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Sulfone-Mediated Syntheses of Crocetin Derivatives: Regioselectivity of Highly Functionalized Building Blocks

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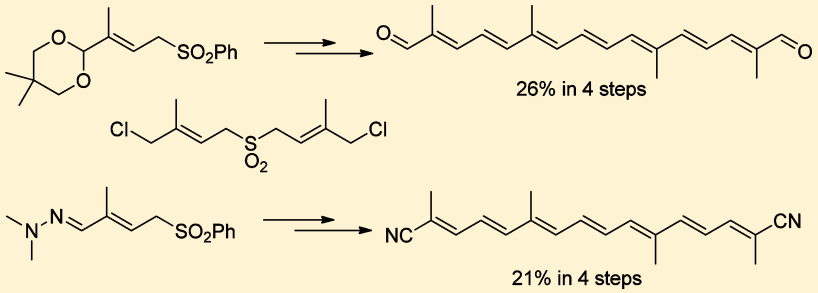
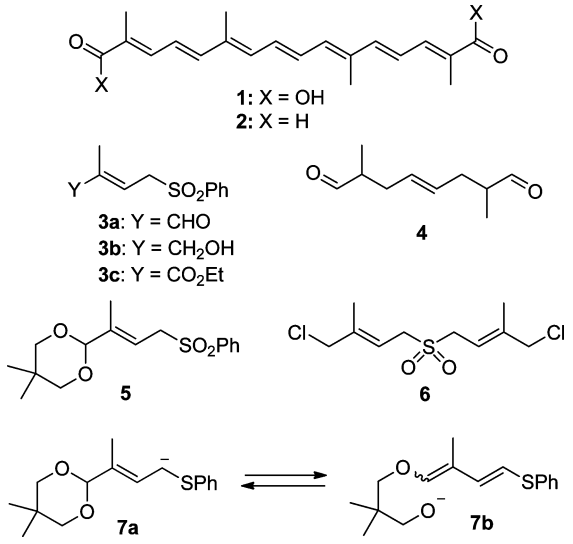
Supporting Information



ABSTRACT: New C_5 sulfone building blocks containing a masked polar end group have been devised for the efficient synthesis of carotenoids with polar termini. Chemoselectivity or the regiochemical issue of the highly functionalized units has been carefully addressed depending on the soft or hard nature of electrophiles. These building blocks have been successfully applied to the syntheses of crocetin derivatives, crocetin dial and the novel crocetin dinitrile.

Carotenoids are nonpolar hydrocarbons, in which alternating carbon−carbon double and single bonds bestow a radical (or singlet oxygen) quenching ability as well as characteristic red color.[1] Crocetin (**1**) is an unusual natural carotene compound, which contains polar carboxyl end groups instead of the nonpolar cyclohexene ring moieties (Scheme 1). Contrary to the hydroxyl groups of xanthophylls, the carboxyl groups of crocetin are directly attached to the conjugated polyene chain, which makes the synthesis of this carotenoid more challenging.[2] Synthetically, the apocarotenoid, crocetin dialdehyde (**2**), has drawn more attention as a useful synthetic intermediate for further elaboration by the Wittig reaction to the C_{40} carotenoids of industrial application such as β-carotene and lycopene.[3]

Scheme 1. Building Blocks for Crocetin Dialdehyde (2) Devised for the Sulfone-Mediated Synthesis



We have developed sulfone-mediated synthetic methods of carotenoids, in which various C_5 and C_{10} building blocks have been devised for the efficient assembly of the conjugated polyene chain of nonpolar carotenoids.[4] A strategy based on sulfone chemistry afforded several advantages in carotenoid synthesis in that sulfone intermediates are stable and easy to crystallize and produce mainly *E*-alkenes in the elimination.[5] Retrosynthesis of crocetin dialdehyde (**2**) based on the sulfone-mediated coupling−double elimination strategy intuitively requires highly functionalized building block **3a**, the C_5 allylic sulfone containing a formyl end group, and 2,7-dimethyloct-4-enedial (**4**) (Scheme 1).[4e] Because of the incompatibility of the functionalities in **3a** under basic coupling conditions, a masked form of the formyl group was required. Several umpolungs of **3a** were evaluated for their reactivity: hardness or softness as well as regioselectivity of the resulting carbanion. We herein disclose the details of the study described above and delineate the synthesis of crocetin derivatives by using the new C_5 building blocks.

We initially considered hydroxymethyl or ester functionality (e.g., **3b** or **3c**) in place of the formyl group in C_5 building

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block **3a** (Scheme 1). However, the anionic reactivities of the regioisomeric conjugated hydroxymethyl-sulfone and conjugated sulfone-ester have been reported to be unfavorable.[6] Because hydroxymethyl-sulfone suffered from low yields due to the elimination of the hydroxyl group even in the dianionic form and the wrong regioselectivity has been obtained in allylation of sulfone-ester, we concentrated on the study of the protected formyl group.

Acetal protection of **3a** with neopentyl glycol provided highly stable allylic sulfone **5**. However, this crystalline material was not soluble in most organic solvents, including THF and MeOH, which did not allow the coupling reaction with dial **4** at low temperatures. Protection with ethylene glycol or 1,3-propanediol improved the solubility but did not allow smooth coupling with dial **4** either. Cleavage of acetals was noticed under the coupling condition using *n*-BuLi in THF at −78 °C. The corresponding allylic sulfide **7** with neopentyl glycol protection was then prepared to maintain the stability as well as to circumvent the solubility problem of sulfone. Unfortunately, the coupling reaction with dial **4** (*n*-BuLi in THF at −78 °C) did not proceed either, presumably because of the conversion of **7a** into the more stabilized ring opening alkoxide **7b**.[7]

