Synthesis and Characterization of Alkyl-, Alkenyl-, Acyl- and Nitrogen-substituted Derivatives of the Potent Phototoxin α-Terthiophene

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Some alkyl-, alkenyl-, acyl- and nitrogen- derivatives of α-terthienyl **1** have been synthesized in an effort to expand the potential insecticidal activity profile of this compound. The introduction of substituents was carried out directly on the α-terthienyl molecule. Three compounds were isolated in the nitration reaction and the compounds have been identified as 5-nitro-2,2':5',2''-terthiophene **5**, 3'-nitro-2,2':5',2''-terthiophene **6** and 3-nitro-2,2':5',2''-terthiophene **7** respectively. Preliminary results of biological acitivity are reported.

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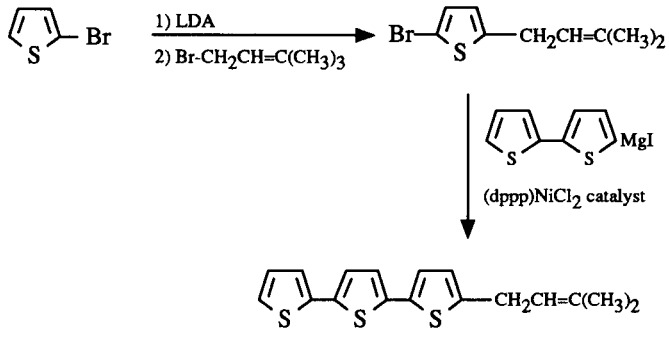
2,2':5',2''-Terthiophene **1** (α-T) is a plant secondary metabolite biosynthetically related to polyacetylenes which occurs in species of the plant family *Asteraceae*. The phototoxic activity [1a,b] of this substance has been linked to the generation of singlet oxygen and has been confirmed by mechanistic [2,3] and fundamental photochemical studies [4].

In a recent paper [5] we reported the synthesis and characterization of alkyl-, halo- and hetero-substituted derivatives of α-terthiophene. It was shown that 5-methyl-2,2':5',2''-terthiophene **2**, 5-iodo-2,2':5',2''-terthiophene **3** and 5,5''-diiodo-2,2':5',2''-terthiophene **4** derivatives were more efficient larvicides than the parent compound. To continue the evaluation of structure-activity relationships we have synthesized other derivatives in which the electronic effects of the substituents could be compared to the biological activity observed.

General Approach to the Synthesis of Derivatives.

In our previous report [5], the synthesis of derivatives was accomplished by the nickel-catalyzed cross-coupling reaction. The catalyst used was dichloro[1,3-bis-(diphenylphosphino)propane]-nickel(II) ($Ni[dppp]Cl_2$) [6] (Scheme 1).

Scheme 1



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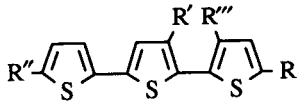
Except for the synthesis of **15**, the substituents in the derivatives reported in this paper were introduced directly on the 2,2':5',2''-terthiophene **1** molecule.

Nitrogen Containing Substituents.

Treatment of 2,2':5',2''-terthiophene **1** with fuming nitric acid and acetic anhydride in methylene chloride gave a mixture of products [7]. Three nitro derivatives were detected [8a,b] and their yields determined by gc



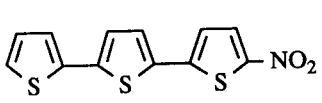
1	R=R'=R''=R'''= H	**10**	R'=R'''=H, R=R''=CN
2	R'=R''=R'''=H, R=CH_3	**11**	R'=R''=R'''=H, R=$CONH_2$
3	R'=R''=R'''=H, R=I	**12**	R'=R''=R'''=H, R=(E)-CH=$CHCO_2CH_3$
4	R'=R'''=H, R=R''=I	**13**	R'=R''=R'''=H, R=$CH_2CH_2CO_2CH_3$
5	R'=R''=R'''=H, R=NO_2	**14**	R'=R''=R'''=H, R=$CH_2CH_2CO_2H$
6	R=R''=R'''=H, R'=NO_2	**15**	R'=R''=R'''=H, R=$CH_2CH=C(CH_3)_2$
7	R=R'=R''=H, R'''=NO_2	**16**	R'=R''=R'''=H, R=$COPhCO_2CH_3$
8	R'=R''=R'''=H, R=NH_2	**17**	R'=R'''=H, R=R''=$COPhCO_2CH_3$
9	R'=R''=R'''=H, R=CN	**18**	R'=R''=R'''=H, R=$COPhCO_2H$

