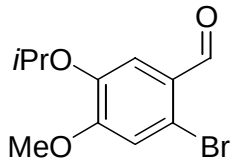
Supporting Information

for

Iodine Induced Reaction Cascades for the Rapid Construction of Variously Substituted Benzothiophenes.

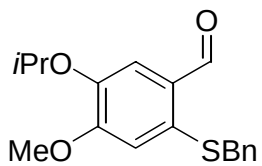
Karl O. Hessian and Bernard L. Flynn*



2-Bromo-5-isopropoxy-4-methoxybenzaldehyde (**12**)

NBS (11.21 g, 63.0 mmol) was added to a solution of **11** (8.73 g, 45.0 mmol) in DMF (10 mL) at room temperature, and heated to 80 ˚C. After 7 h, the solution was cooled to room temperature, diluted with diethyl ether (200 mL), washed with $Na_2S_2O_{5(aq)}$ (5% w/v, 200 mL), water (2 x 200 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (25 g). The solid residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether 95 : 5, then 9 : 1) to give the product **12** as a white solid (11.65 g, 94 %), mp = 78 - 79 ˚C.

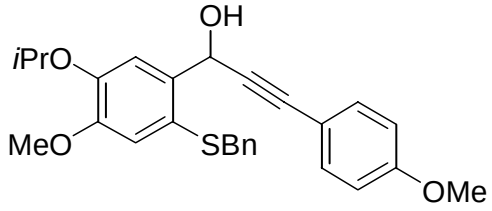
^{1}H-NMR ($CDCl_3$) δ 10.16 (s, 1H), 7.41 (s, 1H), 7.04 (s, 1H), 4.61 (septet, *J* = 6.0 Hz, 1H), 3.92 (s, 3H), 1.36 (d, *J* = 6.0 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 190.8 (C), 155.6 (C), 147.1 (C), 126.4 (C), 120.0 (C), 115.8 (C-H), 113.5 (C-H), 71.5 (C-H), 56.4 (CH_3), 21.8 (CH_3). LRMS m/z (calculated for $C_{11}H_{13}O_3{}^{81}Br$) = 274 (21) (M^+), 232 (100). HRMS Calculated for $C_{11}H_{13}O_3{}^{81}Br$ = 274.0028. Found = 274.0024. IR (KBr disc, cm^{-1}) = 2971, 1681, 1587, 1508, 1432, 1386, 1268, 1217, 1158, 1109.



Benzyl 2-formyl-4-isopropoxy-5-methoxyphenylsulfide (**13**)

Benzyl mercaptan (4.51 mL, 38.4 mmol) was added dropwise over 0.25 h to a stirred suspension of NaH (1.76 g, 43.9 mmol) in THF (75 mL) at 0 ˚C (icebath). To this was added a solution of **12** (10.0 g, 36.6 mmol) in THF (25 mL), and the reaction heated to 45 ˚C for 12 h. After this time, the reaction was cooled to room temperature, diluted with dichloromethane (200 mL), washed with $HCl_{(aq)}$ (5%, 100 mL), $NaOCl_{(aq)}$ (1%, 100 mL) and water (3 x 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (18 g). The solid residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether 4 : 1) to give the product **13** as a yellow solid (10.29 g, 89 %), mp = 49 - 51 ˚C.

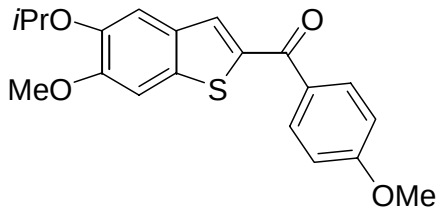
^{1}H-NMR ($CDCl_3$) δ 10.19 (s, 1H), 7.33 (s, 1H), 7.21 - 7.05 (m, 5H), 6.76 (s, 1H), 4.59 (septet, *J* = 6.1 Hz, 1H), 3.95 (s, 2H), 3.74 (s, 3H), 1.34 (d, *J* = 6.1 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 190.3 (C), 154.3 (C), 147.2 (C), 136.9 (C), 132.1 (C), 130.1 (C), 128.7 (C-H), 128.3 (C-H), 127.1 (C-H), 116.9 (C-H), 112.9 (C-H), 71.0 (C-H), 55.9 (-CH_3), 41.4 (CH_2), 21.6 (-CH_3). LRMS m/z = 316 (26) (M^+), 274 (11), 225 (17), 183 (59). HRMS Calculated for $C_{18}H_{20}O_3S$ = 316.1133. Found = 316.1144. IR (KBr disc, cm-1) = 2988, 2861, 1666, 1578, 1495, 1439, 1388, 1334, 1262, 1158, 700.



1-(2-Benzylthioxy-5-isopropoxy-4-methoxyphenyl)-3-(4-methoxyphenyl)prop-2-yn-ol (**14**)

n-Butyllithium (6.51 mL, 13.0 mmol) was added dropwise to a solution of *gem*-dibromostyrene (2.28 g, 6.51 mmol) in THF (20 mL) at -78 ˚C (dry-ice / acetone bath). The solution was warmed to room temperature and stirred for 0.5 h, then recooled to -78 ˚C. After this time a solution of **13** (2.00 g, 6.33 mmol) in THF (6 mL) was added and left to stir for 0.25 h. The reaction was bought to room temperature again, quenched with $NH_4Cl_{(aq)}$ (10%, 100 mL), taken up into diethyl ether (150 mL), washed with water (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (8 g). The solid residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether 3 : 2) to give the product **14** as a yellow resin (2.72 g, 96%).

