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Novel methods for the synthesis of 5-substituted-3-carboxy-2,5- and 4,5-dihydrothiophenes and 5-substituted 2- and 3-sulfolenes

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Abstract—Various approaches to the syntheses of 5-substituted-3-carbomethoxy-2,5-dihydrothiophenes and their product sulfolenes, required as synthetic precursors for tangutorine, are described. An efficient route to 3,5-disubstituted-4,5-dihydrothiophenes and hence 3,5-disubstituted-2-sulfolenes by radical chemistry is also described.

1. Introduction

Dihydrothiophenes are highly useful as synthetic intermediates for a wide range of purposes, containing both a sulfur atom and a reactive double bond. 2,3-Dihydrothiophenes have been used as intermediates in the synthesis of thionucleosides and penicillin analogues while 2,5-dihydrothiophenes have shown considerable potential as antivirals.[1]

Sulfolenes, the oxidation products of dihydrothiophenes, have found application in synthesis as masked diene precursors for Diels Alder reactions. Both 2- and 3-sulfolenes can be converted to 1,3-dienes with predictable double bond geometry.[2]

Our group has an interest in the total synthesis of the bioactive alkaloid tangutorine.[3] Our approach via intramolecular Diels Alder reaction required either a 2 or 3-sulfolene (**1** or **2**, respectively) as a masked diene precursor (Scheme 1).[4]

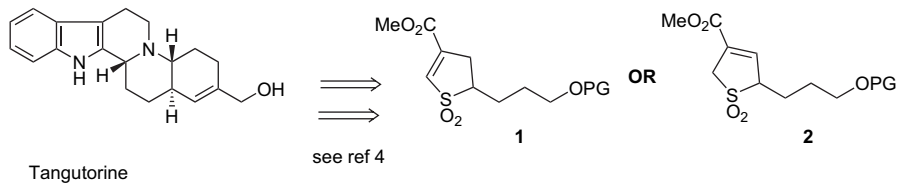
Here we describe novel chemistry leading to syntheses of compounds of the form **1** and **2**. The approach to 2-sulfolenes **1** via 4,5-dihydrothiophenes utilises radical chemistry, while the successful synthesis of 3-sulfolenes **2** and their corresponding dihydrothiophenes makes use of a conjugate addition/Claisen reaction protocol.

2. Results and discussion

2.1. Synthesis of 5-substituted-3-carboxy-2,5-dihydrothiophenes and their 1,1-dioxides

Approaches to the synthesis of 3-carboxy-2,5-dihydrothiophenes generally involve formation of the double bond by phosphorus chemistry.[5] 5-Substituted 3-carboxy examples in the literature are rare since direct alkylation of the readily available 3-carboxy-2,5-dihydrothiophenes and 1,1-dioxy derivatives to give 5-substitution is impossible.[6] The 5-carboxymethyl derivative is known via intramolecular conjugate addition of a thiol and the 5-ethyl compound has been made by McIntosh and Sieler.[7] The 5-trifluoromethyl-3-cyano-2,5-dihydrothiophene has been made by addition of cyanide to a ketone followed by elimination.[8]

Our first target was compound **3**, a 5-substituted-3-carboxy-2,5-dihydrothiophene. Initially an approach based on an intramolecular Dieckmann cyclisation was investigated



Scheme 1.

Keywords: Sulfolene; Dihydrothiophene; Xanthate radical transfer.
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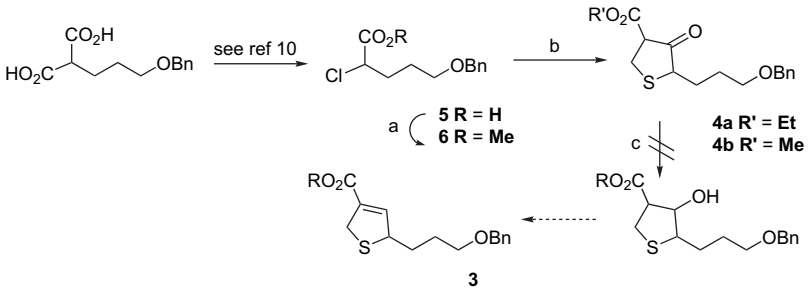
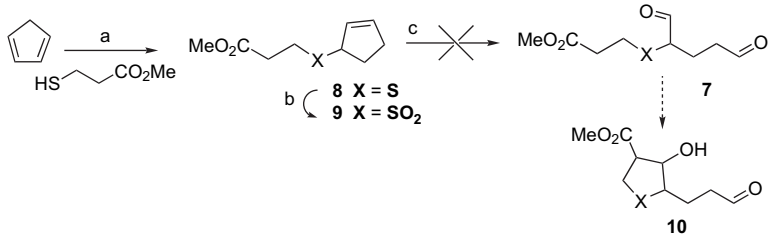


Scheme 2. Reagents and conditions: (a) MeOH, $SOCl_2$, 0 °C, then rt, 16 h, 80%; (b) (i) $MeO_2CCH_2CH_2SH$, NaH, Et_2O/DMF, 0 °C, then rt, 18 h, 64%; (ii) NaOMe, toluene, 0 °C, then reflux 3 h, 44%; (c) $NaBH_4$ or $LiBH_4$ or $NaCNBH_3$, various solvents and temperatures.

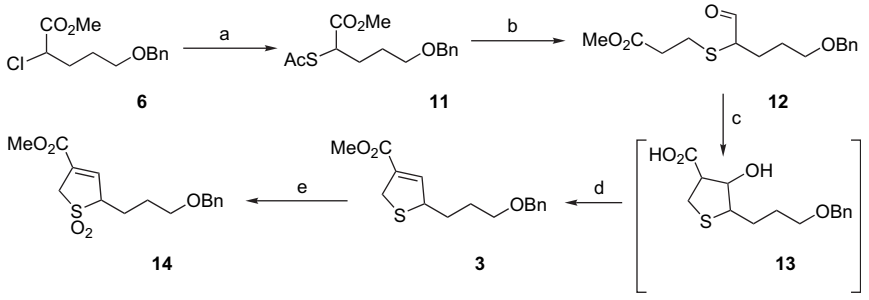
since Cheney's group had shown previously that this approach could be used to form the keto-ester **4a** by chlorination of a known malonic acid derivative to give **5** after decarboxylation, substitution with a thiol and intramolecular Dieckmann cyclisation.[9] This route was followed from the methyl ester **6** giving, in our hands, a moderate overall yield of β-keto ester **4b** (Scheme 2). The seemingly simple reduction to the corresponding hydroxy ketone could not be realised in acceptable yield under any of the conditions attempted. The enol form of **4b** predominated in a ratio of around 1.7:1 and it is likely that basic reducing agents such as borohydride would simply form an enolate but sodium cyanoborohydride at lower pH was equally unsuccessful. As a result, a variation on this theme was adopted, using an intramolecular Claisen reaction.

Our first route via an intramolecular Claisen reaction was based on the cyclisation of a dialdehyde **7** to give hydroxy ester **10** directly. Cyclopentadiene was reacted with methyl-3-mercaptopropionate in the presence of ethyl aluminium dichloride to give the sulfide **8** (Scheme 3).[10] Ozonolysis of **8**, or its S-oxidation product **9**, under various conditions resulted in complex mixtures of products from which neither **7**, cyclisation product nor any derivatives could be isolated.

