Studies on the Dimerization of 2-Benzylidene-1-indanone

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It has been observed that 2-(*E*)-benzylidene-1-indanone (**1**) undergoes dimerization under basic conditions. The reaction is highly stereoselective and provides almost exclusively dimer **2b** using $NaHCO_3$/DMF, guanidine carbonate/DMF, or Cs_2CO_3/CH_3CN. The structure and the relative stereochemistry of compound **2b** were initially established on the basis of COSY, HMQC, HMBC, and NOESY NMR correlation techniques. The structure and the stereochemistry were then confirmed by X-ray crystallographic analysis. Two other stereoisomers were obtained, in minor proportions, by varying the experimental conditions. A fourth isomer was also produced using 2-(*Z*)-benzylidene-1-indanone as the starting material.

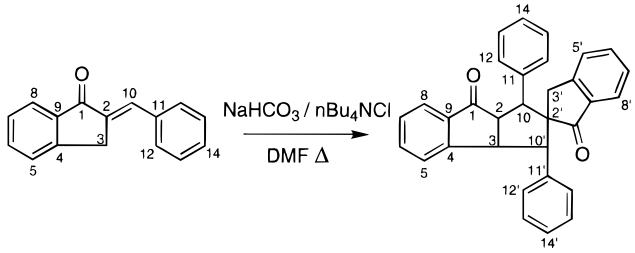
Introduction

Vinylic substitution reactions on an enone functionality by an aryl group catalyzed by palladium are well documented in the literature.[1] Generally, these reactions are performed in DMF in the presence of a base and an ammonium salt such as nBu_4NCl. While attempting to perform such a substitution on 2-(*E*)-benzylidene-1-indanone (**1**), using the preceding protocol, we observed the exclusive formation of an unexpected dimer (**2**) (Scheme 1). Fascinated by this dimerization in which five contiguous stereogenic centers are created from an achiral molecule, we decided to explore the stereochemical outcome of this reaction.

Results and Discussion

Initial studies showed that the palladium salt is not necessary for this dimerization to occur since the reaction takes place efficiently in the absence of palladium acetate as has been previously demonstrated.[2] Thus, 2-(*E*)-benzylidene-1-indanone (**1**) was subjected to varying basic conditions (Table 1) in order to evaluate the isomeric distribution of dimer **2** (Scheme 2). In this study, only three of the sixteen possible diastereoisomers of dimer **2** were observed, and each was isolated and fully characterized. Their relative stereochemistry was established by NMR techniques. As exemplified in Table 1, dimer **2** was isolated in moderate (entries 1, 2, and 3) to high yields (entry 5) as experimental conditions were changed. However, in all cases, isomer **2b** was predominantly formed in contrast with a previous report.[2] Using $NaHCO_3$/DMF as a base (Table 1, entry 1) it was possible to isolate a second stereoisomer (**2a**) in 5% yield. A third isomer (**2c**)[3] was also produced in 10% yield using PrOH/NaOPr/urea conditions (Table 1, entry 4).[2] When cesium carbonate was used as the base (Table 1, entry 5) dimer **2b** was formed in high yield.

Scheme 1



1 **2**

Table 1. Reaction Conditions and Isolated Yields for the Reaction of 1 to Give the Various Isomers of Dimer 2

		yield, %[a]		
entry	conditions	**2a**	**2b**	**2c**
1	DMF/$NaHCO_3$/100 °C/2 days	5	69	0[b]
2	DMF/guanidine carbonate/ 100 °C/18 h	0[c]	64	0[d]
3	PrOH/NaOPr/urea/100 °C/5 h	12	56	0
4	PrOH/NaOPr/urea/100 °C/2 h	−[e]	−[e]	10
5	CH_3CN/Cs_2CO_3/room temperature/18 h	0	93	4[f]

[a] Isolated yields. [b] Crude NMR analysis shows traces of isomer **2c** ≅ 2%. [c] Crude NMR shows 2% of isomer **2a**. [d] Crude NMR after 3 h shows 2% of isomer **2c**. [e] Not isolated. Experimental and purification conditions optimized in order to isolate isomer **2c**. [f] Isomer **2c** was isolated as a mixture with isomer **2b**.

