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An intramolecular Diels–Alder route to novel tetracyclic benzo[*b*]thiophene derivatives

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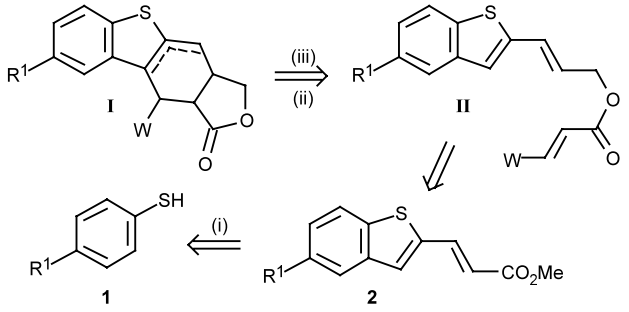
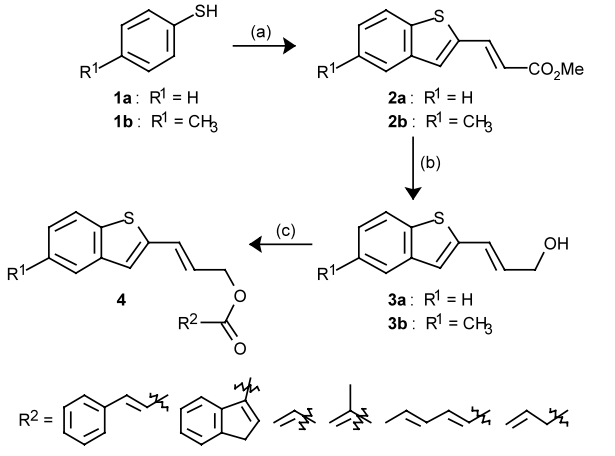
Abstract—A one-pot route to 3-benzo[*b*]thiophen-2-yl-acrylates (**2**) from the corresponding thiophenols (**1**) is reported. Ester reduction and subsequent hydroxyl esterification deliver *psuedo* trienoates (**II**) which undergo an intramolecular Diels–Alder (IMDA) reaction to give two 2-oxa-9-thiacyclopenta[*b*]fluoren-3-one products (**I**)—the major Diels–Alder product rearomatizes to **7**. © 2002 Elsevier Science Ltd. All rights reserved.

Benzo[*b*]thiophene derivatives present interesting synthetic targets and encompass numerous biological activities.[1] While they have been synthesized through various methods,[2] the intramolecular Diels–Alder (IMDA) reactions of benzo[*b*]thiophene derivatives have not been studied extensively.[3] We have investigated this IMDA reaction with the objective of producing novel benzo[*b*]thiophene-containing tetracyclic structures (**I**; Scheme 1) and present here (i) a one-pot preparation of 2-substituted benzo[*b*]thiophene derivative **2** from thiophenol **1**,[4] (ii) the reactivity and stereoselectivity of IMDA reactions of benzo[*b*]thiophene derivatives (**II**), and (iii) observations regarding rearomatization of **I** subsequent to the IMDA reaction.

2-Substituted benzo[*b*]thiophene derivative **2** was prepared from thiophenol **1** (Scheme 2) by *ortho* lithiation with *n*BuLi and TMEDA in cyclohexane[5] followed by treatment of the *ortho*-lithiated phenylthioate with DMF in THF. Subsequent addition of methyl 4-bromocrotonate gave esters **2**—the consequence of *ortho* formylation, *S*-alkylation, and intramolecular aldol condensation. When *ortho* formylation was accomplished with DMF diluted in cyclohexane, the reaction mixture was difficult to stir, resulting in low product yield (15–20%). Substituting THF for cyclohexane largely solved this problem and formation of **2** followed by DIBAL-H reduction of the crude dienoate delivered



Scheme 1. An intramolecular Diels–Alder approach to tetracyclic benzo[*b*]thiophenes.



Scheme 2. Preparation of benzo[*b*]thiophene-based *pseudo* trienoates. (a) (i) *n*BuLi, TMEDA, cyclohexane, rt, 24 h, (ii) DMF, THF, rt, 12 h, (iii) methyl 4-bromocrotonate, rt, 6 h; (b) DIBAL-H, 0°C, 2 h; (c) R^2CO_2H, DCC, DMAP, CH_2Cl_2, rt, 2 h.