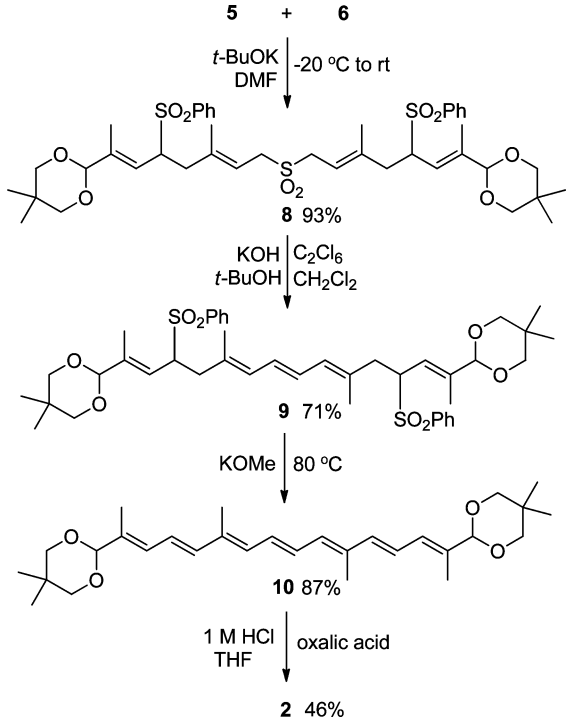
The solubility problem of C_5 building block **5** can be alleviated at higher temperatures in DMF (e.g., 1 g of **5** per 30 mL of DMF at 25 °C), and bis(chloroallylic)sulfone **6** should be utilized as a coupling partner to avoid the retro-aldol reaction, inherent in dial **4** at high temperatures. Thus, a 2-fold excess of allylic sulfone **5** (over **6**) was dissolved in sufficient DMF at room temperature, and *t*-BuOK was added to deprotonate the α-hydrogen. The anionic solution of **5** in DMF was then cooled to −20 °C and allowed to react with **6** to produce coupling product **8** in 93% yield (Scheme 2). The presence of three rigid sulfone functionalities allowed easy purification of this coupling product just by washing with MeOH.

The Ramberg−Bäcklund reaction of bis-allylic sulfone **8** produced triene **9** in 71% yield. The Ramberg−Bäcklund reaction utilizing CCl_4 as both a chloronium (Cl^+) source and a solvent should be modified because the reagent has been banned for environmental reasons.[4a,8] Almost the same result was obtained using only 2 equiv of C_2Cl_6 over **8** as a halogen source in CH_2Cl_2, where the base, *t*-BuOK, was slowly generated by the reaction of KOH and *t*-BuOH.[9] Triene **9** containing two rigid sulfone groups was easily purified again just by washing with MeOH.

A small amount of the *Z* isomer at C_8 (≤20%) was noticed in the ^{1}H NMR spectrum of **9**, but the *E*/*Z* mixture was subjected to the dehydrosulfonation condition under KOMe in a benzene/cyclohexane mixture at 80 °C to produce the fully conjugated polyene acetal **10** in 87% crude yield. An analytical sample was prepared by trituration with diethyl ether to give all-(*E*)-**10**. The crude acetal product **10** was hydrolyzed by 1 M HCl in THF to give crocetin dial (**2**) in 46% isolated yield after silica gel chromatographic separation, which was further purified by trituration with MeOH. Crocetin dial (**2**) was thus synthesized in 26% overall yield (four steps) from C_5 acetal building block **5**.

Hydrazone protection of **3a** with *N*,*N*-dimethylhydrazine provided highly stable C_5 building block **11a**, in which a very interesting regiochemical reactivity issue emerged because of the coexistence of anion-stabilizing sulfone and hydrazone functionalities. Furthermore, hydrazone is known to be transformed into nitrile by oxidation,[10] which would allow

Scheme 2. Synthesis of Crocetin Dialdehyde (2) Using Allylic Sulfone 5 with Acetal Protection



the efficient synthesis of a new type of crocetin derivative, crocetin dinitrile. We thus systematically studied the reactivity (chemoselectivity) of C_5 allylic sulfone **11a** and allylic sulfide **11b** with hydrazone protection toward the base-promoted alkylation with hard (acetaldehyde) and soft (iodomethane) electrophiles. Even though there were some variations in the yields of the reaction products, different metallic bases (NaHMDS or *t*-BuLi) provided a similar trend in the chemoselectivity of alkylation of the C_5 building blocks with hydrazone protection (Scheme 3).

There is a clear difference between allylic sulfone **11a** and allylic sulfide **11b** in the chemoselectivity of alkylation with acetaldehyde. This hard electrophile reacted at the hard α-carbon to the hydrazone in allylic sulfide **11b** to produce **12b** in up to 70% yield, while γ-alkylation of the hydrazone in allylic sulfone **11a** was observed to produce **13a** in only 39% yield. This was a manifestation of the anion stabilizing effect of sulfone, which directed α-alkylation (γ to the hydrazone) but deactivated anionic reactivity. On the other hand, iodomethane as a soft electrophile reacted only at the soft γ-carbon to the hydrazone to produce **15a** and **15b** from allylic sulfone **11a** and allylic sulfide **11b**, respectively. It was interesting to note that no α-alkylation product **14a** or **14b** was observed in either case.

The utility of novel C_5 allylic sulfone **11a** with hydrazone protection was demonstrated in the synthesis of a new crocetin derivative, crocetin dinitrile (**19**) (Scheme 4). As was expected from the previous regioselectivity study, allylic sulfone **11a** matched well with C_{10} allylic chloride **6** rather than aldehyde **4** for the base-promoted coupling (*t*-BuOK in DMF) to give trisulfone **16** in 72% yield. The Ramberg−Bäcklund reaction under the modified condition utilizing C_2Cl_6 as a halogen source in CH_2Cl_2 uneventfully produced triene **17** in 56% yield (3.5:1 *E*/*Z* mixture at C_8 based on ^{1}H NMR analysis). Base-promoted elimination of benzenesulfonyl groups (KOMe at 80 °C) produced fully conjugated polyene **18** with hydrazone in

