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# Photochemical Approach to the Synthesis of Naturally Occurring Thienylacetylenes

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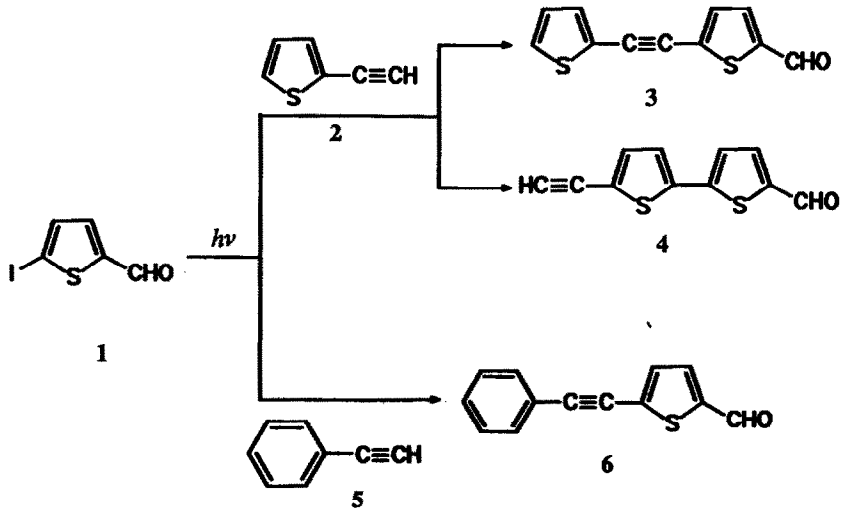
*Abstract*: Three naturally occurring thienylacetylenes are synthesized through a photochemical coupling of 5-iodo-2-thienyl derivatives and 5-trimethylsilyl-2-thienylacetylene.

Recently we have reported that the irradiation of 5-iodothiophene-2-carbaldehyde (**1**) in the presence of 2-ethynylthiophene (**2**) gave a mixture of two compounds: a thienylacetylene **3** and a bithiophene **4** (Scheme 1).[1]

On the contrary, the same reaction, performed in the presence of phenylacetylene (**5**), gave only **6** in 54% yield. Compound **6** is a naturally occuring thiophene isolated in *Bidens cosmoides, Bidens forbesii, Bidens hillenbrandiana, Bidens menziesii, Bidens micrantha, Bidens torta*,[2] and *Coreopsis grandiflora*,[3] and

**Scheme 1**



then the described photochemical approach can represent an useful synthetic method. Also compound **3** is a naturally occurring compound isolated in *Berkheya armata, Berkheya herbacea, Berkheya purpurea*, and *Berkheya rigida*;[4,5] unfortunately our photochemical approach required very diluted solutions ($10^{-3}$ M) and then prevented us from obtaining large quantity of this compound. Nevertheless, naturally occurring thiophenes isolated in numerous members of the *Compositae* showed interesting biological properties as phototoxic compounds.[6] The biological properties of these compounds have been related to the capabilities of this type of compounds to be photosensitizers of singlet oxygen.[7] In the case of compound **3** we were not able to find any datum about both photochemical and phototoxic properties. Then, the development of a general synthetic method can be a significant target in order to obtain compounds to be tested for their photochemical and biological properties.

Compound **3** can be obtained from 2,2'-bithienylacetylene via a Vilsmeier-Haack reaction.[8] 2,2'-Bithienylacetylene can be obtained by using several methodologies that required multistep sequences and not very high yields.[8-10]

In this paper we want to report our photochemical approach to the synthesis of **3** and related compounds.