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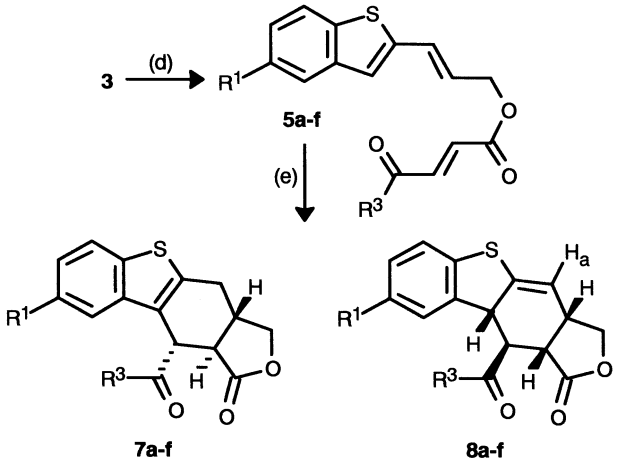
hydroxy diene **3**[6] in 37–41% overall yield from thiophenol **1**. DCC-mediated esterification of **3** with various acrylic acid derivatives gave esters **4** in good yield (84–98%). Unfortunately, these *pseudo* trienoates failed as IMDA substrates—even under harsh, sealed tube reaction conditions (e.g. 255°C, 7 days). These disappointing results clearly indicate that (2-vinyl)-benzo[*b*]thiophene derivatives afford poor diene reactivity for the IMDA reaction. Attempts at Lewis acid catalyzed IMDA with these substrates were equally ineffective, leading to extensive starting material decomposition.

This lack of IMDA reactivity led us to investigate doubly activating the dienophile moiety of *pseudo* trienoate **4**. Thus, alcohols **3**[7] were esterified to **5** in moderate yields (57–84%; Scheme 3) by treatment with (*E*)-4-oxobut-2-enoic acid derivatives[8] under DCC/DMAP coupling conditions. We were pleased to find that heating toluene solutions of these doubly activated *pseudo* trienoates at 115–140°C in sealed tubes deliver one major Diels–Alder product[9] together with a minor Diels–Alder product (Scheme 3) and a trace amount of an aldehyde. Spectroscopic studies established this aldehyde to be (*E*)-3-(benzo[*b*]thiophen-2-yl)-2-propen-1-al, which was apparently formed by a thermal ene reaction of **5**.

HMQC experiments identified two CH_2 correlation peaks for each major IMDA product (**7**), but only one CH_2 correlation peak for each minor IMDA product



(d) (*E*)-R^3-CH=CH-CO_2H, DCC, DMAP, CH_2Cl_2, rt, 2 h. (e) Toluene, sealed tube, 115-140 °C, 12-20 h.

Reactants	R^1	R^3	Ratio **7:8**	Reaction °C/h	Yield
5a	H	Me	61:39	120/12	62%
5b	Me	Me	62:38	115/20	52%
5c	H	Ph	76:24	140/12	61%
5d	Me	Ph	74:26	140/14	75%
5e	H	2-Cl-Ph	80:20	140/14	65%
5f	Me	2-Cl-Ph	75:25	140/14	64%

Scheme 3. IMDA of *psuedo* trienoate **5**.

(**8**). Moreover, the ^1H NMR signal at ca. 5.5 ppm (H_a) in **8** is clearly correlated with the ^{13}C NMR signal at ca. 115 ppm. From these NMR experiments, it was clear that the major product contains a rearomatized benzo[*b*]thiophene structure, while the minor product does not. That these two IMDA products are not in dynamic equilibrium was established by exposing pure **7c** and pure **8c** to IMDA reaction conditions for 10 h; neither IMDA product isomerized to the other. Finally, the structures of major (e.g. **7f**) and minor (e.g. **8d**) IMDA products were confirmed by X-ray crystallographic analysis (Fig. 1).