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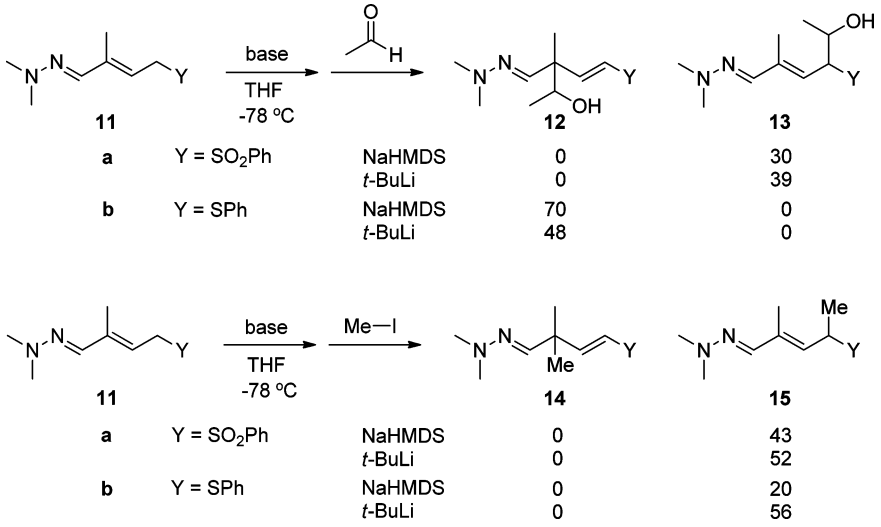
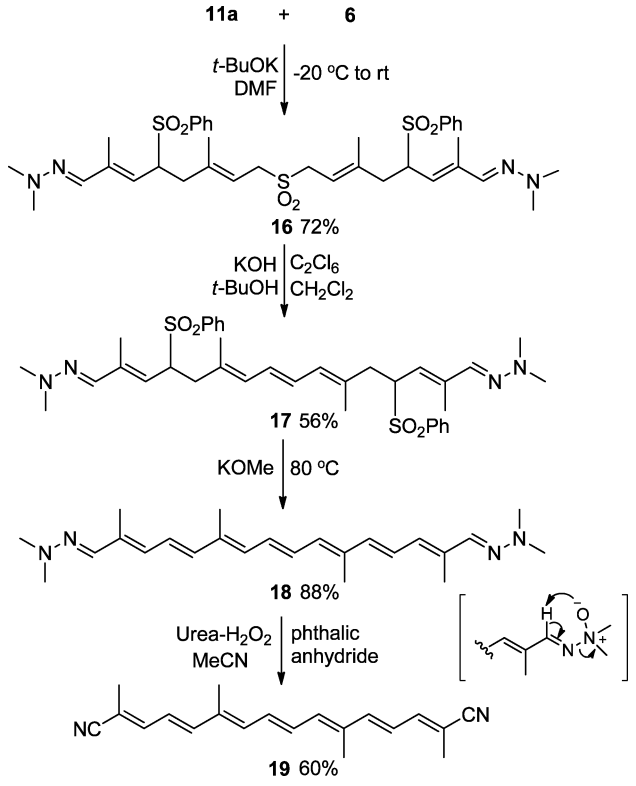
Scheme 3. Regioselectivity of Allylic Sulfone 11a and Allylic Sulfide 11b with Dimethylhydrazone Protection in Base-Promoted Alkylation with Acetaldehyde and Iodomethane



Scheme 4. Synthesis of Crocetin Dinitrile (19) Using Allylic Sulfone 11a with Dimethylhydrazone Protection



88% crude yield. An analytical sample of **18** was easily prepared by trituration with MeOH.

Deprotection of the hydrazone was not a trivial task especially because of the unstable nature of the carotenoid polyene chain under acidic conditions. However, oxidation of the tertiary amine in dimethylhydrazone induced smooth intramolecular oxidative dehydrogenation of the resulting ammonium oxide to generate nitrile functionality (see the brackets in Scheme 4).[10] Crocetin dinitrile (**19**) was obtained in 60% isolated yield from the oxidation of hydrazone **18** by monoperphthalic acid, which was generated *in situ* from the reaction of urea-hydrogen peroxide (UHP) and phthalic anhydride in acetonitrile. With novel C_5 building block **11a** with hydrazone protection as the starting point, crocetin dinitrile (**19**) was synthesized in 21% overall yield (four steps).

In summary, we developed new types of C_5 building blocks, which are amenable to the sulfone-mediated synthesis of carotenoids with polar end groups. The regiochemical issue of the highly functionalized C_5 building blocks was carefully addressed, and the utility of them was demonstrated in the efficient syntheses of crocetin dial (**2**) and crocetin dinitrile (**19**). The carotenoids with nitrile termini are especially valuable for easy coordination to various metal surfaces.

EXPERIMENTAL SECTION

General Experimental. ^{1}H and ^{13}C NMR spectra were recorded on 400 and 100 MHz NMR spectrometers, respectively, in deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal reference. High-resolution mass spectroscopy was performed using a magnetic sector analyzer. Solvents for extraction and chromatography were reagent grade and used as received. Column chromatography was performed by the method of Still with silica gel 60, 70−230 mesh ASTM supplied by Merck using a gradient mixture of EtOAc and hexanes. Reactions were performed in a well-dried flask under an argon atmosphere unless noted otherwise.

***(E)*-2-Methyl-4-(phenylsulfonyl)but-2-enal (3a).** To a stirred solution of (*E*)-4-chloro-2-methylbut-2-enal[11] (11.10 g, 94.0 mmol) in MeOH (100 mL) was added *p*-TsOH (0.50 g 2.80 mmol). The mixture was stirred at room temperature for 1 h, and $NaSO_2Ph$ (15.40 g, 94.0 mmol) was added. The reaction mixture was stirred at room temperature for 12 h, concentrated under reduced pressure, and then treated with 1 M HCl (100 mL). The resulting mixture was stirred at room temperature for 1 h, extracted with CH_2Cl_2, washed with 1 M HCl and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude solid product was purified by being washed with ether to give **3a** (10.10 g, 45.0 mmol) in 48% yield as white solid: R_f = 0.07 (1:4 EtOAc/hexane); mp 112−115 °C; ^{1}H NMR δ 1.48 (s, 3H), 4.13 (d, J = 8.0 Hz, 2H), 6.45 (dt, J_d = 1.6 Hz, J_t = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 2H), 7.70 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 9.46 (s, 1H); ^{13}C NMR δ 9.2, 56.3, 128.2, 129.4, 134.3, 136.3, 138.3, 145.4, 193.5; IR (KBr) 3071, 2992, 2936, 2848, 1694, 1461, 1312, 1242, 1176, 1144, 1083, 1003, 919, 812, 746, 695, 578 cm^{-1}; HRMS (CI$^+$) calcd for $C_{11}H_{13}O_3S$ 225.0585, found 225.0578.

