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Synthesis of Monosulphur and Monoselenium Analogues of Psoralen

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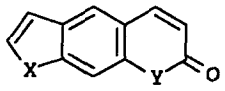
Abstract: The synthesis of new, highly efficient DNA photoinactivating agents comprising an atom of sulfur or selenium in place of oxygen in the psoralen system is described.

Psoralens (derivatives of furo[3,2-g][1]benzopyran-7-one **9e**) are commonly used in the photochemotherapy of vitiligo, psoriasis and more recently in extracorporal photochemotherapy[1,2] as well as reagents for the biophysical study of nucleic acids.[3,4,5] Furthermore, psoralen derivatives are now recognized as effective agents for the blood cell products purification because they turned out to be very effective virucidal agents especially against enveloped viruses like the herpes virus or the human immunodeficiency virus type-1 (HIV-1).[6] Psoralens have been shown to intercalate nucleic acids and undergo [2+2] photocycloadditions to adjacent pyrimidine bases.[7] Among the different approaches which have been followed to obtain psoralens with better photobinding activity one consists in the synthesis of hetero-analogues.

So far, some nitrogen,[8,9,10,11] sulphur[12,13] and selenium[13] analogues or its derivatives have been described. The replacement of the endocyclic oxygen atoms by sulphur and/or selenium provides new heteropsoralens expected to show modified geometry, enophilic character, and enhanced light absorption at 365 nm compared to the parent compound since replacement of the oxygen atom in either benzofuran[14] and 2H-benzopyran-2-one[15] by other chalcogens results in a bathochromic effect. It has also been shown that benzothiopyran-2-one,[16] benzothiophene[17,18] and benzoselenophene[19,20] afford light induced [2+2] cycloadditions. Furthermore, the substitution of the oxygen atoms by sulphur or selenium should improve the yield of the excited triplet state which is generally admitted to be responsible for the [2+2] photoreaction of the natural psoralens.[21] We wish to report here the synthesis of the four heteropsoralens where sulphur or selenium replaces only one of the two endocyclic oxygen atoms of psoralen (Scheme 1), namely 7H-selenopyrano[3,2-f][1]benzofuran-7-one **9a**, 7H-thiopyrano[3,2-f][1]benzofuran-7-one **9b**, 2H-selenolo[3,2-g][1]-benzopyran-2-one **9c** and 2H-thieno[3,2-g][1]benzopyran-2-one **9d**.

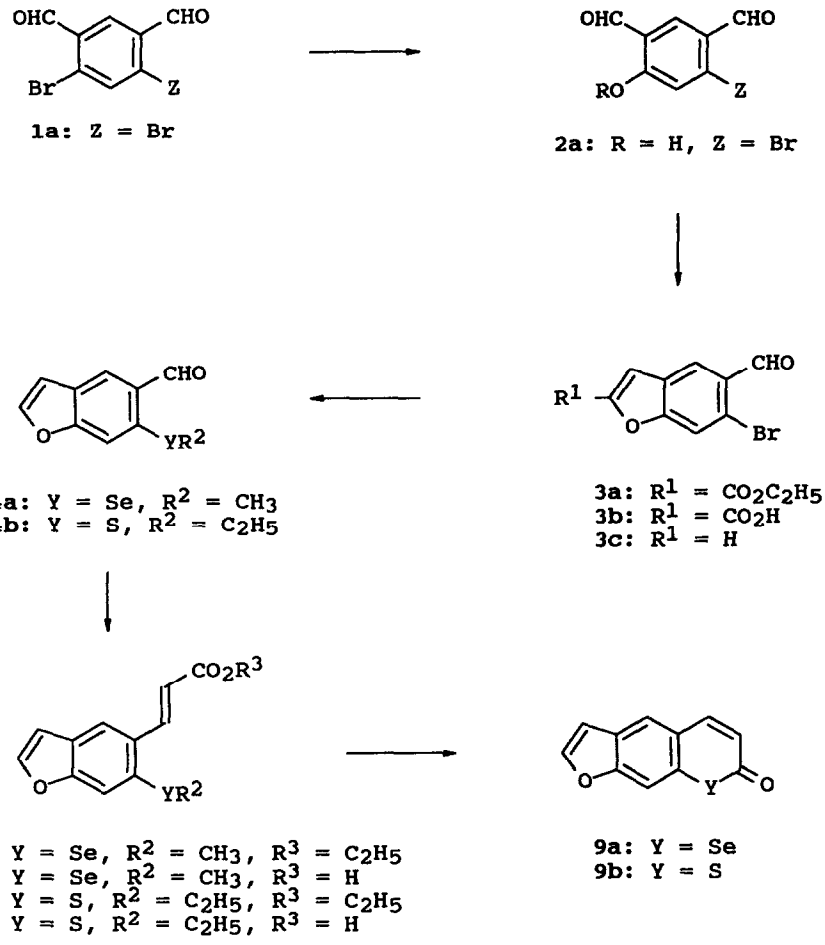


9a: X = O, Y = Se
9b: X = O, Y = S
9c: X = Se, Y = O
9d: X = S, Y = O
9e: X = O, Y = O