Clearly, the IMDA reaction of **5** can proceed via a transition state in which the ketone carbonyl occupies the *endo* position or via a transition state in which the ester carbonyl occupies the *endo* position. The former would lead to the unobserved IMDA adduct **6** while the latter would deliver the observed product **8**. The *endo*-ketone cycloaddition (i.e. **5**→**6**) followed by C,C-double bond isomerization would deliver **7**, which is in fact the major product in each cycloaddition reaction. In contrast, the minor *endo*–ester cycloadduct (**8**) does not undergo C,C-double bond isomerization to the benzo[*b*]thiophene substructure (i.e. to the unobserved product **9**). We were surprised at the apparent thermodynamic energetics in the **6**/**7** versus **8**/**9** equilibration processes and set out to establish computational energy differences for these two C,C-double bond isomerizations. Using Wavefunction's Spartan software with the MMFF94 forcefield, we calculated that the lowest energy conformer of isomerized **7c** is 0.70 kcal/mol more stable than the lowest energy conformer of IMDA product **6c** (see Scheme 4). While relative energies of such small magnitude must be viewed with reservation, this result suggests that the observed isomerization of **6c** to **7c** is energetically favored. Since the thermal [1,3] sigmatropic rearrangement **6c**→**7c** would be antarafacial, we assume this isomerization proceeds by a stepwise process. However, cycloadduct **8c** is formed simultaneously with **6c** (→**7c**) and could presumably avail itself to a similar stepwise isomerization leading to **9c**. Calculations show that this process is energetically disfavored with the lowest energy conformer of IMDA product **8c** calculated to be 6.28 kcal/mol more stable than unobserved product **9c**.

The experimental results presented in Scheme 3 demonstrate that both *endo*-ketone and *endo*-ester pathways

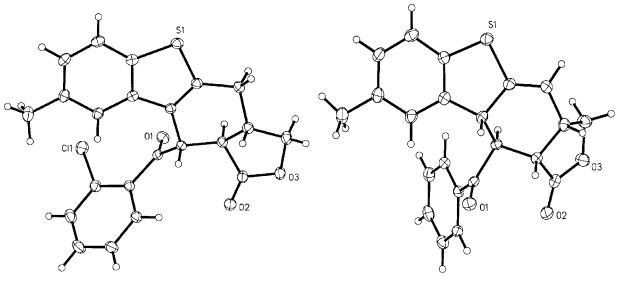
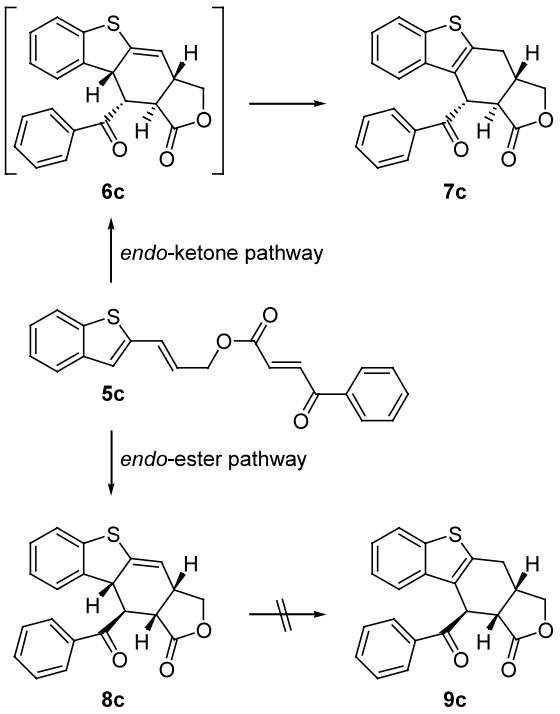


Figure 1. X-Ray structures of **7f** and **8d**.



Scheme 4. C,C-double bond isomerization in 2-oxa-9-thia-cyclopenta[*b*]-fluoren-3-ones.

are operative in the cycloaddition of **5**. Moreover, MMFF94 calculations indicate the final product distribution (cf. Scheme 4) is determined by the relative energetics of stepwise olefin isomerizations (**6c→7c** and **8c→9c**).

