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PAPER

Using light and a molecular switch to 'lock' and 'unlock' the Diels–Alder reaction†

Zach Erno,‡ Amir Mahmoud Asadirad,‡ Vincent Lemieux and Neil R. Branda*

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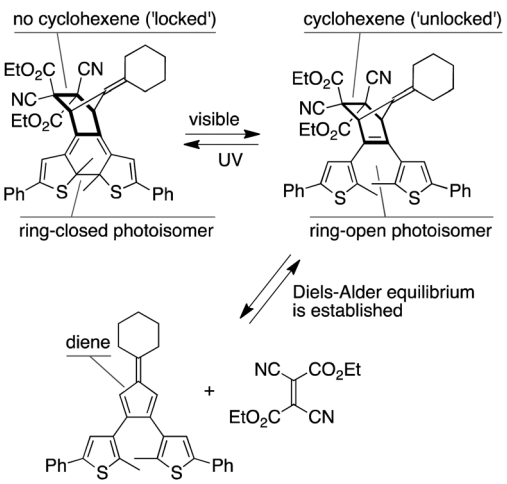
Light is used to 'gate' the Diels–Alder reaction using a photoresponsive dithienylfuran backbone and turn the reversibility of the Diels–Alder reaction 'off' and 'on' at 100 °C. These features make the reported system an excellent candidate for developing the next generation of self-healing polymers and photothermal drug delivery vehicles.

Introduction

The reversibility of the Diels–Alder reaction and its sensitivity to temperature make it an attractive motif to develop technologies that benefit from molecular assembly through covalent bonds at one set of conditions (*low to moderate temperatures*) and fragmentation of the components at another (*high temperatures*).[1,2] One example is in dynamic combinatorial chemistry, where its reversibility facilitates rapid exchange of diene–dienophile partners to generate chemical libraries that can be screened in real time for host–guest binding interactions.[3] New functional materials based on the retro-Diels–Alder reaction have also grown rapidly in number and this versatile reaction has been used to cleave dendrimers[4,5] and surfactants,[6] help remendable polymers spontaneously heal damaged regions at the molecular level,[7–9] and release payloads from nanoparticle-based vehicles for potential drug delivery applications.[10]

However, the true usefulness of these control strategies is limited by shortcomings inherent in the nature of the thermally regulated Diels–Alder equilibrium. Exposure of molecules or materials to elevated temperatures may be difficult to avoid or even essential in certain working environments, causing premature thermolysis of the molecular components, cleavage of synthetic tethers or loss of mechanical strength and integrity in remendable polymers. Dynamic combinatorial libraries can also undergo significant changes in composition as the temperature is varied, making it difficult or even impossible to isolate and characterize desired target molecules at ambient conditions. A second stimulus that would selectively 'gate' the reversibility of the thermal Diels–Alder reaction would overcome this limitation and offer the end-user the control to turn 'off' and 'on' the bond-forming and cleaving reactions 'on-command'.

We recently published a system that illustrates the concept of using light to 'lock' the Diels–Alder reaction based on the photoreactions of the well-known dithienylethene molecular architecture (Scheme 1).[11] It involves two reversible reactions, the first requiring two types of light as the stimuli. Because the ring-closed polycycles of dithienylethenes have linearly conjugated π-electron backbones, they undergo photochemical bond-breaking reactions when exposed to visible light (*these compounds are highly coloured*)[12,13] and produce their ring-open counterparts, which owing to the lack of linear conjugation between their two 'arms' are colourless. Exposing the ring-open polycycles to ultraviolet light activates the hexatrienes, triggers the reverse reactions and regenerates the ring-closed versions.



Scheme 1 Conceptual scheme of photo-locking the Diels–Alder reaction using the dithienylethene molecular system. Only after ring-opening the ring-closed isomer can the reverse Diels–Alder reaction take place.