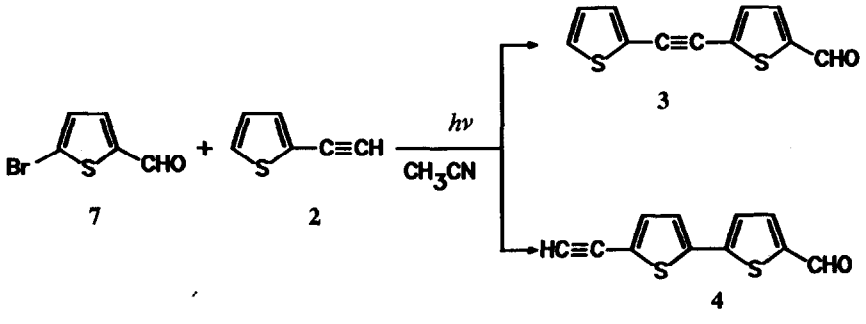
**Result and Discussion**

The formation of compounds **3** and **4** in the reaction of **1** with **2** can be explained considering the formation of a solvent separated radical ion pair due to a single electron transfer between halothiophene derivative (the acceptor) and the alkyne (the donor).[1]

On the basis of this mechamism we can favour the formation of **3** using reagents able to give only contact ion pair. We could obtain these conditions using as substrate an halothiophene derivative with higher $E_{1/2}^{Red}$ than 5-iodothiophene-2-carbaldehyde. At this purpose we used 5-bromothiophene-2-carbaldehyde (**7**). In fact, in a previous paper we showed that in furan derivatives there was a neat difference in polarographic behaviour between iodo and bromo substituted compounds.[11]

The irradiation of **7** in the presence of **2** showed that there was an increase in selectivity. In fact the ratio between **3** and **4** was 6:1 instead of 3:1 as reported in Ref. 1 (Scheme 2). However this result is not synthetically useful because we observed a sharp decrease in the reactivity. After 3 h irradiation we obtained only 15% conversion of **7**.

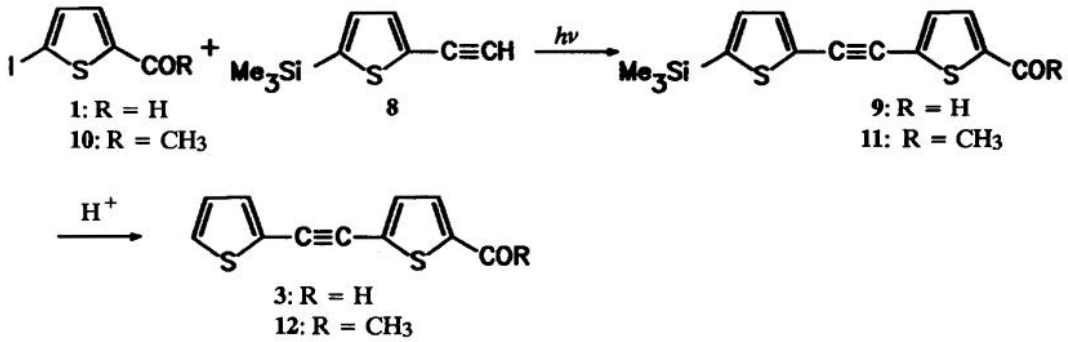
**Scheme 2**




7 2 3 4

This method does not allow us to obtain **3** as only product. Then we have tested whether protected alkynes can be used. In order to test this hypothesis we have used 2-ethynyl-5-trimethylsilylthiophene (**8**) as reagent. The irradiation of **1** in the presence of **8** furnished only **9** in 65% yield. Compound **9** can be converted in the naturally occurring thiophene **3** in acidic medium in 85% yield (Scheme 3).[12]

**Scheme 3**




The above described synthetic sequence can be used in the synthesis of other naturally occurring thienylacetylenes. In fact, the irradiation of 2-acetyl-5-iodothiophene (**10**) in the presence of **8** gave 2-acetyl-5-(5'-trimethylsilyl-2'-thienylethynyl)thiophene (**11**) in 81% yield. Compound **11** can be deprotected by using the same procedure above described in 91% yield to give 2-acetyl-5-(2'-thienylethynyl)thiophene (**12**) (Scheme 3). Compound **12** is a naturally occurring thienylacetylene isolated in *Berkheya armata* and *Berkheya rigida*.[4,5]