Scheme 1

Our synthetic strategy called for the preparation of a 4,6-disubstituted isophthalaldehyde containing one leaving group (e.g. bromine) and one phenol or ether function. The access to these unknown disubstituted isophthalaldehydes however is not straightforward by formylation of mono- or disubstituted phenols which proved to require tedious multistep synthesis with several purifications. We then investigated the synthesis of the isophthalaldehydes **2a** and **2b** starting from the known 4,6-dibromoisophthalaldehyde[22] **1a** (Scheme 2). This compound (**1a**) which is easily obtained from m-xylene contains two activated halogen atoms and appeared to be the precursor of choice of **2a** and **2b**. However, direct nucleophilic substitution of aryl halides by alkoxide and especially hydroxide anions requires high temperatures and the hydroxide anion which is a rather poor nucleophile could lead to Cannizzaro-type reactions with the isophthalaldehyde **1a**. In order to make the nucleophilic substitution by the hydroxide anion feasable the nucleophilicity of the hydroxide anion has to be enhanced. This has been done in a solvent where the anion is poorly solvated and the cation very well. In DMSO where this condition is met 4,6-dibromoisophthalaldehyde **1a** reacts with an excess of potassium hydroxide in five minutes to yield 54% of the phenol **2a**. Surprisingly, the Cannizzaro reaction prevails at room temperature but at higher temperatures, e.g. 70 - 150 °C, only the rapid nucleophilic substitution of the halogen is observed. No reaction takes place when the potassium cation is replaced by the less solvated sodium cation. Other dipolar aprotic solvents like acetonitrile or DMF yield respectively the starting material and 4-bromo-6-(N,N-dimethylamino)isophthalaldehyde.

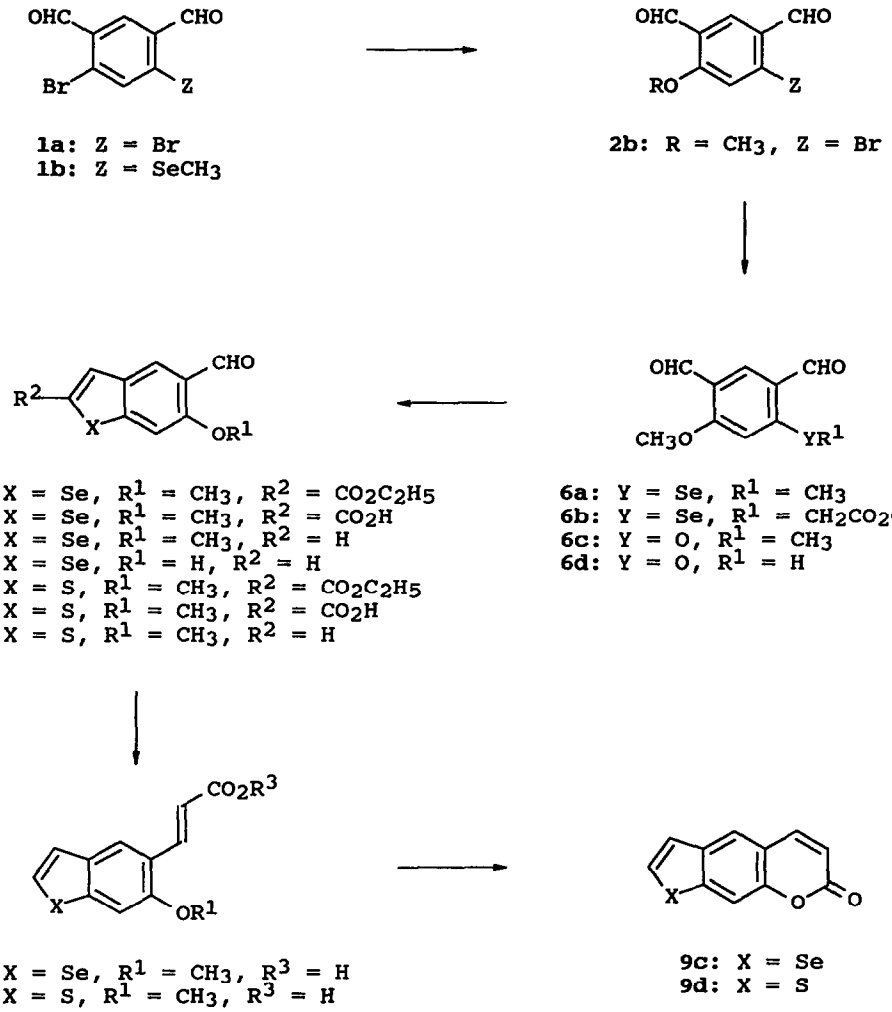
In order to synthesize the psoralen analogues containing a furan moiety, the phenol **2a** is transformed in one step and 75 % yield into the benzofuran derivative **3a** by reaction with ethylbromoacetate in DMF. Hydrolysis of the ester function of the benzofuran derivative **3a** followed by the decarboxylation of the resulting carboxylic acid **3b** affords 6-bromo-5-formylbenzo[b]furan **3c**. This compound (**3c**) provides both the selenoether **4a** or the thioether **4b** by nucleophilic substitution of the halogen atom by either methaneselenolate or ethanethiolate anions.