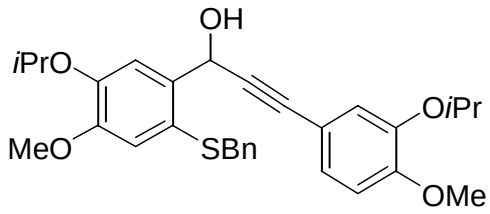
^{1}H-NMR ($CDCl_3$) δ 7.43 (d, *J* = 8.6 Hz, 2H), 7.42 (s, 1H), 7.32 - 7.22 (m, 5H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.79 (s, 1H), 6.08 (d, *J* = 4.6 Hz, 1H), 4.68 (septet, *J* = 6.0 Hz, 1H), 4.05 (s, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 2.51 (d, *J* = 4.6 Hz, 1H), 1.45 (dd, *J* = 2.0, 6.0 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 159.3 (C), 149.2 (C), 147.6 (C), 137.9 (C), 137.1 (C), 132.8 (C-H), 128.8 (C-H), 128.1 (C-H), 126.8 (C-H), 122.7 (C), 118.6 (C-H), 114.5 (C), 113.8 (C-H), 113.6 (C-H), 88.0 (C), 85.8 (C), 70.9 (C-H), 62.6 (C-H), 55.6 (-CH_3), 54.9 (-CH_3), 41.4 (-CH_2), 21.8 (-CH_3), 21.5 (-CH_3). LRMS m/z = 448 (18) (M^+), 357 (53), 315 (25). HRMS Calculated for $C_{27}H_{28}O_4S$ = 448.1708. Found = 448.1707. IR (NaCl film, cm^{-1}) = 3487, 2975, 2837, 1604, 1508, 1440, 1385, 1290, 1249, 1173.



5-Isopropoxy-2-(3-isopropoxy-4-methoxybenzoyl)-6-methoxybenzo[*b*]thiophene (**18**)

Iodine (272 mg, 1.07 mmol) was added to a solution of **14** (470 mg, 1.05 mmol) in dichloromethane (10 mL) and left to stir. After 0.5 h, the solution was diluted with dichloromethane (40 mL), washed with $Na_2S_2O_{5(aq)}$ (10%, 50 mL), and water (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (4 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether 5 : 3) to give the product **18** as a yellow solid (337 mg, 90%) mp = 115 - 117 ˚C.

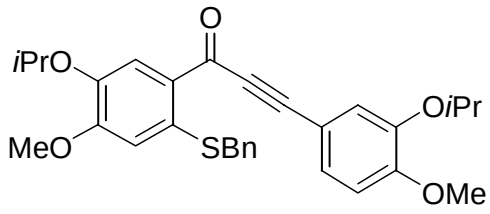
^{1}H-NMR ($CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 7.72 (s, 1H), 7.30 (s, 1H), 7.27 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 4.57 (septet, *J* = 6.1 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 1.41 (d, *J* = 6.1 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 187.8 (C), 162.9 (C), 152.1 (C), 146.8 (C), 141.4 (C), 137.0 (C), 132.7 (C), 131.5 (C-H), 131.3 (C-H), 130.7 (C), 113.6 (C-H), 110.3 (C-H), 103.9 (C-H), 71.7 (C-H), 56.1 (-CH_3), 55.5 (-CH_3), 21.9 (-CH_3). LRMS m/z = 356 (65) (M^+), 314 (100), 271 (25). HRMS Calculated for $C_{20}H_{20}O_4S$ = 356.1082. Found = 356.1084. IR (KBr disc, cm^{-1}) = 2974, 2837, 1601, 1571, 1503, 1462, 1355, 1290, 1231, 1172.



1-(2-Benzylthioxy-5-isopropoxy-4-methoxyphenyl)-3-(3-isopropoxy-4-methoxyphenyl)prop-2-yn-ol (**20**)

n-Butyllithium (10.2 mL, 20.4 mmol) was added dropwise to a solution of *gem*-dibromostyrene (3.57 g, 10.2 mmol) in THF (25 mL) at -78 ˚C (dry-ice / acetone bath). The solution was warmed to room temperature and stirred for 0.5 h, then recooled to -78 ˚C. After this time a solution of **13** (3.16 g, 10.0 mmol) in THF (6 mL) was added and left to stir for 0.5 h. The reaction was bought to room temperature, quenched with $NH_4Cl_{(aq)}$ (10%, 100 mL), taken up into diethyl ether (150 mL), washed with water (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (8 g). The solid residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether 3 : 2) to give the product **20** as a yellow resin (4.91 g, 97%).

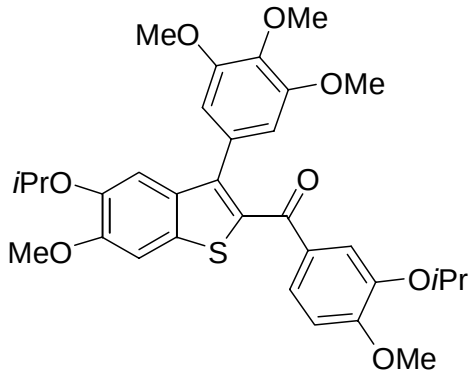
^{1}H-NMR ($CDCl_3$) δ 7.30 (s, 1H), 7.25 - 7.09 (m, 5H), 7.01 (dd, *J* = 1.8, 8.3 Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.75 (s, 1H), 6.07 (d, *J* = 5.1 Hz, 1H), 4.62 (septet, *J* = 6.1 Hz, 1H), 4.45 (septet, *J* = 6.1 Hz, 1H), 3.99 (s, 2H), 3.83 (s, 3H), 3.70 (s, 3H), 2.40 (d, *J* = 5.1 Hz, 1H), 1.38 (dd, *J* = 3.7, 6.1 Hz, 6H), 1.33 (d, *J* = 6.1 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 150.9 (C), 149.7 (C), 146.8 (C), 138.2 (C), 137.5 (C), 129.1 (C-H), 128.5 (C-H), 127.2 (C-H), 125.2 (C-H), 123.0 (C), 119.0 (C-H), 118.6 (C-H), 114.8 (C), 114.2 (C-H), 111.6 (C-H), 87.9 (C), 86.4 (C), 71.4 (C-H), 71.3 (C-H), 63.0 (C-H), 56.0 (-CH_3), 55.9 (-CH_3), 41.8 (-CH_2), 22.2 (-CH_3), 21.8 (-CH_3). LRMS m/z = 506 (43) (M^+), 415 (100). HRMS Calculated for $C_{30}H_{34}O_5S$ = 506.2126. Found = 506.2131. IR (NaCl film, cm^{-1}) = 2978, 1592, 1504, 1386, 1264, 1110, 1044.



