Synthesis and Characterization of Photoswitchable Lipids Containing Hemithioindigo Chromophores

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The synthesis of four lipids containing the hemithioindigo chromophore as part of the fatty acid is described. Heck reaction of bromophenyl thioacetate esters with acrylonitrile, followed by reduction, ester hydrolysis, and Friedel−Craft acylation−cyclization gave a substituted thioindoxyl that condensed with an alkoxy benzaldehyde to produce the hemithioindigo. "Solventless" nitrile hydrolysis followed by mixed anhydride coupling of the acid with glycerophosphocholine produced lipids bearing two hemithioindigo chromophores. The photochemistry of various hemithioindigo derivatives was studied to confirm the expected photoisomerization in both homogeneous organic solution, and in vesicle bilayer membranes. Characteristic changes in the UV−visible spectra are consistent with fully reversible *Z*−*E* photoisomerization. Chromatographic separation of the *Z* and *E* isomers of a compound containing a single hemithioindigo chromophore confirmed the spectroscopic analysis and provided a quantitative analysis of the compositions of *Z*−*E* isomer mixtures.

The lipid composition of biomembranes varies dramatically between cells and subcellular components yet is tightly regulated to preserve defined lipid composition profiles in specific membranes.[1,2] Moreover, most membranes contain large amounts of lipids that alone do not form planar bilayers.[3] As a consequence, most biomembranes are actively maintained in a state of "curvature stress" in which the tendency of each bilayer leaflet to curl to a nonplanar conformation is opposed by hydrophobic interactions between the leaflets.[4] Proteins embedded in the lipid bilayer alter this balance by providing additional hydrophobic interactions.[5] This is a reciprocal relationship: a "hydrophobic coupling" exists between the curvature stress of the membrane and the conformational state of the protein. Ultimately this can lead to a regulation of protein function through control of the physical properties of the membrane lipids.[4]

On a molecular level, curvature stress is directly related to the shape of individual lipid molecules. A "shape parameter" (*s*) has been described that relates the hydrated headgroup area (a_0), the overall length (l), and the volume (v) of the alkyl chains to the phase preference of pure lipids ($s = v/a_0l$).[6] Lipids that are roughly cylindrical ($s \sim 1$) form lamellar bilayer phases. Increasing the headgroup area, and/or decreasing the tail volume decreases *s* and leads to micellar phases ($s \sim 0.5$). Conversely decreasing headgroup area and/or increasing chain volume leads to "inverted" lipid phases ($s > 1$) such as reverse micelles.

The control of the lipid shape parameter provides a potential mechanism to modulate membrane processes such as transmembrane transport,[7] transfection,[8] or bilayer fusion.[9,10] Irreversible destabilization of bilayer vesicles (liposomes) has been widely examined using pH changes to alter headgroup repulsions,[11−13] or light-induced polymerizations to alter chain packing.[14] Reversible photochemical switching, e.g., *Z*/*E* photoisomerization, is a particularly appealing option for controlling lipid shape, and examples of retenoic acid,[15] azobenzene,[16,17] and spiropyran[18]-derived lipids have been examined as triggers for release of vesicle contents, presumably via defects in the bilayer. Similarly, vesicle fusion can be irreversibly initiated photochemically by photopolymerization processes that induce lipid phase separation.[19,20] The product vesicles of such a process are

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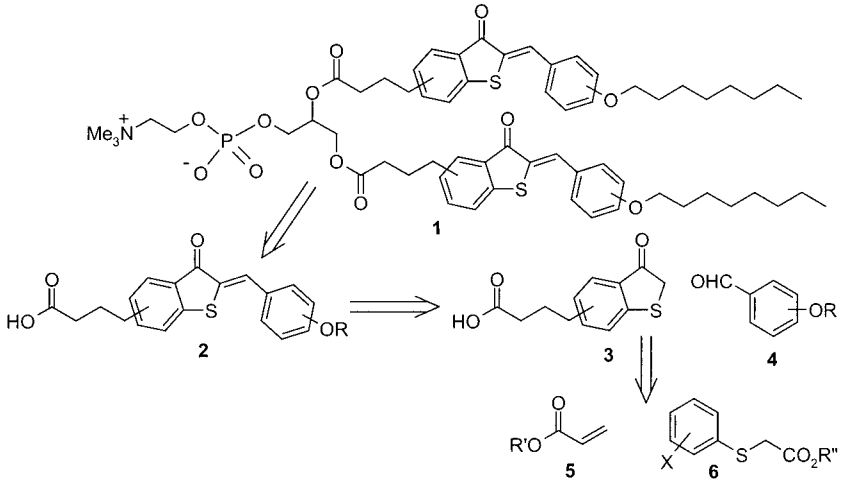
Scheme 1. Proposed Synthesis of Target Lipid 1



typically unstable and fusion is usually followed by enhanced bilayer permeability.

Reversible control of membrane or transporter functions, via reversible control of curvature stress, has not been achieved, yet is highly desirable for some applications such as the initiation and control of bilayer fusion. We envisage a reversibly photoisomerizable lipid that would preserve the bilayer barrier in both forms, yet would provide sufficient shape change on photoisomerization to influence curvature stress and thence some responsive membrane process. Photochemical reversibility in an oriented membrane medium is sometimes limited relative to homogeneous solution as the anisotropic environment inhibits some types of large structural reorganizations.[21] The ideal switch would also be freely miscible in membrane lipids and resist aggregation and phase separation. Aggregation of azobenzenes in lipids leads to membrane disruption on photoisomerization, while the same lipid dispersed as monomers does not alter bilayer permeability.[22] Good miscibility is essential, given the importance of lateral mobility of lipids in the dynamics of bilayer fusion.[20]

Hemithioindigos, although relatively little studied,[23−28] are appealing candidates as components of photoswitchable lipids. They are reversibly photochromic and the less-stable *E*-isomer is sufficiently stable to be isolated by chromatography.[29] They are photochemically robust, resisting photofatigue over thousands of cycles.[29] Most importantly, a surfactant derivative has been shown to be reversibly photoisomerized in dialkylammonium vesicles.[30] The structural changes accompanying isomerization will vary depending on the positions of the substituents, thus a simple series of regioisomers can be used to explore the multiple requirements of the target lipid. This paper describes the design, synthesis, and photochemical characterization of switchable lipids based on the hemithioindigo chromophore (**1**). The use of these lipids to influence membrane processes will be reported separately.

Results and Discussion

Scheme 1 shows a general structure of the target lipids prepared (**1**) together with an analysis of the proposed synthesis. The lipid should be available from bis-esterification of phosphoglycerol by a hemithioindigo carboxylic acid (**2**). The key intermediate **2** could be derived by Knoevenagel condensation of a substituted thioindoxyl (**3**) and a benzaldehyde derivative (**4**). The thioindoxyl could be derived from a halo-substituted thiophenol derivative (**6**) and an acrylate (**5**) by a Heck coupling and reduction sequence, and a Friedel−Crafts acylation−cyclization process. Other routes are possible, differing only in the sequence of the various steps. The chemical stability of thioindoxyl and hemithioindigo intermediates to the proposed reactions was unknown at the outset, but it was clear that selective differentiation of the esters in **5** and **6** would be required to ensure that the cyclization process proceeded as desired.

Scheme 2 shows exploratory chemistry that refined the synthetic plan of Scheme 1. *p*-Bromothiophenoxide was alkylated with ethyl bromoacetate to give the thioether **6a** that was hydrolyzed to the acid **7**. Conversion to the acid chloride was followed by $AlCl_3$-catalyzed cyclization to the bromothioindoxyl **8**. In general, thoindoxyl derivatives are unstable with respect to oxidation to thioindigos, thus Knoevenagel condensation with benzaldehyde derivatives was done with freshly prepared **8** to give the hemithioindigos **9** or **10** in moderate yield (66 and 74%, respectively). The phenol **9** could be alkylated to give **10** although the yield was modest,[29] thus the one-step process from alkylated benzaldehydes such as **4a** is superior.

In parallel, the bromo ester **6a** or the bromo acid **7** underwent palladium-catalyzed coupling[31] with acrylic acid (**5a**), or in somewhat better yield with methyl

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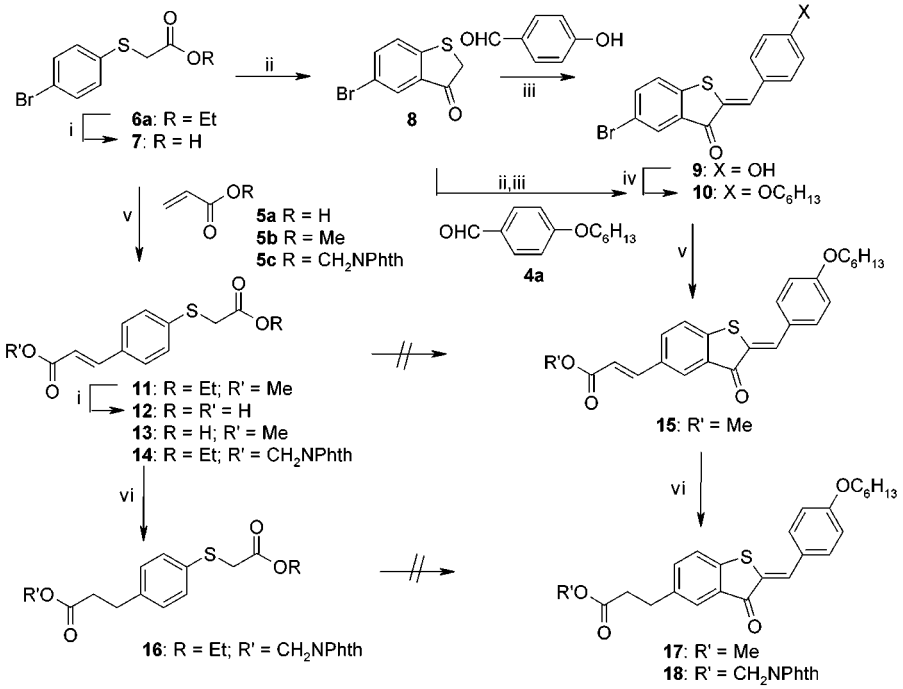
Scheme 2. Syntheses of Hemithioindigo Intermediates[a]

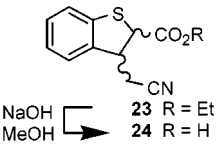


[a] Key: (i) NaOH, MeOH, reflux, 3 h; 93% (**7**), 85% (**12**); (ii) (a) $SOCl_2$, reflux, 1 h, (b) $AlCl_3$, $(ClCH_2)_2$, 0 °C to RT, 1 h; (iii) piperidine (cat.), benzene, reflux, 2 h; 66% (**9**), 74% (**10**); (iv) KOH, DMSO, RT, 30 min; 16%; (v) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N, 100 °C, 24 h; 27% (**11**), 10% (**13**), 27% (**15**); (vi) $Rh(PPh_3)_3Cl$ (3 mol %), H_2 (60 psi), benzene/EtOH, RT, 10 d; 95% (**16**), incomplete (**17**).

acrylate (**5b**), to give the expected *trans*-alkenes **11**, **12**, and **13**. The yields in all the Heck couplings discussed are poor (generally less than 45%) and were resistant to improvement over a range of changes in reaction conditions, solvents, and catalysts. More serious is the failure of the acids **12** or **13** to undergo cyclization and coupling with aldehydes to produce the required hemithioindigos such as **15**. Alkene **15** could be produced in low yield from **10** using the conditions used previously with the thioethers. Reduction of **15** to **17** either failed outright (H_2−Pd/C; H_2−Pt gave unreacted starting material) or was extremely sluggish (H_2−$Rh(PPh_3)_3Cl$). Thus it appears that reduction must precede hemithioindigo formation, and a differentially protected form of the diacid **12** is required. Our initial choice was the phthalimidomethyl ester, reported to be resistant to Friedel−Crafts acylation conditions.[32,33] In the event, the coupling of the phthalimidomethyl acrylate (**5c**) proceeded as expected to give **14**, and the alkene was successfully reduced using Wilkinson's catalyst to give the diester **16**. Attempts to selectively deprotect the ethyl ester while preserving the phthalimidomethyl ester failed (LiBr−pyridine; LiI−DMF; TMSCl−NaI−CH_3CN; KO*i*Bu); the differential reactivity differences are too small in this system.