It was clear that an aldehyde in the side chain could not be supported and would need to be masked for the Claisen route to succeed. This entailed the synthesis of **12** with a protected hydroxy function (Scheme 4). The methyl ester **6** was reacted with thioacetic acid to give **11**. This was fully reduced, used in a conjugate addition to methyl acrylate and then selectively oxidised to the aldehyde **12**. This cyclised to a mixture of hydroxy acids **13**, which were not isolated but used directly. The concomitant saponification of the ester was disappointing since it later had to be replaced but adjustment of the conditions failed to suppress this side-reaction. Mesylation, elimination and re-esterification provided the desired dihydrothiophene **3** in an overall yield of 34% from the aldehyde. This is the first time an intramolecular Claisen approach has been used to prepare 5-substituted-3-carboxy-2,5-dihydrothiophenes and though the overall route is long it is reasonably efficient. S-oxidation proceeded in acceptable yield with Oxone to give **14**. To the best of our



Scheme 3. Reagents and conditions: (a) $EtAlCl_2$, toluene, rt, 36 h, 68%; (b) Oxone, water, 0 °C, 1 h, 92%; (c) O_3, various solvents and work-up procedures or $NaIO_4$, various solvents and temperatures.



Scheme 4. Reagents and conditions: (a) NaH, AcSH, Et_2O/DMF, 0 °C–rt, 20 h, 82%; (b) (i) $LiAlH_4$, Et_2O, 0 °C, 1 h, 88%; (ii) methyl acrylate, NEt_3, rt, 18 h, 87%; (iii) oxalyl chloride, NEt_3, DMSO, CH_2Cl_2, −50 °C–rt, 1 h, 93%; (c) NaOMe, toluene, 0 °C, then reflux, 2 h; (d) (i) MsCl, NEt_3, CH_2Cl_2, 0 °C, 1 h; (ii) 2 M HCl; (iii) $SOCl_2$, MeOH, rt, 1 h, 34% over four steps; (e) Oxone, MeOH, 0 °C, 30 min, 55%.

knowledge this is the first 5-substituted-3-carboxy-3-sulfolene to be synthesised.[11]

2.2. Synthesis of 5-substituted-3-carboxy-4,5-dihydrothiophenes and their 1,1-dioxides

Past approaches for the synthesis of 3-carboxy-4,5-dihydrothiophenes have involved rearrangements of thiolactones and enethiols, eliminations and cyclopropylphosphonium chemistry.[12] The methodology we adopted was Zard's xanthate radical transfer protocol.[13] This had been shown to be an excellent method for the preparation of xanthate-substituted acetals, themselves good precursors for 4,5-dihydrothiophenes.

The xanthate precursor **18** was prepared from methyl methoxyacrylate **16** in 37% overall yield (Scheme 5). Purification of **18** proved difficult as a number of minor side-products were formed, this accounts for the rather poor yield. The radical addition, under Zard's standard conditions, proceeded well with a good yield of product **19** obtained. The product was then subjected to cleavage of the xanthate and acid-catalysed cyclisation, which provided the dihydrothiophene **20**. Compound **20** was subjected to gentle cleavage with methoxide giving **21** before oxidation to the target sulfolene **22**, in just over 25% yield from the starting olefin.

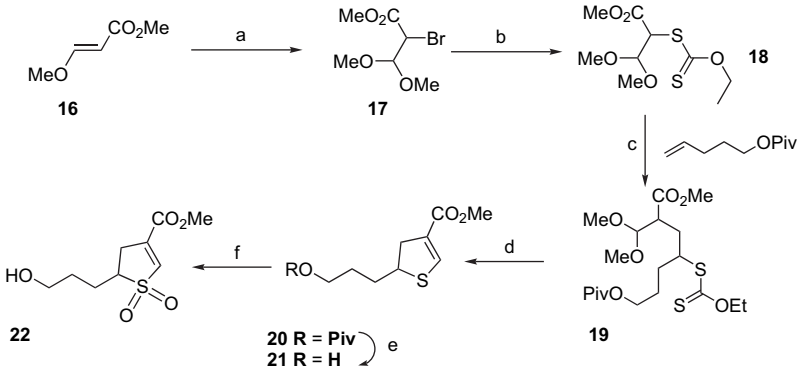
Because the ester was found to be labile in a later Pictet Spengler reaction (see Ref. 4), the synthesis of **27**, the corresponding nitrile to **22**, was also undertaken (Scheme 6). While synthesis of the xanthate **23** and the radical addition to 1-pivaloyloxy-pent-4-ene giving **24** were both straightforward and proceeded in similar yields to those obtained in the ester series, xanthate cleavage and cyclisation were more challenging. Ethylenediamine appeared to react with the nitrile in **24** and produced a complex mixture of products, leading us to investigate a series of bases (NH_3, KOH, NaOH, NaOMe) and reducing agents ($LiBH_4$, $NaBH_4$) all of which led to cleavage of the pivalate as well as the xanthate. The resulting hydroxy thiol was not isolated but exposure to acidic ion-exchange resin to remove the acetal followed by trifluoroacetic acid induced it to cyclise giving, as the major product, **25**, a 3-cyano-4,5-dihydrothiophene with a trifluoroacetate protection. Cleavage and oxidation were straightforward giving **27** in a comparable yield to that obtained for **22**.

In conclusion, new routes have been developed for the synthesis of two important classes of sulfur heterocycle and their *S,S*-dioxo forms bearing difficult substitution patterns.

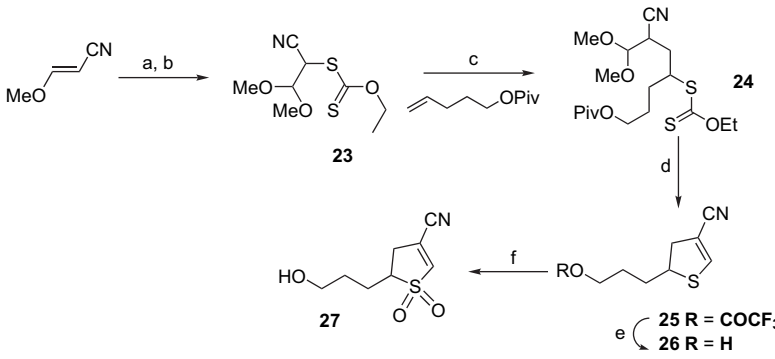
3. Experimental

3.1. General

Melting points were determined on a Gallenkamp electrothermal apparatus and are uncorrected. Infrared absorption



Scheme 5. Reagents and conditions: (a) NBS, MeOH, 0 °C; (b) (i) NaI, Et_2O, rt, 1 h; (ii) KSC(S)OEt, Et_2O, 0 °C–rt, 18 h, 37% for three steps; (c) lauroyl peroxide (16 mol %), 1,2-DCE, reflux, 2 h, 89%; (d) (i) ethylenediamine, EtOH, rt, 1 h; (ii) TFA, CH_2Cl_2, rt, 1 h, 71%; (e) NaOMe, MeOH, 0 °C–rt, 20 h, 70%; (f) Oxone, MeOH, H_2O, 0 °C, 15 min, 55%.