1-(2-Benzylthioxy-5-isopropoxy-4-methoxyphenyl)-3-(3-isopropoxy-4-methoxyphenyl)prop-2-ynone (**21**)

MnO_2 (5 g, 10 eq.) was added to a solution of **20** (500 mg, 0.988 mmol) in THF (10 mL) and left to stir. After 2 h, the solution was filtered, rinsing with dichloromethane (4 x 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the product **21** as a yellow solid (490 mg, 98%), mp = 118 - 119 ˚C.

^{1}H-NMR ($CDCl_3$) δ 7.91 (s, 1H), 7.46 - 7.22 (m, 6H), 7.14 (d, *J* = 1.8 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.76 (s, 1H), 4.54 (septet, *J* = 6.1 Hz, 1H), 4.17 (s, 2H), 3.89 (s, 3H), 3.75 (s, 3H), 1.40 (d, *J* = 6.1 Hz, 6H), 1.38 (d, *J* = 6.1 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 176.3 (C), 154.5 (C), 152.8 (C), 147.2 (C), 143.6 (C), 137.0 (C), 136.6 (C), 128.9 (C-H), 128.7 (C-H), 127.4 (C-H), 127.2 (C), 127.1 (C-H), 121.2 (C-H), 119.3 (C-H), 112.3 (C), 111.7 (C-H), 109.5 (C-H), 93.6 (C), 87.0 (C), 72.1 (C-H), 71.6 (C-H), 56.1 (-CH_3), 56.0 (-CH_3), 32.0 (-CH_2), 22.1 (-CH_3), 22.0 (-CH_3). LRMS m/z = 504 (12) (M^+), 413 (100). HRMS Calculated for $C_{30}H_{32}O_5S$ = 504.1970. Found = 504.1964. IR (KBr disc, cm^{-1}) = 2974, 2928, 2188, 1593, 1541, 1509, 1439, 1266, 1202, 1178.

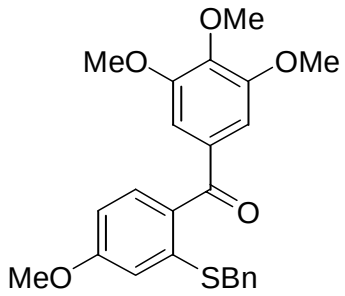


5-Isopropoxy-2-(3-isopropoxy-4-methoxybenzoyl)-6-methoxy-3-(3,4,5-trimethoxyphenyl)benzo[*b*]thiophene (**24**)

3,4,5-trimethoxyphenyllithium **22** was generated by addition of *t*-butyllithium (0.71 mL, 1.17 mmol) to a solution of 3,4,5-trimethoxyiodobenzene (173 mg, 0.588 mmol) in THF (3 mL) at -78 ˚C (dry-ice / acetone bath) which was left to stir for 0.25 h. After this time, a solution of **21** (237 mg, 0.469 mmol) in THF (2 mL) was added. After stirring for a further 0.25 h, the solution was warmed to room temperature and quenched with $NH_4Cl_{(aq)}$ (10%, 30 mL), extracted with diethyl ether (40 mL), washed with water (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude brown residue was dissolved in dichloromethane (5 mL) and a solution of iodine (119 mg, 0.469 mmol) in dichloromethane (2 mL) added and the reaction mixture left to

stir for a further 0.25 h. This as diluted with diethyl ether (30 mL), washed with $Na_2S_2O_{5(aq)}$ (5%, 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether 2 : 3) to afford the product **24** as a yellow resin (213 mg, 78%).

^{1}H-NMR ($CDCl_3$) δ 7.31 (s, 1H), 7.27 - 7.20 (m, 3H), 6.61 (d, *J* = 8.4 Hz, 1H), 6.50 (s, 2H), 4.47 (septet, *J* = 6.1 Hz, 1H), 4.42 (septet, *J* = 6.1 Hz, 1H), 3.96 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.72 (s, 6H), 1.36 (d, *J* = 6.1 Hz, 6H), 1.28 (d, *J* = 6.1 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 186.3 (C), 154.1 (C), 153.0 (C), 151.9 (C), 147.2 (C), 146.8 (C), 140.3 (C), 136.2 (C), 134.6 (C), 132.7 (C), 130.9 (C), 131.4 (C), 124.8 (C-H), 116.0 (C-H), 110.3 (C-H), 109.8 (C-H), 107.6 (C-H), 104.0 (C-H), 71.8 (C-H), 71.7 (C-H), 61.4 (CH_3), 56.4 (CH_3), 56.2 (CH_3), 56.0 (CH_3), 21.9 (CH_3). LRMS m/z = 580 (100) (M^+), 538 (12), 496 (30). HRMS Calculated for $C_{32}H_{36}O_8S$ = 580.2130. Found = 580.2136. IR (NaCl film, cm^{-1}) = 2612, 2590, 1853, 1602, 1546, 1523, 1410, 1120, 1075.

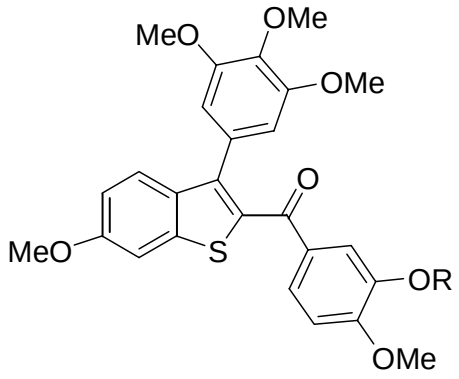


Benzyl 2-(3, 4, 5-trimethoxybenzoyl)-5-methoxyphenyl sulfide (**27**)

n-Butyllithium (0.28 mL, 0.56 mmol) was added to benzyl 2-iodo-5-methoxyphenyl sulfide (200 mg, 0.56 mmol) in THF (5 mL) at -78 ˚C (dry-ice / acetone bath), and stirred for 0.25 h. After this time, a solution of trimethoxybenzoylchloride (135 mg, 0.58 mmol) in THF (2 mL) was added, and the solution stirred for a further 0.5 h, and then warmed to room temperature. The solution was diluted with diethyl ether (50 mL), washed with $NH_4Cl_{(aq)}$ (10%, 50 mL), and water (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether 4 : 1, 3 : 2) to give the product **27** as a white solid (181 mg, 76%), mp = 136 – 138 °C.