Table I
^{1}H NMR Data [a] for Nitrogen Derivatives

Compound	H-4 (d, 1H)	H-3 (d, 1H)	H3' (d, 1H)	H-4' (d, 1H)	H3" (d, 1H)	H-4" (dd, 1H)	H-5" (dd, 1H)	(Hz) $J_{3,4}$	$J_{3',4'}$	$J_{3",4"}$	$J_{4",5"}$	$J_{3",5"}$
5	7.83	7.05	7.26	7.12	7.22	7.04	7.28	4.00	3.00	3.00	5.20	1.15
6	7.12	7.57	7.53 [b]	7.64 [c]	7.23	7.06	7.33	3.75	5.16 [d]	3.61	5.13	1.17
7	7.61	7.16 [e]	7.47	7.06	7.26	7.04	7.27	5.78 [f]	3.93	3.74	5.07	1.17
8 [g]	6.08	6.76	6.83	7.00	7.11	6.48	7.17	3.72	3.75	3.64	5.10	1.18
9	7.81	7.30	7.46	7.42	7.38	7.12	7.50	3.50	3.50	3.50	5.50	1.00
10 [h]	7.98	7.58	7.62	7.62	7.58	7.98	–	4.00	–	4.00	–	–
11	7.67	7.33	7.29	7.25	7.33	7.10	7.46	3.50	3.50	3.50	5.00	1.00

[a] Deuteriochloroform (300 MHz) for **5-8**, acetone-d_6 for **9,11** and DMSO-d_6 for **10**; abbreviations used; s(singlet), d(doublet), dd(doublet of doublets). [b] δ 7.53, H-5. [c] Singlet. [d] $J_{4,5}$ = 5.16 Hz. [e] δ 7.16, H-5. [f] $J_{4,5}$ = 5.78 Hz. [g] $CONH_2$ substituent at C-5. [h] 5,5"-Disubstituted.

analysis. Pure substances were obtained by column chromatography and the compounds were identified as 5-nitro-2,2':5',2"-terthiophene **5** (82%), 3'-nitro-2,2':5',2"-terthiophenne **6** (1%) and 3-nitro-2,2':5',2"-terthiophene **7** (17%) respectively in order of increasing polarity.



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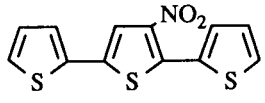

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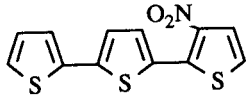

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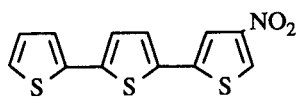

7a

The major product was easily identified as **5** on the basis of its ^{1}H nmr spectrum (see Table I) and characterized by a significant downfield shift of the C-4 proton adjacent to the nitro group. The structure of **6** was identified as the 3'-nitro-2,2':5',2"-terthiophene derivative by the lone singlet in the ^{1}H nmr at 7.64 and two proton patterns corresponding to two unsubstituted thienyl rings, one proton pattern being more deshielded than the other due to the nitro group. The structure elucidated for **7** is 3-nitro-2,2':5',2"-terthiophene. The key evidence for this is the doublet of doublets for the C-4, C-5 protons (see Table I). The absence of singlets in the ^{1}H nmr spectrum, ruled out the 4-nitro derivative **7a** as a possible structure.

Catalytic hydrogenation of 5-nitro-2,2':5',2"-terthiophene **5** with 10% palladium on carbon in ethyl acetate afforded 5-amino-2,2':5',2"-terthiophene **8** in 66% yield.

Treatment of 2,2':5',2"-terthiophene **1** with chlorosulfonyl isocyanante at −30° in dichloromethane generated the *N*-chlorosulfonyl derivative of α-terthiophene-5-carboxamide which, on addition of dimethylformamide, afforded 5-cyano-2,2':5',2"-terthiophene **9** in 75% yield, [9a,b]. The reaction with the chlorosulfonyl isocyanate was found very sensitive to reaction conditions and, if perfomed at room temperature, the yield of mononitrile derivative decreased, and some of the disubstituted derivative 5,5"-dicyano-2,2':5',2"-terthiophene **10** (31%) was formed.

Treatment of the 5-cyano derivative **9** with sodium hydroxide in ethanol gave after separation of the crude product (71% yield) a yellow solid identified as 5-carboxamide-2,2':5',2"-terthiophene **11**.

Alkyl and Alkenyl Derivatives.