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(*E*)-5,5-Dimethyl-2-[4-(phenylsulfonyl)but-2-en-2-yl]-1,3-dioxane (5). To a stirred solution of **3a** (4.20 g, 18.74 mmol) in toluene (100 mL) were added neopentyl glycol (9.76 g, 93.73 mmol) and *p*-TsOH (0.10 g, 0.56 mmol). The reaction mixture was heated at 120 °C for 8 h in a reflux condenser equipped with a Dean−Stark column. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The crude product was diluted with CH_2Cl_2, washed with 1 M NaOH and H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by being washed with ether to give **5** (5.40 g, 17.40 mmol) in 93% yield as white solid: R_f = 0.55 (2:3 EtOAc/hexane); mp 164−166 °C; ^{1}H NMR δ 0.73 (s, 3H), 1.17 (s, 3H), 1.39 (s, 3H), 3.46 (d, J = 10.8 Hz, 2H), 3.62 (d, J = 10.8 Hz, 2H), 3.85 (d, J = 8.0 Hz, 2H), 4.67 (s, 1H), 5.70 (t, J = 8.0 Hz, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 11.6, 21.8, 22.9, 30.1, 55.5, 77.1, 103.1, 114.6, 128.5, 129.1, 133.7, 138.5, 142.5; IR (KBr) 2965, 2872, 1642, 1478, 1455, 1399, 1315, 1152, 1115, 1092, 1017, 984, 882, 733, 612 cm^{-1}; HRMS (CI$^+$) calcd for $C_{16}H_{23}O_4S$ 311.1317, found 311.1319.

(*E*)-5,5-Dimethyl-2-[4-(phenylthio)but-2-en-2-yl]-1,3-dioxane (7). The mixture of (*E*)-2-methyl-4-(phenylthio)but-2-enal[12] (2.100 g, 10.92 mmol), neopentyl glycol (11.35 g, 0.109 mol), and *p*-TsOH (0.55 mmol, 104 mg) in benzene (50 mL) was heated to reflux in a round-bottomed flask, equipped with a Dean−Stark trap and a condenser, for 20 h. The mixture was cooled to room temperature, diluted with ether, washed with a 1 M NaOH solution (3 × 50 mL) and H_2O (50 mL), dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The crude orange oily product (2.957 g) was purified by SiO_2 flash column chromatography to give **7** (1.687 g, 6.06 mmol) as a light yellow oil: R_f = 0.63 (8:2 hexane/EtOAc); ^{1}H NMR δ 0.72 (s, 3H), 1.20 (s, 3H), 1.70 (s, 3H), 3.47 (d, J = 10.8 Hz, 2H), 3.58 (d, J = 7.6 Hz, 2H), 3.63 (d, J = 10.8 Hz, 2H), 4.69 (s, 1H), 5.77 (t, J = 7.6 Hz, 1H), 7.15−7.21 (m, 1H), 7.24−7.30 (m, 2H), 7.31−7.36 (m, 2H); ^{13}C NMR δ 11.2, 21.7, 22.8, 30.0, 31.2, 77.0, 77.0, 77.0, 104.0, 124.1, 126.0, 128.7, 129.5, 136.3; IR (KBr) 2961, 2865, 1700, 1600, 1479, 1401, 1241, 1106, 1032, 993, 937, 751, 694 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{16}H_{23}O_2S$ 279.1419, found 279.1414.

2,2′-(2*E*,2′*E*,6*E*,6′*E*)-8,8′-Sulfonylbis[6-methyl-4-(phenylsulfonyl)octa-2,6-diene-8,2-diyl]bis(5,5-dimethyl-1,3-dioxane) (8). To a stirred solution of **5** (5.00 g, 16.12 mmol) in DMF (150 mL) was added *t*-BuOK (2.20 g, 19.35 mmol). The mixture was stirred at room temperature for 30 min and cooled to −20 °C. A solution of **6**[4c] (2.18 g, 8.06 mmol) in DMF (4 mL) was then added. The resulting mixture was stirred at −20 °C for 2 h, warmed to room temperature, and stirred for 2 h. The reaction mixture was treated with H_2O (300 mL) and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by being washed with MeOH to give **8** (6.14 g, 7.48 mmol, a mixture of diastereomers) in 93% yield as white solid: R_f = 0.13 (2:3 EtOAc/hexane); mp 183−185 °C; ^{1}H NMR δ 0.71 (s, 6H), 1.13 (s, 6H), 1.19 (s, 6H), 1.65 (s, 6H), 2.44 (dd, J = 13.6, 11.2 Hz, 2H), 3.01 (dd, J = 13.6, 2.4 Hz, 2H), 3.38 (d, J = 10.8 Hz, 4H), 3.56 (d, J = 10.8 Hz, 4H), 3.92 (ddd, J = 11.2, 10.8, 2.4 Hz, 2H), 4.54 (s, 2H), 4.56 (diastereomers in ^{1}H NMR) (s, 2H), 5.21 (t, J = 11.2 Hz, 2H), 5.23 (diastereomers in ^{1}H NMR) (t, J = 11.6 Hz, 2H), 5.38 (d, J = 10.8 Hz, 2H), 7.48−7.55 (m, 4H), 7.61−7.67 (m, 2H), 7.82−7.86 (m, 4H); ^{13}C NMR (peaks from diastereomers are given in parentheses) δ 11.9 (11.5), 16.9 (16.8), 21.7 (21.3), 22.9, 30.1, 37.3 (37.4), 51.0, 55.4, 62.2, 77.2 (71.7), 102.6 (103.0), 114.5 (114.4), 120.1, 129.1 (128.5), 129.4 (128.9), 133.8 (133.7), 140.4 (136.9), 142.3 (142.5); IR (KBr) 2963, 2869, 1682, 1461, 1405, 1315, 1156, 1113, 1029, 991, 884, 757, 701, 611 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{42}H_{59}O_{10}S_3$ 819.3270, found 819.3281.