^{1}H-NMR ($CDCl_3$) δ 7.31 - 7.22 (m, 3H), 7.18 - 7.09 (m, 3H), 6.92 (s, 1H), 6.85 (d, *J* = 2 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 4.21 (s, 2H), 3.95 (s, 3H), 3.83 (s, 3H), 3.80 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 182.6 (C), 154.6 (C), 151.9 (C), 143.1 (C), 142.9 (C), 140.1 (C-H), 130.4 (C), 129.7 (C). 125.0

(C), 120.3 (C-H), 119.5 (C-H), 116.0 (C-H), 111.4 (C-H), 110.7 (C-H), 106.3 (C-H), 61.3 (CH_3), 56.6 (CH_3), 56.4 (CH_3), 41.4 (CH_2). LRMS m/z = 424 (32) (M^+), 333 (100). HRMS Calculated for $C_{24}H_{24}O_5S$ = 424.1981. Found = 424.1977. IR (KBr disc, cm^{-1}) = 2643, 2597, 1784, 1602, 1433, 1306, 1295, 1110.

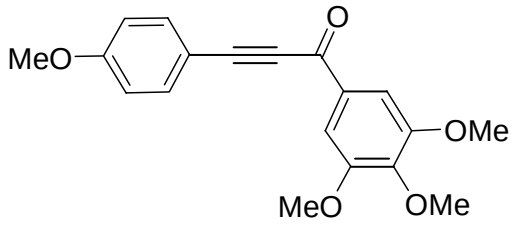


2-(3-Isopropoxy-4-methoxybenzoyl)-6-methoxy-3-(3,4,5-trimethoxyphenyl)benzo[*b*]thiophene (**29**)

n-Butyllithium (1.02 mL, 2.04 mmol) was added dropwise to a solution of *gem*-dibromostyrene (357 mg, 1.02 mmol) in THF (5 mL) at -78 ˚C (dry-ice / acetone bath). The solution was warmed to room temperature and stirred for 0.5 h, then recooled to -78 ˚C. After this time a solution of **27** (424 mg, 1.00 mmol) in THF (2 mL) was added and left to stir for 0.5 h. The reaction was bought to room temperature, quenched with $NH_4Cl_{(aq)}$ (10%, 30 mL), taken up into diethyl ether (30 mL), washed with water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude brown residue was dissolved in dichloromethane (5 mL) and stirred for 0.1 h. After this time a solution of iodine (254 mg, 1.00 mmol) in dichloromethane (3 mL) was added and left to stir for a further 0.25 h, then diluted with diethyl ether (30 mL), washed with $Na_2S_2O_{5(aq)}$ (5%, 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether 4:1, 3:1, 1:1) to afford the product **29** as a white solid (430 mg, 82%).

^{1}H-NMR ($CDCl_3$) δ 7.12 - 7.06 (m, 3H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.91 (dd, *J* = 2.1, 8.0 Hz, 1H), 6.70 (s, 2H), 6.65 (d,*J* = 8.0 Hz, 1H), 4.58 (septet, *J* = 6.0 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.77 (s, 6H), 1.39 (d, *J* = 6.0 Hz, 6H). ^{13}C-NMR ($CDCl_3$) δ 187.1 (C), 156.3 (C), 151.0 (C), 149.6 (C), 147.0 (C), 144.6 (C), 139.9 (C), 134.7 (C), 131.9 (C), 133.2 (C), 128.6 (C), 127.2 (C), 124.9 (C-H), 118.2 (C-H), 114.9 (C-H), 111.8 (C-H), 108.4 (C-H), 106.7 (C-H), 103.9 (C-H),

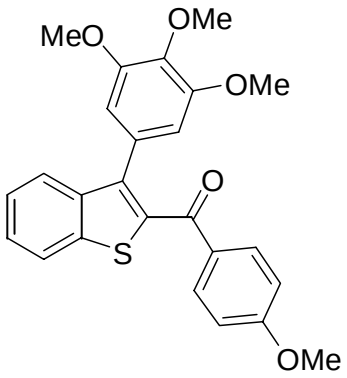
71.7 (C-H), 61.7 (CH_3), 56.4 (CH_3), 56.3 (CH_3), 56.1 (CH_3), 21.9 (CH_3). LRMS m/z = 522 (20), 462 (70), 327 (100). HRMS Calculated for $C_{29}H_{30}O_7S$ = 522.1713. Found = 522.1714.



3-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1one (**30**)

n-Butyllithium (20.0 mL), 40.0 mmol) was added to a solution of *gem*-dibromostyrene (5.55 g, 19.0 mmol) in THF (50 mL) at -78 ˚C (dry-ice / acetone bath). The solution was stirred at this temperature for 0.25 h, and then warmed to room temperature and left to stir for a further 0.5 h. The solution was recooled to -78 ˚C, and 3,4,5-trimethoxybenzaldehyde (3.84 g, 19.6 mmol) was added. After stirring for 0.5 h, the solution was again bought to room temperature and left to stir for 0.25 h. After this time, the solvent was substantially removed under reduced pressure, diluted with diethyl ether (200 mL), washed with NH_4Cl(aq) (10%, 150 mL), and water (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude brown residue was dissolved in dichloromethane (40 mL) and manganese dioxide (15 g) added. After stirring for 1 h, the solution was filtered to remove the manganese dioxide, and concentrated under reduced pressure to afford the product **30** as a cream solid (6.13 g, 99%).

