 124.5, 124.6, 124.9, 125.0, 126.5, 126.6, 126.8, 127.5, 128.3, 128.6, 129.0, 129.7, 129.9, 130.1, 132.2, 132.3, 134.1, 134.8, 135.5, 138.7, 138.9, 139.4, 139.7, 140.8, 167.7, 168.9.

Anal. Calcd for $C_{42}H_{34}N_2O_2$ (*syn*/*anti*-mixture of **18**): C, 84.25; H, 5.72; N, 4.68. Found: C, 83.90; H, 6.04; N, 4.46.

***β*-Truxinic Acid (10)**[17]**.** A suspension of a mixture of *syn*- and *anti*-**18** (0.050 g, 0.084 mmol) in 5 mL of 30% aqueous hydrochloric acid was stirred at 110 °C for 24 h in a closed vessel. The resulting mixture was allowed to come to room temperature, basified with NH_4OH, and extracted with chloroform to quantitatively recover **16**. The aqueous layer was then acidified to pH 2 with concentrated hydrochloric acid, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was then crystallized from acetic acid, filtered, washed with 10% hydrochloric acid, and freeze-dried to afford 0.020 g of **10** (0.068 mmol, 81%) as a white powder.

^{1}H NMR (DMSO) δ 3.77 (d, J = 5.9 Hz, 2H), 4.18 (d, J = 5.8 Hz, 2H), 6.94−7.09 (m, 10H), 12.38 (s, 2H). ^{13}C NMR (DMSO) δ 43.0, 44.9, 126.3, 128.1, 128.3, 139.7, 174.4.

3. Synthesis of 10 and 26 with Template 21. 1,8-Bis(4′-acetamidophenyl)naphthalene (20). A solution of 1,8-diiodonaphthalene (0.57 g, 1.4 mmol), 4-acetamidophenylboronic acid (**19**) (0.64 g, 3.6 mmol), $Pd(PPh_3)_4$ (0.41 g, 0.36 mmol), and K_2CO_3 (0.89 g, 6.5 mmol) in 21 mL of nitrogen-purged ethanol:toluene:water (1:1:1) was stirred at 95 °C for 20 h. The resulting mixture was allowed to come to room temperature, quenched with water, and extracted with EtOAc and THF (1:1). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:EtOH 95:5 to 4:1) afforded 0.51 g (1.3 mmol, 90%) of **20** as a light brown powder.

^{1}H NMR (DMSO) δ 1.97 (s, 5.2 H), 2.03 (s, 0.8 H), 6.82 (d, J = 8.2 Hz, 4H), 7.17 (d, J = 8.3 Hz, 4H), 7.33 (d, J = 6.8 Hz, 2H), 7.56 (dd, J = 7.4, 7.8 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 9.69 (s, 1.8 H), 9.97 (s, 0.2H). ^{13}C NMR (DMSO) δ 24.5, 117.9, 119.8, 125.7, 126.8, 128.6, 129.0, 129.9, 131.1, 134.7, 135.7, 137.6, 137.7, 138.8, 140.1, 168.3, 168.7. Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.42; H, 5.96; N, 7.19.

1,8-Bis(4′-anilino)naphthalene (21). To a solution of 1,8-bis-(4′-acetamidophenyl)naphthalene (**20**) (0.31 g, 0.79 mmol) in 12 mL of ethanol was added 3 M HCl (2.4 mL, 7.1 mmol) and the mixture was stirred at 95 °C for 24 h. The resulting mixture was allowed to come to room temperature, basified with 28% NH_4OH, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:EtOH 97.5:2.5 to 95:5) afforded 0.25 g (0.79 mmol, 100%) of **21** as an off-white powder.

^{1}H NMR δ 2.76 (br s, 4H), 6.33 (d, J = 8.2 Hz, 4H), 6.74 (d, J = 8.2 Hz, 4H), 7.38 (d, J = 7.0 Hz, 2H), 7.50 (dd, J = 7.3, 7.8 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H). ^{13}C NMR δ 114.0, 125.0, 127.9, 129.6, 130.5, 130.7, 134.1, 135.6, 140.7, 144.2. Anal. Calcd for $C_{22}H_{18}N_2$: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.39; H, 6.12; N, 8.77.