Acknowledgements

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7. **General experimental for 1b to 7d**. **Methyl (2*E*)-3-(5-methylbenzo[*b*]thiophen-2-yl)prop-2-enoate (2b)**. A solution of 4-methylbenzenethiol (**1b**, 3.0 g, 24 mmol) and TMEDA (8.5 mL, 53 mmol) in distilled cyclohexane (200 mL) was prepared in a 500 mL three-neck flask equipped with a dropping funnel under a dry nitrogen atmosphere. *n*-BuLi (1.6 M; 33 mL, 53 mmol) in hexanes was added dropwise over 30 min at 0°C and the reaction mixture was stirred for 24 h at rt. To the resulting slightly yellow, turbid solution was added dropwise over 1 h DMF (4.6 mL, 60 mmol) in THF (30 mL) at 0°C. The reaction mixture was stirred for 12 h at rt to give a white turbid solution to which was added a solution of methyl 4-bromocrotonate (4.3 mL, 31 mmol) in distilled cyclohexane (50 mL; dropwise at 0°C). After various color changes occurred (yellow turbid→orange turbid→peach turbid) while stirring for 12 h at rt, a dark green turbid reaction mixture was obtained. Aqueous 1N HCl was added dropwise to make a slightly acidic solution and the organic layer was collected, dried with anhydrous $MgSO_4$, filtered, and concentrated. Column chromatography (10% EtOAc/hex) afforded the title compound as a slightly yellow solid (2.50 g, 10.8 mmol, 45%): $R_f = 0.53$ (EtOAc/hex = 1/2); mp 115.3–115.7°C; FTIR (KBr) 1711, 1629, 1431, 1321 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.81 (s, 3H), 6.28 (d, $J = 15.8$ Hz, 1H), 7.20 (dm, $J = 8.2$ Hz, 1H), 7.37 (s, 1H), 7.55 (s, br, 1H), 7.66 (d, $J = 8.2$ Hz, 1H), 7.86 (d, $J = 15.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 51.8, 118.5, 121.9, 124.2, 127.9, 128.4, 134.5, 137.3, 137.9, 139.4, 139.7, 166.8. Anal. calcd for $C_{13}H_{12}O_2S$: C, 67.22; H, 5.21. Found: C, 67.51; H, 5.35.
(2*E*)-3-(5-Methylbenzo[*b*]thiophen-2-yl)prop-2-en-1-ol (3b). Methyl (2*E*)-3-(5-methylbenzo[*b*]thiophen-2-yl)prop-2-enoate (**2b**, 2.10 g, 9.0 mmol) was dissolved in toluene (30 mL) and DIBAL-H (1.0 M in hexanes; 20 mL, 20 mmol) was added dropwise over 10 min at 0°C. After stirring 1 h

at 0°C, the reaction was quenched by addition of a toluene/methanol (1:1; 20 mL) mixture and a saturated solution of Rochelle's salt (aq.). Aqueous 1N HCl was added to make a slightly acidic solution and the organic layer was collected, dried with anhydrous $MgSO_4$, filtered, and concentrated. Column chromatography (20% EtOAc/hex) afforded the title compound as a slightly yellow solid (1.65 g, 8.1 mmol, 90%): $R_f = 0.34$ (EtOAc/hex = 1/2); mp 115–117°C; FTIR (KBr) 3277, 1492, 1443 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, br, 1H), 2.44 (s, 3H), 4.33 (dd, $J = 5.5$, 1.5 Hz, 2H), 6.28 (dt, $J = 15.8$, 5.5 Hz, 1H), 6.84 (dm, $J = 15.8$, 1H), 7.06 (s, 1H), 7.13 (dd, $J = 8.2$, 1.6 Hz, 1H), 7.47 (s, br, 1H), 7.63 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 63.2, 121.8, 122.7, 123.5, 124.8, 126.4, 130.5, 134.1, 136.0, 140.3, 142.0.