The Wittig reaction of 5-formyl-2,2':5',2"-terthiophene [10] with methyl(triphenylphosphoranylidene)acetate [11] in THF at reflux for 13 hours provided methyl 2,2':5',2"-terthiophene-5-[(*E*)-3"'-acrylate] **12** in 92% yield. The catalytic reduction of **12** with 10% palladium on carbon afforded methyl 2,2':5',2"-terthiophene-5-(3"'-propionate) **13** in 70% yield. Hydrolysis of **13** with sodium hydroxide in methanol/THF (1:1) gave 2,2':5',2"-terthiophene-5-(3"'-propionic acid) **14** as a yellow solid in 85% yield.

Treatment of 2-bromothiophene with a solution of lithium diisopropylamine generated *in situ*, produced 2-bromo-5-lithiothiophene which was treated with 4-bromo-2-methyl-2-butene to give 2-bromo-5-(3'-methyl-2'-butenyl)-thiophene. The Grignard reagent formed by transmetallation with 5-iododithienyl [5] was coupled with 2-bromo-5-(3'-methyl-2'-butenyl)thiophene in low yield (11%) to afford 5-(3"'-methyl-2"'-butenyl)-2,2':5',2"-terthiophene **15** as a yellow solid.

Acyl Derivatives of α-Terthiophene.

Derivatives **16**, **17** and **18** were prepared by nucleophilic substitution reaction of 2,2':5',2"-terthiophene **1** with one equivalent of phthalic anhydride which resulted in a mixture of mono and diacid products. Without further purification, the resultant mixture was methylated with a freshly distilled diazomethane solution. Purification of the mixture gave a major product, the methyl monosubstituted ester derivative **16** (35%) and also a minor product **17** (44%) identified as the methyl disubstituted ester derivative. Hydrolysis of the methyl monosubstituted ester

16 with a sodium hydroxide solution in methanol at room temperature for 18 hours generated the pure monoacid identified as 4,5-[(1'''-carboxy)-2'''-benzoic acid]-2,2':5',2''-terthiophene **18** in 93% yield.

Biological Activity Tests.

Using the standard phototoxicity test with yeast culture which is a good indicator of phototoxicity to mosquito larvae (see Table II) compounds **1, 2, 11** and **18**, showed good phototoxic activity, while compounds **4, 5, 7, 9, 10, 13** showed moderate to low activity. Compounds **3, 12, 16** and **17** were inactive under the test conditions. The results indicate that most but not all derivatives of **1** retain phototoxicity as a biological activity and are a potential source of new photosensitizing molecules. The relationship of structure to phototoxic activity is complex and will be examined in a subsequent manuscript.

Table II

Phototoxicity Tests: Inhibitory Effects of Thiophenes on *Saccharomyces cereviceae* under Near-UV and Dark Conditions

Compound	Mean Size of Zone of Inhibition (mn) +near UV	dark
1	7	0
2	3	0
3	0	0
4	0.5	0
5	1	0
6	NT	NT
7	1	0
8	NT	0
9	2	0
10	2	0
11	3	0
12	0	0
13	0.5	0
14	1	0
15	NT	NT
16	0	0
17	0	0
18	3	0

NT = not available for test. Note: Phototoxic test was undertaken as described in [12]. Ten μg of each compound was applied to a 5 mm diameter filter paper disk, subsequently placed on yeast culture on agar. Irradiation was undertaken with 4 20W black blue tubes for 12 hours ($I = 5$ W/m^2).

EXPERIMENTAL

General.

Melting points were determined on a Hoover Unimelt apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 783 Ratio Recording Infrared spectrophotometer neat, with potassium bromide. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Varian XL-300, with deuteriochloroform as solvent (unless indicated otherwise) and TMS as internal standard. Mass spectra were recorded on a VG mass spectrometer with a DANI 7070 gas chromatograph at the Department of Chemistry, Ottawa-Carleton Chemistry Institute. Chromatographic separations were performed on a preparative, centrifugally accelerated, radial, thin-layer chromatograph (a chromatotron Model 7924), using silica gel PF-254 with calcium sulfate hemihydrate type 60 (Merck 7749) as adsorbent. Tetrahydrofuran (THF) was dried as follows: THF (500 ml), sodium metal (5 g) and benzophenone (10 g) were refluxed under nitrogen until a deep blue color formed and persisted. After an additional 2 hours of gentle reflux, THF was distilled into an oven dried, nitrogen-flushed flask. Most reactions were carried out under nitrogen; hypodermic syringes were used to transfer solutions.

Nitration of 2,2':5',2''-Terthiophene (**1**).