Based on the initial findings, the synthesis of the targets was completed as shown in Scheme 3. The required differential protection of the diacid is achieved via the nitrile that will be subsequently hydrolyzed to expose the acid. The synthesis begins with the Heck coupling of bromo esters **6a**−**c** with acrylonitrile. For the *para* and *meta* isomers, mixed isomers of the alkene products **19a**,**b** were produced in acceptable yields. Compound **19c** from the *ortho* isomer was not produced, but gave instead an isomeric compound lacking an olefin.

The structure of the isomeric product was assigned as **23** based on the following evidence. The compound is isomeric with **19a**,**b** by mass spectrometry and retains a disubstituted benzene, an ethyl ester, and a nitrile group (IR, ^{13}C NMR). The methylene adjacent to the sulfur expected in **19c** appears as a methine (DEPT), together with a second methine having a very similar chemical shift in the ^1H NMR spectrum. A COSY spectrum establishes the fragment S−CH−CH−CH_2, and a decoupled ^{13}C NMR spectrum of the product of base hydrolysis (**24**) establishes both two- and three-bond couplings in the fragment S−CH−CH−CH_2−C(O)OH. Compound **23** would form from **19c** by a deprotonation adjacent to the ester followed by intramolecular Michael reaction and reprotonation.



The hemithioindigo synthesis proceeded from **19a**,**b** by hydrogenation of the mixed alkenes to the saturated nitriles **20a**,**b**. Hydrolysis of the ethyl ester then allowed the hemithioindigos **22a**−**f** to be formed via the procedures previously discussed. Friedel−Crafts cyclization from **21b** results in two isomeric thioindoxyls, thus **22e** and **22f** are formed as a mixture of regioisomers that was subsequently separated by chromatography. The yields of the hemithioindigo synthesis remain poor (20−45%).

The next step required the hydrolysis of the nitrile. Basic conditions sufficient to achieve nitrile hydrolysis (NaOH or KOH, alcohols or ethylene glycol)[34−37] resulted

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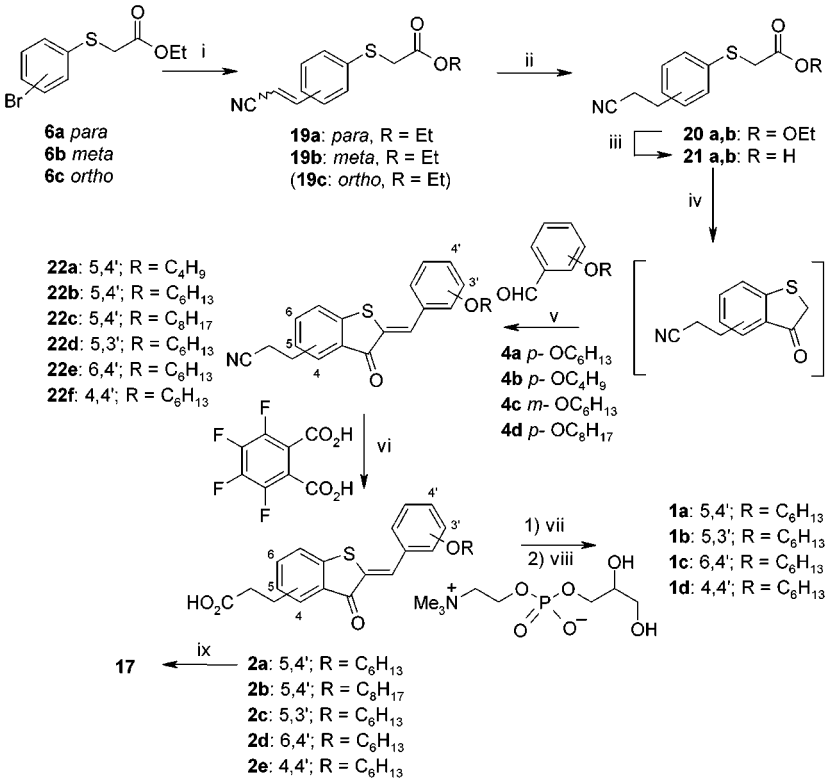
Scheme 3. Synthesis of Hemithioindigo Lipids[a]



[a] Key: (i) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N, 100 °C, 24 h; 78% (**19a**), 60% (**19b**), **19c** not formed, gave **23** (38%); (ii) $Rh(PPh_3)_3Cl$ (3 mol %), H_2 (60 psi), benzene/EtOH, RT, 10 d; 65% (**20a**), 64% (**20b**); (iii) NaOH, MeOH, reflux, 3 h; 90% (**21a**), 84% (**21b**), 75% (**21c**); (iv) (a) $SOCl_2$, reflux, 1 h, (b) $AlCl_3$, $(ClCH_2)_2$, 0 °C to RT, 1 h; (v) piperidine (cat.), benzene, reflux, 2 h; 45% (**22a**), 34% (**22b**), 42% (**22c**), 19% (**22d**), 34% (**22e** + **22f**); (vi) 170 °C, 5 d; 90% (**2a**), 71% (**2b**), 88% (**2c**), 86% (**2d**), 83% (**2e**); (vii) *t*-BuCOCl, Et_3N, CH_2Cl_2, RT, 30 h; (viii) DMAP, CH_2Cl_2, RT, 24 h; 85% (**1a**), 91% (**1b**), 87% (**1c**), 92% (**1d**); (ix) CH_2N_2, Et_2O, RT, 24 h; quant.

in destruction of the hemithioindigo core. The polar products are uncharacterized; some samples suggest that hydroxide attack occurred β to the carbonyl. The hemithioindigo core readily resists acidic conditions (H_2SO_4/H_2O; HBr/AcOH),[38] but so too does the nitrile. "Solventless" hydrolysis employing $CuCl_2 \cdot 2H_2O$ (240 °C, 1 h) resulted in destruction of the hemithioindigo presumably due to the generation of hydroxide.[39] Fusion with phthalic acids,[40] particularly tetrafluorophthalic acid[41] proved to a suitable method to produce the required acids (**2a**−**e**) in good yields. The lipid synthesis was completed following a standard mixed anhydride coupling with the $CdCl_2$ complex of glycerophosphocholine.[22,42,43] The bis-hemithioindigo lipids (**1a**−**d**) were readily isolated and purified by size exclusion chromatography on lipophilic Sephadex. Despite some poor-yielding steps, and some steps that required long reaction times, the overall synthesis is reasonably efficient (10% from bromothiophenol).

The absorption spectra of the hemithioindigos prepared show many of the features reported in previous work.[24,25,29] Figure 1 shows sample spectra for nitrile hemithioindigos (**22**), and Table 1 unites data for single hemithioindigo compounds in a number of solvents. In hexanes, the *Z*-isomer normally has two maxima between 410 and 490 nm depending on substituent.[24] The *E*-isomer absorption occurs as single band, usually 20−30 nm longer in wavelength than the longer wavelength absorption of the *Z*-isomer.[29] Solvents other than hexanes give more poorly resolved spectra in which the absorption peaks are broader and lower in intensity. The exceptions are the *meta*-substituted derivative **22d**, illustrated in Figure 1C, and the corresponding acid **2c**. Even in hexanes the absorption bands are broadened and of low intensity. These are the first hemithioindigo derivatives with a *meta*-substituent on the phenyl. It is not known if this is a general property of this substitution pattern.

Photoisomerization is readily observed in most cases. The *Z*-to-*E* conversion is achieved by irradiation at 406 nm, near the minimum absorbance of the *E*-isomer in most solvents. *E*-to-*Z* conversion can be effected by irradiation at 480 nm, near the maximum in the *E*-isomer absorbance spectrum. Typical spectral changes are shown in Figure 1. The *meta*-substituted derivatives **22d** and **2c** show very little spectral change on irradiation (Figure 1C). Similarly, the bromo-substituted derivative **9** resists isomerization. All photoisomerizations show clear isosbestic points, and the process is apparently completely

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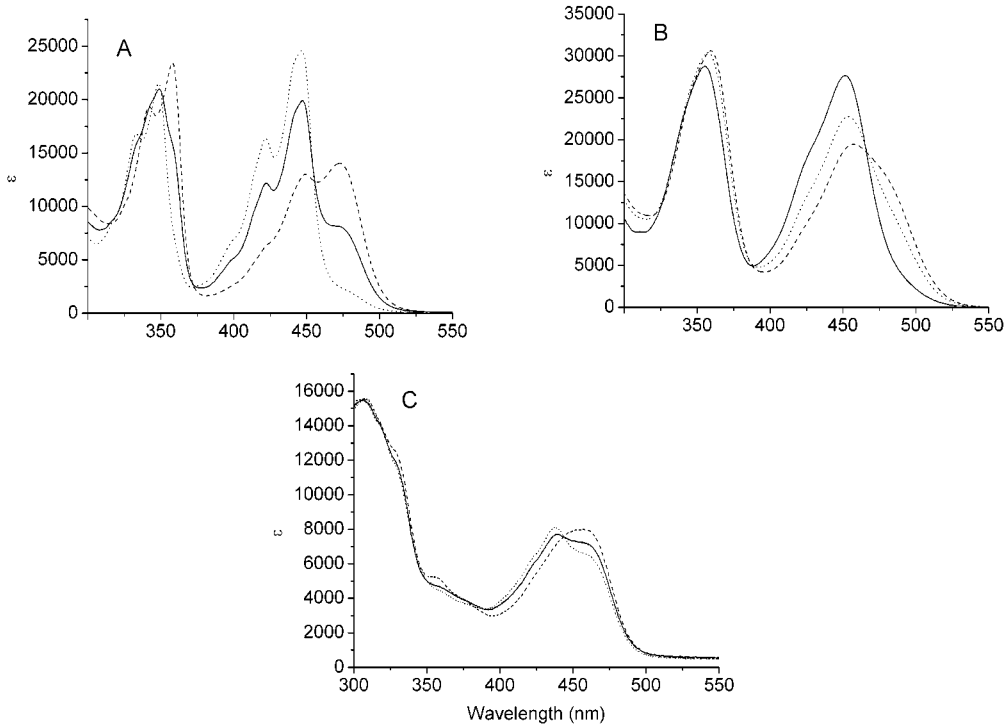

Figure 1. Absorption spectra of single chromophore hemithioindigos. A: **21f** (4.8×10^{-5}M) in hexanes; B: **21b** (3.3×10^{-5}M) in $CHCl_3$; C: **21d** (1.7×10^{-5}M) in hexanes. Solid line − sample from ambient light; dashed line − sample following irradiation at 406 nm; dotted line − sample following irradiation at 480 nm.

Table 1. Absorption Spectra of Hemithioindigo Compounds

compd	λ_{max} (nm) *Z* isomer	λ_{max} (nm) *E* isomer	$\epsilon_o \times 10^{-3}$ ($M^{-1}\,cm^{-1}$) *Z* isomer	solvent
9	423, 446	*b*	22	hexanes
	451	*b*	23	MeOH
10	422, 446	362, 473	22	hexanes
	455	461	16	CH_2Cl_2
22a, **22b**, **22c**	418, 441	357, 467	26	hexanes
	452	459	28	$CHCl_3$
2a, **2b**	441	357, 467	17	hexanes
	452	*c*	11	$CHCl_3$
22d	437	455	9	hexanes
2c	437	455	8	hexanes
2c	446	*c*	7	$CHCl_3$
22e	447	358, 471	25	hexanes
2d	444	467	20	hexanes
2d	453	*c*	11	$CHCl_3$
22f	422, 447	358, 471	25	hexanes
22f	454	*c*	20	$CHCl_3$
2e	421, 444	354, 468	20	hexanes
1a	356, 453	*d*	30	$CHCl_3$
1a	361, 460	462	28	CF_3CH_2OH
1b	310, 444	*d*	10	$CHCl_3$
1c	352, 445	*d*	26	$CHCl_3$
1d	351, 451	454	19	$CHCl_3$

[a] Calculated assuming 100% conversion to the *Z*-isomer in the dark. [b] Insensitive to photoisomerization. [c] Shoulder peak. [d] No apparent change.

reversible over periods of several days involving many hours of irradiation. This is consistent with previous reports of high resistance of hemithioindigos to photofatigue.[29]

As prepared, all hemithioindigos are predominantly in the *Z* form. The ^1H and ^{13}C NMR spectra consistently show a single isomer, with only minor amounts of the *E*-isomer in a few samples. On a preparative scale, irradiation of a chloroform solution of **22b** at 350 nm for 30 min, followed by concentration and chromatography in red light produced *E*-**22b** in quantity sufficient for spectroscopic characterization. The proton and carbon β to the carbonyl show the largest NMR changes: 0.78 ppm upfield shift in the ^1H spectrum and 5 ppm downfield shift in the ^{13}C spectrum. The *ortho*-positions of the phenyl substituent are also significantly perturbed, undergoing a 0.43 ppm downfield shift in the ^1H spectrum. Smaller changes are evident throughout the hemithioindigo core, particularly at the 4 position of the thioindoxyl.