Finally, the irradiation of 2-hydroxyacetyl-5-iodothiophene (**13**) in the presence of **8** gave 2-hydroxyacetyl-5-(5'-trimethylsilyl-2'-thienylethynyl)thiophene **14** in 81% yield (Scheme 4). The subsequent deprotection of **14** in acidic medium gave **15** in 71% yield. In this case we observed both deprotection and acetylation of the hydroxy group. Reduction with $NaBH_4$ gave quantitatively **16** which can be converted into the diol **17** by treatment with NaOH in 67% yield. Compound **17** is a naturally occurring thiophene isolated in *Centaurea sphaerocephala* and never synthetized before.[13]

In conclusion our photochemical approach can represent a suitable synthetic method for the synthesis of this type of compounds.

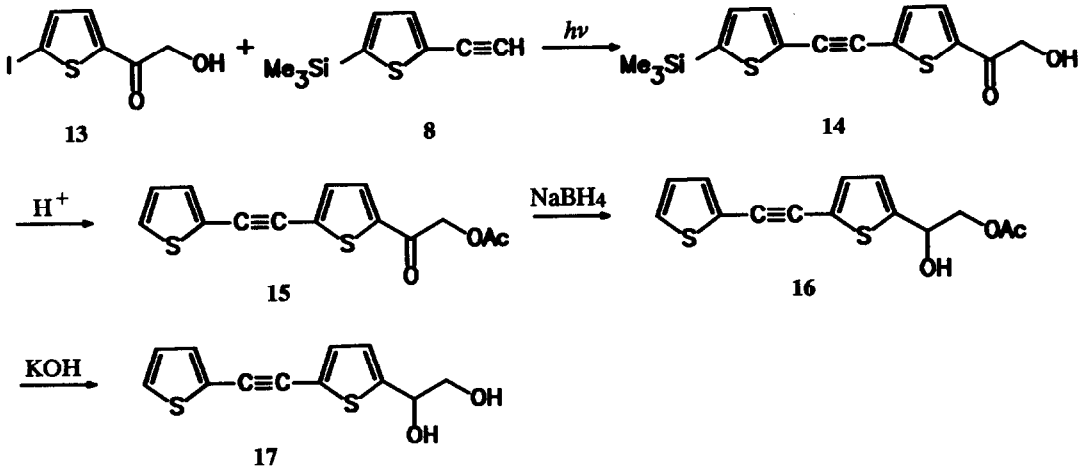
As reported above no datum is available on the phototoxic properties of these compounds. We have tested **12** as singlet oxygen sensitizer. In order to test this capability we have used the reactivity of *trans*-$\alpha,\alpha'$-dimethylstilbene (**18**). In fact, it is known that this compound reacts with singlet oxygen to give **19**, while electron transfer process induces the formation of a mixture of products (Scheme 5).[14]

The irradiation of $5 \times 10^{-2}$ M solution of **18** containing $2 \times 10^{-4}$ M **12** in acetonitrile in a Pyrex tube at 13°C for 4 h with a high pressure mercury arc furnished only the compound **19** while there was no evidence of the formation of the compounds **20-23**. In conclusion we have an evidence that **12** is a singlet oxygen sensitizer and we can exclude the formation of superoxide ion in our system.