Scheme 2

The seleno- or thioethers **4a** and **4b** are then transformed into 5-(2-ethoxycarbonylvinyl)-6-methylselenobenzo[b]furan **5a** and 5-(2-ethoxycarbonylvinyl)-6-ethylthiobenzo[b]furan **5c** respectively by a Wittig-Horner reaction using triethylphosphonoacetate and C-200[23] ($Ba(OH)_2.0.8\ H_2O$) as catalyst. The ester functions of **5a** and **5c** are subsequently hydrolyzed and the resulting acids **5b** and **5d** yield 7H-selenopyrano-[3,2-f][1]benzofuran-7-one **9a** and 7H-thiopyrano[3,2-f][1]benzofuran-7-one **9b** by cyclization with polyphosphoric acid silylester[24] (PPSE).

The synthesis of 2H-selenolo[3,2-g][1]benzopyran-2-one **9c** and 2H-thieno[3,2-g][1]benzopyran-2-one **9d** (Scheme 3) required the intermediate 4-bromo-6-methoxyisophthalaldehyde **2b** which could be obtained in 82% yield by reaction of 4,6-dibromoisophthalaldehyde **1a** with one equivalent of lithium methanolate in methanol (the same reaction of **1a** in DMF, DMSO or acetonitrile affords a mixture of **2a**, **2b** and the starting material **1a**).



Scheme 3

The selenolocoumarin **9c** is then obtained by introducing a selenoether in place of the bromine in 4-bromo-6-methoxyisophthalaldehyde **2a** with potassium methaneselenolate to provide 4-methoxy-6-methylselenoisophthalaldehyde **6a**. Unexpectedly, the reaction of potassium methanolate with the previously described 4-bromo-6-methylselenoisophthalaldehyde **1b**[13] leads to a mixture of 4-methoxy-6-methylselenoisophthalaldehyde **6a**, 4,6-dimethoxyisophthalaldehyde **6c** and the starting material **1b**. The selenoether **6a** is then transformed into 5-formyl-6-methoxybenzo[b]selenophene **7c** in 4 steps: reaction with ethylbromoacetate gives the selenoether **6b** which is cyclized in basic medium into the selenophene derivative **7a**. The ester function of **7a** is hydrolysed to the corresponding carboxylic acid **7b** which is decarboxylated to yield 5-formyl-6-methoxybenzo[b]selenophene **7c**. The vinylogous acid (**8a**) of **7d**, which is prepared by the Perkin reaction, is finally

cyclized into 2H-selenolo[3,2-g][1]benzopyran-2-one **9c** but the yield is only 19% owing to the polymer formation probably by acylation of the selenophene. A higher yield is obtained when 5-formyl-6-methoxybenzo[b]selenophene **7c** is first demethylated to 5-formyl-6-hydroxybenzo[b]selenophene **7d** with lithium chloride[25] in boiling DMF. The phenol **7d** is then transformed into the selenolocoumarin **9c** by a classical Perkin reaction.