Furthermore, 2-(*Z*)-benzylidene-1-indanone (**3**) was prepared using a modified procedure of George[4] and subjected to guanidine/DMF conditions. A new diastereoisomer (**2d**) was thus obtained in 15% yield presumably by the dimerization of two *Z* isomer molecules (Scheme 3). Isomer **2b** was also produced in 26% yield in this reaction. Since 2-(*Z*)-benzylidene-1-indanone (**3**) is converted to the *E* isomer (**1**) under these experimental conditions, the new isomer **2d** could also be derived from the dimerization of one *Z* monomer with one *E* monomer. It is likely that dimer **2b** was produced via the condensation of two molecules having the *E* stereochemistry.

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1997.

(1) See: Amoress, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1988**, *45*, 813 and cited references.

(2) Wendelin, W.; Schermanz, K.; Britmaier, E. *Monatsh. Chem.* **1988**, *119*, 355.

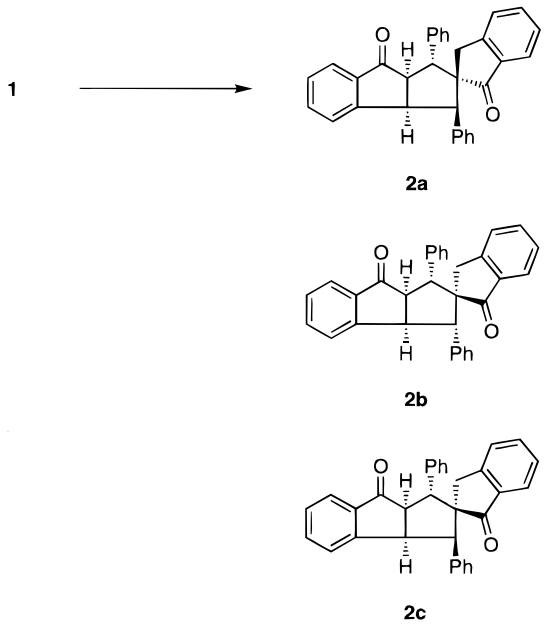
(3) The isomer **2c** was found to be unstable under the NaOPr/urea/PrOH conditions. After 5 h at 100 °C isomer **2c** was not detected.

(4) George, H.; Roth, H. J. *Tetrahedron Lett.* **1971**, *43*, 4057.

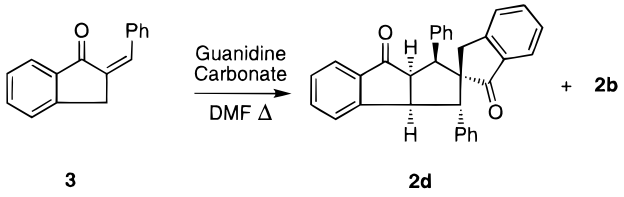
(5) Derome, A.; Williamson, M. *J. Magn. Reson.* **1990**, *88*, 177.

S0022-3263(97)00402-7 CCC: $14.00

Scheme 2



Scheme 3



The structure of dimer product **2** was determined by NMR using a combination of DQF-COSY,[5] NOESY, HMQC,[6] and HMBC[7] techniques. From the 1D proton and carbon spectra, a doubling of the expected number of peaks was observed, indicating that a dimer was the likely product. The protons were assigned using DQF-COSY and NOESY data, and protonated carbons were assigned with the HMQC experiment. All quaternery carbons were then identified from the HMBC data. Careful examination of the HMBC spectrum showed several extra cross peaks in addition to those expected for the monomers. Long-range correlations from H-3 to C-10′, from H-10 to C-1′, C-2′, and C-3′, from H-10′ to C-3 and C-4, and from H-3′ to C-10 are only consistent with the spiro-fused ring system shown in the schemes.

The relative stereochemistry of each dimer could then be determined from the NOESY experiment. For example, in the case of isomer **2b**, the relative stereochemistry of the H-2 and H-3 protons is likely cis due to the difficulty in forming a trans-fused 5,5 ring system. This stereochemistry is confirmed by the observation of an intense NOE cross peak between H-2 and H-3 in the NOESY spectrum. Cross peaks are also observed between H-3 and one of the diastereotopic methylene protons at H-3′ and between H-2 and the other diastereotopic methylene proton at H-3′. Therefore the H-3′ methylene group must be on the same side of the molecule as are protons H-2 and H-3. The observation of a cross peak between H-10 and H-10′ indicates that these two protons are on the same side of the five-membered ring. Upon examination of the region of the NOESY spectrum containing the aromatic signals, strong NOE cross peaks between H-3 and H-12′ and between H-2 and H-12 are found. Only the stereochemistry shown for isomer **2b** in Scheme 2 satisfies all of the observed NOEs. Thus, in this particular isomer, protons H-2, H-3, and H-3′ and the two phenyl rings are on the same side of the fused ring system.