## Experimental

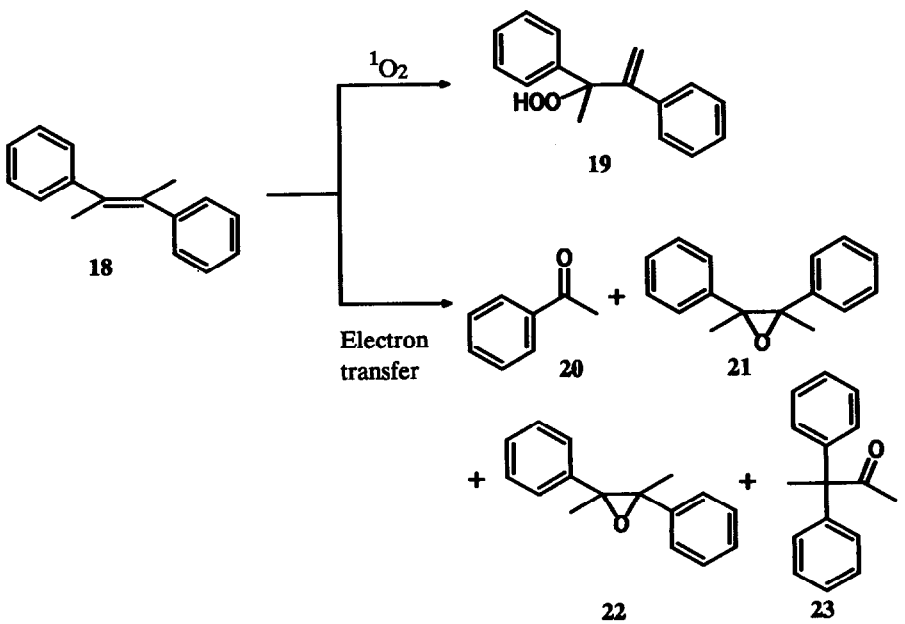
M.p.s were obtained with a Mettler FP81 cell equipped with a Mettler FP80 central processor. $^1H$ NMR spectra were recorded with a Varian Gemini 200 MHz with $CDCl_3$ as solvent. Mass spectra were obtained with a Hewlett-Packard 5971A mass selective detector connected with a Hewlett-Packard 5890 gas chromatographic instrument and with a Hewlett-Packard 9000 central processor. IR spectra were obtained on a Shimadzu IR-470 spectrophotometer. UV spectra were recorded with a Varian DMS-90 spectrophotometer. GLC analyses were performed with Hewlett-Packard 5880A and 5890 instruments (flame- ionization detector). Commercial Merck silica gel was used for column chromatography.

**Scheme 4**




13 8 14 15 16 17

**Scheme 5**



**Starting Materials**

5-Bromothiophene-2-carbaldehyde (**7**) was prepared from 2,5-dibromothiophene by reaction with BuLi and dimethylformamide (DMF).[15] The latter compound was obtained *via* a reaction between thiophene and bromine in the presence of AcOH.[16] 2-Ethynylthiophene (**2**) was prepared from thiophene-2-carbaldehyde by reaction with $CBr_4/PPh_3$ in $CH_2Cl_2$ and subsequent reaction of the dibromoalkene with MeLi and then water.[17] 5-Iodothiophene-2-carbaldehyde (**1**) was obtained from thiophene-2-carbaldehyde through reduction with $NaBH_4$, iodination of the corresponding alcohol with iodine and HgO, and subsequent oxidation of 5-iodothiophene-2-methanol with PCC (pyridinium chlorochromate).[6] 2-Ethynyl-5-trimethylsilylthiophene (**8**) was prepared as described for 2-ethynylthiophene starting from 5-trimethylsilylthiophene-2-carbaldehyde.[18] 2-Acetyl-5-iodothiophene (**10**) was prepared from 2-iodothiophene by reaction with $Ac_2O$ in the presence of $H_3PO_4$.[19] 2-Iodothiophene was prepared from thiophene by reaction with iodine and HgO.[20] 2-Hydroxyacetyl-5-iodothiophene (**13**) was prepared from 2-bromoacetyl-5-iodothiophene through reaction with $HCO_2Na$ in MeOH.[21] 2-Bromoacetyl-5-iodothiophene was obtained from 2-acetyl-5-iodothiophene *via* reaction with bromine in $CCl_4$.[21] $\alpha,\alpha'$-Dimethylstilbene (**18**) was synthesized by reductive coupling of acetophenone in the presence of $TiCl_4$ and Zn.[22] Crystallization from ethanol yielded pure *trans*-$\alpha,\alpha'$-dimethylstilbene (m.p. 102-103°C).