To a solution of α-terthiophene **1** (1.24 g, 5 mmoles) in 10 ml of methylene chloride with 10 ml of acetic anhydride at 5° was added with stirring, 3.5 ml of a solution composed of fuming nitric acid (3 ml) in glacial acetic acid (30 ml). The reaction mixture was stirred at room temperature for 6 hours. Hydrolysis with 60 ml of water produced 1.3 g of a red precipitate which was collected by filtration, washed with water, and air dried. The red solid was analyzed by gc using a capillary column showing a mixture of three products. The material was chromatographed on a flash silica column eluting with hexane gradually increasing to 5% ethyl acetate/hexane. A red-brown solid was isolated and the major product was determined by gc to be the 5-nitro-2,2':5',2''-terthiophene **5** (82%), mp 150-156°; ^{1}H nmr (see Table I); ir (potassium bromide): ν max 3100, 1535, 1505, 1490, 1455, 1430, 1330, 1045, 840, 800, 710 cm^{-1}; eims: m/z (%), 293 (100), 203 (65), 127 (22), 69 (30), 45 (56); hrms: Calcd. for $C_{12}H_7O_2S_3N$, 292.964. Found: 292.962.

Anal. Calcd. for $C_{12}H_7O_2S_3N$: C, 49.13; H, 2.40; S, 32.78. Found: C, 49.19; H, 2.51; S, 32.59.

The second substance eluted was identified as 3'-nitro-2,2':5',2''-terthiophene **6** (1%) as an orange solid, mp 125-126°; ^{1}H nmr: (see Table I); ir (potassium bromide): ν max 3100, 1540, 1510, 1490, 1450, 1430, 1330, 1230, 1180, 1050, 840, 800, 730, 710 cm^{-1}; eims: m/z (%), 293 (100), 246 (26), 203 (48), 135 (64), 44 (100); hrms: Calcd. for $C_{12}H_7O_2S_3N$, 293.366. Found: 292.962.

Anal. Calcd. for $C_{12}H_7O_2S_3N$: C, 49.13; H, 2.40; S, 32.78. Found: C, 49.43; H, 2.61; S, 32.58.

A third substance, 3-nitro-2,2':5',2''-terthiophene **7**, was obtained as a red solid, mp 125-126°; ^{1}H nmr: (see Table I); ir (potassium bromide): ν max 3100, 1565, 1540, 1510, 1430, 1375, 1325, 1185, 1045, 840, 800, 735, 715 cm^{-1}; eims: m/z (%), 293 (100), 203 (48), 135 (64), 44 (100); hrms: Calcd. for $C_{12}H_7O_2S_3N$, 293.366. Found: 292.962.

Anal. Calcd. for $C_{12}H_7O_2S_3N$: C, 49.13; H, 2.40; S, 32.78. Found: C, 49.43; H, 2.37; S, 32.54.

5-Amino-2,2':5',2''-terthiophene (**8**).

To a solution of 5-nitro-2,2':5',2''-terthiophene **5** (100 mg, 0.34 mmole) dissolved in 15 ml of ethyl acetate was added 20 mg of 10% palladium on carbon. The hydrogenation was carried out under a positive pressure of hydrogen and the reaction consumed 90 ml of hydrogen over a 6.5 hours period. The reaction was monitored by tlc analysis and showed the absence of starting material at that time and the 5-amino derivative appeared as a pale grey spot after spraying with sulfuric acid. The catalyst was filtered and the brown solid chromatographed on a silica column

eluting with hexane/ethyl acetate to afford 59 mg (66%) of **8** as a green solid, mp 85-89°; ^{1}H nmr: (see Table I); eims: m/z (%), 263 (100), 231 (5.5), 203 (9.9), 166 (2.3), 131 (13); hrms: Calcd. for $C_{12}H_9S_3N$, 262.989. Found: 262.988. Compound **8** was too unstable to attempt elemental analysis.

5-Cyano-2,2':5',2''-terthiophene (**9**).

To a solution of α-terthiophene **1** (2 g, 8.05 mmoles) in methylene chloride (40 ml) was added over a 10 minute period chlorosulfonyl isocyanate (5.25 ml, 8.5 mmoles) in 10 ml of methylene chloride at −30°. The *N*-chlorosulfonyl amide separated as a minute crystalline solid and the mixture was stirred until the temperature reached 10°. Dimethylformamide (17.05 ml, 7.9 mmoles) was added to the cold solution (−30°) during a 5 minute period and the mixture was stirred at −30° for 1 hour. The temperature gradually rose to room temperature and cubes of ice were added. After the ice had melted, 100 ml of water were added and the organic layer separated. The aqueous layer was extracted with 4 x 100 ml of methylene chloride and the organic layer combined and washed with 3 x 15 ml water. The solvent was removed under reduced pressure and chromatographed on silica gel plate (chromatotron) with methylene chloride as eluent to afford 1.65 g of **9** as an orange solid (75%), mp 104-105°; ^{1}H nmr: (see Table I); ir (potassium bromide): ν max 3100, 2220, 1460, 1425, 1230, 1210, 1160, 1050, 845, 800, 715, 530, 480 cm^{-1}; eims: m/z (%), 273 (100), 191 (100), 146 (20), 43 (10).