Scheme 6. Reagents and conditions: (a) NIS, MeOH, 0 °C–rt, 3 h, 88%; (b) KSC(S)OEt, Et_2O, 0 °C–rt, 22 h, 47%; (c) lauroyl peroxide (16 mol %), 1,2-DCE, reflux, 6 h, 90%; (d) (i) NaOMe, MeOH, 0 °C–rt, 24 h; (ii) Amberlite H-120; (iii) TFA, CH_2Cl_2, rt, 1 h, 41% over three steps; (e) KOH, MeOH/H_2O, 0 °C, 1 h, 63%; (f) Oxone, MeOH/H_2O, 0 °C, 1 h, 65%.

spectra were recorded on a Bruker VECTOR-200 instrument, as liquid films or solutions in chloroform. NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker AC-400 instrument, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C NMR. Chemical shifts are reported in parts per million relative to trimethylsilane as an internal standard. Mass spectra (MS) were measured on a JEOL JMS-DX303 or JEOL JMN-SX-102A instruments, chemical ionisation with methane was used throughout. All new compounds were determined to be >95% pure by signal/noise ratio in the ^{13}C NMR. Flash chromatography was carried out with silica gel, Merck Type 60 (70–325 mesh ASTM) or Merck Type 60 (230–400 mesh ASTM). Compounds **5**,[9] and **16**–**18**[14] were prepared by literature procedures.

3.1.1. Methyl 5-(3-benzyloxypropyl)-4-oxo-tetrahydrothiophene-3-carboxylate (4b). To a solution of 5-benzyloxy-2-chloro-pentanoic acid **5** (9.76 g, 40.2 mmol) in methanol (500 mL), cooled to 0 °C, was added dropwise thionyl chloride (5.00 mL, 61.7 mmol). Once the addition was completed, the reaction mixture was stirred at rt for 16 h. Most of the methanol was evaporated in vacuo and the residual oil was taken up in ether (50 mL), washed with water (2×30 mL), saturated sodium bicarbonate (2×30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 4:1) gave methyl 5-benzyloxy-2-chloro-pentanoate (**6**) (8.25 g, 80%) as pale yellow oil, R_f (Pet. ether/EtOAc 4:1) 0.39; ν_{max} (cm^{-1}) (thin film) 1755 (C=O), 1176–1104 (C–O), 1027 (C–O); δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.68–1.86 (2H, m, CH_2CH$_2$), 1.98–2.22 (2H, m, CH_2CH), 3.51 (2H, t, J=6.1 Hz, CH_2O), 3.78 (3H, s, CH_3O), 4.33 (1H, dd, J=8.2, 5.8 Hz, CH), 4.50 (2H, s, CH_2 benzyl), 7.19–7.31 (5H, m, CH aromatic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 26.0, 31.7, 52.6, 56.9, 68.9, 72.7, 127.4, 128.2, 138.1, 169.9; *m/z* 257 ([M+H]$^+$, 40%), HRMS $C_{13}H_{18}ClO_3$ [M+H]$^+$ required 257.0944, found 257.0939.

To a suspension of sodium hydride (1.25 g, 31.25 mmol) in ether (10 mL) cooled to 0 °C was added dropwise methyl 3-mercapto-propionate (4.31 g, 35.15 mmol) in ether (40 mL). The mixture was stirred for 15 min at 0 °C, then for 1.5 h at rt. The mixture was cooled to 0 °C and methyl 5-benzyloxy-2-chloro-pentanoate (**6**) (7.30 g, 28.44 mmol) in dry ether (30 mL) was added dropwise, followed by dry DMF (30 mL). After 20 min stirring at 0 °C, the mixture was stirred for 18 h at rt. The residual oil was distilled under reduced pressure to give methyl 5-benzyloxy-2-(2-methoxycarbonyl-ethylsulfanyl)-pentanoate as a colourless oil (6.20 g, 64%), bp 199–200 °C/0.2 mmHg; ν_{max} (cm^{-1}) (thin film) 1735 (C=O), 1102 (C–O); δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.61–2.05 (4H, m, 2×CH_2), 2.60 (2H, dt, J=7.2, 2.8 Hz, CH_2CO), 2.81–2.93 (2H, m, CH_2S), 3.30 (1H, dd, J=8.1, 6.8 Hz, CH), 3.48 (2H, t, J=6.1 Hz, CH_2O), 3.69 (3H, s, CH_3O), 3.74 (3H, s, CH_3O), 4.49 (2H, s, CH_2O benzyl), 7.27–7.38 (5H, m, CH aromatic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 26.2, 27.4, 28.2, 34.5, 46.4, 51.8, 52.3, 69.5, 72.9, 127.6, 128.4, 138.4, 172.0, 173.0; *m/z* 341 ([M+H]$^+$, 40%), HRMS $C_{17}H_{25}O_5S$ required 341.1417, found 341.1420.

To a solution of sodium methoxide [from sodium (3.0 g, 130.4 mmol) and methanol (80 mL)], cooled to 0 °C was slowly added methyl 5-benzyloxy-2-(2-methoxycarbonyl-ethylsulfanyl)-pentanoate (6.7 g, 19.7 mmol) in toluene (50 mL). The reaction mixture was stirred at 0 °C for 1 h, then heated at reflux for 3 h. Most of the solvent was removed in vacuo and the residue was diluted with water (50 mL), cooled, acidified with acetic acid (50 mL) and extracted with toluene (3×60 mL). The organic layers were washed with water (2×50 mL), brine (2×50 mL), evaporated in vacuo, diluted in ether (50 mL) and shaken with a saturated aqueous solution of cupric acetate (35 mL). Layers were separated and the aqueous layer was extracted with ether (50 mL). The combined ethereal layers were concentrated in vacuo to a third of original volume and Pet. ether (30 mL) was added to initiate crystallisation. The green crystals were collected by filtration and washed with water (3×10 mL) and Pet. ether (2×10 mL).

The crystals were suspended in ether (100 mL) and 2 M sulfuric acid (50 mL) was added. The layers were separated and the organic layer was washed with 2 M sulfuric acid (2×50 mL), water (2×50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give methyl 5-(3-benzyloxypropyl)-4-oxo-tetrahydrothiophene-3-carboxylate (**4b**) as a dark brown oil (2.65 g, 44%) as a mixture of keto and enol forms in a ratio of 1:1.7, respectively, ν_{max} (cm^{-1}) (thin film) 1731 (C=O), 1665 (C=O), 1625, 1105, 1028; δ ^{1}H NMR (400 MHz, $CDCl_3$) (keto form exists as a mixture of diastereomers partially discernible in ^{13}C NMR) 1.64–2.19 (4H, m, 2×CH_2), 3.13 (1H, ddd, J=11.9, 8.1, 3.9 Hz, CHS), 3.32–3.50 (4H, m, CH_2O+CH_2S), 3.72–3.74 (1H, m, CHCO$_2$Me), 3.78 (3H, s, CH_3O), 4.49 (2H, s, CH_2O benzyl), 7.27–7.37 (5H, m, CH aromatic); (enol form) 1.64–2.19 (4H, m, CH_2), 3.43 (2H, t, J=5.7 Hz, CH_2O), 3.68 (2H, dd, J=7.6, 2.7 Hz, CH_2S), 3.79 (3H, s, CH_3O), 4.22–4.23 (1H, m, CHS), 4.50 (2H, s, CH_2O benzyl), 7.27–7.37 (5H, m, CH aromatic), 10.98 (1H, s, OH); δ ^{13}C NMR (100 MHz, $CDCl_3$) (keto form) 24.4 and 26.5, 26.9, 27.5, 27.7, 52.2, 52.8, 55.5, 55.6, 69.1, 69.2, 69.4, 73.0, 127.5, 128.3, 138.3, 138.4, 168.2, 168.4, 206.5, 207.2; (enol form) 27.2, 27.8, 31.4, 52.0, 53.5, 69.4, 72.9, 98.7, 127.6, 128.3, 138.2, 148.5, 172.0; *m/z* 309 ([M+H]$^+$, 21%), HRMS $C_{16}H_{24}NO_4S$ [M+NH$_4$]$^+$ required 326.1426, found 326.1421.