**2,5-Dibromothiophene.** B.p. 210-218°C (lit.,[23] 210.5-211°C); $^1$H NMR $\delta$: 6.67 (2 H, s); IR $\nu_{max}$: 1518, 1410, 1202, 982, 948, 860, and 782 cm$^{-1}$; MS *m/z*: 212, 210, and 208.

**5-Bromothiophene-2-carbaldehyde (7).** B.p. 138-140°C/30 mmHg (lit.,[24] 80-83°C/2 mmHg); $^1$H NMR $\delta$: 9.83 (1 H, s), 7.58 (1 H, d, *J* 4 Hz), and 7.20 (1 H, d, *J* 4 Hz); IR $\nu_{max}$: 2818, 2740, 2720, 1668, 1523, 1415, 1391, 1377, 1322, 1303, 1220, 1201, 1185, 1055, 977, 802, 755, 749, and 633 cm$^{-1}$; MS *m/z*: 160, 159, 158, and 157.

**2-Ethynylthiophene (2).** B.p. 44-46°C/18 mmHg (lit.,[25] 54- 60°C/20 mmHg); $^1$H NMR $\delta$: 7.22 (2 H, m), 6.93 (1 H, dd, $J_1$ 4 Hz, $J_2$ 5 Hz), and 3.13 (1 H, s).

**5-Iodothiophene-2-carbaldehyde (1).** M.p. 47-49°C (lit.,[15] 49°C); $^1$H NMR $\delta$: 9.60 (1 H, s), and 7.25 (2 H, s); IR $\nu_{max}$: 2820, 2735, 2718, 1680, 1512, 1410, 1388, 1377, 1318, 1219, 1200, 1051, 952, and 663 cm$^{-1}$; MS *m/z*: 238 and 237.

**5-Trimethylsilyl-2-ethynylthiophene (8).** B.p. 52-54°C/20 mmHg; $^1$H NMR $\delta$: 7.35 (1 H, d, *J* 3.5 Hz), 7.12 (1 H, d, *J* 3.5 Hz), 3.42 (1 H, s), and 0.36 (9 H, s); MS *m/z*: 180 and 165.

**2-Iodothiophene.** B.p. 73°C/15 mmHg (lit.,[20] 73°C/15 mmHg); $^1$H NMR $\delta$: 7.07 (2 H, m), and 6.56 (1 H, m); IR $\nu_{max}$: 1397, 1343, 1335, 1218, 1080, 1043, 948, 840, 820, 736, and 690 cm$^{-1}$; MS *m/z*: 210.

**2-Acetyl-2-iodothiophene (10).** M.p. 128-129°C (lit.,[19] 129°C); $^1$H NMR $\delta$: 7.20 (2 H, s), and 2.06 (3 H, s); IR $\nu_{max}$: 1665, 1400, 1358, 1315, 1268, 959, and 908 cm$^{-1}$; MS *m/z*: 252.

**2-Hydroxyacetyl-5-iodothiophene (13).** $^1$H NMR $\delta$: 7.32 (2 H, s), 4.69 (1 H, d, *J* 4.5 Hz) and 3.22 (1 H, t, *J* 4.5 Hz); MS *m/z*: 268 and 237.

***Photochemical reaction of 5-bromothiophene-2-carbaldehyde with 2-ethynylthiophene.***

5-Bromothiophene-2-carbaldehyde (**7**) (402 mg, 2.1 mmoles) was dissolved in $CH_3CN$ (300 ml) in the presence of 2-ethynylthiophene (**2**) (3 g, 27.8 mmoles). The mixture was outgassed with $N_2$ for 1 h. The