4D LABS, Department of Chemistry, Simon Fraser University, 8888 University Drive, Burnaby, B.C., Canada. E-mail: nbranda@sfu.ca; Fax: +1 778 7823765; Tel: +1 778 7828061

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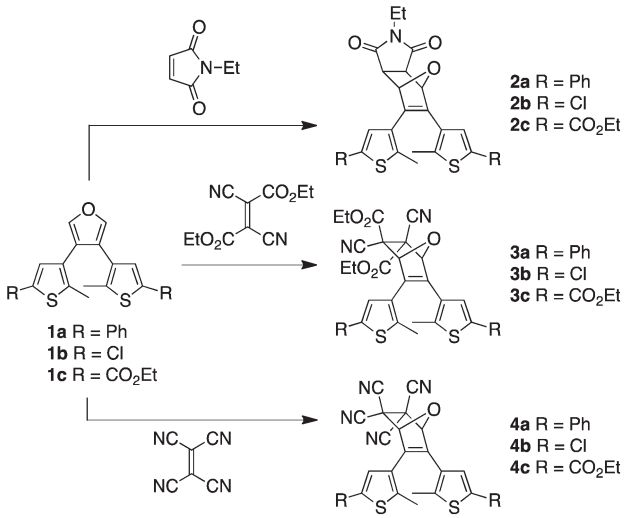
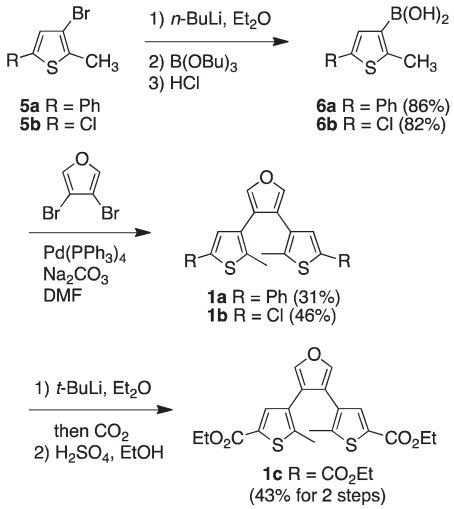
‡ Authors made equal contributions.



Scheme 2 Three variations of the dithienylfuran diene can react with three different dienophiles to produce nine bicyclic dithienylethene ring-open isomers.



Scheme 3 Synthesis of the dithienylfurans used in the studies described in this report.

The important differentiating structural feature of the two polycycles (ring-closed *vs.* ring-open) is the absence or presence of the cyclohexene ring shown in bold in the scheme. While the ring-open isomer has the cyclohexene necessary for the reverse Diels–Alder reaction to proceed, its ring-closed counterpart does not. It is, therefore, effectively 'locked' and visible light is required to 'unlock' it. Our observations are that the ring-open polycycle is highly unstable and spontaneously breaks into its Diels–Alder fragments, fulvene (labeled 'diene' in the scheme) and diethyl dicyanofumarate. This constitutes the second reversible reaction of the system. Depending on the reaction conditions (concentration, temperature, stoichiometry), the Diels–Alder equilibrium favours the starting material or products.[14]

The 'lockable' feature of our published system makes it attractive for applications that benefit from spontaneous thermolysis at ambient temperatures upon exposing the ring-closed isomer to visible light. However, other environments of use may require systems whose equilibria favour bond formation at ambient temperatures. This need demands the design of molecular switching systems capable of regulating the Diels–Alder equilibrium over a wider temperature range than is currently possible. In this report, we describe the effects of different dienes, dienophiles and thiophene substituents on 'gating' the Diels–Alder equilibria using light and demonstrate that the concept can be applied to reactions that occur only at elevated temperatures.

We chose to base our molecular design on the dithienylfuran architecture (Scheme 2) knowing that furan-based Diels–Alder dienes tend to undergo thermolysis at higher temperatures[15–17] than those based on fulvenes.[18,19] We selected three representative dienophiles representing a range of chemical reactivities due to their varying electron-deficiencies. *N*-Ethylmaleimide was chosen as the least reactive,[4–6,10,14,20,21] diethyl dicyanofumarate as having intermediate reactivity[3,11] and tetracyanoethylene as the most reactive dienophile.[22,23] The last variable we included were the specific functional groups decorated onto the two thiophene rings. Phenyl (**1a**), chloro (**1b**) and ethoxycarbonyl (**1c**) groups impart different combinations of steric and electronic contributions to the Diels–Alder reaction equilibria and may also affect the temperature dependency. In this report, we describe the syntheses of the three dithienylfuran dienes, their reactivities with three the dienophiles, the reversible photochemical ring-closing reactions of their Diels–Alder products when exposed to UV and visible light, and their ability to 'gate' the reversible cycloaddition reaction.

In general, we noticed that the reactivities of all the dithienylfuran compounds towards all the dienophiles are greatly diminished relative to that of the previously studied fulvene (in most cases, the Diels–Alder equilibrium does not favour the products at all).[13] Of the two successful Diels–Alder partners, we highlight one (**1c** + maleimide → **2c**) that can be used to 'lock' the reaction (it is resistant to spontaneous ring-opening even at elevated temperatures over extended periods of time) and facilitate 'on'-or-'off' control by undergoing repeated bidirectional photoisomerization with minimal photofatigue.