2,2′-[(2*E*,6*E*,8*E*,10*E*,14*E*)-6,11-Dimethyl-4,13-bis(phenylsulfonyl)hexadeca-2,6,8,10,14-pentaene-2,15-diyl]bis(5,5-dimethyl-1,3-dioxane) (9). To a stirred solution of **8** (3.27 g, 3.98 mmol) in CH_2Cl_2 (80 mL) were added *t*-BuOH (32 mL) and C_2Cl_6 (1.89 g, 7.96 mmol). The mixture was stirred at room temperature for 10 min, and pulverized KOH (2.23 g, 39.82 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, and most of solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2, washed with a 10% $NaHCO_3$ solution, dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The crude product was purified by being washed with MeOH to give **9** (2.14 g, 2.84 mmol, a mixture of diastereomers) in 71% yield as light yellow solid: R_f = 0.35 (2:3 EtOAc/hexane); mp 166−169 °C; ^{1}H NMR δ 0.71 (s, 6H), 1.13 (s, 6H), 1.19 (s, 6H), 1.67 (s, 6H), 2.40 (dd, J = 13.6, 10.8 Hz, 2H), 3.01 (dd, J = 13.6, 2.8 Hz, 2H), 3.40 (d, J = 10.8 Hz, 4H), 3.57 (d, J = 10.8 Hz, 4H), 3.89 (ddd, J = 11.2, 10.0, 2.8 Hz, 2H), 4.58 (s, 2H), 5.41 (d, J = 10.0 Hz, 2H), 5.82−5.91 (m, 2H), 6.15−6.24 (m, 2H), 7.44−7.55 (m, 4H), 7.57−7.68 (m, 2H), 7.77−7.86 (m, 4H); ^{13}C NMR (peaks from diastereomers are given in parentheses) δ 11.7 (11.8), 16.8 (16.7), 21.8, 22.8, 30.1, 37.6, 63.0, 63.1, 102.8, 120.6 (120.8), 124.0 (123.5), 127.9 (128.7), 128.8, 129.4 (129.5), 132.8, 133.5 (133.6), 137.4, 141.6; IR (KBr) 2964, 2871, 1724, 1641, 1483, 1460, 1399, 1316, 1153, 1116, 1037, 991, 735, 698, 624 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{42}H_{57}O_8S_2$ 753.3495, found 753.3509.

Crocetin Dialdehyde, Neopentyl Diacetal (10). To a stirred solution of **9** (1.50 g, 1.99 mmol) in benzene (20 mL) and cyclohexane (30 mL) was added KOMe (4.19 g, 59.76 mmol). The reaction mixture was heated at 80 °C for 8 h and cooled to room temperature. The mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude product was diluted with CH_2Cl_2, washed with a 10% $NaHCO_3$ solution, dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to give crude **10** (0.86 g, 1.73 mmol) in 87% yield as an orange solid. An analytical sample was prepared by trituration with diethyl ether: R_f = 0.55 (1:4 EtOAc/hexane); mp 117−120 °C; ^{1}H NMR δ 0.75 (s, 6H), 1.23 (s, 6H), 1.89 (s, 6H), 1.94 (s, 6H), 3.51 (d, J = 10.8 Hz, 4H), 3.67 (d, J = 10.8 Hz, 4H), 4.77 (s, 2H), 6.17−6.26 (m, 2H), 6.29 (d, J = 10.8 Hz, 2H), 6.35 (d, J = 14.8 Hz, 2H), 6.49 (dd, J = 14.8, 10.8 Hz, 2H), 6.55−6.68 (m, 2H); ^{13}C NMR δ 12.1, 12.8, 21.9, 23.0, 30.2, 77.3, 104.6, 123.7, 128.6, 130.1, 132.7, 134.1, 136.2, 138.9; UV (CH_2Cl_2) λ_{max} (ε) 382 (16408), 402 (25547), 429 nm (25969); IR (KBr) 2934, 2867, 1746, 1470, 1390, 1277, 1190, 1110, 1026, 959, 888, 813, 654 cm^{-1}; HRMS (EI$^+$) calcd for $C_{30}H_{44}O_4$ 468.3239, found 468.3242.

Crocetin Dialdehyde (2). To a stirred solution of the crude polyene acetal **10** described above in THF (10 mL) were added 1 M HCl (20 mL) and oxalic acid (0.33 g, 3.46 mmol). The reaction mixture was stirred at room temperature for 1 h, extracted with EtOAc, washed with 1 M HCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **2** (0.23 g, 0.79 mmol) in 46% yield as a red solid. An analytical sample was prepared by trituration with MeOH: R_f = 0.23 (1:4 EtOAc/hexane); mp 189−192 °C; ^{1}H NMR δ 1.91 (s, 6H), 2.03 (s, 6H), 6.41−6.52 (m, 2H), 6.68−6.82 (m, 6H), 6.90−7.00 (m, 2H), 9.47 (s, 2H); ^{13}C NMR δ 9.7, 12.8, 123.7, 132.0, 136.7, 137.1, 137.4, 145.4, 148.8, 194.5; UV (CH_2Cl_2) λ_{max} (ε) 422 (51422), 446 (78763), 475 nm (77058); IR (KBr) 3044, 2932, 2839, 2726, 1683, 1624, 1570, 1448, 1418, 1330, 1272, 1198, 982, 845, 747, 698, 645 cm^{-1}; HRMS (CI$^+$) calcd for $C_{20}H_{25}O_2$ 297.1855, found 297.1852.