Dimer **2b** was then submitted for X-ray crystallographic analysis in order to confirm that the relative stereochemistry derived by NMR was correct. The solution to the X-ray crystal structure[8] of **2b** is shown in Figure 1 and is consistent with the derived NMR structure.[9] As a result, the configuration of the other isomers of **2** were determined by NMR only.

The structures and relative stereochemistries of isomers **2a** and **2d** were determined by NMR in a fashion similar to that described for dimer **2b**. Analysis of dimer **2c** proved to be problematic due to extensive line broadening of several of the key proton and carbon signals as a result of chemical exchange. Cooling the sample in acetone-d_6 to −53 °C caused the lines to sharpen sufficiently to determine the structure and relative stereochemistry of **2c** to be that shown in Scheme 2. Interestingly, it is clear that the chemical exchange phenomenon results from restricted rotation about the C-10′, C-11′ bond. At −53 °C the rate of rotation about this bond is slow enough to destroy the chemical equivalency of the two H-12′ protons and the two H-13′ protons. As a result, unique signals are observed for each of the five protons on this aromatic ring.

A potential mechanism for the formation of dimer **2** is shown in Scheme 4. The first step of the reaction is the abstraction of one of the methylene protons of **1** to give a cross-conjugated enolate. This enolate can then perform an intermolecular Michael addition on a second molecule of monomer **1**. The newly generated enolate is then free to undergo an intramolecular Michael addition to generate the desired ring system which when protonated produces dimer **2**.

In conclusion, we have shown that the base-catalyzed dimerization of 2-(*E*)-benzylidene-1-indanone (**1**) provides mainly dimer **2b**. Modification of the reaction conditions can produce two other dimers, **2a** and **2c**, in minor amounts. A fourth dimer is formed in low yield when 2-(*Z*)-benzylidene-1-indanone (**3**) is used as a starting material. The NMR techniques used were sufficient for the determination of the relative stereochemistry of the dimers as was demonstrated with dimer **2b** where the X-ray structure is in complete agreement with that obtained from the NMR analysis. The relative stereochemistry of the major dimer **2b** under all reaction conditions tried was different than that obtained in the two previous studies.[2,10]

Experimental Section

General. Melting points (uncorrected) were determined in an open capillary tube. All reactions were performed in the dark to avoid olefin isomerization. Proton and carbon NMR spectra were recorded at 500 and 125 MHz, respectively. ^{1}H

(6) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565.
(7) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.

(8) Manuscript in preparation.
(9) During the period of peer review of the manuscript, a report appeared[10] which also describes the dimerization of **1**. However, the reported dimer which is spectroscopically identical to dimer **2b** and has the same melting point as **2b** has been assigned a relative stereochemistry that disagrees with that described in this manuscript.
(10) Houlihan, W. J.; Shapiro, M. J.; Chin, J. A. *J. Org. Chem.* **1997**, *62*, 1529.

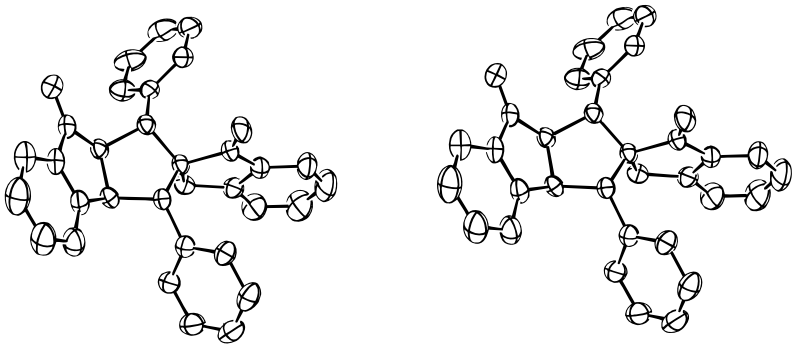
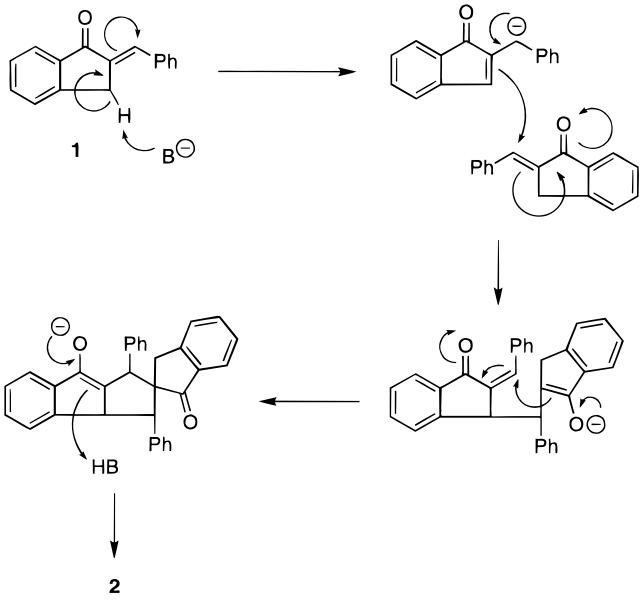