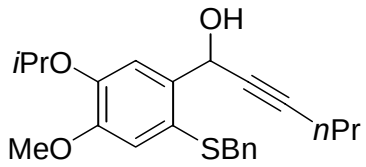
^{1}H-NMR ($CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.48 (s, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 3.95 (s, 6H), 3.93 (s, 3H), 3.84 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ 176.7 (C), 161.6 (C), 152.9 (C), 143.3 (C), 134.8 (C-H), 132.2 (C), 114.3 (C-H), 111.8 (C), 106.7 (C-H), 94.0 (C), 86.6 (C), 60.8 (CH_3), 56.1 (CH_3), 55.3 (CH_3). LRMS m/z = 326 (100) (M^+), 283 (56), 255 (11), 225 (57), 225 (10). HRMS Calculated for $C_{19}H_{18}O_5$ = 326.1154. Found = 326.1151. IR (KBr disc, cm^{-1}) = 2820, 1742, 1584, 1517, 1365, 1203, 1009, 960.



2-(4-Methoxybenzoyl)-3-(3,4,5-trimethoxyphenyl)benzo[*b*]thiophene (**32**)

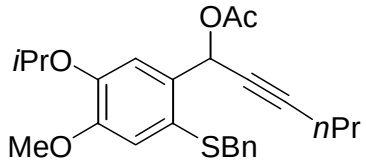
i-Propylphenylsulfide (190 mg, 1.25 mmol) was added to a solution of *n*-butyllithium (0.60 mL, 1.20 mmol) and TMEDA (278 mg, 2.40 mmol) in THF (4 mL) at 0 ˚C (ice-bath), the solution was allowed to warm to room temperature and stirred for 10 h. The resultant solution of 2-lithio-isopropylphenylsulfide **31** was then cooled to -78 ˚C (dry-ice / acetone bath) and a solution of **30** (326 mg, 1.00 mmol) in THF (8 mL) added. This solution was left to stir for a further 0.5 h at -78 ºC, before warming to room temperature for further 0.5 h. The solution was then diluted with diethyl ether (30 mL), and washed with $NH_4Cl_{(aq)}$ (10%, 30 mL), and water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude brown residue was diluted with an acetonitrile / water solution (5 mL, 9 : 1), and iodine added (111 mg, 0.44 mmol) added. The solution was left to stir for 2 h, and then diluted with diethyl ether (30 mL), washed with $Na_2S_2O_5$ (5%, 30 mL), water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, eluent CH_2Cl_2 / diethyl ether / hexanes, 1:1:8, 1:2:7, 1:4:5, 2:5:3), to give the product **32** as a white solid (144 mg, 83%), mp = 162 - 164 ˚C.

^{1}H-NMR ($CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.53 - 7.42 (m, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.55 (s, 2H), 3.77 (s, 3H), 3.73 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ 186.9 (C), 154.8 (C), 152.4 (C), 149.6 (C), 146.6 (C), 141.8 (C), 140.1 (C), 139.5 (C), 138.1 (C), 131.9 (C-H), 130.0 (C), 127.8 (C-H), 125.4 (C-H), 124.3 (C-H), 123.9 (C-H), 118.2 (C-H), 114.0 (C-H), 61.2 (CH_3), 56.0 (CH_3), 55.4 (CH_3). LRMS m/z = 434 (22) (M^+). HRMS Calculated for $C_{25}H_{22}O_5S$ = 434.1256. Found = 434.1260. IR (KBr disc, cm^{-1}) = 2774, 2698, 1730, 1502, 1366, 1322, 1294, 1170, 1008, 996.



Benzyl 2-(1-hydroxy-2-hexynyl)-4-isopropoxy-5-methoxyphenyl sulfide (**33**)

n-Butyllithium (1.50 mmol, 0.75 mL) was added dropwise to a solution of 1-pentyne (136 mg, 2.00 mmol) in THF (3 mL) at -78 ˚C, and left to stir for 0.15 h. After this time, a solution of **13** (400 mg, 1.27 mmol) in THF (2 mL) was added and the reaction warmed to room temperature. After stirring for 0.25 h, the reaction was diluted with diethyl ether (30 mL), washed with $NH_4Cl_{(aq)}$ (10%, 30 mL), water (30 mL), dried over $MgSO_4$, and then concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether, 9:1, 4:1, 3:2) to give the product as a colourless oil (482 mg, 99%).
^{1}H-NMR ($CDCl_3$) δ 7.25 (s, 1H), 7.23 - 7.19 (m, 3H), 7.11 - 7.05 (m, 2H), 6.72 (s, 1H), 5.86 (brs, 1H), 4.59 (septet, *J* = 6.1 Hz, 1H), 3.96, 3.95 (2 x diastereotopic CH_2), 3.68 (s, 3H), 2.23, 2.22 (2 x t, 7.0 Hz, diastereotopic CH_2), 1.53 (sextet, *J* = 7.2 Hz, 2H), 1.37 (dd, *J* = 3.3, 6.1 Hz, 6H, 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 149.5 (C), 147.7 (C), 138.0 (C), 137.5 (C), 128.9 (C-H), 128.3 (C-H), 126.9 (C-H), 122.9 (C), 118.7 (C-H), 114.0 (C-H), 86.9 (C), 80.4 (C), 71.1 (C-H), 62.5 (C-H), 55.8 (-CH_3), 41.6 (-CH_2), 22.0 (-CH_3), 21.9 (-CH_2), 21.7 (-CH_3), 20.7 (-CH_2), 13.4 (-CH_3). LRMS m/z = 384 (35) (M^+), 293 (100), 251 (38), 225 (57), 209 (25). HRMS Calculated for $C_{23}H_{28}O_3S$ = 384.1759. Found = 384.1763. IR (NaCl film, cm^{-1}) = 3499, 2966, 2932, 1594, 1499, 1385, 1255, 1201, 1112, 1045, 699.