(*E*)-1,1-Dimethyl-2-[(*E*)-2-methyl-4-(phenylsulfonyl)but-2-enylidene]hydrazine (11a). To a stirred solution of **3a** (2.84 g, 12.66 mmol) in CH_2Cl_2 (40 mL) were added 1,1-dimethylhydrazine (1.34 g 13.93 mmol) and Et_3N (3.84 g, 37.99 mmol). The reaction mixture was stirred at room temperature for 3 h, diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **11a** (2.50 g, 8.86 mmol) in 70% yield as a light yellow solid: mp 102−105 °C; R_f = 0.52 (2:3 EtOAc/hexane); ^{1}H NMR δ 1.50 (s, 3H), 2.86 (s, 6H), 3.99 (d, J = 8.4 Hz, 2H), 5.47 (t, J = 8.4 Hz, 1H), 6.90 (s, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.64 (t, J = 7.6 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 11.5, 42.6, 56.5, 114.6, 128.4, 129.1, 133.6, 135.5, 138.8, 143.0; IR (KBr) 2991, 2926, 1637, 1563, 1455, 1310, 1250, 1175, 1142, 1096,

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1063, 923, 895, 778, 741, 689, 540 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_{19}N_2O_2S$ 267.1167, found 267.1171.

(*E*)-1,1-Dimethyl-2-[(*E*)-2-methyl-4-(phenylthio)but-2-enylidene]hydrazine (11b). To a stirred mixture of (*E*)-2-methyl-4-(phenylthio)but-2-enal[12] (3.30 g, 17.16 mmol) and dimethylhydrazine hydrochloride salt (2.48 g, 25.75 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (5.20 g, 51.48 mmol). The mixture was stirred vigorously at room temperature for 1 day under an argon atmosphere, diluted with CH_2Cl_2 (50 mL), and partitioned with a 4% KOH solution (50 mL). The organic layer was separated, dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **11b** (2.543 g, 10.85 mmol) in 63% yield as a yellow oil: R_f = 0.54 (8:2 hexane/EtOAc); ^1H NMR δ 1.80 (s, 3H), 2.83 (s, 6H), 3.73 (d, J = 8.0 Hz, 2H), 5.63 (t, J = 8.0 Hz, 1H), 6.96 (s, 1H), 7.15−7.22 (m, 1H), 7.24−7.31 (m, 2H), 7.33−7.38 (m, 2H); ^{13}C NMR δ 11.5, 32.3, 42.8, 42.8, 125.9, 126.1, 128.7, 129.8, 136.2, 137.5, 137.9; IR (KBr) 2970, 2861, 2789, 1699, 1581, 1483, 1448, 1260, 1140, 1089, 1029, 906, 852, 743, 694 cm^{-1}; HRMS (FAB^+) calcd for $C_{13}H_{19}N_2S$ 235.1269, found 235.1262.

(*E*)-3-[(*E*)-(2,2-Dimethylhydrazono)methyl]-3-methyl-5-(phenylthio)pent-4-en-2-ol (12b). To a stirred solution of **11b** (0.56 g, 2.41 mmol) in THF (15 mL) at −78 °C was added a 1 M THF solution of NaHMDS (2.89 mL, 2.89 mmol). The mixture was stirred for 30 min, and acetaldehyde (0.47 g, 10.84 mmol) was added. The resulting mixture was stirred at −78 °C for 3.5 h, quenched with a 10% NH_4Cl solution (10 mL), extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **12b** (0.58 g, 2.08 mmol) in 70% yield as a yellow oil.

The reaction of **11b** (0.29 g, 1.26 mmol) and acetaldehyde (0.28 g, 6.28 mmol) in THF (10 mL) at −78 °C for 2.5 h with *t*-BuLi (1.7 M hexane solution, 0.89 mL, 1.51 mmol) as a base produced **12b** (0.17 g, 0.61 mmol) in 48% yield after purification by silica gel flash column chromatography: R_f = 0.22 (5:1 hexane/EtOAc); ^1H NMR δ 1.14 (d, J = 6.4 Hz, 3H), 1.17 (s, 3H), 2.75 (s, 6H), 4.00 (dq, J_d = 2.0 Hz, J_t = 6.4 Hz, 1H), 4.50 (br s, 1H), 6.14 (d, J = 15.6 Hz, 1H), 6.21 (d, J = 15.6 Hz, 1H), 6.38 (br s, 1H), 7.18−7.25 (m, 1H), 7.27−7.36 (m, 4H); ^{13}C NMR δ 17.3, 21.0, 42.9, 48.6, 72.5, 123.3, 126.3, 128.9, 129.1, 136.0, 138.1, 142.1; IR (KBr) 3430, 2985, 2872, 2798, 1596, 1488, 1451, 1381, 1255, 1128, 1091, 1021, 955, 922, 829, 740, 689, 628 cm^{-1}; HRMS (CI^+) calcd for $C_{15}H_{23}N_2OS$ 279.1531, found 279.1535.

(4*E*,6*E*)-6-(2,2-Dimethylhydrazono)-5-methyl-3-(phenylsulfonyl)hex-4-en-2-ol (13a). To a stirred solution of **11a** (0.26 g, 0.97 mmol) in THF (10 mL) at −78 °C was added a 1 M THF solution of NaHMDS (1.16 mL, 1.16 mmol). The mixture was stirred for 30 min, and acetaldehyde (0.19 g, 4.36 mmol) was added. The resulting mixture was stirred at −78 °C for 2.5 h, quenched with a 10% NH_4Cl solution (10 mL), extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **13a** (0.09 g, 0.29 mmol) in 30% yield as a light yellow solid.

The reaction of **11a** (0.17g, 0.65 mmol) and acetaldehyde (0.14 g, 3.27 mmol) in THF (10 mL) at −78 °C for 2.5 h with *t*-BuLi (1.7 M hexane solution, 0.46 mL, 0.78 mmol) as a base produced **13a** (0.08 g, 0.26 mmol) in 39% yield after purification by silica gel flash column chromatography: R_f = 0.32 (3:2 hexane/EtOAc); mp 120−123 °C; ^1H NMR δ 1.19 (d, J = 6.4 Hz, 3H), 1.38 (d, J = 1.6 Hz, 3H), 2.86 (s, 6H), 3.13 (d, J = 2.4 Hz, 1H), 3.89 (dd, J = 11.2, 1.6 Hz, 1H), 4.79 (dq, J_d = 1.6 Hz, J_q = 6.4 Hz, 1H), 5.73 (d, J = 11.2 Hz, 1H), 6.97 (br s, 1H), 7.50−7.56 (m, 2H), 7.62−7.67 (m, 1H), 7.82−7.88 (m, 2H); ^{13}C NMR δ 11.7, 20.6, 42.6, 65.0, 69.6, 115.6, 128.7, 129.0, 133.9, 135.7, 137.9, 144.2; IR (KBr) 3474, 2978, 2937, 1553, 1442, 1363, 1321, 1289, 1257, 1225, 1141, 1099, 1053, 928, 901, 835, 725, 673 cm^{-1}; HRMS (CI^+) calcd for $C_{15}H_{23}N_2O_3S$ 311.1429, found 311.1427.