The thienocoumarin **9d** is obtained by first reacting 4-bromo-6-methoxyisophthalaldehyde **2b** with potassium ethylthioglycolate to afford 2-ethoxycarbonyl-5-formyl-6-methoxybenzo[b]thiophene **7e** in 65 % yield. This ester **7e** is saponified and the corresponding acid **7f** is decarboxylated to 5-formyl-6-methoxybenzo[b]thiophene **7g**. The vinylogous acid **8b** of this aldehyde which is obtained by a Knoevenagel reaction has been cyclized in PPSE to provide 2H-thieno[3,2-g][1]benzopyran-2-one **9d**.

The UV spectra, the photobiological activity[26] and the singlet oxygen quantum yield[27] of these thio- and selenopsoralens are published elsewhere.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated reactions were carried out in commercial pure grade solvents without further purification. THF was distilled from sodium and potassium. Analytical grade anhydrous K_2CO_3, LiCl and pure grade KOH (min. 85%, Janssen) were used. The standard isolation procedure comprises pouring the reaction mixture into ice/water mixture, filtration of the precipitate and redissolution in CH_2Cl_2, washing with 1N $NaHCO_3$, drying ($MgSO_4$) and evaporation of the solvent under reduced pressure. Analytical thin-layer chromatography (TLC) was done with silica plates (Macherey-Nagel) and 70-230 mesh silica gel (E. Merck) was used for column chromatography.

Melting points were determined with a Kofler hotplate melting point apparatus and are uncorrected. ^1H NMR spectra (in $CDCl_3$) are referenced to HMDSO and coupling constants, *J*, are in hertz. ^{13}C NMR spectra are referenced to $CDCl_3$. ^{77}Se chemical shifts are relative to dimethylselenide. Mass spectra were recorded by direct introduction under 70 eV IP. Isotopic distributions are in agreement with theory and only the most abundant isotopes (^{79}Br, ^{80}Se) are mentioned. Elemental analyses were performed by the Institute of Pharmacy (Liege, Belgium).

4-Bromo-6-hydroxyisophthalaldehyde 2a: A mixture of 9.6 g (171 mmol) of potassium hydroxide and 50 ml of DMSO at 90°C is added to a solution of 10 g (34 mmol) of **1a** in 150 ml of DMSO at 90°C. The reaction medium is stirred vigorously for 5 min and poured into iced water. After acidification with conc. HCl, the precipitate is extracted by 2 x 200 ml $CHCl_3$. The aqueous layer is discarded and the organic solution extracted with 1N NaOH. The basic phase is acidified and the precipitate extracted with $CHCl_3$. The organic layer is washed twice with brine, dried and the solvent evaporated under reduced pressure. The product **2a** is pure enough to be used in the next step but can be purified by column chromatography (toluene/ethyl acetate 80/20) followed by recrystallization in toluene/heptane. Yield 4.8 g (54 %) of white plates. mp 160°C. ^1H NMR (400 MHz) δ 11.46 (s, 1H), 10.23 (s, 1H), 9.93 (s, 1H), 8.20 (s, 1H), 7.29 (s, 1H); MS *m/z* 228 (60), 227 (100), 199 (9). Anal. Calcd for $C_8H_5O_3Br$: C, 41.95; H, 2.20. Found: C, 42.11; H, 2.21.

4-Bromo-6-methoxyisophthalaldehyde 2b: To a solution of 0.476 g (68.6 mmol) of lithium in 250 ml of dry methanol, 20 g (68.5 mmol) of **1a** are added. After 4 h at the reflux temperature the solution is allowed

to cool and poured into 500 ml of iced water. The precipitate is filtered, washed with water and dissolved in CH_2Cl_2. The organic layer is dried and the solvent evaporated. The resulting solid is pure enough to be used in the next steps. Yield 13.7 g (82%). An analytical sample melts at 171-172°C (toluene). ^1H NMR (400 MHz) δ 10.36 (s, 1H), 10.21 (s, 1H), 8.36 (s, 1H), 7.25 (s, 1H), 4.02 (s, 1H); MS *m/z* 242 (100), 241 (81), 227 (21), 154 (52). Anal. Calcd for $C_9H_7BrO_3$: C, 44.47; H, 2.90. Found: C, 44.57; H, 2.93.