1,8-Bis(4′-cinnamamidophenyl)naphthalene (22). To **21** (0.049 g, 0.16 mmol) in 5 mL of THF was added a solution of cinnamoyl chloride (0.05 g, 0.33 mmol) in 2 mL of THF at 0 °C, and the solution was stirred for 22 h at room temperature. The resulting mixture was quenched with 1 M NaOH and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was suspended in 10 mL of CH_2Cl_2 and filtered twice to recover the desired product (0.05 g. 0.10 mmol), and the filtrate was then subjected to flash chromatography on silica gel (hexanes:THF 2:1) to afford a total of 0.074 g (0.15 mmol, 93%) of **22** as a white powder.

^{1}H NMR (DMSO) δ 6.73 (d, J = 15.7 Hz, 2H), 6.87 (d, J = 8.0 Hz, 4H), 7.25−7.60 (m, 20H), 8.0 (d, J = 7.8 Hz, 2H), 9.99 (s, 2H). ^{13}C NMR (DMSO) δ 122.9, 125.8, 128.0, 128.8, 129.1, 129.3, 130.0, 130.1, 131.1, 135.2, 135.7, 137.6, 138.1, 140.1, 140.2, 163.7. Anal. Calcd for $C_{40}H_{30}N_2O_2$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.56; H, 5.60; N, 4.80.

Cyclobutane Derivative (23). A suspension of **22** (0.22 g, 0.39 mmol) in 54 mL of nitrogen-purged acetone was placed in a quartz vessel and subjected to 48 h of UV irradiation with a 400 W, medium pressure wide band mercury lamp placed 1 cm away. A fan was used to maintain the solution at room temperature. The solvent was then removed. Purification of the residue by flash chromatography on silica gel (CH_2Cl_2) afforded 0.18 g (0.32 mmol, 82%) of **23** as a white solid.

^{1}H NMR δ 3.78 (d, J = 9.7 Hz, 1H), 4.36 (dd, J = 10.6, 11.2 Hz, 1H), 4.50−4.64 (m, 2H), 6.31 (d, J = 7.8 Hz, 2H), 6.48 (d, J = 7.1 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 6.98 (d, J = 7.6 Hz, 2H), 7.05−7.20 (m, 10H), 7.42 (br s, 1H), 7.50−7.60 (m, 5H), 7.82 (d, J = 7.4 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.97 (dd, J = 1.4, 7.8 Hz, 2H). ^{13}C NMR δ 43.4, 44.8, 47.4, 48.4, 119.2, 119.4, 119.5, 119.8, 125.1, 126.7, 127.3, 128.2, 128.4, 128.8, 129.0, 129.8, 130.1, 130.4, 130.9, 131.2, 135.6, 135.8, 137.6, 138.0, 139.1, 139.2, 139.4, 139.5, 168.9, 170.4. Anal. Calcd for $C_{40}H_{30}N_2O_2$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.42; H, 5.59; N, 4.76.

***β*-Truxinic Acid (10).** A suspension of **23** (0.054 g, 0.094 mmol) in 6 mL of 30% aqueous hydrochloric acid was stirred at 110 °C for 24 h in a closed vessel. The resulting mixture was allowed to come to room temperature, basified with NH_4OH, and extracted with chloroform to quantitatively recover **21**. The aqueous layer was then acidified to pH 2 with concentrated hydrochloric acid, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was then crystallized from acetic acid, filtered, washed with 10% hydrochloric acid, and freeze-dried to afford 0.025 g of **10** (0.085 mmol, 90%) as a white powder.

^{1}H NMR (DMSO) δ 3.77 (d, J = 5.9 Hz, 2H), 4.18 (d, J = 5.8, 2H), 6.94−7.09 (m, 10H), 12.38 (s, 2H). ^{13}C NMR (DMSO) δ 43.0, 44.9, 126.3, 128.1, 128.3, 139.7, 174.4.