Results and discussion

We synthesized dithienylfuran derivatives **1a** and **1b** using a two-fold Suzuki cross-coupling reaction between 3,4-dibromofuran and the corresponding thiopheneboronic acids (Scheme 3). The former heterocycle was prepared by the oxidative cyclocondensation of (*E*)-2,3-dibromo-2-butene-1,4-diol in chromic acid following a literature procedure.[24] The latter two heterocycles were prepared from the known bromothiophenes **5a**[25] and **5b**[26] by lithium–halogen exchange, boronylation and hydrolysis of the resulting boronate esters in a three-step, one-pot procedure.[27] The two-fold Suzuki cross-coupling reaction occurred in moderately poor yields, with the dominant side products formed from reductive dehalogenation of the mono-coupled intermediate.[28] The dithienylfuran dicarboxylic acid was prepared from the dichloro derivative (**1b**) by a two-step, one-pot procedure involving lithium–halogen exchange followed by carboxylation with gaseous CO_2 and acidification. The poor solubility of the resulting diacid in nonpolar organic solvents encouraged us to convert

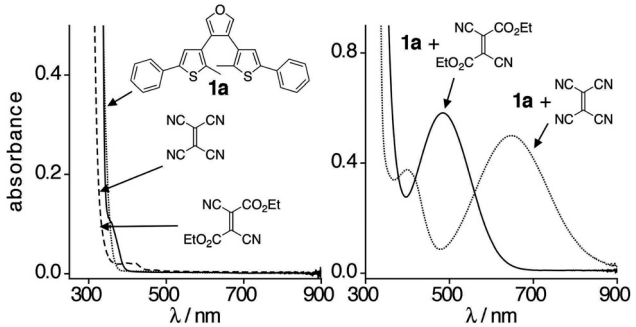


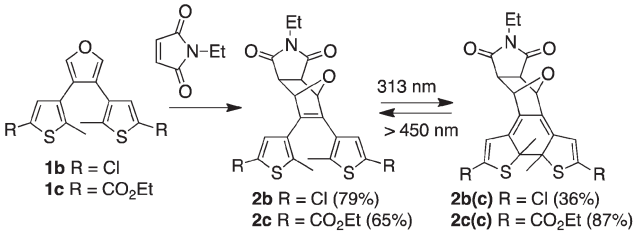
Fig. 1 UV-vis absorbance spectra of $CHCl_3$ solutions of **1a**, diethyl dicyanofumarate and tetracyanoethylene (left) and mixtures of **1a** with diethyl dicyanofumarate and tetracyanoethylene (right). All solutions were 30 mM with respect to the chromophores and measured at 20 °C.

the diacid into its corresponding diester (**1c**), which was done under Fisher esterification conditions with ethanol.[29]

To our surprise, dithienylfuran dienes **1a** and **1c** did not react with diethyl dicyanofumarate or tetracyanoethylene despite their being the most reactive dienophiles. No attempts were made to carry out similar reactions using dithienylfuran **1b** due to its tendency to undergo rapid photodegradation during photochemical ring-closing as will be shown later in this manuscript. A more accurate statement would be that no cycloaddition products could be observed under various conditions (different reactant stoichiometries, solvents, and temperatures: see Table S1 in the ESI† for details). This could imply that the reaction does, in fact, occur but the equilibrium lies so dominantly to favour the starting materials that even trace amounts of product cannot be observed by ^{1}H NMR spectroscopy. Given our goals were to develop high-temperature reactions, we did not pursue these studies any further but concentrated our efforts on the other derivatives. The diphenyl derivative (**1a**) did undergo formation of charge transfer complexes with these dienophiles as suggested by the appearance of a distinct colour (the two starting materials are colourless) as shown in Fig. 1.