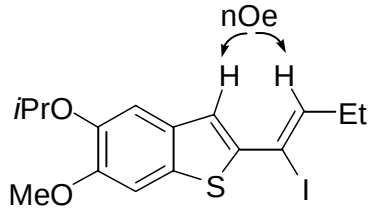


Benzyl 2-(1-acetoxy-2-hexynyl)-4-isopropoxy-5-methoxyphenyl sulfide (**34**)

n-Butyllithium (1.50 mmol, 0.75 mL) was added dropwise to a solution of 1-pentyne (136 mg, 2.00 mmol) in THF (3 mL) at -78 ˚C, and left to stir for 0.15 h. After this time, a solution of **13** (400 mg, 1.27 mmol) in THF (2 mL) was added and the reaction warmed to room temperature.

After 0.15 h, acetic anhydride (306 mg, 3.00 mmol) was added, and the reaction left to stir for a further 0.2 h. After this time, the reaction was diluted with diethyl ether (30 mL), washed with $NH_4Cl_{(aq)}$ (10%, 30 mL), water (30 mL), dried over $MgSO_4$ and then concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether, 9:1, 4:1) to give the product **34** as a colourless oil (524 mg, 97%).

^{1}H-NMR ($CDCl_3$) δ 7.24 (s, 1H), 7.22 - 7.14 (m, 3H), 7.12 - 7.07 (m, 2H), 6.93 (s, 1H), 6.60 (s, 1H), 4.58 (septet, *J* = 6.1 Hz, 1H), 3.92 (s, 2H), 3.59 (s, 3H), 2.24, 2.23 (2 x t, 7.0 Hz, diastereotopic CH_2), 2.07 (s, 3H), 1.53 (sextet, *J* = 7.1 Hz, 2H), 1.38 (d, *J* = 6.1 Hz, 6H), 0.96 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 169.3 (C), 149.5 (C), 147.1 (C), 138.8 (C), 133.6 (C), 129.1 (C-H), 128.6 (C-H), 126.4 (C-H), 124.0 (C), 118.2 (C-H), 114.6 (C-H), 87.8 (C), 77.9 (C), 70.9 (C-H), 64.0 (C-H), 55.6 (CH_3), 41.2 (CH_2), 22.0 (CH_3), 21.8 (CH_2), 21.5 (CH_3), 20.9 (CH_3), 20.4 (CH_2). LRMS m/z = 426 (20) (M^+), 335 (100). HRMS Calculated for $C_{25}H_{30}O_4S$ = 426.1795. Found = 426.1787. IR (NaCl film, cm^{-1}) = 2920, 2841, 1760, 1475, 1410, 1115, 1036, 970.

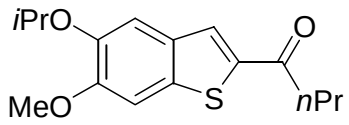


2-[(*Z*)-1-Iodobut-1-enyl]-5-isopropoxy-6-methoxybenzo[*b*]thiophene (**36**)

A solution of iodine (84 mg, 0.330 mmol) dissolved in CH_2Cl_2 (2 mL) was added to a solution of **34** (138 mg, 0.325 mmol) in CH_2Cl_2 (10 mL), and left to stir for 0.3 h. After this time, the solution was quenched with $Na_2S_2O_5$ (10%, 30 mL), extracted with diethyl ether (40 mL), washed with water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether, 19:1, 9:1) to give the product **36** as a colourless resin (128 mg, 98%).

^{1}H-NMR ($CDCl_3$) δ 7.32 (s, 1H), 7.17 (s, 1H), 7.12 (s, 1H), 6.11 (t, *J* = 6.8 Hz, 1H), 4.53 (septet, *J* = 6.1 Hz, 1H), 3.89 (s, 3H), 2.37 (quintet, *J* = 7.2 Hz, 2H), 1.40 (d, *J* = 6.1 Hz, 6H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 150.1 (C), 146.3 (C), 142.4 (C), 139.5 (C-H), 132.3 (C), 126.0 (C-H), 109.9 (C-H), 104.2 (C-H), 95.1 (C), 71.6 (C-H), 56.1 (-CH_3), 30.9 (-CH_2), 21.9 (-CH_3), 12.7 (-CH_3). LRMS m/z = 402 (51) (M^+), 359 (5), 275 (100), 233 (36). HRMS Calculated for

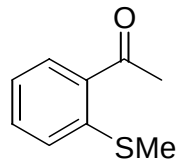
$C_{16}H_{19}O_2SI$ = 402.0151. Found = 402.0151. IR (NaCl film, cm^{-1}) = 2972, 2932, 1602, 1513, 1480, 1437, 1298, 1235, 1207, 1174, 1112, 1056. A 1D NOE difference spectrum was performed at 500 MHz with saturation of the olefinic triplet at 6.11 ppm. This produced significant enhancement of the methylene and methyl groups and the hydrogen at C3. The enhancement of the H at C3 is indicative of a *syn*-relationship of the olefinic H and the benzothiophene ring.



2-Butanoyl-5-isopropoxy-6-methoxybenzo[*b*]thiophene (**37**)

Iodine (209 mg, 0.82 mmol) was added to a solution of **33** (310 mg, 0.81 mmol) in ethanol (5 mL) and left to stir. After 0.5 h, the solution was diluted with diethyl ether (50 mL), washed with $Na_2S_2O_{5(aq)}$ (10%, 40 mL), and water (40 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, hexanes / diethyl ether, 9:1, 4:1) to give the product **37** as a white solid (232 mg, 98%), mp = 114 - 116 ˚C.

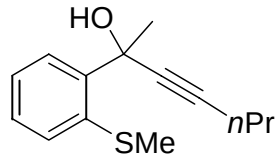
^{1}H-NMR ($CDCl_3$) δ 7.80 (s, 1H), 7.27 (s, 1H), 7.24 (s, 1H), 4.56 (septet, *J* = 6.0 Hz, 1H), 3.93 (s, 3H), 2.92 (t, *J* = 7.3 Hz, 2H), 1.81 (sextet, 2H), 1.40 (d, *J* = 6.0 Hz, 6H), 1.01 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 194.4 (C), 152.1 (C), 146.8 (C), 141.9 (C), 136.8 (C), 132.6 (C), 128.7 (C-H), 110.2 (C-H), 103.9 (C-H), 71.6 (C-H), 56.1 (-CH_3), 40.9 (-CH_2), 21.8 (-CH_3), 18.4 (-CH_2), 13.8 (-CH_3). LRMS m/z = 292 (57) (M^+), 250 (60), 222 (48), 207 (100), 179 (23) 164 (14). HRMS Calculated for $C_{16}H_{20}O_3S$ = 292.1133. Found = 292.1134. IR (KBr disc, cm^{-1}) = 2969, 2934, 1641, 1601, 1511, 1458, 1432, 1357, 1290, 1261, 1203, 1152, 1055, 1015.