mixture was then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water-jacket. After 3 h the mixture was diluted with $CHCl_3$ and washed with brine. The neutral organic phase was dried ($Na_2SO_4$). Removal of the solvent yielded a crude product which was chromatographed on $SiO_2$. Elution with $CHCl_3$-*n*-hexane (3:2) gave pure **3** (59 mg) and **4** (10 mg). **3**: m.p. 78-79°C (lit.,[19] 79°C); $^1H$ NMR $\delta$: 9.83 (1 H, s), 7.66 (1 H, d, $J$ 5 Hz), 7.38 (2 H, m), 7.29 (1 H, d, $J$ 5 Hz), and 7.03 (1 H, dd, $J_1 = J_2$ 4 Hz); IR $\nu_{max}$: 2720, 2200, and 1670 $cm^{-1}$; MS *m/z*: 220 (12%), 219 (19), 218 (100), 217 (56), 190 (6), 189 (13), and 145 (24); **4**: very dense oil; $^1H$ NMR $\delta$: 9.93 (1 H, s), 7.7 (2 H, m), 7.3 (2 H, m), and 3.45 (1 H, s); IR $\nu_{max}$: 3305, 2200, 1665, 1450, 1410, and 910 $cm^{-1}$; MS *m/z*: 220 (11%), 219 (19), 218 (100), 217 (55), 189 (11), and 145 (26).

**5-(5'-Trimethylsilyl-2'-thienylethynyl)thiophene-2-carbaldehyde (9).** 5-Iodothiophene-2-carbaldehyde (1 g, 4.2 mmoles) was dissolved in $CH_3CN$ (320 ml) in the presence of 2-ethynyl-5-trimethylsilylthiophene (2.5 g, 13.9 mmoles). The solution was outgassed with $N_2$ for 1 h and then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water-jacket. After 9 h the mixture was diluted with $CHCl_3$ and washed with 0.1 M $Na_2S_2O_3$ and then with brine. The neutral organic phase was dried ($Na_2SO_4$). Removal of the solvent yielded a crude product which was chromatographed on $SiO_2$. Elution with benzene gave pure **9** (792 mg, 65%); $^1H$ NMR $\delta$: 9.84 (1 H, s), 7.64 (1 H, d, $J$ 4 Hz), 7.36 (1 H, d, $J$ 3.5 Hz), 7.27 (1 H, d, $J$ 4 Hz), 7.13 (1 H, d, $J$ 3.5 Hz), and 0.31 (9 H, s); IR $\nu_{max}$: 2195, 1668, 1637, 1604, 1507, 1451, 1416, 1394, and 1388 $cm^{-1}$; MS *m/z*: 292 (18%), 291 (27), 290 (96), 277 (27), 276 (38), 275 (100), 231 (4), 193 (13), 185 (6), 171 (6), 137 (34), 115 (15), 113 (8), 101 (9), 91 (7), 87 (6), 75 (11), 73 (8), 69 (6).

**5-(2'-Thienylethynyl)thiophene-2-carbaldehyde (3).** Compound **9** (659 mg, 2.27 mmoles) was dissolved in AcOH (50 ml) in the presence of $H_2SO_4$ (1 N in AcOH, 38 ml). The mixture was stirred for 12 h and then treated with $NaHCO_3$ until neutrality. The mixture was then extracted with $Et_2O$ and washed with brine. The neutral organic phase was dried over $Na_2SO_4$ and the removal of the solvent yielded a crude product which was chromatographed on $SiO_2$. Elution with $CHCl_3$-*n*-hexane (4:1) gave pure **3** (421 mg, 85%). For spectroscopic data see above.