(2*E*)-3-(5-methylbenzo[*b*]thiophen-2-yl)prop-2-enyl (2*E*)-4-oxo-4-phenylbut-2-enoate (5d). A solution of (*2E*)-4-oxo-4-phenyl-2-butenoic acid (0.15 g, 0.87 mmol), DCC (0.18 g, 0.87 mmol), (2*E*)-3-(5-methylbenzo[*b*]thiophen-2-yl)prop-2-en-1-ol (**3b**, 0.12 g, 0.62 mmol) and DMAP (7 mg, 0.06 mmol) in dichloromethane (20 mL), was stirred for 2 h at rt. The *N*,*N*-dicyclohexylurea ppt was removed by filtration and the filtrate was washed with water, dried ($MgSO_4$), filtered, and concentrated. Column chromatography (20% EtOAc/ hex) afforded the title compound as a slightly yellow solid (0.18 g, 0.51 mmol, 81%): $R_f = 0.65$ (EtOAc/hex = 1/2); mp 98–99°C; FTIR (KBr) 1723, 1670, 1593, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 4.91 (dd, $J = 6.4$, 1.3 Hz, 2H), 6.22 (dt, $J = 15.6$, 6.4 Hz, 1H), 6.92 (d, br, $J = 15.6$ Hz, 1H), 6.94 (d, $J = 15.6$ Hz, 1H), 7.12–7.16 (m, 1H), 7.14 (s, br, 1H), 7.48–7.56 (m, 3H), 7.60–7.66 (m, 2H), 7.96 (d, $J = 15.6$ Hz, 1H), 7.99–8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 65.3, 121.8, 123.6, 123.8, 124.1, 126.7, 128.5, 128.83, 128.84, 132.0, 133.8, 134.2, 136.2, 136.4, 136.8, 140.1, 141.1, 165.2, 189.3.

IMDA of 5d. A solution of **5d** (0.20 g, 0.55 mmol) in toluene (5 mL) was stirred for 14 h at 140°C in a sealed tube. The solvent was evaporated under vacuum. Column chromatography (20% EtOAc/hex) afforded two white solids: **7d** (110 mg) [$R_f = 0.38$ (EtOAc/hex = 1/2); mp 277.7–278.5°C; FTIR (KBr) 1771, 1681, 1592 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.78–2.91 (m, 1H), 3.04–3.29 (m, 3H), 4.16 (dd, $J = 10.8$, 8.8 Hz, 1H), 4.63 (dd, $J = 8.8$, 6.8 Hz, 1H), 5.14 (dm, $J = 10.6$ Hz, 1H), 6.84 (s, br, 1H), 7.03 (d, br, $J = 7.5$ Hz, 1H), 7.55–7.62 (m, 3H), 7.65–7.72 (m, 1H), 8.20 (d, br, $J = 7.2$ Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 28.8, 39.8, 43.9, 47.5, 71.6, 122.0, 122.1, 125.9, 127.8, 128.8, 128.9, 129.0, 133.7, 134.0, 137.6, 137.9, 138.3, 174.9, 201.2. Anal. calcd for $C_{22}H_{18}O_3S$: C, 72.91; H, 5.01. Found: C, 72.95; H, 5.14.] and **8d** (39 mg) [$R_f = 0.47$ (EtOAc/hex = 1/2); FTIR (KBr) 1746, 1682, 1467, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 3H), 3.23 (m, 1H), 3.32 (m, 1H), 4.09 (m, 1H), 4.24 (dd, $J = 9.2$, 4.4 Hz, 1H), 4.49 (dd, $J = 9.0$, 6.6 Hz, 1H), 4.63 (dm, $J = 10.4$ Hz, 1H), 5.67 (dd, $J = 3.5$, 2.6 Hz, 1H), 6.55 (s, 1H), 6.93 (d, $J = 8.2$ Hz, 1H), 7.05 (d, $J = 8.1$ Hz, 1H), 7.20–7.31 (m, 2H), 7.50 (m, 1H), 7.61 (m, 1H), 8.13 (dd, $J = 8.4$, 1.3 Hz, 1H); see X-ray structure in Fig. 1] in a combined total yield of 75% (149 mg, 0.41 mmol).

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9. **IMDA product 7a**. $R_f = 0.33$ (EtOAc/hex = 1/2); mp 146–147°C; FTIR (KBr) 1777, 1698, 1432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 2.69–2.89 (m, 2H), 2.97–3.06 (m, 1H), 3.14–3.21 (m, 1H), 4.15 (dd, $J = 10.5$, 8.8 Hz, 1H), 4.26 (m, 1H), 4.63 (dd, $J = 8.6$, 6.6 Hz, 1H), 7.28–7.35 (m, 2H), 7.37–7.42 (m, 1H), 7.74–7.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 31.2, 39.7, 46.2, 49.8, 71.4, 121.2, 122.7, 124.5, 124.7, 127.2, 137.3, 137.8, 138.9, 174.7, 208.7. Anal. calcd for $C_{16}H_{14}O_3S$: C, 67.11; H, 4.93. Found: C, 67.32; H, 5.05.