2-Acylphenyl methyl sulfide (**41**)

2-Bromoacetophenone (3.98 g, 20.0 mmol) was added to a stirred solution of sodium methylthiolate (1.56 g, 22.0 mmol) in THF (15 mL) and heated to 75 ˚C (oil bath) and left to stir. After 10 h, the reaction was cooled to room temperature, diluted with ethyl acetate (80 mL), washed with $HCl_{(aq)}$ (5%, 80 mL), $NaOCl_{(aq)}$ (1%, 80 mL) and water (3 x 80 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give the product as an orange solid (3.32 g, 100 %).

^{1}H-NMR ($CDCl_3$) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.43 (dt, *J* = 1.5, 8.3 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.15 (dt, *J* = 1.1, 7.7 Hz, 1H), 2.58 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ 198.7 (C), 142.4 (C), 133.9 (C), 132.1 (C-H), 130.9 (C-H), 124.6 (C-H), 123.2 (C-H), 28.0 (CH_3), 15.6 (CH_3). This data was in accord with that previously published for **41**.[a]

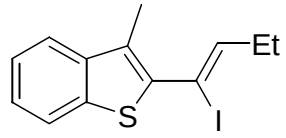


2-(2'-Thiomethoxyphenyl)-hept-3-yn-2-ol (**42**)

Cerium chloride (242 mg, 0.650 mmol) was dried in a Schlenk tube under vaccum at 145 ˚C (oil bath). After 2 h of stirring, the tube was cooled to room temperature, and THF (2.5 mL) was added, and the flask left to stir for a further 2 h, and then cooled to -78 ˚C (dry -ice / acetone bath). Meanwhile, *n*-butyllithium (0.30 mL, 0.60 mmol) was added to a second schlenk tube containing a solution of 1-pentyne (40.8 mg, 0.60 mmol) in THF (2.5 mL) at -78 ˚C. After 0.15 h, the lithium acetylide solution was transferred by canula to the cerium chloride solution. After stirring for a further 1 h at -78 ˚C, a solution of **41** (83 mg, 0.50 mmol) in THF (1 mL) was added, and the solution left to stir for 4 h then warmed to room temperature. After this time, the solution was diluted with diethyl ether (40 mL), washed with $NH_4Cl_{(aq)}$ (10%, 40 mL) and water (40 mL), dried over $MgSO_4$ and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica gel, eluent hexanes / diethyl ether, 99:1, 95:5, 9:1) to give the product **42** as a colourless oil (102 mg, 87%).

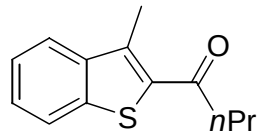
^{1}H-NMR ($CDCl_3$) δ 7.64 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.40 (dd, *J* = 1.5, 7.7 Hz, 1H), 7.25 (dt, *J* = 1.5, 7.7 Hz, 1H), 7.18 (dt, *J* = 1.5, 7.7 Hz, 1H), 4.40 (brs, 1H), 2.51 (s, 3H), 2.22 (t, *J* = 7.0 Hz, 2H), 1.92 (s, 3H), 1.55 (sextet, *J* = 7.1 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 144.1 (C), 135.6 (C), 130.4 (C-H), 128.0 (C-H), 125.9 (C-H), 125.6 (C-H), 86.2 (C), 84.0 (C), 69.6

(C), 29.8 (CH_3), 21.9 (CH_2), 20.8 (CH_2), 18.6 (CH_3), 13.5 (CH_3). LRMS m/z = 234 (8) (M^+), 219 (50), 205 (35), 191 (39), 151 (100). HRMS Calculated for $C_{14}H_{18}OS$ = 234.1078. Found = 234.1074. IR (NaCl film, cm^{-1}) = 3436, 2963, 2931, 2871, 2240, 1673, 1587, 1462, 1434, 1044, 756, 736.



2-(1'-Iodobut-1'-enyl)-3-methylbenzo[*b*]thiophene (**43**)

Iodine (172 mg, 0.677 mmol) was added to a solution of **42** (155 mg, 0.662 mmol) in CH_2Cl_2 (10 mL) and stirred for 0.5 h. After this time, the solution was quenched with $Na_2S_2O_5$ (10%, 30 mL), extracted with diethyl ether (40 mL), washed with water (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica (2 g). The residue was subjected to flash chromatography (silica gel, hexanes) to give the product b42 as a yellow oil (206 mg, 95%).
^{1}H-NMR ($CDCl_3$) δ 7.76 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.67 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.42 - 7.35 (m, 2H), 5.89 (t, *J* = 6.8 Hz, 1H), 2.38 (quintet, *J* = 7.3 Hz, 2H), 2.34 (s, 3H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 145.4 (C-H), 141.1 (C), 140.1 (C), 138.3 (C), 128.7 (C), 124.9 (C-H), 124.2 (C-H), 122.3 (C-H), 122.1 (C-H), 91.8 (C), 30.8 (CH_2), 12.7 (CH_3), 12.6 (CH_3). LRMS m/z = 328 (44) (M^+), 201 (100), 185 (42), 171 (52). HRMS Calculated for $C_{13}H_{13}SI$ = 327.9783. Found = 327.9783. IR (NaCl film, cm^{-1}) = 3060, 2966, 2931, 1459, 1434, 1183, 1122, 829, 753, 727.