3.1.2. Methyl 3-(cyclopent-2-enylsulfanyl)-propionate (8). To 3-methyl mercaptopropionate (23.76 g, 0.191 mol) at 10 °C under argon was added a 25 wt % solution of ethyl aluminium dichloride in toluene (4.4 mL, 0.006 mol), then freshly cracked cyclopentadiene (18.37 g, 0.278 mol) was added dropwise via cannula. After 1 h of vigorous stirring, the solution was warmed to rt for 36 h. The dark green reaction mixture was poured into water (200 mL), diluted with diethyl ether (200 mL) and partitioned. The aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic extracts (yellow solution) were washed with water (2×100 mL), then brine (2×100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual crude orange oil was distilled under reduced pressure to give methyl 3-(cyclopent-2-enylsulfanyl)-propionate (**8**) as a brown oil (24.22 g, 68%), bp 89–92 °C/0.1 mmHg; ν_{max} (cm^{-1}) (thin film) 3056, 1730 (C=O), 1609, 1172 (C–O); δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.89–1.96 (1H, m, one of allylic CH_2), 2.28–2.39 (2H, m, CH_2), 2.43–2.55 (1H, m,

one of allylic CH_2), 2.61 (2H, dd, J=11.3, 4.3 Hz, CH_2CO_2Me), 2.79 (2H, dd, J=11.3, 4.3 Hz, CH_2S), 3.70 (3H, s, CH_3OCO), 3.85–3.92 (1H, m, CH), 5.70–5.73 (1H, m, CH olefinic), 5.87 (1H, ddd, J=5.9, 3.9, 1.9 Hz, CH olefinic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 25.3, 31.6, 31.7, 34.9, 49.9, 51.7, 131.3, 132.9, 172.4; m/z 187 ([M+H]$^+$, 100%), HRMS $C_9H_{15}O_2S$ [M+H]$^+$ required 187.0793, found 187.0788.

3.1.3. Methyl 3-(cyclopent-2-enylsulfonyl)-propionate (9). Oxone® (27.0 g, 43.83 mmol) in water (210 mL) was added over 30 min to a solution of 3-(cyclopent-2-enylsulfanyl)-propionic acid methyl ester (**8**) (5.20 g, 27.9 mmol) in methanol (60 mL) cooled to 0 °C. After 30 min stirring, the reaction mixture was extracted with ethyl acetate (3×75 mL). The combined organic extracts were dried over $MgSO_4$. The solvents were removed under reduced pressure to give a colourless oil, which was purified by flash chromatography (Pet. ether/EtOAc: 1:1) yielding methyl 3-(cyclopent-2-enylsulfonyl)-propionate (5.60 g, 92%) as colourless needles, mp 39–41 °C; R_f (Pet. ether/EtOAc 1:1) 0.41; ν_{max} (cm^{-1}) (thin film) 1739 (C=O), 1439, 1366, 1121 (C–O); δ ^{1}H NMR (400 MHz, $CDCl_3$) 2.26–2.45 (2H, m, ring CH_2), 2.46–2.55 (1H, m, one of allylic CH_2), 2.60–2.70 (1H, m, one of allylic CH_2), 2.88 (2H, t, J=7.5 Hz, CH_2CO), 3.23 (2H, tq, J=13.8, 7.5 Hz, CH_2SO$_2$), 3.73 (3H, s, CH_3O), 4.17–4.23 (1H, m, CH), 5.80 (1H, qd, J=5.7, 2.3 Hz, CH olefinic), 6.27 (1H, ddd, J=5.7, 4.3, 2.3 Hz, CH olefinic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 24.1, 26.0, 32.2, 44.9, 52.4, 70.4, 122.8, 140.6, 171.1; m/z 219 ([M+H]$^+$, 100%), HRMS $C_9H_{18}NO_4S$ [M+NH$_4$]$^+$ required 236.0957, found 236.0952.

3.1.4. Methyl 2-acetylsulfanyl-5-benzyloxy-pentanoate (11). To a suspension of a 60% dispersion of sodium hydride (0.43 g, 10.75 mmol) in diethyl ether (20 mL) was added dropwise thioacetic acid (0.8 mL, 10.89 mmol) in ether (5 mL) at 0 °C after which the mixture was stirred for 5 min at 0 °C, then for 1 h at rt. The mixture was then cooled to 0 °C and methyl 5-benzyloxy-2-chloro-pentanoate (**6**) (2.08 g, 8.11 mmol) in ether (5 mL) was added, followed by DMF (5 mL). The solution was kept at 0 °C for 10 min, then stirred at rt for 20 h and diluted with water (20 mL). The aqueous layer was extracted with ether (3×25 mL). The combined organic layers were washed with water (3×20 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 4:1) gave methyl 2-acetylsulfanyl-5-benzyloxy-pentanoate (**11**) (1.97 g, 82%) as a yellow oil, R_f (Pet. ether/EtOAc 4:1) 0.39; ν_{max} (cm^{-1}) (thin film) 1739 (C=O), 1698 (C=O), 1197, 1110 (C–O); δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.62–1.78 (2H, m, CH_2CH$_2$), 1.81–1.90 (1H, m, one of CH_2CHS), 2.04 (1H, dddd, J=16.9, 9.8, 7.2, 5.9 Hz, one of CH_2CHS), 2.35 (3H, s, CH_3CO), 3.47 (2H, t, J=6.3 Hz, CH_2O), 3.72 (3H, s, CH_3O), 4.23 (1H, t, J=7.2 Hz, CHS), 4.49 (2H, s, CH_2O benzyl), 7.27–7.38 (5H, m, CH aromatic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 27.2, 28.6, 30.2, 45.6, 52.6, 69.3, 72.9, 127.6, 128.3, 138.4, 172.0, 193.7; m/z 297 (M$^+$, 10%), HRMS $C_{15}H_{20}O_4S$ required 297.1155, found 297.1159.

3.1.5. Methyl 3-(4-benzyloxy-1-formyl-butylsulfanyl)-propionate (12). To a suspension of lithium aluminium hydride (1.07 g, 26.79 mmol) in ether (50 mL) cooled to 0 °C was added dropwise 2-acetylsulfanyl-5-benzyloxy-pentanoate (**11**) (1.99 g, 6.71 mmol) in ether (20 mL) over 15 min. Once the addition was complete, the mixture was stirred for 15 min at 0 °C, then for 1 h at rt and carefully quenched at 0 °C with wet ether (75 mL; Et_2O/H_2O 1:1, v/v). Once the mixture had turned white, it was transferred into a separating funnel and 2 M aqueous H_2SO_4 (50 mL) was added. The layers were separated and the aqueous layer was extracted with ether (3×30 mL). The combined ethereal extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 7:3) gave 5-benzyloxy-2-mercapto-pentan-1-ol (1.34 g, 88%) as a yellow oil, R_f (Pet. ether/EtOAc 7:3) 0.42; ν_{max} (cm^{-1}) (thin film) 3386 (O–H), 1096 (C–O); δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.34 (1H, d, J=8.4 Hz, SH), 1.49–1.93 (4H, m, 2×CH_2), 2.27 (1H, br s, OH), 2.89 (1H, tdt, J=8.4, 7.4, 4.9 Hz, CH), 3.45–3.51 (3H, m, CH_2OBn+one of CH_2OH), 3.70 (1H, dd, J=11.2, 4.9 Hz, one of CH_2OH), 4.50 (2H, s, CH_2 benzyl), 7.27–7.37 (5H, m, CH aromatic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 27.1, 31.4, 43.6, 67.8, 69.7, 72.9, 127.6, 128.3, 138.3; m/z 227 ([M+H]$^+$, 8%), HRMS no satisfactory data assignment could be obtained.