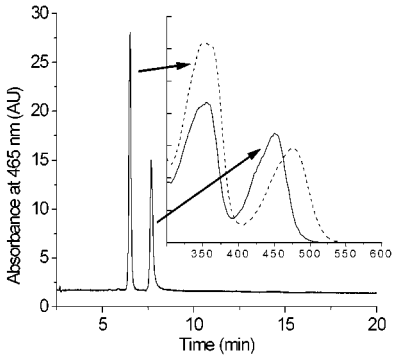

Figure 2. Chromatogram of an isomer mixture of **17** produced by irradiation at 406 nm analyzed by reverse-phase HPLC (C_{18} column, acetonitrile-methanol−water 98:2:2, 1 mL/min, detect at 465 nm). The inset shows the absorption spectra of the two components, normalized to correct for the concentration ratio (59:41 *E*:*Z*).

Quantitative analysis of the isomer mixture can be achieved by liquid chromatography on a reverse phase column (Figure 2). The data illustrated for **17** are representative of chromatograms of compounds **9** and **22a**−**f**. An isosbestic point for **17** in acetonitrile−methanol−water (96:2:2) occurs at 465 nm, thus the

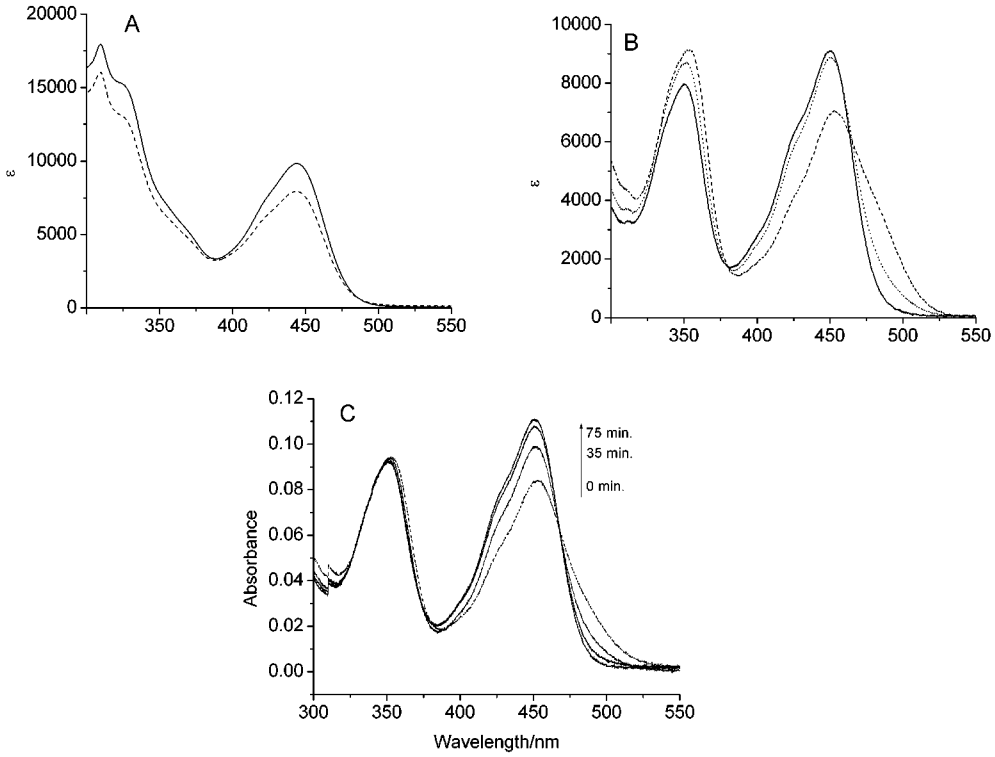

Figure 3. Absorption spectra of bis-hemithioindigo lipids. A: **1b** (6.7×10^{-6}M) in $CHCl_3$; B: **1d** (1.6×10^{-5}M) in $CHCl_3$; C: thermal recovery of **1d** (5.8×10^{-6} M) in $CHCl_3$ under ambient light. Solid line − sample from ambient light; dashed line − sample following irradiation at 406 nm; dotted line − sample following irradiation at 480 nm.

integrated areas of peaks detected at 465 nm can be used to determine the isomer composition (59:41 *E*:*Z* in the sample used for Figure 2). The assignment of isomers to the two peaks in the chromatogram follows directly from the spectra of the two components (inset to Figure 2).

The following features of the photoisomerization of single hemithioindigo compounds are established. (1) The *Z* isomer is the thermodynamically favored form. The composition of mixtures held in the dark for prolonged periods is 98 ± 2% *Z*: 2 ± 2% E (for **17**). (2) Irradiation at 406 nm, or 445 nm produces a photostationary state enriched in the *E*-isomer. The composition varies somewhat with the compound, the irradiation conditions, and the solvent. Compound **17** is typical: the photostationary state is 65% *E*-**17** after 10 min of irradiation in acetonitrile−methanol−water (96:2:2). The photostationary states achieved with the compounds reported here, are significantly less enriched in the *E*-isomer relative to previous reports.[29] (3) Similarly, irradiation at longer wavelength (480 or 490 nm) produces a photostationary state enriched in the *Z*-isomer. This is not the thermodynamic equilibrium mixture as there is still a significant amount of the *E*-isomer present. For **17** in acetonitrile−methanol−water (96:2:2), irradiation at 490 nm for 10 min produces a stationary state that is 93% *Z*-**17**. If left in the dark, this mixture reverts slowly to the equilibrium mixture. (4) Ambient light (fluorescent, indirect daylight) is sufficient to establish a mixture in stock solutions of the compounds. The composition varies with the "conditions", but is typically between 60 and 70% *Z*-isomer a day after the solution is prepared. (5) In the dark at room temperature, solutions enriched in the *E*-isomer slowly revert to the *Z*-isomer. The process is first-order with a half-life of 8−9 h ($k \approx 2 \times 10^{-5}$ s^{-1}) for a range of compounds and solvents. This is 2−3 orders of magnitude faster than reported previously.[29] (6) In ambient light the rate of approach to the apparent photostationary state is also first order with rate about 10-fold faster ($t_{1/2} \approx 50$ min).

The experiments with single-chromophore hemithioindigos indicate that switching to the *E*-isomer will be incomplete, and that once formed, the *E*-isomer will revert to the *Z* isomer relatively quickly, even in the dark. The bis-hemithioindigo lipids are therefore predicted to consist of: a thermodynamically stable *Z*,*Z*-isomer, a pair of *E*,*Z*- and *Z*,*E*-isomers, and an *E*,*E*-isomer. If a photostationary state of 60% *E*-isomer per hemithioindigo is assumed to follow from irradiation at 406 nm, the mixture will be 16% *Z*,*Z*, 48% *Z*,*E* + *E*,*Z*, and 36% *E*,*E*. This composition might be altered if chromophores do not act independently. Figure 3 shows typical spectral changes observed for the bis-hemithioindigo lipids **1a**−**d**. Some lipids and solvents show virtually no photochromism, as illustrated by **1b** in $CHCl_3$ (Figure 3A). The apparent bleaching of the peak centered at 465 nm is reversible with a half-life in the dark of 8 h, consistent with previous examples of *E*-to-*Z* thermal reversion of a hemithioindigo. Other lipids show more pronounced changes following irradiation at 406 nm, as exemplified by **1d** (Figure 3B). The broadening and longer wavelength shift of the band at 460 nm is consistent with an increased proportion of *E*-isomer. The changes in this case are reversible as well (Figure 3C). Chromatographic conditions suitable for the quantification of the isomer mixtures produced could not be developed. Four partly overlapped components could be separated, each of which had a hemithioindigo absorption spectrum. However, the four-component system is too complex to provide a single isosbestic point, so the quantitative analysis of this mixture requires a more sophisticated approach than was possible with the single-chromophore systems discussed above.

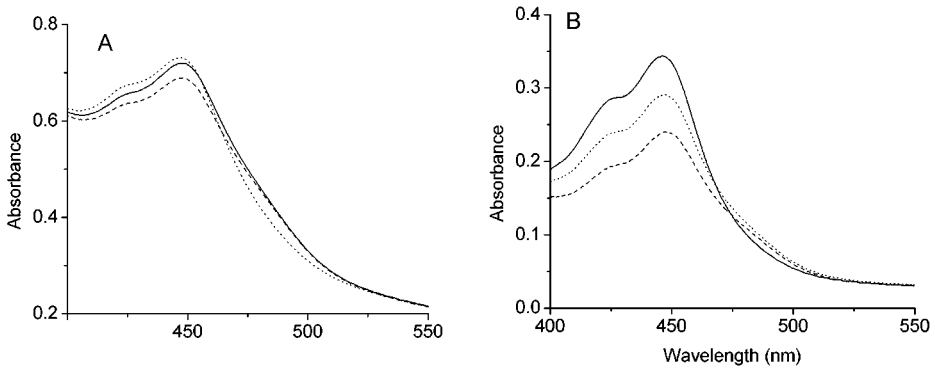

Figure 4. Absorption spectra of hemithioindigo lipids dispersed in phosphatidylserine vesicles (1:9 wt/wt). A: **1c**, B: **1d**. Solid line − sample from ambient light; dashed line − sample following irradiation at 406 nm; dotted line − sample following irradiation at 480 nm.

Hemithioindigo lipids **1a**−**d** were readily incorporated into phosphatidylserine (PS) vesicles. A mixed lipid film was prepared by evaporation of a $CHCl_3$ solution of PS and **1a**−**d**. Vesicles prepared from this film by a freeze−thaw technique[44] followed by sizing through an extruder[45] and gel filtration showed incorporation of hemithioindigo in the vesicle fraction. Pure **1a**−**d** did not disperse into aqueous buffers under the mild conditions used to form the vesicles, forming rather platelets that clogged the extruder filter. The proportion of **1a**−**d** in PS could be varied freely up to about 20 wt %. At higher proportions of hemithioindigo lipid, platelets appeared on the extruder filter indicating incomplete incorporation in the PS vesicle formed. Typical absorption spectra of hemithioindigo lipids in PS vesicles are shown in Figure 4. No clear photochromism was found in any preparation. However, the absorption band about 450 nm is reversibly altered by irradiation at 406 and 480 nm in a manner that is consistent with previous examples of hemithioindigo switching in homogeneous solution. Both the apparent "bleaching" at 450 nm and the modest broadening to longer wavelength following irradiation at 406 nm are consistent with a *Z*-to-*E* photoisomerization (Figure 4B). The rate of thermal return to the initial spectrum under ambient light conditions was comparable to previous cases ($t_{1/2} \approx 45$ min) as well. The results, while not clear-cut, are consistent with the minor changes noted in previous work with single hemithioindigos in vesicle membranes.[30] It is unlikely that the isomerized lipid is ejected from the bilayer, as these, and previously reported hemithioindigos,[25] exhibit significant solvatochromism. A significant red-shift of 15−20 nm would be expected if the chromophore migrated to a more polar environment, such as the surface of a vesicle.

In conclusion, we have prepared a class of lipids containing hemithioindigo chromophores in the acyl chains. The isolated chromophore can be reversibly switched between two geometric isomers in organic solvents; however, the conversion to the less-stable *E*-isomer is incomplete at the photostationary state. Thermal reversion to the *Z*-isomer is slow in the dark, but is accelerated in ambient light. The hemithioindigo lipids are readily incorporated into PS vesicles where they apparently undergo the same type of reversible photoisomerization and slow thermal reversion reactions as in homogeneous solution. These lipids thus offer the potential for the reversible control of membrane processes via control of curvature stress. Our progress in this area will be reported separately.