**2-Acetyl-5-(5'-trimethylsilyl-2'-thienylethynyl)thiophene (11).** 2-Acetyl-5-iodothiophene (1 g, 3.97 mmoles) was dissolved in $CH_3CN$ (320 ml) in the presence of 2-ethynyl-5-trimethylsilylthiophene (2.5 g, 13.9 mmoles). The solution was outgassed with $N_2$ for 1 h and then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water-jacket. After 6 h the mixture was diluted with $CHCl_3$ and washed with 0.1 N $Na_2S_2O_3$ and then with brine. The neutral organic phase was dried over $Na_2SO_4$. The removal of the solvent yielded a crude product which was chromatographed on $SiO_2$. Elution with $CHCl_3$-*n*-hexane (4:1) gave pure **11** (978 mg, 81%). Very dense oil; $^1H$ NMR $\delta$: 7.56 (1 H, dd, $J_1$ 3 Hz, $J_2$ 0.8 Hz), 7.34 (1 H, dd, $J_1$ 3 Hz, $J_2$ 0.8 Hz), 7.20 (1 H, dd, $J_1$ 4 Hz, $J_2$ 1 Hz), 7.12 (1 H, dd, $J_1$ 4 Hz, $J_2$ 1 Hz), 2.50 (3 H, s), and 0.30 (9 H, s); IR $\nu_{max}$: 2195, 1660, 1400, 1355, 1300, 1265, and 980 $cm^{-1}$; MS *m/z*: 306 (17%), 305 (27), 304 (94), 291 (27), 290 (40), 289 (100), 207 (13), 199 (6), 171 (7), 137 (39), 115 (16), 101 (12), 91 (8), 87 (8), 75 (11), 73 (10).

**2-Acetyl-5-(2'-thienylethynyl)thiophene (12).** Compound **11** (1.04 g, 3.34 mmoles) was dissolved in AcOH (50 ml) in the presence of $H_2SO_4$ (1 N in AcOH, 38 ml). The mixture was stirred for 12 h and then neutralized with $NaHCO_3$. The mixture was extracted with $Et_2O$. The neutral organic phase was dried over $Na_2SO_4$ and the removal of the solvent yielded a crude product which was chromatographed on $SiO_2$. Elution with $CHCl_3$-*n*-hexane (4:1) gave pure **12** (721 mg, 3.1 mmoles, 91%). M.p. 128-129°C (lit.,[19] 129°C); $^1H$ NMR $\delta$: 7.54 (1 H, d, $J$ 4 Hz), 7.3 (2 H, m), 7.19 (1 H, d, $J$ 4 Hz), 7.00 (1 H, dd, $J_1$ 5 Hz, $J_2$ 4 Hz), and 2.50 (3 H, s); IR $\nu_{max}$: 2200, 1730, 1660, 1445, 1405, 1360, 1330, 1275, and 960 $cm^{-1}$; MS *m/z*: 234

(10%), 233 (15), 232 (93), 219 (11), 218 (16), 217 (100), 190 (4), 189 (23), 146 (6), 145 (59), 109 (5), 94 (7), 93 (7), 87 (7), 69 (10).

**2-Hydroxyacetyl-5-(5'-trimethylsilyl-2'-thienylethynyl)thiophene (14).** 2-Hydroxyacetyl-5-iodothiophene (1 g, 3.73 mmoles) was dissolved in $CH_3CN$ (320 ml) in the presence of 2-ethynyl-5-trimethylsilylthiophene (5 g, 27.78 mmoles). The solution was outgassed with $N_2$ for 1 h and then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water-jacket. After 8 h the mixture was diluted with $CHCl_3$ and washed with 0.1 N $Na_2S_2O_3$ and then with brine. The neutral organic phase was dried over $Na_2SO_4$ and the removal of the solvent yielded a crude product which was chromatographed on $SiO_2$. Elution *n*-hexane-$Et_2O$ (2:3) gave pure **14** (975 mg, 81%). Very dense oil; $^1H$ NMR $\delta$: 7.59 (1 H, d, *J* 4 Hz), 7.35 (1 H, d, *J* 3.5 Hz), 7.22 (1 H, d, *J* 4 Hz), 7.12 (1 H, d, *J* 3.5 Hz), 4.75 (2 H, s), 3.27 (1 H, broad s), and 0.3 (9 H, s); IR $\nu_{max}$: 3480, 2977, 2942, 2861, 2200, 1741, 1671, 1372, 1240, 1070, and 1048 $cm^{-1}$.