We also did not observe any products when the phenyl derivative of the dithienylfuran (**1a**) was treated with *N*-ethylmaleimide. Dienes **1b** and **1c** did, however, produce bicyclic compounds **2b** and **2c**, respectively under appropriate conditions. When equimolar quantities of **1b** and the dienophile were reacted in $CDCl_3$, the reaction appeared to proceed sluggishly at room temperature according to ^{1}H NMR spectroscopy, with little to no observable product being formed after 24 h. Increasing the temperature of the reaction to 60 °C had little effect even after 19 h. A temperature of 70 °C seems to be the activation threshold and the Diels–Alder product **2b** was observed after just 4 h at this temperature. The product was identified to consist exclusively in its isomeric *exo* form.[7,30] After allowing the reaction to continue at 70 °C for another 20 h, the bicyclic product (**2b**) could be isolated in 79% yield by column chromatography. The cycloaddition reaction of diester **1c** with *N*-ethylmaleimide was carried out under identical conditions. No detectable product was formed after 24 h at room temperature or at 60 °C for 20 h. Once again, heating the reaction at 70 °C for 38 h produced the *exo* product (**2c**) in 65% isolated yield (Scheme 4).

The photoinduced ring-closing of Diels–Alder products **2b** (in CD_2Cl_2) and **2c** (in CD_3CN) was monitored by UV-vis



Scheme 4 Synthesis of Diels–Alder products **2b** and **2c** and their photochemical ring-closing and ring-opening reactions.

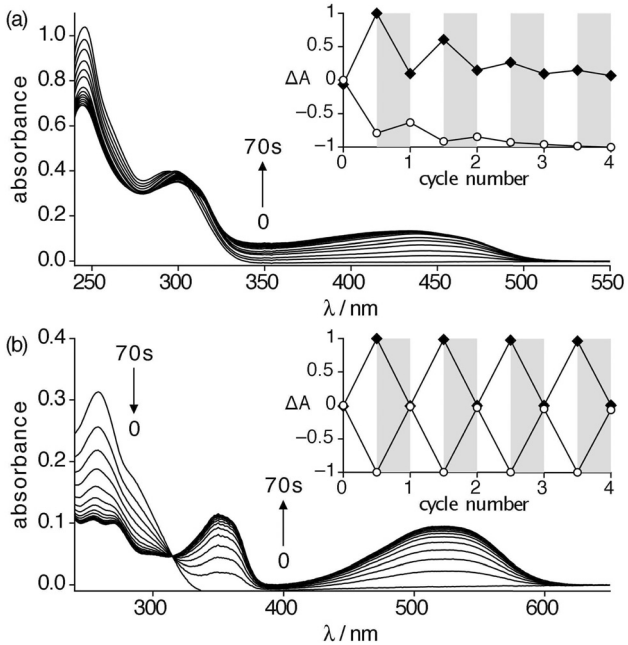


Fig. 2 Changes in UV-vis absorbance spectra when solutions of (a) **2b** in CD_2Cl_2 (10^{-6} M) and (b) **2c** in CD_3CN (10^{-6} M) are irradiated with 313 nm light every 5 s for a total of 70 s. The inset plots show the changes in the absorbances corresponding to the (◯) ring-open (247 nm for **2b** and 258 nm for **2c**) and (◆) ring-closed isomers (434 nm for **2b(c)** and 521 nm for **2c(c)**) upon alternate irradiation with 313 nm light (un-shaded) and >450 nm light (shaded). All measurements were acquired at 20 °C.

absorbance and ^{1}H NMR spectroscopy, with spectra acquired intermittently after irradiation with 313 nm light for 5 and 120 second intervals, respectively. In both cases, the changes in the UV-vis absorption spectra are typical for dithienylethene derivatives (Fig. 2). Exposing the solutions to UV light produced an immediate decrease in the intensity of the high-energy absorbance bands (centered at 247 nm for **2b** and 258 nm for **2c**) and the appearance of new broad absorbance bands in the visible region of the spectra (centered at 434 nm for **2b** and 521 nm for **2c**), which can be attributed to ring-closed isomers (**2b(c)** and **2c (c)**). These spectral changes account for the changes in colour of the solutions from colourless to yellow in the case of **2b** and red in the case of **2c**. When these coloured solutions are irradiated with light of wavelengths longer than 450 nm, the colours disappear and the original spectra are generated as ring-opening is induced, confirming that photoisomerization of these species is bidirectional.