(*E*)-1,1-Dimethyl-2-[(*E*)-2-methyl-4-(phenylsulfonyl)pent-2-enylidene]hydrazine (15a). To a stirred solution of **11a** (0.29 g, 1.08 mmol) in THF (10 mL) at −78 °C was added a 1 M THF solution of NaHMDS (1.30 mL, 1.30 mmol). The mixture was stirred for 30 min, and iodomethane (0.77 g, 5.42 mmol) was added. The resulting mixture was stirred at −78 °C for 30 min, warmed to room temperature, and stirred for 2.5 h. The reaction mixture was quenched with a 10% NH_4Cl solution (10 mL), extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **15a** (0.10 g, 0.36 mmol) in 43% yield as a yellow oil.

The reaction of **11a** (0.19g, 0.73 mmol) and iodomethane (0.20 g, 1.46 mmol) in THF (10 mL) at −78 °C for 30 min and then at room temperature for 2.5 h with *t*-BuLi (1.7 M hexane solution, 0.52 mL, 0.88 mmol) as a base produced **15a** (0.11g, 0.38 mmol) in 52% yield after purification by silica gel flash column chromatography: R_f = 0.62 (3:2 hexane/EtOAc); ^1H NMR δ 1.43 (d, J = 1.2 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 2.85 (s, 6H), 4.08 (dq, J_d = 10.4 Hz, J_q = 6.8 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 6.88 (br s, 1H), 7.48−7.56 (m, 2H), 7.60−7.65 (m, 1H), 7.81−7.88 (m, 2H); ^{13}C NMR δ 11.7, 14.0, 42.7, 60.1, 122.7, 128.9, 129.0, 133.5, 135.8, 137.7, 141.1; IR (KBr) 2950, 2873, 2797, 1632, 1571, 1456, 1319, 1157, 1095, 1010, 890, 876, 824, 772, 733, 691, 643 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{21}N_2O_2S$ 281.1324, found 281.1324.

(*E*)-1,1-Dimethyl-2-[(*E*)-2-methyl-4-(phenylthio)pent-2-enylidene]hydrazine (15b). To a stirred solution of **11b** (0.21 g, 0.90 mmol) in THF (10 mL) at −78 °C was added a 1 M THF solution of NaHMDS (1.09 mL, 1.09 mmol). The mixture was stirred for 30 min, and iodomethane (0.64 g, 4.52 mmol) was added. The reaction mixture was stirred at −78 °C for 2.5 h and quenched with a 10% NH_4Cl solution (10 mL). The mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography to give **15b** (0.040 g, 0.18 mmol) in 20% yield as a yellow oil.

The reaction of **11b** (0.42 g, 1.78 mmol) and iodomethane (1.26 g, 8.88 mmol) in THF (10 mL) at −78 °C for 30 min and then at room temperature for 2.5 h with *t*-BuLi (1.7 M hexane solution, 1.26 mL, 2.14 mmol) as a base produced **15b** (0.25 g, 1.01 mmol) in 56% yield after purification by silica gel flash column chromatography: R_f = 0.67 (4:1 hexane/EtOAc); ^1H NMR δ 1.38 (d, J = 6.4 Hz, 3H), 1.65 (s, 3H), 2.82 (s, 6H), 4.19 (dq, J_d = 10.0 Hz, J_q = 6.4 Hz, 1H), 5.44 (d, J = 10.0 Hz, 1H), 6.95 (br s, 1H), 7.22−7.29 (m, 3H), 7.38−7.43 (m, 2H); ^{13}C NMR δ 11.7, 21.3, 42.2, 42.9, 127.3, 128.7, 133.2, 133.7, 134.7, 135.1, 138.4; IR (KBr) 3071, 2974, 2865, 2784, 1571, 1480, 1448, 1380, 1275, 1193, 1120, 1034, 915, 847, 752, 705 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{21}N_2S$ 249.1425, found 249.1424.

(2*E*,2′*E*)-2,2′-{(2*E*,2′*E*,6*E*,6′*E*)-8,8′-Sulfonylbis[2,6-dimethyl-4-(phenylsulfonyl)octa-2,6-dien-8-yl-1-ylidene]}bis(1,1-dimethylhydrazine) (16). To a stirred solution of **11a** (1.50 g, 5.31 mmol) in DMF (20 mL) at −20 °C was added *t*-BuOK (0.70 g, 6.37 mmol). The mixture was stirred at −20 °C for 30 min, and a solution of **6** (0.70 g, 2.66 mmol) in DMF (2 mL) was added. The resulting mixture was stirred at −20 °C for 2 h, warmed to room temperature, and stirred for 2 h. The mixture was then quenched with a 10% NH_4Cl solution (10 mL), extracted with CH_2Cl_2, washed with a 10% NH_4Cl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **16** (1.40 g, 1.92 mmol) in 72% yield as a light yellow solid: R_f = 0.05 (2:3 EtOAc/hexane); mp 144−146 °C; ^1H NMR δ 1.33 (d, J = 1.2 Hz, 6H), 1.62 (s, 6H), 2.48 (dd, J = 13.6, 11.2 Hz, 2H), 2.84 (s, 12H), 3.01 (dd, J = 13.6, 3.2 Hz, 2H), 3.48 (d, J = 7.6 Hz, 2H), 4.09 (ddd, J = 11.2, 10.0, 3.2 Hz, 2H), 5.14 (d, J = 10.0 Hz, 2H), 5.27 (t, J = 7.6 Hz, 2H), 6.81 (s, 2H), 7.48−7.55 (m, 4H), 7.60−7.66 (m, 2H), 7.78−7.84 (m, 4H); ^{13}C NMR δ 11.7, 16.7, 37.9, 42.7, 51.3, 63.2, 114.2, 129.8, 129.0, 129.1, 129.3, 133.8, 137.5, 140.8, 142.8; IR (KBr) 2936, 2868, 2791, 1696, 1637, 1565, 1453, 1313, 1155, 1092, 1051, 754, 695, 609 cm^{-1}; HRMS (FAB^+) calcd for $C_{36}H_{51}N_4O_6S_3$ 731.2971, found 731.2975.