Triethylamine (2.50 mL, 17.85 mmol) was added to 5-benzyloxy-2-mercapto-pentan-1-ol (5.12 g, 22.62 mmol) at rt. The mixture was stirred for 10 min, then methyl acrylate (5.00 mL, 54.62 mmol) was added dropwise. The reaction mixture was stirred for 18 h, concentrated and purified by flash chromatography (Pet. ether/EtOAc 3:2) to give methyl 3-(4-benzyloxy-1-hydroxymethyl-butylsulfanyl)-propionate (6.31 g, 87%) as a yellow oil, R_f (Pet. ether/EtOAc 3:2) 0.24; ν_{max} (cm^{-1}) (thin film) 3445 (O–H), 1731 (C=O), 1247–1094; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.44–1.84 (4H, m, 2×CH_2), 1.93 (1H, br s, OH), 2.59 (2H, t, J=7.3 Hz, CH_2CO), 2.72–2.84 (3H, m, CH_2S+CH), 3.47–3.54 (3H, m, CH_2OBn+one of CH_2OH), 3.67 (1H, dd, J=12.7, 7.9 Hz, one of CH_2OH), 3.70 (3H, s, CH_3O), 4.50 (2H, s, CH_2O benzyl), 7.27–7.38 (5H, m, CH aromatic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 25.1, 26.9, 28.1, 34.6, 49.1, 51.7, 64.1, 69.7, 72.7, 127.4, 127.5, 128.2, 138.2, 172.2; m/z 313 ([M+H]$^+$, 5%), HRMS $C_{16}H_{25}O_4S$ [M+H]$^+$ required 313.1474, found 313.1469.

To a solution of oxalyl chloride (1.9 mL, 2.7 g, 21.6 mmol) in dichloromethane (45 mL), cooled to between −50 and −60 °C under argon, was added a solution of DMSO (3.8 mL, 4.2 g, 53.5 mmol) in dichloromethane (42 mL). The reaction mixture was stirred for 3 min and then a solution of methyl 3-(4-benzyloxy-1-hydroxymethyl-butylsulfanyl)-propionate (6.3 g, 20.2 mmol) in dichloromethane (19 mL) was added over 5 min and the mixture was stirred for 15 min. Triethylamine (14.0 mL, 10.1 g, 99.9 mmol) was then added and the reaction mixture was allowed to warm to rt and stirred for 1 h. Water (50 mL) was added and the aqueous layer was extracted with dichloromethane (3×100 mL). The combined organic extracts were washed with brine (3×100 mL), 2 M aqueous HCl (2×100 mL), water (4×100 mL), saturated aqueous Na_2CO_3 (2×100 mL), water (2×100 mL), dried over $MgSO_4$, filtered and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 3:2) gave methyl 3-(4-benzyloxy-1-

formyl-butylsulfanyl)-propionate (**12**) (5.8 g, 93%) as a yellow oil, R_f (Pet. ether/EtOAc 3:2) 0.60; ν_{max} (cm^{-1}) (thin film) 1732 (C=O), 1712 (C=O), 1177, 1100; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.68–1.97 (4H, m, 2×CH_2), 2.54–2.59 (4H, m, COCH_2, SCH_2), 3.16 (1H, ddd, J=8.0, 6.3, 4.5 Hz, CH), 3.49 (2H, t, J=5.7 Hz, CH_2O), 3.69 (3H, s, CH_3O), 4.48 (2H, s, CH_2O benzyl), 7.27–7.38 (5H, m, CH aromatic), 9.20 (1H, d, J=4.5 Hz, CHO); δ ^{13}C NMR (100 MHz, $CDCl_3$) 24.6, 24.9, 27.1, 34.2, 51.8, 53.0, 69.2, 72.9, 127.6, 128.3, 138.2, 171.8, 193.6; m/z 311 ([M+H]$^+$, 100%), HRMS $C_{16}H_{23}O_4S$ [M+H]$^+$ required 311.1317, found 311.1314.

3.1.6. 5-(3-Benzyloxypropyl)-3-carboxymethyl-2,5-dihydrothiophene (3). To a solution of sodium methoxide [prepared from sodium (0.77 g, 33.58 mmol) in methanol (30 mL)] cooled to 0 °C was added dropwise methyl 3-(4-benzyloxy-1-formyl-butylsulfanyl)-propionate (**12**) (5.80 g, 18.68 mmol) in toluene (10 mL) over 20 min. Once addition was complete the reaction mixture was heated under reflux for 2 h, cooled and diluted with water (100 mL). Most of the methanol was removed in vacuo and the mixture was acidified with 2 M aqueous HCl (50 mL) and extracted with ether (3×100 mL). The combined organic extracts were washed with water (2×100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in dry dichloromethane (40 mL) and cooled to 0 °C before triethylamine (10.00 mL, 0.07 mol) was added and the reaction mixture was stirred for 5 min. Methanesulfonyl chloride (2.00 mL, 0.02 mol) was added and the mixture was stirred at 0 °C for 10 min, then for 45 min at rt, diluted with dichloromethane (50 mL), washed with 2 M aqueous HCl (2×20 mL), dried over $MgSO_4$, filtered and concentrated. The residual oil was dissolved in MeOH (50 mL) and cooled to 0 °C. Thionyl chloride (5.00 mL, 68.50 mmol) was added dropwise and the reaction mixture was stirred at rt for 1 h and then concentrated. Purification by flash chromatography (Pet. ether/EtOAc 9:1) gave 5-(3-benzyloxypropyl)-3-carboxymethyl-2,5-dihydrothiophene (**3**) (1.85 g, 34% from aldehyde **12**) as a pale brown oil, R_f (Pet. ether/EtOAc 9:1) 0.25; ν_{max} (cm^{-1}) (thin film) 1720 (C=O), 1648 (C=C), 1257, 1089; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.66–1.95 (4H, m, 2×CH_2), 3.49 (2H, t, J=6.2 Hz, CH_2O), 3.76 (3H, s, CH_3O), 3.84–3.94 (2H, m, CH_2S), 4.31–4.41 (1H, m, CH), 4.50 (2H, s, CH_2O benzyl), 6.79 (1H, dd, J=4.7, 2.1 Hz, CH olefinic), 7.27–7.37 (5H, m, CH aromatic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 27.6, 34.2, 36.6, 51.9, 55.0, 69.7, 72.9, 127.6, 128.3, 134.0, 138.4, 144.6, 164.4; m/z 293 ([M+H]$^+$, 25%), HRMS $C_{16}H_{18}O_3S$ required for [M−2] 290.0971, found 290.0967.

3.1.7. 5-(3-Benzyloxypropyl)-3-carbomethoxy-3-sulfolene (14). To an ice-cooled solution of 5-(3-benzyloxypropyl)-3-carboxymethyl-2,5-dihydrothiophene (**3**) (661 mg, 2.26 mmol) in methanol (25 mL) was added dropwise a solution of Oxone® (7.00 g, 11.39 mmol) in water (50 mL). Once addition was complete the reaction mixture was stirred for 30 min at the same temperature, diluted with water (50 mL), extracted with dichloromethane (3×50 mL), dried with $MgSO_4$, filtered and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 1:1) gave 5-(3-benzyloxypropyl)-3-carbomethoxy-3-sulfolene (**14**) (401 mg, 55%) as a viscous brown oil, R_f (Pet. ether/EtOAc 1:1) 0.41; ν_{max} (cm^{-1}) (thin film) 1717 (C=O), 1642 (C=C), 1256, 1089, 739; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.79–2.15 (4H, m, 2×CH_2), 3.50–3.59 (2H, m, CH_2S), 3.81 (3H, s, CH_3O), 3.94–3.97 (3H, m, CH_2O+CHS), 4.50 (2H, s, CH_2O benzyl), 6.96–6.98 (1H, m, CH olefinic), 7.26–7.37 (5H, m, CH aromatic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 27.3, 33.0, 52.2, 56.7, 64.2, 70.1, 73.1, 127.4, 128.5, 133.8, 138.3, 144.2, 164.8; m/z 325 ([M+H]$^+$, 35%), HRMS $C_{16}H_{21}O_5S$ required 325.1101, found 325.1109.