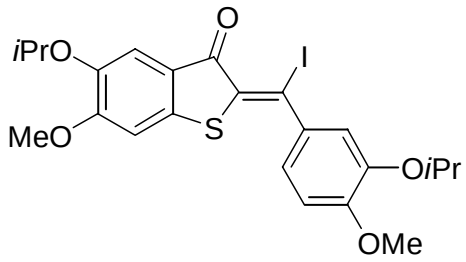


2-Butanoyl-3-methylbenzo[*b*]thiophene (**44**)

Iodine (232 mg, 0.914 mmol) was added to a solution of **42** (210 mg, 0.897 mmol) in ethanol (6 mL) and left to stir. After 0.5 h, the solution was diluted with diethyl ether (50 mL), washed with $Na_2S_2O_{5(aq)}$ (10%, 40 mL), and water (40 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The residue was subjected to flash chromatography (silica

gel, hexanes / diethyl ether, 9:1, 8:2) to give the product **44** as a white solid (182 mg, 93%), mp = 51 - 53 ˚C.

^{1}H-NMR ($CDCl_3$) δ 7.85 (dd, *J* = 1.5, 7.7 Hz, 2H), 7.45 (dt, *J* = 1.5, 7.7 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.76 (s, 3H), 1.81 (sextet, *J* = 7.3 Hz, 2H), 1.03 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ 195.8 (C), 140.4 (C), 139.7 (C), 139.0 (C), 135.1 (C), 127.3 (C-H), 124.5 (C-H), 124.0 (C-H), 122.6 (C-H), 44.6, (CH_2), 17.8 (CH_2), 13.8 (CH_3). LRMS m/z = 218 (28) (M^+), 175 (100), 147 (18). HRMS Calculated for $C_{13}H_{14}OS$ = 218.0765. Found = 218.0765. IR (KBr disc, cm^{-1}) = 2960, 2927, 2869, 1673, 1515, 1462, 1428, 1364, 1297, 1186, 1159, 1082, 753, 730.



2-(α-iodo-3'-isopropoxy-4'-methoxybenzylidene)-5-isopropoxy-6-methoxybenzo[*b*]thiophen-3-one:

Iodine (124 mg, 0.488 mmol) was added to a solution of **21** (240 mg, 0.476 mmol) in CH_2Cl_2 (8 mL) and stirred for 0.5 h. After this time, the solution was quenched with $Na_2S_2O_{5(aq)}$ (30 mL), extracted with diethyl ether (3 x 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure onto silica gel (2 g). The solid residue was subjected to flash chromatography (silica gel, hexanes : diethyl ether, 3:2, 2:3 sequential elution), to give the product thioaurone as a yellow oil (230 mg, 90%), and the product thioflavone as a white solid (10 mg, 4%).

Lower Rf Isomer ^{1}H-NMR, initially formed product upon addition of iodine to **21**, most likely (*E*)-**41**:

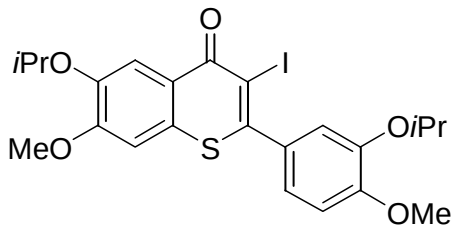
^{1}H-NMR ($CDCl_3$) δ 7.39 (s, 1H), 7.09 (dd, *J* = 2.1, 8.4 Hz, 1H), 7.05 (d, *J* = 2.1, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 1H), 4.63 - 4.46 (m, 2H), 3.90 (s, 6H), 1.42 - 1.35 (m, 6H).

Higher Rf Isomer ^{1}H-NMR, formed upon thermal isomerization of initial product, most likely (*Z*)-**41**:

^{1}H-NMR ($CDCl_3$) δ 7.08 (s, 1H), 7.04 (dd, *J* = 2.0, 8.4 Hz, 1H), 6.96 (d, *J* = 2.0 Hz), 6.83 (d, *J* = 8.4 Hz, 1H), 6.80 (s, 1H), 4.52 (septet, *J* = 6 Hz, 1H), 4.48 (septet, *J* = 6 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 1.39 (d, *J* = 6 Hz, 6H), 1.34 (d, *J* = 6 Hz, 6H).

Following spectra obtained on combined isomers (*E,Z*)-**41**:

^{13}C-NMR ($CDCl_3$) δ 178.9 (x2) (C), 165.1 (C), 157.3 (C), 157.1 (C), 151.2 (x2) (C), 146.6 (C), 146.4 (C), 146.2 (x2) (C), 139.1 (C), 138.0 (C), 137.5 (C), 134.4 (C), 133.2 (C), 126.6 (C), 124.8 (C), 122.1 (C-H), 121.8 (C-H), 115.9 (C-H), 115.6 (C-H), 114.1 (C), 112.0 (C-H), 111.4 (C-H), 111.0 (C-H), 110.6 (C-H), 105.1 (C-H), 103.6 (C-H), 98.7 (C), 71.5 (C-H), 71.4 (x2) (C-H), 71.3 (C-H), 56.4 (x2), 56.0 (x2) (CH_3), 21.9 (CH_3), 21.8 (CH_3). LRMS m/z = 540 (71) (M^+), 456 (100), 329 (22), 226 (29). HRMS Calculated for $C_{23}H_{25}O_5SI$= 540.0467. Found = 540.0465.



3-iodo-6-isopropoxy-2-(3'-isopropoxy-4'-methoxyphenyl)-7-methoxythioflavone 46:

^{1}H-NMR ($CDCl_3$) δ 8.02 (s, 1H), 7.26 (s, 1H), 6.99 – 6.95 (m, 2H), 6.93 (s, 1H), 4.78 (septet, *J* = 6.0 Hz, 1H), 4.58 (septet, *J* = 6.0 Hz, 1H), 3.97 (s, 3H), 3.93 (s, 3H), 1.46 – 1.40 (m, 12H). LRMS m/z = 540 (40) (M^+), 413 (100), 371 (25), 329 (15), 269 (30). HRMS Calculated for $C_{23}H_{25}O_5SI$= 540.0467. Found = 540.0464.