Figure 1. Stereoview of the ORTEP representation of **2b**. Non-hydrogen atoms are represented by ellipsoids corresponding to 20% probability. Hydrogen atoms are omitted for clarity.

Scheme 4



chemical shifts (δ) were reported in ppm relative to the residual solvent lines of $CHCl_3$ and acetone-d_5 at 7.24 and 2.04 ppm, respectively, and ^{13}C chemical shifts were reported relative to the solvent lines of $CDCl_3$ and acetone-d_6 at 77.0 and 29.8 ppm, respectively.

2-(*E*)-Benzylidene-1-indanone (1). To a mixture of 1-indanone (2.00 g, 15.1 mmol) and benzaldehyde (1.72 g, 16.2 mmol) in EtOH (20 mL) was added concentrated HCl (100 μL). The resulting mixture was heated at 80 °C for a period of 18 h. The reaction mixture was cooled to rt to give a yellow solid. The solid was filtered and washed with EtOH to provide 2.15 g (65%) of the title compound: ^1H NMR (500 MHz, acetone-d_6, 295 K) δ 7.82−7.77 (m, 3H), 7.71−7.66 (m, 2H), 7.57 (t, J = 2.2 Hz, 1H), 7.51 (t, J = 7.4 Hz, 2H), 7.50−7.46 (m, 1H), 7.44 (t, J = 7.3 Hz, 1H), 4.13 (d, J = 2.2 Hz, 2H); ^{13}C NMR (125 MHz, acetone-d_6, 295 K) δ 193.5, 150.4, 138.2, 135.9, 135.7, 135.0, 133.1, 131.1, 130.0, 129.3, 128.0, 127.0, 124.0, 32.4; HRMS calcd for $C_{16}H_{13}O$ $[M + H]^+$ 221.0966, found 221.0966.