**2-Acetoxyacetyl-5-(2'-thienylethynyl)thiophene (15).** Compound **14** (316 mg, 0.99 mmoles) was dissolved in AcOH (190 ml) in the presence of $H_2SO_4$ (1 N in AcOH, 140 ml). The mixture was stirred for 18 h and then the mixture was neutralized with $NaHCO_3$ and extracted with $Et_2O$. The neutral organic phase was dried ($Na_2SO_4$) and the removal of the solvent yielded a crude product which was chromatographed on $SiO_2$. Elution with AcOEt-*n*-hexane (1:2) gave **15** (204 mg, 71%). Very dense oil; $^1H$ NMR $\delta$: 7.62 (1 H, d, *J* 4 Hz), 7.31 - 7.37 (2 H, m), 7.22 (1 H, d, *J* 4 Hz), 7.02 (1 H, dd, $J_1$ 5 Hz, $J_2$ 4 Hz), 5.17 (2 H, s), and 2.20 (3 H, s); IR $\nu_{max}$: 2200, 1746, 1676, 1445, 1411, 1373, 1324, 1251, 1248, 1243, 1239, 1236, 1197, 1185, 1178, 1169, 1165, 1159, 1121, 1088, 1048, 1046, and 908 $cm^{-1}$.

**2-(1,2-Dihydroxyethyl)-5-(2'thienylethynyl)thiophene (17).** Compound **15** (58 mg, 0.2 mmoles) was dissolved in MeOH (5 ml) and treated with $NaBH_4$ (20 mg). After 15' the mixture was poured into diluted $H_2SO_4$ at 0°C and extracted several times with $Et_2O$. The neutral organic phase was dried over $Na_2SO_4$ and the removal of the solvent yielded a crude product which was dissolved in MeOH (5 ml) and treated with 2 N NaOH (2 ml). The mixture was stirred at 60°C for 3 h. After neutralization with diluted $H_2SO_4$ the mixture was extracted with $CHCl_3$. The neutral organic phase was dried over $Na_2SO_4$. The removal of the solvent yielded a crude product which was chromatographed on $SiO_2$. Elution with $CHCl_3$-MeOH 97:3 gave pure **17** (33 mg, 67%). $^1H$ NMR $\delta$: 7.29 (1 H, dd, $J_1$ 5 Hz, $J_2$ 1 Hz), 7.25 (1 H, dd, $J_1$ 4 Hz, $J_2$ 1 Hz), 7.13 (1 H, d, *J* 4 Hz), 6.99 (1 H, dd, $J_1$ 5 Hz, $J_2$ 4 Hz), 6.89 (1 H, d, *J* 4 Hz), 5.01 (1 H, dd, $J_1$ 7 Hz, $J_2$ 4 Hz), 3.7 - 3.9 (2 H, m), 2.6 (1 H, broad s), 2.1 (1 H, broad s); IR $\nu_{max}$: 3595, 3405, 2200, 1600 $cm^{-1}$.

**Photochemical oxidation of *trans*-$\alpha,\alpha'$-dimethylstilbene.**

A solution (50 ml) containing $2 \times 10^{-4}$ M **12** and $5 \times 10^{-2}$ M **18** in acetonitrile was irradiated in a Pyrex tube surrounded by a Pyrex water jacket connected to a Haake F3 thermostat to maintain the temperature at 13.0 $\pm$ 0.1°C with a 500 W high pressure mercury arc (Helios-Italquartz) surrounded by a Pyrex water jacket in the presence of a flux of oxygen. After 4 h, the solvent was removed at room temperature on a rotary evaporator; residual oil was analyzed via $^1H$ NMR ($CDCl_3$) $\delta$: 7.0 - 7.5 (10 H, m), 5.49 (2 H, dd, $J_1$ 8 Hz, $J_2$ 1 Hz), 1.84 (3 H, s).

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