Experimental Section

General Procedure I: Ether Synthesis.[46,47] A suspension of KOH (132 mmol, 4 equiv) in 50 mL of DMSO was treated with hydroxybenzaldehyde (33 mmol, 1 equiv) and an alkyl halide (49.0 mmol, 1.5 equiv). This suspension was stirred vigorously at room temperature for 30 min, and then quenched with water (150 mL). The product was extracted with CH_2Cl_2 (2 × 75 mL), and then washed with water (3 × 75 mL), dried, and concentrated to a yellow liquid. The crude product was purified by distillation (Kugelrohr, 5×10^{-2} atm), affording a clear liquid.

General Procedure II: Thioether Synthesis.[48] A solution of bromothiophenol (230 mmol) and ethyl bromoacetate (240 mmol, 1.05 equiv) in 60 mL of benzene was refluxed, under N_2. DBU (240 mmol, 1.05 equiv), in 60 mL of benzene, was added over 10 min, and the solution was refluxed for 2 h. The DBU salt precipitate was filtered, and the filtrate was concentrated to yield a light yellow liquid. This crude product was distilled, (Kugelrohr, 5×10^{-2} atm), yielding a clear liquid (bp ca. 120 °C).

General Procedure III: Heck Reactions.[49] A mixture was prepared containing an aryl bromide (1 equiv), a freshly distilled alkene (1.5 equiv), NEt_3 (1.5 equiv), $Pd(OAc)_2$ (0.05 equiv), and $P(Ph)_3$ (0.10 equiv). The flask was purged with argon, sealed with a septum, sonicated to a fine suspension, and then heated at 100 °C for 24−72 h. The mixture was cooled and filtered, and the solid was washed twice with ether. Concentration of filtrate resulted in a golden solution. The purification procedures varied with compound as described below.

General Procedure IV: Hemithioindigo Synthesis.[29] A phenyl thioacetic acid (7.81 mmol) in an excess of $SOCl_2$ (5 mL) was refluxed, under N_2, for 1 h. The excess thionyl chloride was removed under vacuum. The resultant acid chloride, in 15 mL of $(ClCH_2)_2$, was cooled in a salt ice bath to below 0 °C. $AlCl_3$ (9.4 mmol, 1.2 equiv) was added to the cooled solution, under rapid stirring, over a 2 min period. The solution was stirred with cooling for another 10 min, removed, and left

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stirring at room temperature (23 °C), for a further 40 min. The reaction was quenched with ice/water, and product was extracted with CH_2Cl_2, dried, concentrated, and dried under vacuum for 15 min. This yellow solid thioindoxyl slowly decomposed and so was used as soon as possible. A solution of the indoxyl, a benzaldehyde derivative (8.2 mmol, 1.05 equiv), and 2 drops of piperidine in 50 mL of benzene was refluxed for 2 h. The course of the reaction and the purification procedure varied with compound and is described individually.

General Procedure V: Nitrile Hydrolysis.[41] The nitrile (0.3 mmol, 1 equiv) and tetrafluorophthalic acid (1 equiv) were added to a Carius tube and sealed under vacuum. The vessel was heated at 170 °C for 5 days. The solid crude product was dissolved in $CHCl_3$/MeOH and was passed through a LH-20 column with $CHCl_3$/MeOH, 4:3, as eluent, to give a yellow solid.

General Procedure VI: Lipid Synthesis.[22] A solution of hemithioindigo carboxylic acid (0.29 mmol), $(CH_3)_3CCOCl$ (3.0 mmol, 10 equiv), and NEt_3 (1.4 mmol, 5 equiv) in CH_2Cl_2 was stirred, under N_2, for 35 h. The reaction was monitored by TLC ($CHCl_3$/MeOH/H_2O, 65:25:4). The crude mixed anhydride was concentrated and dried under vacuum, for 8 h, to remove unreacted $(CH_3)_3CCOCl$ and NEt_3. The mixed anhydride was dissolved in 5 mL of CH_2Cl_2, added to a suspension of dried GPC−$CdCl_2$ complex (0.115 mmol, 0.4 equiv) and DMAP (0.230 mmol, 0.8 equiv) in CH_2Cl_2 (10 mL), and stirred for 23 h. The solution was concentrated and eluted through an ion exchange column of Rexyn-I-300 to remove the $CdCl_2$ and DMAP ($CHCl_3$/MeOH/H_2O, 65:25:4). The crude product was concentrated and then redissolved in $CHCl_3$/MeOH, 4:3, and passed through a Sephadex LH-20 column to yield the pure lipid as a yellow solid.

4-Hexyloxybenzaldehyde (4a)[50] was prepared by procedure I, from 1-bromo hexane and *p*-hydroxybenzaldehyde in 64% yield. Bp 120 °C. ^{1}H NMR ($CDCl_3$): δ = 9.82 (s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.98 (t, J = 6.6, 2H), 1.76 (qn, J = 6.6 Hz, 2H), 1.43 (qn, J = 6.6 Hz, 2H), 1.31 (m, 4H), 0.87 (t, J = 7.4, 3H). ^{13}C NMR ($CDCl_3$): δ = 190.7, 164.2, 131.9, 129.6, 114.6, 68.3, 31.4, 28.9, 25.5, 22.5, 13.9. CI MS *m*/*z* (%): 247 (4), 235 (16), 207 (100).

4-Butoxybenzaldehyde (4b)[50] was prepared by procedure I, from 1-bromobutane and *p*-hydroxybenzaldehyde in 48% yield. Bp 80 °C. ^{1}H NMR ($CDCl_3$): δ = 9.85 (s, 1H), 7.80 (d, J = 8.1 Hz, 2H), 6.96 (d, J = 8.1 Hz, 2H), 4.01 (t, J = 6.6, 2H), 1.77 (qn, J = 8.1 Hz, 2H), 1.48 (sx, J = 7.4, 2H), 0.96 (t, J = 7.4, 3H). ^{13}C NMR ($CDCl_3$): δ = 190.6, 164.1, 131.8, 129.6, 114.6, 67.9, 30.9, 19.0, 13.7. CI MS *m*/*z* (%): 219 (6), 207 (22), 179 (100).

3-Hexlyoxybenzaldehyde (4c) was prepared by procedure I, from 1-bromohexane and *m*-hydroxybenzaldehyde in 83% yield. ^{1}H NMR ($CDCl_3$): δ = 9.94 (s, 1H), 7.42 (s, 1H), 7.40, 7.36, 7.15 (m, 1H), 3.98 (t, J = 6.6, 2H), 1.77 (qn, J = 6.6 Hz, 2H), 1.44 (m, 2H), 1.31 (m, 8H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 192.2, 159.7, 137.7, 129.9, 123.2, 121.9, 112.7, 68.3, 31.5, 29.0, 25.6, 22.5, 14.0. CI MS *m*/*z* (%): 235 (15), 207 (100).

4-Octoylxybenzaldehyde (4d)[50] was prepared by procedure I, from 1-bromooctane and *p*-hydroxybenzaldehyde. Distillation (120 °C) gave an impure product. Chromatography of the distillate (silica, 50 g, 1:3 ethyl acetate:hexanes) was employed to yield a thick clear liquid (17% yield). ^{1}H NMR ($CDCl_3$): δ = 9.86 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.02 (t, J = 6.6, 2H), 1.79 (qn, J = 6.6 Hz, 2H), 1.45 (m, 2H), 1.30 (m, 8H), 0.87 (t, J = 7.4 Hz, 3H). ^{13}C NMR MHz ($CDCl_3$): δ = 190.8, 164.2, 132.0, 129.7, 114.7, 68.4, 31.8, 29.3, 29.2, 29.0, 25.9, 22.6, 14.1. CI MS *m*/*z* (%): 263 (20), 235 (100).

(*N*-Phthalimido)methyl Acrylate (5c). A solution of acrylic acid (3.47, 48 mmol) and dicyclohexylamine, (8.71 g, 48 mmol,1 equiv) in 150 mL of DMF was heated to 65 °C, in an inert atmosphere. *N*-Chloromethylphthalimide (9.41 g, 48 mmol) in 100 mL of DMF was added over 10 min, and the solution was stirred for a further 30 min. The ammonium salt precipitate was filtered and the supernatant concentrated. The crude product was recrystallized from toluene, yielding a white solid (5.97 g, 25.8 mmol, 54%), mp = 142−143 °C. ^{1}H NMR ($CDCl_3$): δ = 7.91 (AB, J = 5.2, 3.0 Hz, 2H), 7.76 (AB, J = 5.2, 3.0 Hz, 2H), 7.42 (ABX, J = 16.9, 1.5 Hz, 1H), 6.07 (ABX, J = 16.9, 10.3 Hz, 1H), 5.85 (ABX, J = 10.3, 1.5 Hz, 1H), 5.78 (s, 2H). ^{13}C NMR 75.47 MHz ($CDCl_3$): δ = 166.7, 164.8, 134.6, 132.2, 131.7, 127.4, 124.0, 60.8. CI MS *m*/*z* (%): 260, 232 (100), 176, 160. Anal. Calcd for $C_{12}H_9O_4N$ (%): C, 62.34; H, 3.92; N, 6.06. Found C, 62.49; H, 4.05; N, 5.82.

Ethyl [(4-bromophenyl)thio]acetate (6a) was prepared by procedure II, from 4-bromothiophenol in 91% yield. ^{1}H NMR ($CDCl_3$): δ = 7.34 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.55 (s, 2H), 1.16 (t, J = 7.3 Hz, 3H). ^{13}C NMR 75.47 MHz ($CDCl_3$): δ = 169.1, 134.3, 132.0, 131.4, 120.8, 61.5, 36.3, 14.1. Anal. Calcd for $C_{10}H_{11}O_2SBr$ (%): C 43.65; H 4.03; O 11.63; S 11.65; Br 29.04. Found: C 43.54; H 4.03; O 11.25; S 11.97; Br 29.21.

Ethyl [(3-Bromophenyl)thio]acetate (6b) was prepared by procedure II, from 3-bromothiophenol in 77% yield. ^{1}H NMR 300 MHz ($CDCl_3$): δ = 7.49 (s, 1H), 7.27 (m, 2H), 7.09 (t, J = 8.1 Hz, 1H), 4.12 (q, J = 7.4 Hz, 2H), 3.59 (s, 2H), 1.18 (t, J = 7.4 Hz, 3H). ^{13}C NMR 75.47 MHz ($CDCl_3$): δ = 169.2, 137.5, 131.9, 130.3, 129.8, 128.0, 122.8, 61.7, 36.2, 14.1. Anal. Calcd for $C_{10}H_{11}O_2SBr$ (%): C 43.65; H 4.03; O 11.63; S 11.65; Br 29.04. Found: C 44.06; H 4.07; O 11.14; S 11.96; Br 28.77.

Ethyl [(2-Bromophenyl)thio]acetate (6c) was prepared by procedure II, from 2-bromothiophenol in quantitative yield. ^{1}H NMR 300 MHz ($CDCl_3$): δ = 7.52 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.03 (t, J = 8.1 Hz, 1H), 4.14 (q, J = 6.6 Hz, 2H), 3.64 (s, 2H), 1.20 (t, J = 6.6 Hz, 3H). ^{13}C NMR 75.47 MHz ($CDCl_3$): δ = 168.9, 136.2, 129.3, 127.8, 127.5, 123.9, 61.6, 35.4, 13.9. Anal. Calcd. for $C_{10}H_{11}O_2SBr$ (%): C 43.65; H 4.03; O 11.63; S 11.65; Br 29.04. Found: C 43.87; H 4.10; O 11.07; S 12.09; Br 28.87.

[(4-Bromophenyl)thio]acetic Acid (7). Ester **6a** (8.72 g, 32 mmol) was dissolved in 100 mL of MeOH containing NaOH (1.52 g, 38.0, 1.2 equiv) and was stirred at reflux for 3 h. The acid salt was concentrated and dried under vacuum. The resultant solid was dissolved in H_2O and acidified to pH < 1. The white precipitate was filtered and dried (3.65 g, 15 mmol, 39%), mp = 117−119 °C. ^{1}H NMR ($CDCl_3$): δ = 7.41 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 3.63 (s, 2H). ^{13}C NMR MHz ($CDCl_3$): δ = 175.0, 133.6, 132.3, 131.7, 121.5, 36.5. CI MS *m*/*z* (%): 249, 247 (50), 231, 229 (40), 203, 201 (100). Anal. Calcd for $C_8H_7O_2Br$ (%): C 38.69; H 2.86. Found: C 38.18; H 2.85.