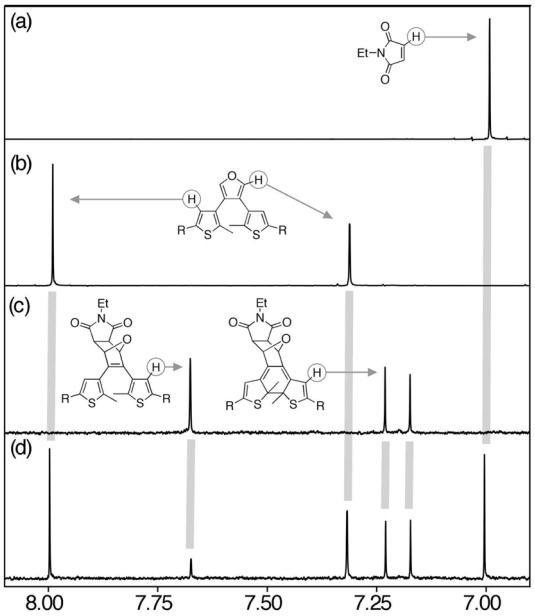


Fig. 3 Partial ^{1}H NMR spectra of a DMSO-d_6 solution of (a) *N*-ethylmaleimide, (b) diene **1c**, (c) a 1 : 1 mixture of **2c** and **2c(c)** generated by reacting **1c** with *N*-ethylmaleimide, isolating the Diels–Alder product and irradiating with 313 nm light until the appropriate ratio was reached, and (d) the same 1 : 1 mixture after heating at 100 °C for 24 h.[32]

The distinguishing difference between the two isomers is the dichloro derivative's exhibiting limited photochromic behaviour. UV irradiation generates a photostationary state that contains only a small amount of the ring-closed isomer (36%) and induces significant decomposition as evident from ^{1}H NMR spectroscopy. This degradation is consistent with the lack of an isosbestic point in the UV-vis absorption spectra and the reduction in the amounts of both isomers as the system is cycled between its states using both types of light (inset to Fig. 2a). Both the low photoconversion and degradation are typical among dithienylethenes bearing chloro substituents.[31] The diester derivative **2c**, on the other hand, showed much better photochromic behaviour and reached a photostationary state consisting of 87% of the ring-closed isomer (**2c(c)**) with insignificant amounts of side-products being formed as monitored by ^{1}H NMR spectroscopy. Also, a clear isosbestic point can be observed in the UV-vis absorption spectra as the system is induced to undergo ring-closing and by the minimal reduction in the absorbances corresponding to either isomer as the system is cycled between its two forms (inset to Fig. 2b).

The concept of a 'light-gated' Diels–Alder reaction was demonstrated only for compound **2c** given the poor behaviour of the chloro derivative. We achieved this using a DMSO-d_6 solution containing equal amounts of the ring-open isomer (**2c**) and its ring-closed counterpart (**2c(c)**), which was produced by periodically irradiating a solution of the pure ring-open isomer with 313 nm light until the desired concentration of its corresponding photoisomer was observed by ^{1}H NMR spectroscopy (Fig. 3c). When this solution was heated at 100 °C for 24 h, a composite spectrum in which *N*-ethylmaleimide and dithienylfuran **1c** was observed, indicating that the reverse Diels–Alder reaction had taken place. The fact that the peaks corresponding to the ring-open isomer were the only ones to reduce in intensity shows that the reverse Diels–Alder reaction only occurs using this isomer as the starting material. The peaks for the ring-closed isomer did not change in intensity, revealing its thermal stability under these conditions. This observation is supported by a calculation of the mole fraction of each component based on peak integrals, which reveals that the amount of **2c** present in the mixture has decreased in proportion to the amounts of *N*-ethylmaleimide and **1c** generated, whereas the amount of **2c(c)** remains unchanged.

Conclusions

We have developed 3,4-dithienylfuran systems that can undergo the Diels–Alder reaction with suitable dienophiles to provide molecular photoswitches. These species can then be made to undergo bidirectional ring-closing and ring-opening isomerization reactions in response to irradiation with UV and visible light, respectively. We have also established that the changes in molecular structure accompanying ring-closure turn off the reversibility of the Diels–Alder reaction. Irradiation with visible light regenerates the ring-open isomer as well as its ability to undergo the reverse Diels–Alder reaction. These systems are significant in their potential to address the limitations of numerous beneficial technologies in synthetic chemistry and materials science, and our future studies will evaluate dithienylfuran-based molecular switches in those contexts.

Experimental

General methods

All solvents and reagents used for synthesis, chromatography, UV-vis spectroscopy measurements and photolysis studies were purchased from Aldrich or Fisher and used as received, unless otherwise noted. Solvents for NMR analysis were purchased from Cambridge Isotope Laboratories and used as received. Column chromatography was performed using silica gel 60 (230–400 mesh) Silicycle Inc.