3.1.8. Methyl 2-dimethoxymethyl-7-(2,2-dimethylpropionyloxy)-4-ethoxythiocarbonylsulfanyl-heptanoate (19). To a refluxing solution of methyl 2-ethoxythiocarbonylsulfanyl-3,3-dimethoxypropionate (**18**) (1.80 g, 6.71 mmol) and 2,2-dimethyl-propionic acid pent-4-enyl ester (1.26 g, 7.42 mmol) in 1,2-dichloroethane (15 mL, previously degassed by refluxing under an atmosphere of argon for 2 h) was added lauroyl peroxide (0.56 g, 1.34 mmol) portionwise (0.14 g every hour for 4 h) as a solid charge. The reaction mixture was then heated under reflux for a further 2 h, cooled and concentrated under reduced pressure. Further purification by flash chromatography gave methyl 2-dimethoxymethyl-7-(2,2-dimethylpropionyloxy)-4-ethoxythiocarbonylsulfanyl-heptanoate (**19**) (2.61 g, 89%) as an inseparable mixture of diastereoisomers (1.1:1) as a yellow oil, R_f (Pet. ether/EtOAc 4:1) 0.34; ν_{max} (cm^{-1}) (thin film) 2958, 2873, 1730 (C=O), 1444, 1158, 1055; δ ^{1}H NMR (400 MHz, $CDCl_3$) (major diastereomer) 1.19 (9H, s, 3×CH_3), 1.41 (3H, t, J=7.1 Hz, CH_3CH$_2$), 1.56–2.14 (6H, m, 3×CH_2), 3.02 (1H, ddd, J=11.2, 7.0, 3.0 Hz, CHCO$_2$Me), 3.32 (3H, s, CH_3O), 3.36 (3H, s, CH_3O), 3.39–3.43 (1H, m, CHS), 3.71 (3H, s, CH_3OCO), 4.01–4.08 (2H, m, CH_2OPiv), 4.51 (1H, d, J=7.0 Hz, CHOMe), 4.59–4.62 (2H, m, CH_2OCS); (minor diastereomer) 1.20 (9H, s, 3×CH_3), 1.42 (3H, t, J=7.2 Hz, CH_3CH$_2$), 1.56–2.14 (6H, m, 3×CH_2), 2.87 (1H, ddd, J=9.8, 7.8, 4.2 Hz, CHCO$_2$Me), 3.34 (3H, s, CH_3O), 3.36 (3H, s, CH_3O), 3.39–3.43 (1H, m, CHS), 3.73 (3H, s, CH_3OCO), 4.01–4.08 (2H, m, CH_2OPiv), 4.49 (1H, d, J=7.8 Hz, CHOMe), 4.59–4.62 (2H, m, CH_2OCS); δ ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer) 13.3, 25.8, 27.1, 31.2, 32.2, 38.7, 46.5, 49.4, 52.0, 53.1, 54.6, 63.8, 69.9, 104.4, 172.8, 178.4, 213.9; (minor diastereomer) 15.2, 25.8, 27.1, 29.7, 32.7, 38.7, 47.0, 49.0, 51.9, 53.4, 54.6, 63.6, 69.8, 104.7, 172.6, 178.4, 213.5; m/z 407 ([M−MeO$^\bullet$]$^+$, 12%), HRMS no satisfactory data assignment could be obtained.

3.1.9. Methyl 5-[3-(2,2-dimethylpropionyloxy)-propyl]-4,5-dihydrothiophene-3-carboxylate (20). To a solution of methyl 2-dimethoxymethyl-7-(2,2-dimethylpropionyloxy)-4-ethoxythiocarbonylsulfanyl-heptanoate **19** (1.12 g, 2.56 mmol) in ethanol (10 mL) was added ethylenediamine (2.00 mL, 29.76 mmol). Once addition was complete, the reaction mixture was stirred at rt for 1 h, concentrated under reduced pressure, diluted with dichloromethane (70 mL) and water (20 mL) and then acidified with a solution of 1 M HCl (50 mL). The layers were separated and the organic layer was washed with water (2×50 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residual oil was then diluted with dichloromethane (20 mL) and trifluoroacetic acid (3.00 mL, 38.62 mmol) was then added via syringe. The reaction mixture was stirred at rt for 1 h, diluted with dichloromethane (50 mL), washed with water

(20 mL), saturated $NaHCO_3$ (2×15 mL), water (2×15 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated to give a yellow oil. Further purification by flash chromatography gave methyl 5-[3-(2,2-dimethylpropionyloxy)-propyl]-4,5-dihydrothiophene-3-carboxylate (**20**) (0.52 g, 71%) as a yellow oil, R_f (Pet. ether/EtOAc 4:1) 0.39; ν_{max} (cm^{-1}) (thin film) 1727 (C═O), 1708 (C═O), 1579, 1480, 1437, 1363, 1156, 1079; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.20 (9H, s, 3×CH_3), 1.71–1.98 (2H, m, CH_2CH_2), 2.06–2.16 (2H, m, CH_2CH), 2.61 (1H, ddd, J=17.9, 6.8, 2.5 Hz, one of ring CH_2), 3.24 (ddd, 1H, J=1.7, 8.2, 17.9 Hz, one of ring CH_2), 3.39 (1H, td, J=14.7, 7.4 Hz, CH), 3.86 (3H, s, CH_3OCO), 4.13 (2H, dt, J=6.3, 1.7 Hz, CH_2O), 7.31–7.32 (1H, m, CH olefinic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 25.0, 26.2, 27.2, 32.5, 38.8, 53.1, 60.1, 63.2, 137.4, 140.0, 162.9, 178.4; m/z 287 ([M+H]$^+$, 12%), HRMS $C_{14}H_{23}O_4S$ [M+H]$^+$ required 287.1312, found 287.1314.

3.1.10. Methyl 5-(3-hydroxypropyl)-4,5-dihydrothiophene-3-carboxylate (21). To a solution of methyl 5-[3-(2,2-dimethylpropionyloxy)-propyl]-4,5-dihydrothiophene-3-carboxylate (**20**) (247 mg, 1.23 mmol) in methanol (2 mL), cooled to 0 °C, was added via syringe a 1 M solution of NaOMe in methanol (1.00 mL, 1.00 mmol). The reaction mixture was allowed to return to rt and then stirred for 20 h, acidified to pH 4 with Amberlite resin IR-120[H], filtered, washed with methanol (3×2 mL) and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 3:2) afforded methyl 5-(3-hydroxypropyl)-4,5-dihydrothiophene-3-carboxylate (**21**) (173 mg, 70%) as a yellow oil, R_f (Pet. ether/EtOAc 3:2) 0.21; ν_{max} (cm^{-1}) (thin film) 3429 (OH), 1703 (C═O), 1577, 1080; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.32 (1H, br s, OH), 1.62–1.69 (2H, m, CH_2CH$_2$), 1.76–1.82 (2H, m, CH_2CH), 2.78 (1H, ddd, J=16.2, 6.2, 1.6 Hz, one of ring CH_2), 3.14 (1H, ddd, J=16.1, 9.4, 2.1 Hz, one of ring CH_2), 3.67 (2H, t, J=6.3 Hz, CH_2O), 3.72 (3H, s, CH_3O), 3.87–3.94 (1H, m, ring CH), 7.33–7.34 (1H, m, CH olefinic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 30.6, 33.2, 39.9, 51.2, 51.5, 62.4, 126.5, 141.7, 163.6; m/z 203 ([M+H]$^+$, 35%), HRMS $C_9H_{15}O_3S$ [M+H]$^+$ required 203.0742, found 203.0736.