5-Bromobenzo[*b*]thiophen-3(2*H*)-one (8) was prepared by the initial stages of procedure IV, from acid **7**. The product is unstable with respect to oxidation and was only characterized spectroscopically: ^{1}H NMR ($CDCl_3$): δ = 7.86 (d, J = 1.8 Hz, 1H), 7.61 (dd, J = 8.5, 1.8 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 3.81 (s, 2H). ^{13}C NMR ($CDCl_3$): δ = 198.5, 153.0, 138.3, 132.6, 129.3, 125.9, 39.8. CI MS *m*/*z* (%): 271, 269 (5), 259, 257 (11), 231, 229 (100).

2-(4-Hydroxyphenylmethylene)-5-bromobenzo[*b*]thiophen-3(2*H*)-one (9) was prepared from **8** and *p*-hydroxybenzaldehyde by the later stages of procedure IV. Upon cooling of the reaction mixture a bright orange solid precipitated. The suspension was washed with $Na_2S_2O_3$ (5%, 25 mL × 2), filtered, and dried under vacuum (1.72 g, 5.16 mmol, 66%). The product was recrystallized from 95% EtOH, mp = 282 °C. ^{1}H NMR (DMSO): δ = 10.46 (s, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.86 (s, 1H), 7.84 (dd, J = 8.8, 2.2 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H). ^{13}C NMR (DMSO): δ = 186.0, 160.5, 144.0, 137.7, 134.8, 133.5, 132.0, 128.5, 126.4, 125.7, 124.5, 118.9, 116.4. CI MS *m*/*z* (%): 363, 361 (19), 335, 333 (100). Anal. Calcd for $C_{15}H_9O_2BrS$: (%): C, 54.07; H, 2.72. Found C, 53.65; H, 2.79.

2-(4-Hexyloxyphenylmethylene)-5-bromobenzo[*b*]thiophen-3(2*H*)-one (10) was prepared by procedure IV, from **7** (0.98 g, 4.3 mmol) and **4b**. The solution was concentrated, and the residue was recrystallized from CH_2Cl_2/hexanes to yield a

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yellow solid (1.34 g, 3.2 mmol, 74%), mp = 129−131 °C. ^{1}H NMR ($CDCl_3$): δ = 8.02 (d, J = 2.2 Hz, 1H), 7.91 (s, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.1 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 1.79 (qn, J = 7.4 Hz, 2H), 1.45 (qn, J = 7.4 Hz, 2H), 1.34 (m, 4H), 0.89 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 187.2, 161.2, 144.6, 137.5, 134.9, 133.2, 132.5, 129.6, 127.2, 126.4, 125.2, 119.3, 115.2, 68.3, 31.5, 29.0, 25.6, 22.6, 14.0. +LSIMS (*m*NBA) *m*/*z* (%): 419, 417 (M + H$^+$, 100). Anal. Calcd for $C_{21}H_{21}O_2BrS$: (%): C, 60.43; H, 5.07. Found C, 60.97; H, 5.51.

Methyl (2*E*)-3-[4-(1-Thia-4-oxa-3-oxohexyl)phenyl]prop-2-enoate (11) was prepared by procedure III, from **6a** (30 mmol) and methyl acrylate (**5b**). The crude product was purified by chromatography (flash silica, 200 g, 60:40 ether: hexanes) and gave a white solid in 37% yield, mp = 47−48 °C. ^{1}H NMR($CDCl_3$): δ = 7.62 (d, J = 16.0 Hz, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.34(d, J = 8.3 Hz, 2H), 6.38 (d, J = 16.0 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR 90.57 MHz ($CDCl_3$): δ = 169.3, 167.4, 143.9, 138.3, 132.5, 128.7, 128.5, 117.6, 61.8, 51.7, 35.7, 14.1. +LSIMS (*m*NBA) *m*/*z* (%): 280 (M$^+$, 100), 249 (43), 207 (35), 175 (30). Anal. Calcd for $C_{14}H_{16}O_4S$ (%): C, 59.98; H, 5.75; O, 22.83; S, 11.44. Found: C, 59.80; H, 5.77; O, 23.00; S, 11.43.

(2*E*)-3-[4-(Carboxymethylthio)phenyl]prop-2-enoic Acid (12). NaOH (0.54 g, 13.6, 2.5 equiv), in 25 mL of MeOH, was added to a solution of **11** (1.53 g, 5.44 mmol) in 50 mL of MeOH, and the mixture was refluxed for 2 h. The acid salt was concentrated and dried under vacuum. The resultant solid was dissolved in H_2O and then acidified to pH < 1. The white precipitate was filtered and dried (1.10 g, 4.62 mmol, 85%), mp = 219−220 °C. ^{1}H NMR MHz (DMSO): δ = 12.63 (br s), 7.62 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 15.4 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 6.50 (d, J = 15.4 Hz, 1H), 3.88 (s, 2H). ^{13}C NMR MHz (DMSO): δ = 170.5, 167.7, 143.3, 138.9, 131.5, 128.8, 127.0, 118.6, 34.2.

Methyl (2*E*)-3-[4-(carboxymethylthio)phenyl]prop-2-enoate (13) was prepared by procedure III, from **7** (7.85 mmol) and methyl acrylate (5b). The crude product was isolated by ether extraction (2 × 25 mL) of the acidic aqueous reaction medium, dried, and concentrated. Recrystallization from 95% ethanol gave **13** as a white solid in 10% yield. ^{1}H NMR (DMSO): δ = 12.9 (br s, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 16.1 Hz, 1H), 7.32 (d, J = 8.3 Hz, 2H), 6.58 (d, J = 16.1 Hz, 1H), 3.88 (s, 2H), 3.70(s, 3H). ^{13}C NMR (DMSO): δ = 170.4, 166.7, 143.8, 139.3, 131.3, 128.8, 126.9, 117.1, 56.1, 34.1.

(*N*-Phthalimido)methyl 4-(1-thia-4-oxa-3-oxohexyl)-cinnamate (14) was prepared by procedure III, from **6a** (2.38 g, 8.66 mmol) and **5c**(2.00 g, 8.66 mmol, 1 equiv). The crude product was dissolved in CH_2Cl_2 (100 mL), and the solution was washed with H_2O (50 mL × 2) and then concentrated. The crude product was recrystallized from ethyl acetate/ hexanes and purified further using centrifugal chromatography ($CHCl_3$) to give a white solid (1.66 g, 3.90 mmol, 45%), mp = 130 °C. ^{1}H NMR ($CDCl_3$): δ = 7.91 (AB, J = 5.9, 2.9 Hz, 2H), 7.76 (AB, J = 5.9, 2.9 Hz, 2H), 7.62 (d, J = 16.2 Hz, 1H), 7.42 (AB, J = 8.1 Hz, 2H), 7.27 (AB, J = 8.1 Hz, 2H), 6.32 (d, J = 16.2 Hz, 1H), 5.82 (s, 2H), 4.14 (q, J = 6.6 Hz, 2H), 3.65 (s, 2H), 1.19 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 169.2, 166.7, 165.5, 145.2, 138.8, 134.6, 132.1, 131.7, 128.6, 128.5, 123.9, 116.5, 61.7, 60.8, 35.5, 14.0. CI MS *m*/*z* (%): 459 (14), 426 (52), 408 (100), 160 (88). Anal. Calcd for $C_{22}H_{19}O_6NS$ (%): C, 62.11; H, 4.50; N, 3.29. Found: C, 61.67; H, 4.50; N, 3.31.

2-(4-Hexyloxyphenylmethylene)-5-(methoxycarbonylethenyl)benzo[*b*]thiophen-3(2*H*)-one (15) was prepared by procedure III, from **10** (0.393 g, 0.94 mmol) and methyl acrylate (**5b**). The product was purified by centrifugal chromatography ($CHCl_3$), eluting unreacted **9**, followed by **14** (0.090 g, 0.21 mmol, 22%), mp = 179−181 °C. ^{1}H NMR ($CDCl_3$): δ = 8.05 (d, J = 1.5 Hz, 1H), 7.95 (s, 1H), 7.69 (d, J = 15.4 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 6.49 (d, J = 15.4 Hz, 2H), 4.01 (t, J = 6.6 Hz, 2H), 3.80 (s, 3H), 1.79 (qn, J = 7.4 Hz, 2H), 1.46 (qn, J = 6.6 Hz, 2H), 1.33 (m, 4H), 0.90 (t, J = 6.6 Hz, 2H). ^{13}C NMR MHz ($CDCl_3$): δ =187.9, 167.1, 161.2, 147.8, 143.2, 134.8, 134.0, 133.2, 132.1, 131.4, 127.4, 126.5, 126.0, 124.3, 118.5, 115.2, 68.3, 51.8, 31.5, 29.1, 25.6, 22.6, 14.0. +LSIMS (*m*NBA) *m*/*z* (%): 423 (60), 289 (100). Anal. Calcd for $C_{25}H_{26}O_4S$: (%): C, 71.06; H, 6.20; O, 15.15; S, 7.57. Found C, 71.37; H, 6.16; O, 14.98.

(*N*-Phthalimido)methyl 4-(1-Thia-4-oxa-3-oxohexyl)-dihydrocinnamate (16). Alkene **14** (2.00 g, 4.70 mmol) and $Rh(PPh_3)_3Cl$ (0.124 g, 0.134 mmol, 0.03 equiv) in 150 mL of degassed 1:1 benzene/ethanol was hydrogenated at room temperature, at 60 psi, for 10 days. The crude product was purified on a silica column (1:1, ethyl acetate/hexanes) to give a clear liquid (1.90 g, 4.45 mmol, 95%). ^{1}H NMR ($CDCl_3$): δ = 7.89 (AB, J = 5.5, 2.9 Hz, 2H), 7.77 (AB, J = 5.5, 2.9 Hz, 2H), 7.26 (d, J = 8.1 Hz, 2H), 7.08 (d, J = 8.1 Hz, 2H), 5.68 (s, 2H), 4.11 (q, J = 6.6 Hz, 2H), 3.62 (s, 2H), 2.88 (t, J = 7.4 Hz, 2H), 2.59 (t, J = 7.4 Hz, 2H), 1.18 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 171.3, 169.5, 166.5, 139.0, 134.5, 132.4, 131.5, 130.4, 128.8, 123.8, 61.3, 60.6, 36.8, 35.1, 30.0, 13.9. +LSIMS (*m*NBA) *m*/*z* (%): 427 (28), 354 (10), 280 (20), 267 (30), 209 (24), 160 (100). Anal. Calcd for $C_{22}H_{21}O_6NS$ (%): C, 61.82; H, 4.95; N, 3.28. Found C, 61.83; H, 4.96; N, 3.33.