Table 1, Entry 1 Reaction Conditions. To a solution of 2-(*E*)-benzylidene-1-indanone (**1**) (1.00 g, 4.54 mmol) in DMF (62 mL) was added an excess of $NaHCO_3$ (1.00 g). The resulting mixture was heated at 100 °C. After a period of 2 days, the reaction mixture was partitioned between CH_2Cl_2 and H_2O. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography (15% EtOAc in hexane) to yield 690 mg (69%) of dimer **2b** and 50 mg (5%) of dimer **2a**. Dimer **2a**: mp 246−248 °C (EtOH); ^1H NMR (500 MHz, $CDCl_3$, 295 K) δ 7.69 (m, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.34 (td, J = 7.5, 1.2 Hz, 1H), 7.27−7.21 (m, 4H), 7.16 (t, J = 7.6 Hz, 1H), 7.14−7.01 (m, 7H), 6.78−6.70 (m, 3H), 5.11 (t, J = 9.2 Hz, 1H), 4.17 (dd, J = 9.5, 8.5 Hz, 1H), 4.06 (d, J = 10.0 Hz, 1H), 3.72 (d, J = 9.7 Hz, 1H), 2.79 (d, J = 17.6 Hz, 1H), 2.71 (d, J = 17.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 295 K) δ 209.0, 207.0, 154,7, 152.1, 139.8, 137.6, 137.2, 136.2, 134.7, 134.2, 130.2, 128.7, 128.2, 128.1, 128.0, 127.4, 127.2, 127.2, 126.6, 125.7, 123.7, 123.7, 69.4, 56.9, 56.6, 53.6, 49.1, 36.6; HRMS calcd for $C_{32}H_{24}O_2$ $[M + H]^+$ 441.1855, found 441.1856. Anal. Calcd for $C_{32}H_{24}O_2$: C, 87.25; H, 5.49. Found: C, 87.00; H, 5.35. Dimer **2b**: mp 225−226 °C (EtOH); ^1H NMR (500 MHz, $CDCl_3$, 295 K) δ 7.75 (d, J = 7.5 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.43 (td, J = 7.3, 1.4 Hz, 1H), 7.38 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 7.5 Hz, 2H), 7.25−7.19 (m, 3H), 7.19−7.02 (m, 8H), 6.93 (d, J = 7.8 Hz, 1H), 4.56 (dd, J = 10.5, 8.7 Hz, 1H), 4.08 (d, J = 10.7 Hz, 1H), 3.92 (dd, J = 10.7, 8.5 Hz, 1H), 3.82 (d, J = 10.7 Hz, 1H), 3.05 (d, J = 17.1 Hz, 1H), 2.98 (d, J = 17.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 295 K) δ 207.7, 205.6, 155.8, 152.8, 137.2, 136.7, 136.5, 135.8, 135.2, 134.7, 128.5, 128.3, 128.3, 128.2, 128.2, 127.2, 127.0, 127.0, 125.7, 125.3, 124.5, 123.4, 70.2, 59.2, 54.1, 53.0, 46.0, 29.6; HRMS calcd for $C_{32}H_{24}O_2$ $[M + H]^+$ 441.1855, found 441.1856. Anal. Calcd for $C_{32}H_{24}O_2$: C, 87.25; H, 5.49. Found: C, 87.70; H, 5.29.

Table 1, Entry 2 Reaction Conditions. To a solution of the monomer **1** (0.500 g, 2.27 mmol) in DMF (7 mL) was added guanidine carbonate (0.205 g , 1.2 mmol). The resulting mixture was heated at 100 °C for a period of 18 h. After the solution was cooled to rt, H_2O (4 mL) was added followed by concentrated HCl until the solution reached a pH of 6. The solid was collected by vacuum filtration to yield isomer **2b** (0.339 g, 68%).

Table 1, Entry 3 Reaction Conditions. Sodium (0.250 g, 1.09 mmol) was dissolved in *n*-propanol (7.0 mL). Thiourea (0.173 g, 2.27 mmol) and monomer **1** (0.500 g, 2.27 mmol) were then added, and the solution was heated at 100 °C. After a period of 5 h, the solution was filtered and the filtrate was allowed to cool to rt and then to 0 °C. The resulting precipitate was collected by filtration and then purified by flash chromatography (15% EtOAc in hexane) to provide 60 mg (12%) of isomer **2a** and 280 mg (56%) of isomer **2b**.

Table 1, Entry 4 Reaction Conditions. The conditions for Table 1, entry 3 were used except the reaction mixture was heated at 100 °C for 2 h. The reaction mixture was then cooled to rt and partitioned between H_2O and CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The resulting residue was purified by flash chromatography (6% EtOAc in toluene) to provide 103 mg of impure isomer **2c** from 0.480 g of monomer **1**. The dimer **2c** was then recrystallized in EtOH to provide 46 mg (10%) of pure material: mp 248−250 °C (EtOH); ^1H NMR (500 MHz, acetone-d_6, 220 K) δ 7.78 (d, J = 7.3 Hz, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.47−7.39 (m, 4H), 7.39−7.30 (m, 3H), 7.29−7.21 (m, 3H), 7.16 (td, J = 7.3, 0.9 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.77 (td, J = 7.8, 1.1 Hz, 1H), 6.52 (d, J = 7.6 Hz, 1H), 6.23 (d, J = 8.2 Hz, 1H), 4.74 (dd, J = 10.1, 8.4 Hz, 1H), 4.15 (d, J = 10.5 Hz, 1H), 3.96 (d, J = 3.4 Hz, 1H), 3.82 (dd, J = 8.1, 3.4 Hz, 1H), 2.91 (d, J = 17.8 Hz, 1H), 2.68 (d, J = 17.8 Hz, 1H); ^{13}C NMR (125 MHz, acetone-d_6, 220 K) δ 208.1, 206.0, 153.9, 152.2, 143.0, 139.3, 136.3, 136.2, 135.0, 132.9, 132.0, 130.4, 129.1, 128.9, 128.8, 128.1, 127.6, 127.5, 127.1, 127.1, 126.8, 126.3, 123.3, 123.0,

66.2, 58.9, 57.7, 71.8, 48.4, 36.6; HRMS calcd for $C_{32}H_{24}O_2$ [M + H]$^+$ 441.1855, found 441.1856.