6-Bromo-2-ethoxycarbonyl-5-formylbenzofuran 3a: A suspension of 4.8 g (21 mmol) of **2a** and 5.8 g (42 mmol) of finely ground K_2CO_3 in 90 ml of DMF is heated to reflux under vigorous stirring. 2.65 ml (24 mmol) of ethylbromoacetate are added at once and the heating is continued for 3 min. The hot solution is poured into iced water and extracted with ether. The organic layer is washed twice with brine, dried and the solvent evaporated. The product is chromatographied through a short silicagel column with toluene/ethyl acetate (80/20) to yield 4.45 g (75 %) of **3a**. mp 109°C (toluene/heptane). ^1H NMR (60 MHz) δ 10.3 (s, 1H), 8.2 (s, 1H), 7.8 (s, 1H), 7.5 (s, 1H), 4.4 (q, 2H), 1.4 (t, 3H); MS *m/z*: 297 (100), 268 (61), 252 (45). Anal. Calcd for $C_{12}H_9O_4Br$: C, 48.51; H, 3.05. Found: C, 48.42; H, 3.01.

Saponification reactions : All saponification reactions were carried out as follows : one mmol of ester is refluxed for 40 min in 3 ml of a water/ethanol mixture (5/7 v/v) containing two mmol of KOH. After cooling, the mixture is washed once with ether, acidified with 6N HCl, filtered and the precipitate washed with water. The precipitate is dried at 110°C. Yields are between 84 and 96%. The acids are used without further purification.

Decarboxylation reactions: General procedure : 10 mmol of the dried acid and 2 g of copper bronze are mixed with 25 ml of freshly distilled quinoline and heated to 185°C until CO_2 evolution stops (5 to 25 min at 185°C, longer heating times lead to lower yields). The reaction mixture is allowed to cool to 60°C and the copper bronze is filtered off and washed with $CHCl_3$. More $CHCl_3$ is added and the solution is washed several times with 2N HCl, once with 1N $NaHCO_3$ and water. The organic layer is dried and the solvent evaporated. The products are purified by column chromatography (toluene).

6-Bromo-5-formylbenzo[b]furan 3c: Yield 62%. mp 91°C (toluene/heptane). ^1H NMR (60 MHz) δ 9.9 (s, 1H), 7.6 (s, 1H), 7.1 (d, J = 2.4, 1H), 7.0 (d, J = 2.4, 1H), 6.2 (s, 1H); MS *m/z* 224 (100), 223 (95), 195 (24). Anal. Calcd for $C_9H_5O_2Br$: C, 48.04; H, 2.24. Found: C, 48.02; H, 2.25

5-Formyl-6-methoxybenzo[b]thiophene 7g: Yield 69 %. mp 81°C (toluene/heptane). ^1H NMR (400 MHz) δ 10.54 (s, 1H), 8.25 (s, 1H), 7.39 (s, 1H), 7.31 (s, 2H), 3.98 (s, 3H); MS *m/z* 192 (100). Anal. Calcd for $C_{10}H_8O_2S$: C, 62.48; H, 4.19; S, 16.68. Found: C, 62.72; H, 4.27; S, 16.69.

5-Formyl-6-methoxybenzo[b]selenophene 7c: Yield 71 %. mp 102°C (toluene/heptane). ^1H NMR (400 MHz) δ 10.45 (s, 1H), 8.1 (s, 1H), 7.75 (d, J = 6, 1H), 7.4 (d, J = 6, 1H), 7.4 (s, 1H), 3.9 (s, 3H); MS *m/z* 240 (100), 225 (21), 224 (16), 196 (33), 180 (21), 170 (32). Anal. Calcd for $C_{10}H_8O_2Se$: C, 50.23; H, 3.37. Found: C, 50.45; H, 3.32.

5-Formyl-6-methylselenobenzo[b]furan 4a: A suspension of 1.4 g (6.2 mmol) of 6-bromo-5-formylbenzo[b]furan **3c** and 2 g (14.5 mmol) of K_2CO_3 in 15 ml of DMF is cooled to 5°C and 0.72 ml (12 mmol) of methaneselenol are added. This mixture is allowed to warm up to room temperature and stirred for 14 h. The mixture is poured into water, extracted with CH_2Cl_2, washed with 1N NaOH, 1N HCl and brine. After drying the solvent is evaporated and the product chromatographied (toluene) to yield 1 g of **4a** (67%). mp 81°C (toluene/heptane). ^1H NMR (60 MHz) δ 10.1 (s, 1H), 8.0 (s, 1H), 7.6 (d, J = 2.4, 1H), 7.5 (s, 1H),

6.8 (d, J = 2.4, 1H), 2.2 ($J_{Se\text{-}CH3}$ = 14, 3H); MS *m/z* 240 (95), 225 (100), 197 (88), 170 (29), 145 (30). Anal. Calcd for $C_{10}H_8O_2Se$: C, 50.23; H, 3.37. Found: C, 50.23; H, 3.36.