1,8-Bis(4′-(3,4-dimethylcinnamido)phenyl)naphthalene (24). A solution of **21** (0.12 g, 0.38 mmol), (*E*)-3-(3,4-dimethylphenyl)-acrylic acid (0.14 g, 0.81 mmol), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide (0.16 g, 0.85 mmol), and DMAP (0.07 g, 0.58 mmol) was stirred in 6 mL of toluene for 23 h at room temperature. The resulting suspension was filtered twice to collect the desired product (0.05 g. 0.10 mmol), and the filtrate was subjected to flash chromatography on silica gel (hexanes: THF 2:1) to afford a total of 0.19 g (0.31 mmol, 80%) of **24** as a white powder.

^{1}H NMR (DMSO) δ 2.11 (s, 6H), 2.17 (s, 6H), 6.33 (d, J = 15.7 Hz, 2H), 6.84 (d, J = 8.4 Hz, 4H), 7.02 (d, J = 7.6 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.17 (s, 2H), 7.28 (d, J = 8.4 Hz, 4H), 7.37 (d, J = 15.5 Hz, 2H), 7.37 (d, J = 7.0 Hz, 2H), 7.57 (dd, J = 7.4, 7.6 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H), 9.86 (s, 2H). ^{13}C NMR (DMSO) δ 19.7, 118.1, 121.7, 125.6, 125.7, 128.8, 128.9, 129.1, 130.1, 130.3, 131.0, 132.8, 135.6, 137.0, 137.7, 137.9, 138.5, 140.1, 140.2, 163.9. Anal. Calcd for $C_{44}H_{38}N_2O_2$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.67; H, 6.16; N, 4.82.

Cyclobutane Derivative (25). A suspension of **24** (0.10 g, 0.16 mmol) in 54 mL of nitrogen-purged acetone was placed in a quartz vessel and subjected to 48 h of UV irradiation, using a 400 W, medium pressure wide band mercury lamp placed 1 cm away. A fan was used to maintain the solution at room temperature. The solvent was then removed, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2) to give 0.08 g (0.13 mmol, 82%) of **25** as a white solid.

^{1}H NMR δ 2.13 (s, 12H), 3.72 (d, J = 10.2 Hz, 1H), 4.36 (dd, J = 10.2, 10.8 Hz, 1H), 4.40−4.54 (m, 2H), 6.31 (d, J = 7.8 Hz, 2H), 6.48 (d, J = 7.4 Hz, 1H), 6.54 (d, J = 7.4 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.76 (br s, 1H), 6.82−6.94 (m, 4H), 7.06 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.46−7.58 (m, 6H), 7.82 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.96 (dd, J = 1.4, 7.8 Hz, 2H). ^{13}C NMR δ 19.3, 19.7, 43.0, 44.4, 48.0, 48.5, 119.3, 124.7, 125.0, 125.7, 128.5, 129.0, 129.4, 129.6, 129.8, 130.0, 130.8, 131.0, 134.8, 135.2, 135.5, 136.2, 136.3, 139.0, 139.6, 169.3, 170.1. Anal. Calcd for $C_{44}H_{38}N_2O_2$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.00; H, 6.28; N, 4.80.

3,4-Bis(3,4-dimethylphenyl)cyclobutane-1,2-dicarboxylic Acid (26). A suspension of **25** (0.06 g, 0.096 mmol) in 6 mL of 30% aqueous hydrochloric acid was stirred at 110 °C for 24 h in a closed vessel. The resulting mixture was allowed to come to room temperature, basified with NH_4OH, and extracted with chloroform to quantitatively recover **21**. The aqueous layer was then acidified to pH 2 with concentrated hydrochloric acid, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was then crystallized from acetic acid, filtered, washed with 10% hydrochloric acid, and freeze-dried to afford 0.031 g of **26** (0.088 mmol, 92%) as a white solid.

^{1}H NMR ($CDCl_3$) δ 2.10 (s, 6H), 2.11 (s, 6H), 3.85 (d, J = 6.1 Hz, 2H), 4.31 (d, J = 6.1 Hz, 2H), 6.60−6.90 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 19.3, 19.7, 44.0, 44.4, 125.2, 129.2, 129.3, 134.5, 135.7, 136.0, 179.7. Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 75.11; H, 7.05.

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Supporting Information Available: Experimental procedures, crystallographic data, and NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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