IMDA product 7b. $R_f = 0.24$ (EtOAc/hex = 1/2); mp 198.8–199.3°C; FTIR (KBr) 1773, 1718, 1601, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 2.61 (s, 3H), 2.67–2.87 (m, 2H), 2.95–3.05 (m, 1H), 3.10–3.19 (m, 1H), 4.14 (dd, $J = 10.4$, 8.8 Hz, 1H), 4.22 (dm, $J = 10.8$ Hz, 1H), 4.62 (dd, $J = 8.6$, 6.6 Hz, 1H), 7.11–7.19 (m, 2H), 7.63 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 28.8, 31.0, 39.7, 46.2, 49.9, 71.4, 121.2, 122.3, 126.2, 126.8, 134.5, 136.1, 137.6, 137.9, 174.7, 208.8. Anal. calcd for $C_{17}H_{16}O_3S$: C, 67.98; H, 5.37. Found: C, 67.81; H, 5.30.

IMDA product 7c. $R_f = 0.30$ (EtOAc/hex = 1/2); mp 271.7–272.4°C; FTIR (KBr) 1774, 1732, 1676, 1623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.78–2.92 (m, 1H), 3.03–3.26 (m, 3H), 4.16 (dd, $J = 10.6$, 9.0 Hz, 1H), 4.63 (dd, $J = 8.8$, 6.8, 1H), 5.19 (d, $J = 10.6$ Hz, 1H), 7.00–7.12 (m, 2H), 7.17–7.25 (m, 1H), 7.51–7.62 (m, 2H), 7.63–7.76 (m, 2H), 8.22 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 39.8, 43.6, 47.6, 71.5, 121.6, 122.6, 124.3, 124.4, 128.3, 128.9, 129.1, 133.8, 137.3, 137.90, 137.92, 138.9, 174.7, 201.0. Anal. calcd for $C_{21}H_{16}O_3S$: C, 72.39; H, 4.63. Found: C, 72.52; H, 4.72.

IMDA product 7e. $R_f = 0.23$ (EtOAc/hex = 1/2); mp 166–168°C; FTIR (KBr) 1774, 1690, 1626, 1586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.74–2.87 (m, 1H), 3.00–3.09 (m, 1H), 3.14–3.27 (m, 2H), 4.17 (dd, $J = 10.9$, 8.6 Hz, 1H), 4.62 (dd, $J = 8.6$, 6.8 Hz, 1H), 5.12 (m, 1H), 7.14–7.20 (m, 1H), 7.24–7.29 (m, 2H), 7.42–7.47 (m, 1H), 7.48–7.51 (m, 2H), 7.73–7.77 (m, 1H), 8.12 (dd, $J = 7.7$, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.7, 39.8, 47.1, 47.4, 71.4, 121.8, 122.5, 124.4, 124.5, 126.9, 127.5, 130.7, 131.5, 132.9, 133.0, 137.2, 138.0, 138.1, 138.8, 174.8, 200.4. Anal. calcd for $C_{21}H_{15}ClO_3S$: C, 65.88; H, 3.95. Found: C, 65.79; H, 3.87.

IMDA product 7f. $R_f = 0.27$ (EtOAc/hex = 1/2); mp 203–205°C; FTIR (KBr) 1769, 1687, 1587, 1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.72–2.87 (m, 1H), 2.99–3.18 (m, 2H), 3.25–3.34 (m, 1H), 4.19 (dd, $J = 11.2$, 8.6 Hz, 1H), 4.62 (dd, $J = 8.6$, 7.0, 1H), 5.05 (d, $J = 10.4$ Hz, 1H), 6.97 (s, 1H), 7.08 (d, $J = 8.1$ Hz, 1H), 7.44–7.62 (m, 4H), 8.18 (dd, $J = 7.3$, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 28.8, 39.7, 46.8, 47.5, 71.4, 122.03, 122.05, 125.9, 126.9, 127.1, 130.6, 131.3, 132.8, 133.0, 134.2, 135.8, 137.5, 138.1, 138.4, 175.0, 200.4. Anal. calcd for $C_{22}H_{17}ClO_3S$: C, 66.58; H, 4.32. Found: C, 66.24; H, 4.33.