6-Ethylthio-5-formylbenzo[b]furan 4b: 930 mg of **3c** (4.13 mmol) and 2.7 g (19.6 mmol) of K_2CO_3 are suspended in 15 ml of DMF. This slurry is cooled to 5°C and 0.9 ml (15.2 mmol) of ethanethiol are added. After 15 min at 5°C, the reaction mixture is refluxed for 2 h. The same isolation procedure as for **4a** affords 852 mg (87%) of **4b**. mp 50°C (toluene/heptane). ^{1}H NMR (60 MHz) δ 10.5 (s, 1H), 8.1 (s, 1H), 7.6 (d, J = 2.4, 1H), 7.5 (s, 1H), 6.75 (d, J = 2.4, 1H), 2.9 (q, 2H), 1.25 (t, 3H); MS *m/z* 206 (100), 178 (90), 150 (56). Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.55. Found: C, 64.16; H, 4.93; S, 15.54.

5-Ethoxycarbonylvinyl-6-methylselenobenzo[b]furan 5a: 800 mg (3.35 mmol) of **4a** are dissolved in 15 ml of dry THF. 0.45 g of $Ba(OH)_2.0.8H_2O$ (C-200),[23] 0.84 ml (4.23 mmol) of triethylphosphonoacetate and 0.08 ml (4.4 mmol) of water are added. This mixture is refluxed for 1 h and allowed to cool. After usual work-up and chromatographic separation on a short column (toluene), 891 mg (87 %) of **5a** are obtained. mp 88°C (hexane). ^{1}H NMR (60 MHz) δ 7.75 (s, 1H), 7.6 (s, 1H), 8.25 (d, J = 16, 2H), 7.55 (d, J = 2.4, 1H), 6.7 (d, J = 2.4, 1H), 6.3 (d, J = 16, 2H), 4.3 (q, 2H), 2.25 (s, 3H), 1.25 (t, 3H); MS *m/z* 310 (11), 265 (6), 223 (26), 215 (80), 187 (100). Anal. Calcd for $C_{14}H_{14}O_3Se$: C, 54.38; H, 4.56. Found: C, 54.43; H, 4.64.

5-Ethoxycarbonylvinyl-6-ethylthiobenzo[b]furan 5c: The same reaction procedure is used as for **5a**. Yield 94%. mp 53°C (hexane). TLC R_f 0.41, $C_6H_5CH_3/CHCl_3$ 17/3. ^{1}H NMR (400 MHz) δ 8.31 (d, J = 15.6, 1H), 7.73 (s, 1H), 7.51 (d, J = 2.3, 1H), 7.50 (s, 1H), 6.61 (d, J = 2.3, 1H), 6.30 (d, J = 15.6, 1H), 4.21 (q, 2H), 2.82 (q, 2H), 1.26 (t, 3H), 1.22 (t, 3H); MS *m/z* 276 (27), 219 (54), 202 (100), 184 (85). Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84; S, 11.60. Found: C, 65.12; H, 6.01; S, 11.43.

7H-Selenopyrano[3,2-f][1]benzofuran-7-one 9a: Polyphosphoric acid silylester has been prepared by refluxing 1.24 g (4.4 mmol) of P_4O_{10} with 2.0 ml (9.4 mmol) of HMDSO in 7 ml of $CHCl_3$ for 1 h. Care must be taken that all P_4O_{10} is dissolved otherwise emulsion formation is observed during the isolation procedure. $CHCl_3$ is evaporated under reduced pressure and 100 mg (0.356 mmol) of **5b** are added. The mixture is heated in an oil bath at 150°C for 30 min and allowed to cool. Ether is added and the oily residue is dissolved. The organic layer is washed with aqueous $NaHCO_3$, dried and the solvent evaporated. The residue is recrystallized (charcoal) from ethanol to yield 38 mg (43%) of **9a**. mp 146°C. ^{1}H NMR (400 MHz) δ 7.84 (s, 1H), 7.70 (d, J = 11.0, 1H), 7.66 (s, 1H), 7.62 (d, J = 2.33, 1H), 6.79 (d, J = 2.33, 1H), 6.44 (d, J = 11.0, 1H); ^{13}C NMR (100.6 MHz) δ 155.5, 146.3, 145.4, 132.7, 127.1, 126.3, 122.7, 122.1, 110.9, 106.4; ^{77}Se NMR (76.4 MHz) δ 631; MS *m/z* 250 (91), 222 (100), 194 (21); Anal. Calcd for $C_6H_{11}O_2Se$: C 53.03; H, 2.43. Found: C, 52.84; H, 2.77.