^{1}H NMR and ^{13}C NMR characterizations of all synthesis precursors to compounds **2a–2c** were performed on Bruker AVANCE 400 BBOF plus direct probe working at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C NMR spectra. The ^{1}H NMR photoisomerization studies of adducts **2b** (in CD_2Cl_2) and **2c** (in CD_3CN) were performed using a Bruker AVANCE 500 TXI inverse ^{1}H/^{13}C/^{19}F probe working at 500.19 MHz for ^{1}H and 125.78 MHz for ^{13}C NMR spectra. Chemical shifts (δ) are reported in parts per millions (ppm) relative to tetramethylsilane (TMS) using the residual solvent peak as a reference standard. Coupling constants (*J*) are reported in hertz. UV-vis absorption spectroscopy was performed using a Varian Cary 300 Bio Spectrometer.

Photochemistry

All ring-closing reactions were carried out using light source from a lamp used for visualizing TLC plates at 313 nm (Spectroline ENF-260C, 3.5 mW cm^{-2}). The ring-opening reactions

were performed using the light of a 300 W halogen photo optic source passed through a 450 nm cutoff filter to eliminate higher energy light.

3,4-Bis(2-methyl-5-phenylthiophen-3-yl)furan (1a). A solution of (2-methyl-5-phenylthiophen-3-yl)boronic acid (**6a**) (0.7 g, 3.1 mmol) in THF (25 mL) was treated with 3,4-dibromofuran (0.34 g, 1.57 mmol) and a saturated aqueous solution of $Na_2CO_3{\cdot}H_2O$ (20 mL). The resulting suspension was deoxygenated with a stream of N_2 and treated with a catalytic amount of $Pd(PPh_3)_4$. The mixture was heated to reflux while stirring magnetically for 3 days, at which time the heating source was removed and the reaction was allowed to cool to room temperature. Et_2O (50 mL) was added to the mixture and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined ether layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography using silica gel (neat hexanes) afforded 200 mg (31%) of white solid. M.p. = 43–45 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.56 (dd, J = 8.4, 1.3 Hz, 4H), 7.36 (tt, J = 1.5, 7.4 Hz, 4H), 7.25 (tt, J = 1.2, 7.4 Hz, 2H), 7.12 (s, 1H), 7.11 (s, 1H), 6.74 (dd, J = 1.2, 2.3 Hz, 1H), 6.73 (dd, J = 1.2, 2.3 Hz, 1H), 2.52 (s, 3H), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ 142.1, 139.6, 134.8, 128.9, 127.1, 126.3, 125.6, 123.0, 15.5. UV-vis (acetonitrile): λ_{max} nm (log ε) 293 (4.64).

3,4-Bis(5-chloro-2-methylthiophen-3-yl)furan (1b). A solution of compound (5-chloro-2-methylthiophen-3-yl)boronic acid (**6b**) (1.18 g, 6.70 mmol) in DMF (25 mL) was treated with 3,4-dibromofuran (608 mg, 3.00 mmol) and $Na_2CO_3{\cdot}H_2O$ (2.0 g, 16.0 mmol). The resulting suspension was purged for 1.5 h with a stream of N_2 and treated with $Pd(PPh_3)_4$ (93 mg, 80 µmol). The mixture was heated at 110 °C and stirred magnetically for 52 h using an oil bath, at which time the heating source was removed and the reaction was allowed to cool to room temperature. Water (100 mL) was added and the mixture was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and solvent was evaporated using a rotary evaporator. Purification of the product by column chromatography (silica gel, neat hexanes) afforded colourless crystals that rapidly developed a yellow/brown colour upon exposure to oxygen and light at ambient temperatures. Recrystallization from CH_2Cl_2 and hexanes under reduced pressure yielded colourless crystals once more, which were stored under N_2 at −20 °C in the dark (451 mg, 46%). M.p. 81–83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 (s, 2H), 6.49 (s, 2H), 2.14 (s, 6H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 147.9, 140.9, 134.4, 127.7, 125.7, 120.2, 13.8. HRMS (CI) m/z calculated for $C_{14}H_{11}Cl_2OS_2$ ($M + H^+$) 328.9, found 329.2.