Methyl 2-(4-hexyloxyphenylmethylene)benzo[*b*]thiophen-3(2*H*)-one-5-(2-ethylcarboxylate) (17) was prepared from **2a** (150 mg, 0.37 mmol) in excess diazomethane in ether. The mixture was stirred at room temperature for 1 h and then evaporated and chromatographed on a silica column ($CHCl_3$: MeOH 9:1) to give a yellow solid (145 mg 0.34 mmol, 93%). ^{1}H NMR ($CDCl_3$): δ = 7.91 (s, 1H), 7.76 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.41 (m, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.01 (t, J = 6.62 Hz, 2H), 3.66 (s, 3H), 2.99 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.79 (qn, J = 6.6 Hz, 2H), 1.33 (qn, J = 6.6 Hz, 2H), 1.23 (m, 4H), 0.89 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 188.5, 172.9, 161.0, 143.0, 138.2, 135.6, 133.9, 133.0, 131.1, 128.5, 126.8, 126.3, 123.9, 115.1, 68.3, 51.7, 35.4, 31.5, 30.3, 29.4, 29.1, 25.7, 22.6, 14.0. +LSIMS (mNBA) *m*/*z* (%) 425.0 (100). Exact mass Calculated for $C_{25}H_{29}O_4S$ 425.1779; found 425.1781

Ethyl [(4-(2-cyanoethenyl)phenyl)thio]acetate (19a) was prepared by procedure III, from **6a** (6.37 g, 23.2 mmol) and freshly distilled acrylonitrile (1.84 g, 34.8 mmol, 1.5 equiv). The crude product (TLC, 1:1 ether:hexanes, R_f = 0.33) was purified by chromatography (silica, 100 g, 55:45 ether:hexanes) to give a yellow liquid that solidified on standing. Kugelrohr distillation (5 × 10^{-2} atm) gave a white solid between 140 and 165 °C (4.46 g, 18.0 mmol, 78%). The isomers could be separated by repeated centrifugal chromatography (1:3 ether: hexanes), *trans* mp = 44−45 °C. ^{1}H NMR ($CDCl_3$): *Trans* δ = 7.30 (m, 3H), 5.78 (d, J = 16.7 Hz, 1H), 4.12 (q, J = 7.1, 2H), 3.64 (s, 2H), 1.17 (t, J = 7.1 Hz, 3H). *Cis* δ = 7.67 (d, J = 8.4 Hz, 2H), 7.30 (m, 3H), 6.99 (d, J = 12.1 Hz, 1H), 5.35 (d, J = 12.0 Hz, 1H), 4.12, (q, J = 7.1, 2H), 3.65 (s, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): *Trans* δ = 168.8, 149.2, 139.5, 131.0, 127.9, 127.5, 117.9, 95.6, 61.5, 34.9, 13.8. *Cis.* δ = 168.8, 147.4, 139.3, 131.0, 129.2, 127.6, 117.1, 94.3, 61.5, 34.9, 13.8. CI MS *m*/*z* (%): 288 (6), 276 (17), 248 (100), 174 (16). Anal. Calcd for $C_{13}H_{13}O_2NS$ (%): C 63.14; H 5.30; N 5.67. Found C, 63.77; H, 5.27; N, 6.05.

Ethyl [(3-(2-cyanoethenyl)phenyl)thio]acetate (19b) was prepared by procedure III, from **6b** (3.16, 11.5 mmol) and acrylonitrile (0.61 g, 11.5 mmol, 1equiv). The crude product was fractionated on a column (silica, 60 g, 2:1 ether:hexanes), followed by centrifugal chromatography (1:3 ether:hexanes), yielding 1.71 g (6.92 mmol, 60%). Separation of isomers was achieved by tedious centrifugal chromatography. ^{1}H NMR ($CDCl_3$): *Trans* δ = 7.46 (s, 1H), 7.42 (d, J = 7.35 Hz, 1H), 7.29 (m, 2H), 5.86 (d, 16.9 Hz), 4.14 (q, J = 6.7 Hz, 2H), 3.62 (s, 2H), 1.19 (t, J = 6.6 Hz, 3H). *Cis* δ = 7.71 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.42 (d, 1H), 7.29 (m, 1H), 7.06 (d, J = 11.8, 1H), 5.46 (d, J = 12.5 Hz, 1H), 4.14 (q, J = 6.7 Hz, 2H), 3.65 (s, 2H), 1.19 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): *Trans* δ = 169.2, 149.5, 136.6, 134.22, 131.7, 129.5, 127.8, 125.6, 117.7, 97.2, 61.6, 36.0, 13.9. *Cis* δ = 169.2, 147.8, 136.3, 134.18, 131.5, 129.6, 129.4, 126.8, 116.9, 96.0, 61.5, 36.1, 13.9. CI MS *m*/*z* (%): 288 (8), 276 (26), 248 (100). HRMS for $C_{13}H_{14}O_2NS$, *m*/*e*: 248.0742, found 248.0763.

Ethyl [(4-(2-Cyanoethyl)phenyl)thio]acetate (20a). The alkene **19a** (7.43 g, 30.1 mmol) and $Rh(PPh_3)_3Cl$ (0.97 g, 1.05 mmol, 0.035 equiv), in 150 mL of degassed 1:1 benzene/ethanol, was stirred under a pressure of 50 psi of hydrogen at room temperature for 9 days. The solution was concentrated, and the residue was triturated with ether, filtered and concentrated again. The crude product was distilled (Kugelrohr, 5×10^{-2} atm) at 160−180 °C, to yield product as a yellowish liquid, acceptably pure for the following step. For higher purity, **18a** was passed through a silica column (1:9, ethyl acetate/toluene), giving a clear liquid (4.85 g, 19.5 mmol, 65%). ^{1}H NMR ($CDCl_3$): δ = 7.32 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H) 4.11 (qua., J = 7.0 Hz, 2H), 3.57 (s, 2H), 2.86 (t, J = 7.3 Hz, 2H), 2.54 (t, J = 7.3 Hz, 2H), 1.17 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 169.4, 136.7, 133.7, 130.2, 128.8, 118.8, 61.3, 36.4, 30.8, 18.9, 13.8. CI MS *m/z* (%): 290 (5), 278 (19), 250 (100), 176 (25). HRMS for $C_{13}H_{15}O_2NS$, *m/e*: 249.0824, found 249.0823.

Ethyl [(3-(2-cyanoethyl)phenyl)thio]acetate (20b) was prepared from **19b** (1.71 g, 6.93 mmol) following the procedure for **20a**. The crude product was purified on a silica column (1:1, ether:hexanes) to give a clear liquid (1.10 g, 4.42 mmol, 64%). ^{1}H NMR ($CDCl_3$): δ = 7.25 (m, 3H), 7.06 (d, J = 7.4 Hz, 1H), 4.14 (q, J = 6.6 Hz, 2H), 3.62 (s, 2H), 2.90 (t, J = 7.4 Hz, 2H), 2.58 (t, J = 7.4 Hz, 2H), 1.20 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 169.5, 138.9, 135.8, 129.4, 129.3, 128.2, 126.7, 118.8, 61.6, 36.3, 31.2, 19.0, 14.0. CI MS *m/z* (%): 278 (28), 250 (85), 204 (37), 176 (100). Anal. Calcd for $C_{13}H_{15}O_2NS$ (%): C, 62.60; H, 6.10; N, 5.60. Found C, 62.58; H, 6.05; N, 5.55.

[(4-(2-Cyanoethyl)phenyl)thio]acetic Acid (21a). Ester **20a** (1.50 g, 6.01 mmol) was dissolved in 50 mL of MeOH containing NaOH (0.29 g, 7.22 mmol, 1.2 equiv) and was stirred at reflux for 3 h. The acid salt was concentrated and dried under vacuum. The resultant solid was dissolved in H_2O and acidified to pH < 1. The white precipitate was filtered and dried. The product was a white solid (1.20 g, 5.43 mmol, 90%), mp = 106−107 °C. ^{1}H NMR ($CDCl_3$): δ = 7.38 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 3.64 (s, 2H), 2.92 (t, J = 7.3 Hz, 2H), 2.59 (t, J = 7.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 175.2, 137.2, 133.4, 130.6, 129.2, 118.9, 36.5, 31.1, 19.2. CI MS *m/z* (%): 262 (10), 250 (26.), 222 (17), 204 (78), 176 (100). Anal. Calcd for $C_8H_{11}O_2NS$: (%): C 59.71; H 5.02; N 6.33. Found C, 59.92; H, 5.00; N, 6.48.

[(3-(2-Cyanoethyl)phenyl)thio]acetic Acid. Ester **20b** (1.10 g, 4.39 mmol) was dissolved in 50 mL of MeOH containing NaOH (0.21 g, 5.38 mmol, 1.2 equiv) and was stirred at reflux for 3 h. The acid salt was concentrated and dried under vacuum. The resultant solid was dissolved in H_2O and acidified to pH < 1. After acidifying the aqueous salt solution, the product was extracted with CH_2Cl_2, dried, and concentrated to give a white solid (0.820 g, 3.71 mmol, 84%), mp = 77−78 °C. ^{1}H NMR ($CDCl_3$): δ = 10.5 (br s, 1H), 7.27 (m, 3H), 7.09 (d, J = 6.6 Hz, 1H), 3.66 (s, 2H), 2.90 (t, J = 7.4 Hz, 2H), 2.59 (t, J = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 175.3, 139.0, 135.2, 129.6, 129.5, 128.5, 127.1, 118.8, 36.2, 31.2, 19.1. CI MS *m/z* (%): Calculated for $C_8H_{11}O_2NS$: (%): C, 59.71; H, 5.02; N, 6.33. Found C, 59.72; H, 5.05; N, 6.07.

2-(4-Butyloxyphenylmethylene)-5-(2-cyanoethyl)benzo[*b*]thiophen-3(2*H*)-one (22a) was prepared by method IV, from acid **21a** (0.293 g, 1.32 mmol) via the acid chloride and cyclization, followed by coupling of the resultant thioindoxyl with **4a** (0.235 g, 1.32 mmol, 1 equiv). A yellow solid precipitated from the cooled reaction mixture, which was filtered and dried under vacuum (0.216 g, 0.595 mmol, 45%), mp = 158 °C. Alternatively the reaction mixture was concentrated and chromatographed (silica, 3:1, $CHCl_3$/hexanes) to afford the product. ^{1}H NMR ($CDCl_3$): δ = 7.91 (s, 1H), 7.75 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.45 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.01 (t, J = 6.3 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.78 (qn J = 7.4 Hz, 2H), 1.48 (sx, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 188.2, 161.0, 145.0, 135.5, 135.2, 134.3, 133.1, 131.3, 127.6, 126.6, 126.2, 124.2, 118.6, 115.1, 67.9, 31.1, 30.9, 19.2, 19.1, 13.8. +LSIMS (*m*NBA) *m/z* (%): 364.1 (100). HRMS (+LSIMS) Calculated for $C_{22}H_{22}O_2NS^+$: 364.1366, found 364.1362.

2-(4-Hexyloxyphenylmethylene)-5-(2-cyanoethyl)benzo[*b*]thiophen-3(2*H*)-one (22b) was prepared by method IV, from acid **21a** (0.600 g, 2.71 mmol) via the acid chloride and cyclization, followed by coupling of the resultant thioindoxyl with **4b** (0.57 g, 2.8 mmol, 1 equiv). A yellow solid precipitated from the cooled reaction mixture, which was filtered and dried under vacuum to give a yellow solid (0.360 g, 0.92 mmol, 34%), mp = 129−131 °C. As isolated the product is the *Z*-isomer: ^{1}H NMR ($CDCl_3$): δ = 7.93 (s, 1H), 7.76 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.48, 7.45 (AB, J = 8.5 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 3.00 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.79 (qn, J = 6.6 Hz, 2H), 1.44 (qn, J = 6.6 Hz, 2H), 1.34 (m, 4H), 0.90 (t, J = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 188.2, 161.1, 145.0, 135.2, 134.3, 133.1, 131.4, 127.7, 126.6, 126.3, 124.3, 118.8, 115.1, 68.3, 31.5, 31.0, 29.0, 25.6, 22.6, 19.2, 14.0. +LSIMS (*m*NBA) *m/z* (%): 392.0 100). HRMS (+LSIMS) Calculated for $C_{24}H_{26}O_2NS^+$: 392.1684, found 392.1670. Anal. Calcd for $C_{24}H_{25}O_2NS$: (%): C, 73.63; H, 6.44; N, 3.58. Found C, 73.20; H, 6.45; N, 3.61.

The *E*-isomer was synthesized by irradiating a chloroform solution of *Z*-**22b**, in a Rayonet reactor, at 350 nm for 30 min. The solution was concentrated, and the isomers were separated by centrifugal chromatography (1:3 hexanes:chloroform), under red light. ^{1}H NMR ($CDCl_3$): δ = 8.19 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 1.5 Hz, 1H), 7.44, 7.34 (AB, J = 8.1 Hz, 2H), 7.15 (s, 1H), 6.91 (d, J = 8.8 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 2.98 (t, J = 6.6 Hz, 2H), 2.62 (t, J = 6.6 Hz, 2H), 1.78 (qn, J = 6.6 Hz, 2H). 1.45 (qn, J = 6.6 Hz, 2H), 1.34 (m, 4H), 0.90 (t, J = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 185.4, 161.5, 144.4, 139.4, 134.8, 134.7, 133.9, 133.9, 133.1, 130.2, 127.0, 126.2, 123.8, 118.7, 114.1, 68.1, 31.5, 31.0, 29.0, 25.6, 22.6, 19.2, 14.0.