7H-Thiopyrano[3,2-f][1]benzofuran-7-one 9b: The same procedure is followed as for the synthesis of **9a** except that the reaction mixture is heated for 5 h at 120°C. Yield 57%. mp 159°C (ethanol). ^{1}H NMR (400 MHz) δ 7.79 (s, 1H), 7.79 (d, J = 10.6, 1H), 7.62 (d, J = 2.05, 1H), 7.54 (s, 1H), 6.79 (d, J = 2.05, 1H), 6.44 (d, J = 10.6, 1H); ^{13}C NMR (100.6 MHz) δ 185.33, 155.27, 146.58, 144.32, 133.52, 127.08, 124.41, 122.36, 121.63, 108.01, 106.39; MS *m/z* 202 (75), 174 (100), 142 (25). Anal. Calcd for $C_{11}H_6O_2S$: C, 65.33; H, 2.99; S, 15.85. Found: C, 65.35; H, 2.94; S, 15.91.

4-Methoxy-6-methylselenoisophthalaldehyde 6a: A suspension of 10 g (41.1 mmol) of **2b** and 10 g (72.4 mmol) of K_2CO_3 in 100 ml DMF is cooled to 5°C. 2.7 ml (45 mmol) of methaneselenol are added and the reaction medium is allowed to warm up slowly to room temperature and is stirred for 14 h. After standard

isolation, the product is chromatographied (toluene/$CHCl_3$, 90/10). Yield 5.7 g (54 %). mp 190-192°C (toluene). ^1H NMR (400 MHz) δ 10.37 (s, 1H), 9.98 (s, 1H), 8.22 (s, 1H), 6.94 (s, 1H), 4.05 (s, 3H), 2.32 (s, 3H); MS *m/z* 258 (54), 243 (100). Anal. Calcd for $C_{10}H_{10}O_3Se$: C, 46.71; H, 3.92. Found: C, 46.57; H, 4.16.

2-Ethoxycarbonyl-5-formyl-6-methoxybenzo[b]selenophene 7a: A mixture of 5 g (19.5 mmol) of **3a** and 30 ml of ethylbromoacetate is refluxed for 2 h, allowed to cool and the precipitate (mainly **6b**) is filtered and washed with petroleum ether (bp 40-60°C). The remaining solid is stirred overnight with 5.4 g (39.1 mmol) of K_2CO_3 in 50 ml DMF. Standard isolation yields 5.3 g (87%) of **7a**. mp 168-169°C (toluene/ethanol). ^1H NMR (400 MHz) δ 10.47 (s, 1H), 8.28 (s, 1H), 8.21 (s, 1H) 7.45 (s, 1H), 4.36 (q, 2H), 3.99 (s, 3H), 1.39 (t, 3H); MS *m/z* 312 (100), 294 (12), 283 (15), 268 (45), 267 (23), 239 (15). Anal. Calcd for $C_{13}H_{12}O_4Se$: C, 50.18; H, 3.89. Found: C, 50.43; H, 3.84.

5-Formyl-6-hydroxybenzo[b]selenophene 7d: 5-Formyl-6-methoxybenzo[b]selenophene **7c** (1 g, 4.2 mmol) and 1.7 g lithium chloride (40 mmol) are refluxed in 50 ml of DMF for 14 h. The reaction mixture is poured into water, basified to pH 13 with 2N NaOH and washed with ether. The aqueous phase is then acidified and extracted with ether. The organic layer is washed twice with brine, dried and evaporated. The resulting phenol **7d** is pure enough to be used in the next step. Column chromatography (toluene/EtOAc, 85/15) of this product affords slightly yellow crystals which darken again on standing. Yield 715 mg (76%). mp 128°C (toluene). ^1H NMR (400 MHz) δ 10.90 (s, br, 1H), 9.95 (s, 1H), 8.95 (s, 1H), 7.85 (d, J = 6.5, 2H), 7.55 (d, J = 6.5, 2H), 7.55 (s, 1H); MS *m/z* 226 (100), 225 (63), 197 (11), 196 (3), 180 (12), 170 (32). Anal. Calcd for $C_9H_6O_2Se$: C, 48.02; H, 2.69. Found: C, 48.24; H, 2.92.