(2*E*,2′*E*)-2,2′-[(2*E*,6*E*,8*E*,10*E*,14*E*)-2,6,11,15-Tetramethyl-4,13-bis(phenylsulfonyl)hexadeca-2,6,8,10,14-pentaene-1,16-

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diylidene]bis(1,1-dimethylhydrazine) (17). To a stirred solution of **16** (0.56 g, 0.76 mmol) in CH_2Cl_2 (20 mL) were added *t*-BuOH (5 mL) and C_2Cl_6 (0.36 g, 1.53 mmol). The mixture was stirred at room temperature for 10 min, and KOH (0.43 g, 7.66 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, and most of solvent was removed under reduced pressure. The crude product was diluted with CH_2Cl_2, washed with 10% $NaHCO_3$, dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure. The crude product was purified by SiO_2 flash column chromatography to give **17** (0.28 g, 0.42 mmol) in 56% yield as a light yellow solid: R_f = 0.28 (2:3 EtOAc/hexane); mp 131−134 °C; ^{1}H NMR δ 1.35 (s, 6H), 1.66 (s, 6H), 2.44 (dd, J = 12.8, 12.0 Hz, 2H), 2.84 (s, 12H), 3.02 (dd, J = 12.8, 2.8 Hz, 2H), 4.11 (ddd, J = 12.0, 10.4, 2.8 Hz, 2H), 5.24 (d, J = 10.4 Hz, 2H), 5.80−5.92 (m, 2H), 6.14−6.25 (m, 2H), 7.00 (br s, 2H), 7.45−7.58 (m, 4H), 7.56−7.66 (m, 2H), 7.67−7.88 (m, 4H); ^{13}C NMR δ 11.6, 16.6, 37.9, 42.6, 63.8, 121.3, 127.8, 128.9, 129.1, 129.3, 133.1, 133.6, 135.7, 137.8, 142.3; IR (KBr) 2933, 2866, 2791, 1697, 1453, 1311, 1151, 1088, 1039, 919, 746, 697, 613 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{36}H_{49}N_4O_4S_2$ 665.3195, found 665.3208.

Crocetin Dimethylhydrazone (18). To a stirred solution of **17** (0.44 g, 0.66 mmol) in benzene (12 mL) and cyclohexane (18 mL) was added KOMe (1.40 g, 19.87 mmol). The reaction mixture was heated at 80 °C for 8 h and cooled to room temperature. The mixture was then filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude product was diluted with CH_2Cl_2, washed with a 10% $NaHCO_3$ solution, dried over anhydrous K_2CO_3, filtered, and concentrated under reduced pressure to give crude conjugated polyene hydrazone **18** (0.22 g, 0.58 mmol) in 88% yield as a red solid. An analytical sample was prepared by trituration with MeOH: R_f = 0.50 (1:4 EtOAc/hexane); mp 115−118 °C; ^{1}H NMR δ 1.98 (s, 6H), 2.02 (s, 6H), 2.90 (s, 12H), 6.20−6.32 (m, 2H), 6.23 (d, J = 11.6 Hz, 2H), 6.35 (d, J = 14.8 Hz, 2H), 6.58−6.69 (m, 2H), 6.68 (dd, J = 14.8, 11.6 Hz, 2H), 7.03 (s, 2H); ^{13}C NMR δ 12.1, 12.8, 43.0, 124.9, 130.0, 131.1, 132.6, 135.8, 136.5, 137.1, 138.5; UV (CH_2Cl_2) λ_{max} (ε) 443 (167508), 472 (226396), 495 nm (197984); IR (KBr) 2996, 2923, 2788, 1544, 1476, 1404, 1273, 1051, 965, 906, 802 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{24}H_{36}N_4$ 380.2940, found 380.2946.

Crocetin Dinitrile (19). The mixture of urea-hydrogen peroxide (0.33 g, 3.47 mmol) and phthalic anhydride (0.26 g, 1.73 mmol) in acetonitrile (10 mL) was stirred vigorously at room temperature for 2 h to give a clear solution. Crude product **18** in CH_2Cl_2 was added; the resulting mixture was stirred at room temperature for 2 h, and most of the solvent was removed under reduced pressure. Crude **18** was diluted with $CHCl_3$, and the undissolved solid was removed by filtration. The filtrate was concentrated under reduced pressure, and the crude product was recrystallized from MeOH to give **19** (0.10 g, 0.35 mmol) in 60% yield as a red solid: R_f = 0.47 (1:4 EtOAc/hexane); mp 100−103 °C; ^{1}H NMR δ 1.97 (s, 6H), 2.01 (s, 6H), 6.35−6.44 (m, 2H), 6.45 (dd, J = 14.8, 10.8 Hz, 2H), 6.55 (d, J = 14.8 Hz, 2H), 6.67−6.77 (m, 2H), 6.81 (d, J = 10.8 Hz, 2H); ^{13}C NMR δ 12.7, 15.3, 106.4, 121.7, 122.0, 131.7, 136.5, 143.9, 144.1; UV (CH_2Cl_2) λ_{max} (ε) 408 (82824), 430 (128500), 457 nm (128102); IR (KBr) 2992, 2214, 1730, 1686, 1619, 1587, 1453, 1390, 1153, 1063, 974, 916, 732, 656 cm^{-1}; HRMS (FAB$^+$) calcd for $C_{20}H_{22}N_2$ 290.1783, found 290.1780.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of compounds **2**, **3a**, **5**, **7**−**10**, **11a**, **11b**, **12b**, **13a**, **15a**, **15b**, and **16**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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