2-(4-Octyloxyphenylmethylene)-5-(2-cyanoethyl)benzo[*b*]thiophen-3(2*H*)-one (22c) was prepared by method IV, from acid **21a** (0.29 g, 1.30 mmol) via the acid chloride and cyclization, followed by coupling of the resultant thioindoxyl with **4d** (0.280 g, 1.20 mmol, 0.92 equiv). A yellow solid precipitated from the cooled reaction mixture, which was filtered and dried under vacuum to give a yellow solid (0.212 g, 0.506 mmol, 42%) with a complex melting behavior. ^{1}H NMR ($CDCl_3$): δ = 7.92 (s, 1H), 7.76 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.51, 7.42 (AB, J = 8.5 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 3.00 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.79 (qn, J = 6.6 Hz, 2H), 1.45 (m, 2H), 1.28 (m, 8H), 0.87 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 188.2, 161.1, 145.0, 135.6, 135.2, 134.3, 133.1, 131.4, 127.7, 126.6, 126.3, 118.7, 115.2, 68.3, 31.8, 31.8, 31.0, 29.3, 29.2, 29.1, 26.0, 22.6, 19.3, 14.1. +LSIMS (*m*NBA) *m/z* (%): 420 (100). Anal. Calcd for $C_{26}H_{29}O_2NS$: (%): C, 74.43; H, 6.97; N, 3.34. Found C, 73.88; H, 7.11; N, 2.96.

2-(3-Hexyloxyphenylmethylene)-5-(2-cyanoethyl)benzo[*b*]thiophen-3(2*H*)-one (22d) was prepared by method IV, from acid **21a** (0.450 g, 2.04 mmol) via the acid chloride and cyclization, followed by coupling of the resultant thioindoxyl with **4c** (0.42 g, 2.04 mmol, 1 equiv). A yellow solid precipitated from the cooled reaction mixture, which was filtered and dried under vacuum to give a yellow solid (0.150 g, 0.384 mmol, 19%), mp = 158 °C. ^{1}H NMR ($CDCl_3$): δ =7.91 (s, 1H), 7.77 (s, 1H), 7.47(AB,s, 2H), 7.36 (t, J = 8.1 Hz, 1H), 7.26 (d, J = 9.6 Hz, 1H), 7.20 (t, J = 2.2 Hz, 1H), 6.95 (dd, J = 8.1, 1.5 Hz, 1H), 4.00 (t, J = 6.6 Hz, 2H), 3.00 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 7.4 Hz, 2H), 1.81 (qn, J = 6.6 Hz, 2H), 1.48 (qn, J = 6.6 Hz, 2H), 1.34 (m, 4H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 188.3, 159.5, 145.2, 135.7, 135.6, 135.3, 134.1, 131.0, 130.5, 130.0, 126.4, 124.3, 123.6, 118.6, 117.1, 116.1, 68.2, 31.6, 30.9, 29.1, 25.7, 22.6, 19.2, 14.0. Anal. Calcd for $C_{24}H_{25}O_2NS$: (%): C, 73.63; H, 6.44; N, 3.56. Found C, 73.45; H, 6.50; N, 3.60.

2-(4-Hexyloxyphenylmethylene)-6-(2-cyanoethyl)benzo[*b*]thiophen-3(2*H*)-one (22e) and 2-(4-hexyloxyphenylmethylene)-4-(2-cyanoethyl)benzo[*b*]thiophen-3(2*H*)-one (22f) were prepared as a mixture by method IV, from acid **21b** (0.820 g, 3.71 mmol) via the acid chloride and cyclization, followed by coupling of the resultant thioindoxyl with **4b** (0.280

g, 1.20 mmol, 0.92 equiv). A yellow solid precipitated from the cooled reaction mixture, which was filtered and dried under vacuum. The regioisomers were separated by column chromatography (silica, 3:1 $CHCl_3$/hexanes). Compound **22e** elutes first followed closely by **22f** in a combined yield of 34%.

22e: (0.240 g, 0.614 mmol), mp = 98−99 °C. ^{1}H NMR ($CDCl_3$): δ = 7.86 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.32 (s, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 3.96 (t, J = 6.6 Hz, 2H), 2.97 (t, J = 7.4 Hz, 2H), 2.65 (t, J = 6.6 Hz, 2H), 1.76 (qn, J = 6.6 Hz, 2H), 1.43 (qn, J = 6.6 Hz, 2H), 1.32 (m, 4H), 0.88 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 187.7, 160.9, 146.7, 145.5, 133.9, 132.9, 129.9, 127.4, 127.1, 126.4, 125.7, 123.4, 118.5, 115.0, 68.1, 31.6, 31.4, 29.0, 25.6, 22.5, 18.7, 13.9. +LSIMS (*m*NBA) *m*/*z* (%): 392 (100). Anal. Calcd for $C_{24}H_{25}O_2NS$: (%): C, 73.63; H, 6.44; N, 3.58. Found C, 73.44; H, 6.56; N, 3.61.

22f: (0.252 g, 0.644 mmol). ^{1}H NMR ($CDCl_3$): δ = 7.81 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.42 (m, 2H), 7.09 (d, J = 7.4 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.98 (t, J = 6.6 Hz, 2H), 3.40 (t, J = 7.4 Hz, 2H), 2.75 (t, J = 6.6 Hz, 2H), 1.78 (qn, J = 6.6 Hz, 2H), 1.45 (qn, J = 6.6 Hz, 2H), 1.33 (m, 4H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 189.0, 160.9, 147.6, 141.0, 134.4, 133.9, 132.9,0.127.7, 127.4, 127.2, 126.5, 123.3, 119.2, 115.0, 68.2, 31.5, 29.0, 28.3, 25.6, 22.5, 18.0, 14.0. +LSIMS (*m*NBA) *m*/*z* (%): 392 (100). Anal. Calcd for $C_{24}H_{25}O_2NS$: (%): C, 73.63; H, 6.44; N, 3.58. Found C, 73.29; H, 6.48; N, 3.54.

2-(4-Hexyloxyphenylmethylene)-5-(2-carboxyethyl)benzo[*b*]thiophen-3(2*H*)-one (2a) was prepared by procedure V, from **22b** (129 mg, 0.323 mmol) and tetrafluorophthalic acid (81 mg, 0.323 mmol, 1 equiv). The product was a yellow solid (119 mg, 0.290 mmol, 90%), mp = 109 °C. ^{1}H NMR ($CDCl_3$): δ = 7.91 (s, 1H), 7.77 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.41 (AB, s, 2H), 6.96 (d, J = 8.8 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 2.99 (t, J = 7.4 Hz, 2H), 2.70 (t, J = 7.4 Hz, 2H), 1.79 (qn, J = 6.6 Hz, 2H), 1.45 (m, 2H), 1.33 (m, 4H), 0.89 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 188.5, 176.9, 161.0, 144.1, 137.8, 135.5, 134.0, 133.1, 131.1, 127.9, 126.7, 126.3, 123.9, 115.1, 68.3, 35.0, 31.5, 29.9, 29.1, 25.6, 22.6, 14.0.+LSIMS (*m*NBA) *m*/*z* (%): 411.1 (65), 289 (100). −LSIMS: 409.1 (100). HRMS (+LSIMS) Calculated for $C_{24}H_{27}O_4S^+$: 411.1630, found 411.1639.

2-(4-Octyloxyphenylmethylene)-5-(2-carboxyethyl)benzo[*b*]thiophen-3(2*H*)-one (2b) was prepared by procedure V, from **22c** (55 mg, 0.13 mmol) and tetrafluorophthalic acid (32 mg, 0.13 mmol, 1 equiv) heated at 180 °C for 5 days. The product was a yellow solid (40 mg, 9.3 × 10^{-2} mmol, 71%), with a complex melting behavior. ^{1}H NMR ($CDCl_3$): δ = 7.91 (s, 1H), 7.76 (s, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.40 (AB, s, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.99 (t, J = 6.6 Hz, 2H), 2.97 (t, J = 7.4 Hz, 2H), 2.70 (t, J = 7.4 Hz, 2H), 1.78 (qn, J = 6.6 Hz, 2H), 1.44 (m, 2H), 1.28 (m, 8H), 0.87 (t, J = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 188.5, 177.9, 161.0, 144.1, 137.9, 135.5, 134.0, 133.1, 127.9, 126.7, 126.3, 123.9, 115.1, 68.3, 35.2, 31.8, 29.9, 29.3, 29.2, 29.1, 26.0, 22.6, 14.1. +LSIMS (*m*NBA) *m*/*z* (%): 439 (100). Anal. Calcd for $C_{26}H_{30}O_4S$: (%): C, 71.20; H, 6.89; O, 14.59, S, 7.31. Found C, 70.97; H, 7.09; O, 12.73; S, 8.08.

2-(3-Hexyloxyphenylmethylene)-5-(2-carboxyethyl)benzo[*b*]thiophen-3(2*H*)-one (2c) was prepared by procedure V, from **22d** (105 mg, 0.263 mmol) and tetrafluorophthalic acid (66 mg, 0.263 mmol, 1 equiv) heated at 160 °C for 3 days. The product was a yellow solid (95 mg, 0.232 mmol, 88%), mp = 116−117 °C. ^{1}H NMR ($CDCl_3$): δ = 7.90 (s, 1H), 7.77 (s, 1H), 7.47, 7.38 (AB, J = 8.5 Hz, 2H), 7.33 (t, J = 8.1 Hz, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.20 (s, 1H), 6.95 (d, J = 8.1 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 3.00 (t, J = 7.4 Hz, 2H), 2.71 (t, J = 7.4 Hz, 2H), 1.80 (qn, J = 6.6 Hz, 2H), 1.47 (m, 2H), 1.35 (m, 4H), 0.91 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 188.6, 178.0, 159.5, 144.2, 138.0, 135.9, 135.4, 133.9, 130.7, 129.9, 126.5, 123.9, 123.5, 117.0, 116.1, 68.2, 35.1, 31.6, 29.8, 29.1, 25.7, 22.6, 14.0. +LSIMS (*m*NBA) *m*/*z* (%): 411 (100). Anal. Calcd for $C_{24}H_{26}O_4S$: (%): C, 70.22; H, 6.38. Found C, 70.10; H, 6.46.

2-(4-Hexyloxyphenylmethylene)-6-(2-carboxyethyl)benzo[*b*]thiophen-3(2*H*)-one (2d) was prepared by procedure V, from **22e** (184 mg, 0.469 mmol) and tetrafluorophthalic acid (112 mg, 0.469 mmol, 1 equiv) heated at 140 °C for 4 days. The product was a yellow solid (166 mg, 0.405 mmol, 86%), mp = 134−135 °C. ^{1}H NMR($CDCl_3$): δ = 7.90 (s, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.33 (s, 1H), 7.12 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 4.00 (t, J = 6.6 Hz, 2H), 3.03 (t, J = 7.4 Hz, 2H), 2.73 (t, J = 7.4 Hz, 2H), 1.79 (qn, J = 6.6 Hz, 2H), 1.45 (qn, J = 6.6 Hz, 2H), 1.33 (m, 4H), 0.89 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 188.2, 177.4, 160.9, 148.3, 146.6, 133.9, 133.0, 129.4, 127.7, 127.1, 126.7, 126.0, 123.5, 115.1, 68.2, 34.7, 31.5, 30.8, 29.1, 25.6, 22.6, 14.0. Anal. Calcd for $C_{24}H_{26}O_4S$: (%): C, 70.22; H, 6.38. Found C, 69.76; H, 6.66.

2-(4-Hexyloxyphenylmethylene)-4-(2-carboxyethyl)benzo[*b*]thiophen-3(2*H*)-one (2e) was prepared by procedure V, from **22f** (193 mg, 0.492 mmol) and tetrafluorophthalic acid (118 mg, 0.492 mmol, 1 equiv) heated at 168 °C for 4 days. The product was a yellow solid (168 mg, 0.410 mmol, 83%), mp = 142−144 °C. ^{1}H NMR ($CDCl_3$): δ =7.87 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.41 (m, 2H), 7.09 (d, J = 7.4 Hz, 1H), 6.97 (d, J = 8.8 H, 2 Hz, 2H), 4.01 (t, J = 6.6 Hz, 2H), 3.44 (t, J = 7.4 Hz, 2H), 2.73 (t, J = 7.4 Hz, 2H), 1.77 (qn, J = 6.6 Hz, 2H), 1.64 (qn, J = 6.6 Hz), 1.34 (m, 4H), 0.90 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 189.2, 178.1, 160.9, 147.4, 143.9, 134.3, 133.6, 133.0, 127.6, 127.5, 127.4, 126.8, 122.5, 115.1, 68.3, 34.5, 31.5, 29.1, 27.6, 25.7, 22.6, 14.0. +LSIMS (*m*NBA) *m*/*z* (%): 411 (100), 393 (69).