2H-Selenolo[3,2-g][1]benzopyran-2-one 9c: 5-Formyl-6-hydroxybenzo[b]selenophene **7d** (350 mg, 1.38 mmol) and 310 mg of anhydrous potassium acetate are refluxed in 2 ml of acetic anhydride for 5 h. After cooling, 3 ml of $CHCl_3$, 3 ml of water and 200 mg of anhydrous potassium acetate are added and the mixture is stirred overnight. More $CHCl_3$ is added and the organic layer decanted and washed with 1M Na_2CO_3, water and dried. After chromatographic purification (toluene/$CHCl_3$, 70/30) the residue yields 32% of **9c**. mp 221°C (ethanol). ^1H NMR (400 MHz) δ 7.96 (d, J = 5.9, 1H), 7.85 (s, 1H), 7.83 (s, 1H), 7.76 (d, J = 9.6, 1H), 7.56 (d, J = 5.9, 1H), 6.40 (d, J = 9.6, 1H); ^{13}C NMR (100.6 MHz) δ 160.58, 150.45, 144.75, 143.67, 138.80, 129.41, 126.72, 123.48, 116.55, 115.73, 113.01; ^{77}Se NMR (76.4 MHz) δ 554 ppm. MS *m/z* 250 (100), 222 (48), 194 (18). Anal. Calcd for $C_{11}H_6O_2Se$: C, 53.03; H, 2.43. Found: C, 52.98; H, 2.51.

2-Ethoxycarbonyl-5-formyl-6-methoxybenzo[b]thiophene 7e: Ethylmercaptoacetate (4.4 ml, 40.1 mmol) is allowed to react at rt with 9.75 g (40.1 mmol) of **2b** and 15 g (108.5 mmol) K_2CO_3 in 100 ml of acetonitrile. Standard isolation and column chromatography (toluene/$CHCl_3$, 85/15) yielded 6.78 g (64 %) of **7e**. mp 158°C (toluene/hexane). ^1H NMR (400 MHz) δ 10.52 (s, 1H), 8.33 (s, 1H), 8.03, (s, 1H), 4.42 (q, 2H), 4.03 (s, 3H), 1.43 (t, 3H); MS *m/z* 264 (100), 246 (14), 236 (18), 219 (59), 218 (39). Anal. Calcd for $C_{13}H_{12}O_4S$: C, 59.08; H, 4.58; S, 12.13. Found: C, 59.26; H, 4.87; S, 12.15.

5-Carboxyvinyl-6-methoxybenzo[b]thiophene 8b: 1.2 g (6.2 mmol) of 5-Formyl-6-methoxybenzo[b]thiophene **7g** are added to a mixture of 5 ml of pyridine, 0.1 ml of piperidine and 2.5 g of malonic acid and heated for 150 min at 95°C and then refluxed for 5 min. This mixture is allowed to cool and poured into 1N HCl. The precipitate is filtered, washed with water and redissolved in 2M $NaHCO_3$. This solution is

treated with charcoal, washed with CH_2Cl_2 and acidified. The precipitate is filtered, washed with water and air dried at 110°C. Yield 0.89 g (64%). mp 241-242°C.

2H-Thieno[3,2-g][1]benzopyran-2-one 9d: 4.57 g of P_4O_{10} (32.2 mmol) are refluxed with 27 ml $CHCl_3$ and 7.23 ml (34.0 mmol) HMDSO for 1 h. The solvent is evaporated and 130 mg of **8b** are added. The mixture is heated in an oil bath at 170°C for 1 h and allowed to cool. $CHCl_3$ is added, the organic layer is washed with water, 1N $NaHCO_3$ and dried. The residue is column chromatographied (toluene/$CHCl_3$, 85/15) to yield 67 mg (60%) of **9d**. mp 191°C (ethanol). ^1H NMR (400 MHz) δ 7.88 (s, 1H), 7.79 (s, 1H), 7.79 (d, J = 9.65, 1H), 6.40 (d, J = 9.65, 1H), 7.46 (d, J = 5.8, 1H), 7.35 (d, J = 5.8, 1H); ^{13}C NMR (100.6 MHz) δ 159.77, 149.76, 142.83, 142.16, 135.44, 126.53, 122.37, 121.27, 115.72, 114.86, 108.78; MS *m/z* 202 (100), 174 (39), 149 (13), 148 (12). Anal. Calcd for $C_{11}H_6O_2S$: C, 65.33; H, 2.99; S, 15.85. Found: C, 65.33; H, 2.98; S, 15.55.

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