Table 1, Entry 5 Reaction Conditions. To a solution of monomer **1** (0.200 g, 0.908 mmol) in CH_3CN (3 mL) was added Cs_2CO_3 (0.775 g, 2.40 mmol). The solution was stirred at rt for 18 h. Crude ^{1}H NMR analysis of a sample extracted with H_2O−EtOAc showed a 5/1 ratio of isomer **2b** and **2c**. The reaction mixture was partitioned between H_2O and CH_2Cl_2. The organic phase was separated, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was recrystallized from EtOH/hexane (2/1) to yield 166 mg (84%) of isomer **2b**. The filtrate was recrystallized to provide 27 mg of a 5/1 mixture of isomers **2c** and **2b**.

2-(*Z*)-Benzylidene-1-indanone (3). 2-(*E*)-Benzylidene-1-indanone (0.500 g, 2.27 mmol) was dissolved in CH_3CN (300 mL) and irradiated with a UV mercury lamp for 4 h while stirring at 10 °C. The solvent was removed under reduced pressure, and the resulting solid was purified by flash chromatography (10% EtOAc in hexane) to provide 336 mg (67%) of the title compound: mp 82−86 °C (EtOAc−hexane); lit.[4] mp 88 °C; ^{1}H NMR (500 MHz, acetone-d_6, 295 K) δ 8.19 (dd, J = 7.7, 2.2 Hz, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.66 (td, J = 7.5, 1.3 Hz, 1H), 7.59 (dt, J = 7.7, 0.9 Hz, 1H), 7.45 (td, J = 7.3, 0.9 Hz, 1H), 7.44−7.37 (m, 3H), 7.13 (t, J = 1.9 Hz, 1H), 3.96 (t, J = 1.5 Hz, 2H); ^{13}C NMR (125 MHz, acetone-d_6, 295 K) δ 192.2, 149.8, 141.1, 139.5, 136.0, 135.9, 135.1, 131.9, 130.3, 128.7, 128.2, 127.0, 124.4, 35.7; HRMS calcd for $C_{16}H_{13}O$ [M + H]$^+$ 221.0966, found 221.0966.

Isomer 2d. To a solution of monomer **3** (0.270 g, 1.23 mmol) in DMF (1 mL) was added guanidine carbonate (0.110 g, 0.61 mmol). The solution was stirred at 100 °C for 1.5 h. The reaction was cooled to rt and quenched with the addition of water. The reaction mixture was extracted with ethyl acetate, and the organic phase was separated, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was then purified by flash chromatography (15% EtOAc in hexane) to provide 70 mg (26%) of isomer **2b** and 40 mg (15%) of isomer **2d**: mp 225−227 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$, 295 K) δ 7.62 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.44 (td, J = 7.5, 1.3 Hz, 1H), 7.36 (t, J = 7.3 Hz, 1H), 7.32−7.26 (m, 3H), 7.23−7.11 (m, 6H), 7.08 (t, J = 7.1 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.89−6.84 (m, 2H), 4.88 (dd, J = 10.8, 8.6 Hz, 1H), 4.47 (dd, J = 10.8, 8.4 Hz, 1H), 3.91 (d, J = 10.8 Hz, 1H), 3.59 (d, J = 10.8 Hz, 1H), 2.67 (d, J = 17.8 Hz, 1H), 2.60 (d, J = 17.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 295 K) δ 209.6, 206.3, 155.4, 152.2, 140.4, 137.9, 136.8, 136.2, 134.9, 134.7, 129.6, 129.0, 128.5, 128.4, 128.0, 127.5, 127.2, 127.1, 125.6, 125.5, 123.7, 123.6, 69.8, 59.3, 57.0, 53.0, 48.9, 35.3; HRMS calcd for $C_{32}H_{24}O_2$ [M + H]$^+$ 441.1855, found 441.1856.

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Supporting Information Available: NMR spectra (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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