3.1.11. 5-(3-Hydroxypropyl)-3-carbomethoxy-2-sulfolene (22). A solution of methyl 5-(3-hydroxypropyl)-4,5-dihydrothiophene-3-carboxylate (**21**) (140 mg, 0.69 mmol) in methanol (2 mL) was added dropwise via syringe to a solution of Oxone® (1.30 g, 2.11 mmol) in water (5 mL), cooled to 0 °C. The reaction mixture was stirred for 15 min at the same temperature, diluted with EtOAc (30 mL) and partitioned. The organic layer was washed with water (2× 5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 1:2) afforded 5-(3-hydroxypropyl)-3-carbomethoxy-2-sulfolene (**22**) (89 mg, 55%) as a thick yellow oil, R_f (Pet. ether/EtOAc 1:2) 0.13; ν_{max} (cm^{-1}) (thin film) 3533–3451 (OH), 1728 (C═O), 1582, 1299, 1133, 1057; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.66 (1H, br s, OH), 1.73–2.15 (4H, m, 2×CH_2), 2.62 (1H, ddd, J=18.0, 6.8, 2.5 Hz, one of ring CH_2), 3.24 (1H, ddd, J=18.0, 8.1, 1.7 Hz, one of ring CH_2), 3.45 (1H, ddd, J=14.8, 8.1, 6.8 Hz, CHCH$_2$), 3.69–3.76 (2H, m, CH_2O), 3.85 (3H, s, CH_3O), 7.29–7.30 (1H, m, CH olefinic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 25.0, 29.7, 32.6, 53.1, 60.4, 62.0, 137.3, 140.2, 163.0; m/z 235 ([M+H]$^+$, 10%), HRMS $C_9H_{15}O_5S$ [M+H]$^+$ required 235.0640, found 235.0636.

3.1.12. *O*-Ethyl *S*-(1-cyano-2,2-dimethoxyethyl)-dithiocarbonate (23). To a well-stirred suspension of *N*-iodosuccinimide (77.09 g, 0.325 mol) in methanol (300 mL), cooled to 0 °C under argon, was added dropwise 3-methoxy-acrylonitrile (28.00 mL, 27.72 g, 0.320 mol). Once addition was complete, the reaction mixture was allowed to return to rt and stirred for a further 3 h. Most of the methanol was removed under reduced pressure and the residue was filtered and extracted with toluene (5× 100 mL). The organic layers were then washed with water (3×150 mL), brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The residual oil was distilled under reduced pressure to yield 2-iodo-3,3-dimethoxy-propionitrile as a yellow oil (68.25 g, 88%), bp 98–101 °C/0.4 mmHg; ν_{max} (cm^{-1}) (thin film) 2839, 2242 (CN), 1117, 1074; δ ^{1}H NMR (400 MHz, $CDCl_3$) 3.48 (3H, s, CH_3O), 3.52 (3H, s, CH_3O), 4.32 (1H, d, J=5.6 Hz), 4.44 (1H, d, J=5.6 Hz); δ ^{13}C NMR (100 MHz, $CDCl_3$) −1.22, 55.4, 56.0, 103.4, 116.6; m/z 242 ([M+H]$^+$, 8%), HRMS $C_5H_{12}N_2O_2I$ [M+NH$_4$]$^+$ required 258.9938, found 258.9941.

To a solution of 2-iodo-3,3-dimethoxy-propionitrile (11.03 g, 45.76 mmol) in acetonitrile (50 mL) was added portionwise potassium *O*-ethyl xanthate (7.56 g, 47.16 mmol) as solid charge over 45 min at 0 °C under argon. Once addition was complete, the reaction mixture was stirred at 0 °C for 30 min, then allowed to return to rt and stirred overnight (22 h). Most of the acetonitrile was removed under reduced pressure and the residue was diluted with Et_2O (400 mL), washed with water (4×100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residual oil was purified by flash chromatography (Pet. ether/EtOAc 4:1) to yield *O*-ethyl *S*-(1-cyano-2,2-dimethoxyethyl)-dithiocarbonate (**23**) as a yellow oil (5.05 g, 47%), R_f (Pet. ether/EtOAc 4:1) 0.32; ν_{max} (cm^{-1}) (thin film) 2839, 2246 (CN), 1112, 1073; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.46 (3H, t, J=7.1 Hz, CH_3CH$_2$), 3.51 (3H, s, CH_3O), 3.52 (3H, s, CH_3O), 4.61 (1H, d, J=4.3 Hz, CHS), 4.71 (2H, q, J=7.1 Hz, CH_2O), 4.83 (1H, d, J=4.3 Hz, CHOMe); δ ^{13}C NMR (100 MHz, $CDCl_3$) 13.7, 42.3, 55.7, 56.3, 71.7, 102.2, 115.6, 209.3; m/z 236 ([M+H]$^+$, 20%), HRMS $C_8H_{14}NO_3S_2$ [M+H]$^+$ required 236.0415, found 236.0411.

3.1.13. 2,2-Dimethylpropionic acid 6-cyano-4-ethoxythiocarbonylsulfanyl-7,7-dimethoxyheptyl ester (24). To a refluxing solution of *O*-ethyl *S*-(1-cyano-2,2-dimethoxyethyl)-dithiocarbonate (**23**) (4.52 g, 19.2 mmol) and 2,2-dimethyl-propionic acid pent-4-enyl ester (3.75 g, 22.0 mmol) in 1,2-dichloroethane (50 mL, previously degassed by heating at reflux under argon for 2 h) was added lauroyl peroxide (1.44 g, 3.6 mmol) portionwise (every hour for 4 h) as a solid charge. The reaction mixture was then heated at reflux for 2 h, cooled and concentrated under reduced pressure. Further purification by flash chromatography (Pet. ether/EtOAc 9:1) afforded an inseparable mixture of diastereoisomers (ratio 1.4:1) of 2,2-dimethylpropionic acid 6-cyano-4-ethoxythiocarbonylsulfanyl-7,7-dimethoxyheptyl ester (**24**) (7.00 g, 90%) as a thick yellow oil, R_f (Pet. ether/EtOAc 9:1) 0.20; ν_{max} (cm^{-1}) (thin film) 2838, 2246 (CN), 1726 (C═O), 1157, 1115, 1048;