1,2-Bis[2-(4-hexyloxyphenylmethylene)benzo[*b*]thiophene-3-(2*H*)-one-5-ylethanoyl]phosphatidylcholine (1a) was prepared by procedure VI, from **2a** (119 mg, 0.290 mmol) as a yellow solid (61 mg, 0.059 mmol, 85%), with a complex melting behavior. $[\alpha]_D$ = +16.6° cm^2 g^{-1} (*c* 0.046, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.77 (s, 1H), 7.76 (s, 1H), 7.64 (s, 1H), 7.63 (s, 1H), 7.56 (d, J = 3.6 Hz, 2H), 7.54 (d, J = 2.8 Hz, 2H), 7.33 (m, AB, 2H), 7.31 (br s, AB, 2H), 6.91 (d, J = 3.6 Hz, 2H), 6.89 (d, J = 2.8 Hz, 2H), 5.19 (m, 1H), 4.36 (m, 3H), 4.11 (dd, J = 12.1, 7.0 Hz, 1H), 3.96 (m, 6H), 3.86 (m, 2H), 3.38 (s, 9H), 2.86 (m, 4H), 2.61 (t, J = 7.8 Hz, 2H), 2.54 (t, J = 7.4 Hz, 2H), 1.75 (m, 4H), 1.41 (m, 4H), 1.32 (m, 8H), 0.89 (m, 6H). ^{13}C NMR ($CDCl_3$): δ =188.2, 172.2, 171.9, 160.8, 143.7, 138.01, 137.97, 135.5, 135.4, 133.55, 133.51, 132.9, 130.9, 130.7, 127.8, 127.7, 126.6, 126.5, 126.0, 123.0, 114.9, 70.7 (d, J = 6.1 Hz), 68.1, 66.2 (d, J = 4.8 Hz), 63.5, 63.1, 59.5, 54.3, 35.1, 34.5, 31.5, 29.8, 29.1, 25.6, 22.6, 14.0. ^{31}P NMR ($CDCl_3$): δ = −0.8. +LSIMS (*m*NBA) *m*/*z* (%): 1042.4 (100). −LSIMS: 1041.3 (100). HRMS (+LSIMS) Calculated for $C_{56}H_{69}NO_{12}S_2P^+$: 1042.3999, found 1042.3993.

1,2-Bis[2-(3-hexyloxyphenylmethylene)benzo[*b*]thiophene-3-(2*H*)-one-5-ylethanoyl]phosphatidylcholine (1b) was prepared by procedure VI, from **2c** (70 mg, 0.171 mmol), as a yellow solid (41 mg, 0.039 mmol, 91%), with complex melting behavior. $[\alpha]_D$ = +7.0°cm^2 g^{-1} (*c* 0.028, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.76 (s, 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.63 (s, 1H), 7.31 (m, 6H), 7.18 (m, 2H), 7.11 (s, 2H), 6.89 (m, 2H), 5.19 (m, 1H), 4.38 (d, J = 12.0 Hz, 1H), 4.31 (m, 2H), 4.11 (dd, J = 12.0, 7.1 Hz, 1H), 3.95 (m, 6H), 3.81 (m, 2H), 2.91 (s, 9H), 2.87 (m, 4H), 2.61 (t, J = 7.3 Hz, 2H), 2.54 (t, J = 7.6 Hz, 2H), 1.76 (m, 4H), 1.44 (m, 4H), 1.33 (m, 8H), 0.87 (m, 6H). ^{13}C NMR ($CDCl_3$): δ = 188.0, 171.8, 171.5, 159.1, 143.6, 137.89, 137.86, 135.6, 135.5, 135.00, 134.96, 133.24, 133.21, 130.29, 130.25, 130.18, 129.5, 125.9, 123.5, 123.1, 116.6, 115.7, 70.6 (d, J = 6.1 Hz), 67.7, 66.1 (d, J = 6.1 Hz), 62.9, 59.0, 54.1, 34.8, 34.6, 31.2, 29.5, 28.8, 25.4, 25.3, 22.2, 13.7. ^{31}P NMR ($CDCl_3$): δ = 1.3. +LSIMS (*m*NBA) *m*/*z* (%): 2084.6 (5), 1042.3 (100). HRMS (+LSIMS) Calculated for $C_{56}H_{69}NO_{12}S_2P^+$: 1042.3999, found 1042.3993.

1,2-Bis[2-(4-hexyloxyphenylmethylene)benzo[*b*]thiophene-3-(2*H*)-one-6-ylethanoyl]phosphatidylcholine (1c) was prepared by procedure VI, from **2d** (114 mg, 0.278 mmol), as a yellow solid (64 mg, 0.061 mmol, 87%), with complex melting behavior. $[\alpha]_D$ = +7.3° cm^2 g^{-1} (*c* 0.023, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.722 (s, 1H), 7.715 (s, 1H), 7.69 (m, 2H), 7.48 (m, 4H), 7.21 (s, 1H), 7.17 (s, 1H), 7.02 (d, J = 8.1 Hz,

1H), 6.96 (d, J = 8.1 Hz, 1H), 6.85 (m, 4H), 5.16 (m, 1H), 4.36 (d, J = 9.8 Hz, 2H), 4.24 (m, 2H), 4.08 (m, 3H), 3.88 (q, J = 6.6 Hz, 4H), 3.75 (m, 2H), 3.31 (s, 9H), 2.85 (m, 4H), 2.60 (m, 4H), 2.53 (t, J = 7.6 Hz, 4H), 1.71 (m, 4H), 1.38 (m, 4H), 1.29 (m, 8H), 0.86 (t, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ = 187.71, 187.61, 172.0, 171.7, 160.8, 148.4, 148.3, 146.3, 146.2, 133.55, 133.47, 132.8, 129.0, 127.5, 127.4, 126.7, 126.46, 126.40, 125.8, 125.7, 123.36, 123.26, 114.9, 71.9 (d, J = 7.4 Hz), 68.1, 66.1 (d, J = 6.1 Hz), 63.2, 59.2 (d, J = 4.9 Hz), 54.2, 34.7, 34.5, 31.5, 30.82, 30.76, 29.0, 25.5, 22.5, 13.9. ^{31}P NMR ($CDCl_3$): δ = 1.2. +LSIMS (*m*NBA) *m*/*z* (%): 2084.6 (10), 1042.3 (100). HRMS (+LSIMS) Calculated for $C_{56}H_{69}NO_{12}S_2P^+$: 1042.3999, found 1042.4005.

1,2-Bis[2-(4-hexyloxyphenylmethylene)benzo[*b*]thiophene-3-(2*H*)-one-4-ylethanoyl]phosphatidylcholine (1d) was prepared by procedure VI, from **2e** (124 mg, 0.302 mmol), as a yellow solid (73 mg, 0.070 mmol, 92%), with a complex melting behavior. $[\alpha]_D$ = +25.8° cm^2 g^{-1} (*c* 0.0433, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.65 (s, 1H), 7.61 (s, 1H), 7.48 (m, 4H), 7.24 (m, 4H), 6.97 (m, 2H), 6.85 (m, 4H), 5.22 (m, 1H), 4.33 (m, 3H), 4.12 (dd, J = 12.0, 7.1 Hz, 1H), 3.91 (m, 6H), 3.83 (m, 2H), 3.37 (s, 9H), 3.30 (m, 4H), 2.61 (m, 4H), 1.73 (m, 4H), 1.41 (m, 4H), 1.31 (m, 8H), 0.87 (m, 6H). ^{13}C NMR ($CDCl_3$): δ = 188.7, 172.6, 172.3, 160.6, 147.0, 143.9, 143.8, 134.2, 133.0, 132.8, 127.4, 127.32, 127.28, 127.22, 127.17, 126.73, 126.67, 122.2, 114.9, 70.8 (d, J = 7.3 Hz), 68.1, 66.3 (d, J = 6.1 Hz), 63.3, 63.0, 59.3, 54.4, 34.4, 34.3, 31.5, 29.1, 27.4, 25.6, 22.6, 14.0. ^{31}P NMR ($CDCl_3$): δ = −0.8. +LSIMS (*m*NBA) *m*/*z* (%): 2084.6 (15), 1042.3 (100). HRMS (+LSIMS) Calculated for $C_{56}H_{69}NO_{12}S_2P^+$: 1042.3999, found 1042.3999.

2-(Carboxyethyl)-3-(cyanoethyl)-2*H*,3*H*-benzo[*b*]thiophene (23) was prepared by procedure III, from **5c** (9.56 g, 34.8 mmol) and acrylonitrile (2.76 g, 52.2 mmol, 1.5 equiv). The crude product was fractionated by chromatography (silica, 100 g, 2:1 ether:hexanes), followed by centrifugal chromatography (1:3 ether:hexanes), yielding 3.27 g of product (13.2 mmol, 38%). ^{1}H NMR($CDCl_3$): δ = 7.18 (m, 4H), 4.19 (m, 4H), 7.76 (t, J = 6.6 Hz, 2H), 1.27(d, J = 8.8 Hz, 3H). ^{13}C NMR MHz ($CDCl_3$): δ = 170.4, 138.28, 138.24, 129.2, 125.5, 124.6, 122.3, 117.4, 62.2, 53.1, 46.2, 21.7, 14.0. CI MS *m*/*z* (%): 288 (9), 276 (23), 248 (100). Anal. Calcd for $C_{13}H_{13}O_2NS$ (%): C, 63.14; H, 5.30; N, 5.67. Found C, 62.85; H, 5.21; N, 5.81.

2-Carboxy- 3-cyanethyl-2*H*,3*H*-benzo[*b*]thiophene (24) was prepared from **22** (0.120 g, 0.486 mmol) and NaOH (0.1 g, excess) in 15 mL of MeOH. The mixture was refluxed for 3 h, cooled, acdified, extracted with CH_2Cl_2 (25 mL × 2), dried, and concentrated to give a white solid (0.080 g, 0.365 mmol, 75%), mp = 142−144 °C. ^{1}H NMR 300 MHz ($CDCl_3$): δ = 9.14 (br s, 1H), 7.20 (m, 4H), 4.15 (d, J = 2.9 Hz, 1H), 4.09 (dt, J = 6.6, 3.7 Hz, 1H), 2.72 (t, J = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 175.9, 138.1, 137.7, 129.4, 125.7, 124.7, 122.4, 117.2, 52.8, 46.1, 21.8. +LSIMS (*m*NBA) *m*/*z* (%): 220 (36), 219 (97), 147 (100). Anal. Calcd for $C_8H_{11}O_2NS$: (%): C, 59.71; H, 5.02; N, 6.33. Found C 59.92; H 5.00; N 6.48.

Photochemical Experiments. Photoisomerization reactions were conducted using a super high pressure mercury lamp (Ushio Inc.) installed in an illuminator (Oriel Corp.) equipped with a shutter control for timing, and a variable wavelength monchromator (PTI). Irradiations were conducted in quartz cells (1 cm path length) held approximately 3 cm from the exit slit of the monochromator. Typically, irradiation times of 10 min of less were sufficient to establish the photostationary states. Analysis of the photoproducts by HPLC was done on a C18 reverse-phase column with 96:2:2 acetonitrile:methanol:water as isocratic eluent. The mixtures were quantified at the wavelength of the isosbestic points determined for the compounds (typically about 465 nm).

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Supporting Information Available: Tables of ^{1}H and ^{13}C NMR chemical shifts of the hemithioindigo core of compounds prepared, and ^{1}H and ^{13}C NMR spectra for compounds **1a**−**d**, **2a**,**e**, **8**, **17**, **19a**, **20a**, and **22a**,**b**,**f**. This material is available free of charge via Internet at http://pubs.acs.org.

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