4,4′-(Furan-3,4-diyl)bis(5-methylthiophene-2-carboxylic acid). A stirred solution of 3,4-bis(5-chloro-2-methylthiophen-3-yl) furan (**1b**) (135 mg, 0.41 mmol) in anhydrous Et_2O (10 mL) was treated with t-BuLi (1.00 mL of 1.5 M solution in pentane, 1.64 mmol) dropwise over 5 min under nitrogen at −78 °C. After 1.5 h of stirring at this temperature, gaseous CO_2 (sublimed from solid CO_2 and passed through a drying tube filled with Drierite) was bubbled under the surface of the reaction mixture for 3 h at −78 °C. After this time, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 1 h, the mixture was treated with aqueous HCl (10 mL, 10%) causing any precipitate to dissolve. The mixture was washed with water (25 mL) and the organic layer was removed and the aqueous layer further extracted with Et_2O (2 × 20 mL). The combined organic layers were extracted with aqueous NaOH (2.5 M, 2 × 100 mL). The combined aqueous layers were treated with concentrated HCl until the pH reached below 1, resulting in the formation of white precipitate, which was collected by vacuum filtration and washed with water. Purification using chromatography on silica gel (9 : 1 : 0.01 CH_2Cl_2 : MeOH : acetic acid) afforded 88 mg (62%) of 4,4′-(furan-3,4-diyl)bis(5-methylthiophene-2-carboxylic acid) as a white solid. M.p. decomposed at 250 °C. IR (KBr): $\tilde{\nu}$ = 1667 cm^{-1} (C═O). ^{1}H NMR (MeOH-d_4, 400 MHz): δ 7.63 (s, 2H), 7.25 (s, 2H), 2.18 (s, 6H). ^{13}C NMR (MeOH-d_4, 400 MHz): δ 225.6, 182.1, 163.8, 161.8, 155.2, 150.0, 140.1, 33.7. HRMS (ESI+) m/z calculated for $C_{16}H_{13}O_5S_2$ ($M + H^+$) 349.0199, found 349.0199.

Diethyl 4,4′-(furan-3,4-diyl)bis(5-methylthiophene-2-carboxylate) (1c). A solution of 4,4′-(furan-3,4-diyl)bis(5-methylthiophene-2-carboxylic acid) (57.0 mg, 0.16 mmol) in anhydrous EtOH (25 mL) was treated with 5 drops of concentrated H_2SO_4. The reaction mixture was heated to reflux and stirred magnetically for 17 h under N_2 and then it was cooled to room temperature. Water (50 mL) was added to the mixture and it was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography using CH_2Cl_2 as the eluent afforded 46 mg (70%) of the product as white crystals. IR (NaCl): $\tilde{\nu}$ = 1716 cm^{-1} (C═O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50 (s, 2H), 7.38 (s, 2H), 4.28 (q, J = 7.1 Hz, 4H), 2.19 (s, 6H), 1.33 (t, J = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 161.1, 143.6, 140.9, 135.0, 129.8, 129.5, 120.2, 60.9, 29.6, 14.4, 14.2. HRMS (CI) m/z calculated for $C_{20}H_{24}NO_5S_2$ ($M + NH_4^+$) 422.1090, found 422.1107.

(3a*R*,4*R*,7*S*,7a*S*)-5,6-Bis(5-chloro-2-methylthiophen-3-yl)-2-ethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (2b). A solution of 3,4-bis(5-chloro-2-methylthiophen-3-yl)furan (**1b**) (18 mg, 55 µmol) in $CHCl_3$ (0.6 mL) was treated with *N*-ethylmaleimide (7.0 mg, 55 µmol) and the mixture was transferred to an NMR tube. The NMR tube was protected from light as it was heated at 70 °C for 73 h in an oil bath. Purification of the product by column chromatography (silica gel, CH_2Cl_2) in the darkness afforded 20 mg (79%) of white crystals. M.p. = 166–167 °C. IR (KBr): $\tilde{\nu}$ = 1694 cm^{-1} (C═O). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.67 (s, 2H), 5.35 (s, 2H), 3.55 (q, J = 7.2 Hz, 2H), 3.06 (s, 2H), 1.95 (s, 6H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (CD_2Cl_2, 600 MHz): δ 176.0 ppm, 138.9, 136.9, 129.4, 127.4, 126.2, 85.6, 48.9, 34.4, 30.2, 14.8, 13.2. HRMS (CI) m/z calculated for $C_{20}H_{18}Cl_2NO_3S_2$ ($M + H^+$) 454.0100, found 454.0110.