δ ^{1}H NMR (400 MHz, $CDCl_3$) (major diastereomer) 1.20 (9H, s, 3×CH_3), 1.45 (3H, t, J=7.1 Hz, CH_3CH$_2$), 1.60–2.06 (6H, m, 3×CH_2), 3.12 (1H, ddd, J=11.3, 5.6, 3.8 Hz, CHCN), 3.41 (3H, s, CH_3O), 3.45 (3H, s, CH_3O), 3.89–3.98 (1H, m, CHS), 4.07 (2H, t, J=3.9 Hz, CH_2OPiv), 4.45 (1H, d, J=5.6 Hz, CHOMe), 4.67 (2H, dq, J=7.1, 3.0 Hz, CH$_3$CH_2O); (minor diastereomer) 1.20 (9H, s, 3×CH_3), 1.44 (3H, t, J=7.1 Hz, CH_3CH$_2$), 1.67–1.89 (4H, m, 2×CH_2), 2.11 (2H, t, J=7.2 Hz, CH_2CHCN), 2.99 (1H, dt, J=7.2, 5.3 Hz, CHCN), 3.43 (3H, s, CH_3O), 3.48 (3H, s, CH_3O), 3.87–3.97 (1H, m, CHS), 4.08 (2H, t, J=5.9 Hz, CH_2OPiv), 4.46 (1H, d, J=5.3 Hz, CHOMe), 4.66 (2H, dq, J=7.1, 1.5 Hz, CH$_3$CH_2O); δ ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereomer) 13.7, 26.0, 27.2, 29.7, 32.4, 34.6, 38.7, 48.5, 54.4, 55.3, 63.6, 70.4, 102.9, 118.9, 178.4, 212.2; (minor diastereomer) 13.8, 25.9, 27.2, 29.7, 32.1, 33.8, 38.7, 48.3, 55.4, 55.5, 63.4, 70.3, 103.1, 118.7, 178.5, 212.8; m/z 374 ([M−MeO$^\bullet$]$^+$, 25%), HRMS no satisfactory data assignment could be obtained.

3.1.14. 3-(3-Cyano-4,5-dihydrothiophene-5-yl)-propyl trifluoroacetate (25). To a solution of sodium methoxide [prepared from sodium (4.36 g, 189 mmol) in methanol (100 mL)] was added dropwise a solution of 2,2-dimethylpropionic acid 6-cyano-4-ethoxythiocarbonylsulfanyl-7,7-dimethoxyheptyl ester (**24**) (2.51 g, 6.21 mmol) in methanol (25 mL) at 0 °C. Once addition was complete, the reaction mixture was allowed to return to rt, stirred for 24 h, acidified to pH 5 with Amberlite H-120 and filtered. Most of the methanol was evaporated and the residue was dissolved in water (50 mL) and extracted with dichloromethane (3×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The residual oil was diluted with dichloromethane (70 mL), and trifluoroacetic acid (3.00 mL, 38.62 mmol) was added dropwise. The reaction mixture was stirred at rt overnight, washed with water (3×30 mL), saturated aqueous $NaHCO_3$ (3×30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Further purification by flash chromatography gave 3-(3-cyano-4,5-dihydrothiophene-5-yl)-propyl trifluoroacetate (**25**) (0.675 g, 41%) as a yellow oil along with deprotected product **26** (0.242 g, 23%), R_f (Pet. ether/EtOAc 4:1) 0.29; ν_{max} (cm^{-1}) (thin film) 3070, 2208 (CN), 1786 (C=O), 1564, 1156; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.77–1.89 (4H, m, 2×CH_2), 2.73 (1H, ddd, J=15.9, 5.7, 1.6 Hz, one of ring CH_2), 3.16 (1H, ddd, J=15.9, 9.3, 2.3 Hz, one of ring CH_2), 3.88–3.95 (1H, m, CHCH$_2$), 4.37 (2H, dt, J=6.1, 2.0 Hz, CH_2O), 7.12–7.13 (1H, m, CH olefinic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 26.1, 32.5, 41.8, 50.3, 67.2, 103.0, 115.6, 115.7, 145.5, 157.6; δ ^{19}F NMR (376 MHz, $CDCl_3$) −75.9 (s, CF_3); m/z 266 ([M+H]$^+$, 17%), HRMS $C_{10}H_{14}F_3N_2O_2S$ [M+NH$_4$]$^+$ required 283.0728, found 283.0726.

3.1.15. 5-(3-Hydroxypropyl)-4,5-dihydrothiophene-3-carbonitrile (26). To a solution of 3-(4-cyano-2,3-dihydrothiophene-2-yl)-propyl trifluoroacetate (**25**) (95.5 mg, 0.36 mmol) in methanol (2 mL) cooled to 0 °C was added dropwise a solution of potassium hydroxide (119 mg, 2.13 mmol) in water (5 mL). Once addition was complete, the reaction mixture was stirred at the same temperature for 10 min, then at rt for 45 min, acidified with 2 M HCl and extracted with EtOAc (3×3 mL). The combined organic extracts were washed with water (3×2 mL), brine (3 mL), dried over $MgSO_4$, filtered and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 4:1 to 1:1) gave 5-(3-hydroxypropyl)-4,5-dihydrothiophene-3-carbonitrile (**26**) (38.4 mg, 63%) as a yellow oil, R_f (Pet. ether/EtOAc 1:1) 0.29; ν_{max} (cm^{-1}) (thin film) 3419 (OH), 2206 (CN), 1562 (C=C), 1057; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.53 (1H, br s, OH), 1.61–1.68 (2H, m, CH_2), 1.78–1.84 (2H, m, CH_2), 2.72 (1H, ddd, J=15.8, 6.2, 1.6 Hz, one of ring CH_2), 3.12 (1H, ddd, J=15.8, 9.3, 2.2 Hz, one of ring CH_2), 3.68 (2H, t, J=6.2 Hz, CH_2O), 3.91–3.98 (1H, m, CH), 7.12 (1H, t, J=1.9 Hz, CH olefinic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 30.4, 32.8, 41.8, 51.1, 62.1, 102.8, 116.0, 146.0; m/z 170 [M+H]$^+$, 30%, HRMS $C_8H_{15}ON_2S$ [M+NH$_4$]$^+$ required 187.0905, found 187.0902.

3.1.16. 5-(3-Hydroxypropyl)-2-sulfolene-3-carbonitrile (27). To a solution of 5-(3-hydroxypropyl)-4,5-dihydrothiophene-3-carbonitrile (**26**) (500 mg, 2.98 mmol) in methanol (5 mL) was added dropwise at 0 °C a solution of Oxone® (9.1 g, 14.80 mmol) in water (50 mL). The reaction mixture was stirred at this temperature for 1 h. Most of the methanol was then evaporated and the residue was extracted with EtOAc (3×30 mL). The combined organic extracts were washed with water (3×20 mL), brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Further purification by flash chromatography (Pet. ether/EtOAc 1:4) gave 5-(3-hydroxypropyl)-2-sulfolene-3-carbonitrile (**27**) (390 mg, 65%) as a thick yellow oil, R_f (Pet. ether/EtOAc 1:4) 0.35; ν_{max} (cm^{-1}) (thin film) 3530 (OH), 2230 (CN), 1309, 1142, 1056; δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.64 (1H, br s, OH), 1.69–2.17 (4H, m, 2×CH_2), 2.72 (1H, ddd, J=17.6, 6.9, 2.6 Hz, one of ring CH_2), 3.22 (1H, ddd, J=17.6, 8.1, 1.7 Hz, one of ring CH_2), 3.47–3.48 (1H, m, CHCH$_2$), 3.73–3.78 (2H, m, CH_2O), 7.30 (1H, m, CH olefinic); δ ^{13}C NMR (100 MHz, $CDCl_3$) 24.8, 29.3, 35.1, 58.8, 61.8, 112.9, 121.6, 142.6; m/z 202 ([M+H]$^+$, 18%), HRMS $C_8H_{12}NO_3S$ required 202.0538, found 202.0534.

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