Diethyl 4,4′-((3a*R*,4*R*,7*S*,7a*S*)-2-ethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindole-5,6-diyl)bis(5-methylthiophene-2-carboxylate) (2c). To a solution of diethyl 4,4′-(furan-3,4-diyl) bis(5-methylthiophene-2-carboxylate) (**1c**) (20 mg, 49 µmol) in $CDCl_3$ (0.6 mL), *N*-ethylmaleimide (6.2 mg, 49 µmol) was

added and the mixture was transferred to a 600 MHz NMR tube. The NMR tube was protected from light and it was heated up to 70 °C using an oil bath. Monitoring the reaction by NMR spectroscopy showed the completion of reaction after 38 h. Purification by column chromatography on silica gel (5% EtOAc in CH_2Cl_2) in the dark afforded the product as white crystals (17 mg, 65%). M.p. = 78–81 °C. IR (KBr): $\tilde{\nu}$ = 1698 cm^{-1} (C═O). ^1H NMR (CD_3CN, 500 MHz): δ 7.56 ppm (s, 2H), 6.38 (s, 2H), 4.28 (q, J = 7.1 Hz, 4H), 3.47 (q, J = 7.2 Hz, 2H), 3.23 (s, 2H), 2.01 (s, 6H), 1.31 (t, J = 7.0 Hz, 6H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (CD_3CN, 600 MHz): δ 177.2, 162.8, 146.4, 140.3, 134.3, 132.3, 132.1, 86.3, 62.5, 49.5, 34.8, 15.6, 14.9, 13.6. HRMS (ESI+) m/z calculated for $C_{26}H_{28}NO_7S_2$ ($M + H^+$) 530.1302, found 530.1338.

Synthesis of ring-closed isomer 2b(c). A solution of (3a*R*,4*R*,7*S*,7a*S*)-5,6-bis(5-chloro-2-methylthiophen-3-yl)-2-ethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (**2b**) (1.52 mM) in CD_2Cl_2 was irradiated with 313 nm light in an NMR tube and its ^1H NMR spectrum was recorded after 1 min. The exposure was continued and a ^1H NMR spectrum of the sample was taken every 2 min until a total of 16 min was reached. The solution turned from colourless to yellow. Further irradiation resulted in the formation of a significant amount of an uncharacterized side product. The photostationary state was calculated to be 36%. ^1H NMR (CD_2Cl_2, 500 MHz): δ 6.11 (s, 1H), 6.10 (s, 1H), 5.23 (s, 1H), 5.19 (s, 1H), 3.49–3.54 (m, 4H), 3.01 (d, J = 6.6 Hz, 1H), 2.94 (d, J = 6.8 Hz, 1H), 1.98 (s, 3H), 1.93 (s, 1H), 1.14 (m, 3H).

Synthesis of ring-closed isomer 2c(c). A solution of diethyl 4,4′-((3a*R*,4*R*,7*S*,7a*S*)-2-ethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindole-5,6-diyl)bis(5-methylthiophene-2-carboxylate) (**2c**) (18.9 mM) in CD_3CN was irradiated with 313 nm light in an NMR tube and its ^1H NMR spectrum was recorded after 2 min. The exposure was continued and a ^1H NMR spectrum of the sample was taken every 2 min until a total of 26 min was reached, followed by spectra taken every 4 min for a total of 34 min. The solution turned from colourless to red. The photostationary state was calculated to be 87%. ^1H NMR (CD_3CN, 500 MHz): δ 6.95 (s, 1H), 6.93 (s, 1H), 5.39 (s, 1H), 5.35 (s, 1H), 4.22–4.25 (m, 4H), 3.43–3.47 (m, 2H), 3.18 (d, J = 6.8 Hz, 1H), 3.07 (d, J = 6.8 Hz, 1H), 1.96 (s, 3H), 1.95 (s, 3H), 1.27–1.30 (m, 6H), 1.06–1.09 (m, 3H).

Thermolysis of isomers 2c and 2c(c). In a 600 MHz NMR tube, a solution of diethyl 4,4′-((3a*R*,4*R*,7*S*,7a*S*)-2-ethyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-epoxyisoindole-5,6-diyl) bis(5-methylthiophene-2-carboxylate) (**2c**) (10^{-4} M) in DMSO-d_6 was irradiated with 313 nm light for 50 s to make a 50 : 50 mixture of **2c** and **2c(c)** isomers. The NMR tube was protected from light and the mixture was heated at 100 °C using an oil bath. The reaction was monitored by ^1H NMR spectroscopy every 24 h and reached its equilibrium after 72 h, at which point 97% of compound **2c** had been converted to *N*-ethylmaleimide and **1c**. The equilibrium constant (K_{eq}) was calculated to be 1.7×10^{-4} M^{-1}.

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32 See ESI† for details.