Anal. Calcd. for $C_{13}H_7S_3N$: C, 57.11; H, 2.58; S, 35.18; N, 5.12. Found: C, 57.10; H, 2.56; S, 35.10; N, 5.13.

5,5''-Dicyano-2,2':5',2''-terthiophene (**10**).

To a solution of α-terthiophene **1** (2.46 g, 0.01 mole) in methylene chloride (20 ml) was added chlorosulfonyl isocyanate (3.5 ml, 0.04 mole) in methylene chloride (3 ml) at room temperature. The reaction mixture was stirred for two hours and left overnight. Work up as in the procedure described for compound **9**, gave 2.4 g (56%) of a mixture of the monocyano derivative **9** (30%) and dicyano derivative **10** (70%), mp 165-170°; ^{1}H nmr: (see Table I); ir (potassium bromide): ν max 2220, 1440, 1050, 870, 815, 800, 560, 510 cm^{-1}; eims: m/z (%), 298 (62), 167 (33), 149 (100), 71 (34), 57 (55), 43 (40).

Anal. Calcd. for $C_{14}H_6S_3N_2$: C, 56.35; H, 2.04; S, 32.23. Found: C, 56.29; H, 2.07; S, 32.41.

2,2':5',2''-Terthiophene-5-carboxamide (**11**).

To an aqueous sodium hydroxide solution (100 ml, 6.8 mmoles) was added 5-cyano-2,2':5',2''-terthiophene **9** (100 mg, 0.36 mmole) dissolved in 15 ml of ethanol. The mixture was stirred for one hour and then heated for four hours at 70°. Analysis (tlc) revealed no starting material at this time. The mixture was hydrolyzed with 10 ml of 2*N* hydrochloric acid to give the precipitated carboxamide **11** (0.97 g). The residue was chromatographed on a silica column eluted with hexane/acetone, increasing gradually to 100%, to afford 75 mg (72%) of the 2,2':5',2''-terthiophene-5-carboxamide **11** as a yellow powder, mp 140-141°; ^{1}H nmr: (see Table I); ir (potassium bromide): ν max 3165, (NH_2) 3390, (CO) 1680, (CN) 1390 and (α-t) 800 cm^{-1}; eims: m/z (%), 291 (100), 275 (29), 273 (22), 203 (25), 149 (35), 129 (26), 107 (39), 91 (96); hrms: Calcd. for $C_{13}H_9OS_3N$: 290.984. Found: 290.984.

Anal. Calcd. for $C_{13}H_9OS_3N$: C, 53.58; H, 3.11; S, 33.01. Found: C, 53.80; H, 3.40; S, 33.26.

Methyl 2,2':5',2''-Terthiophene-5-[(*E*)-3'''-acrylate] (**12**).

To a solution of 5-formyl-2,2':5',2''-terthiophene [10] (715 mg, 2.58 mmoles) in THF (200 ml) was added methyl(triphenylphosphoranylidene)acetate [11] (1.28 g, 3.87 mmoles). The resulting solution was boiled under reflux for 13 hours. The reaction mixture was cooled to room temperature and evaporated to dryness. The residue was dissolved in chloroform (20 ml) and the insoluble product was filtered, washed with chloroform (2 ml) to afford 794 mg of **12** as a yellow solid (92%), mp 199-200°; ^{1}H nmr (deuteriochloroform): δ ppm 7.79 (d, 1H, $J_{CH\text{-}CH}$ = 15 Hz, α-T-CH=), 7.56 (dd, 1H, $J_{5''\text{-}4''}$ = 5.1 Hz, $J_{5''\text{-}3''}$ = 1.1 Hz, H-5''), 7.54 (d, 1H, $J_{4\text{-}3}$ = 3.9 Hz, H-4), 7.39 (d, 1H, $J_{4'\text{-}3'}$ = 3.8 Hz, H-4'), 7.38 (d, 1H, $J_{3\text{-}4}$ = 3.9 Hz, H-3), 7.38 (dd, 1H, $J_{3''\text{-}4''}$ = 3.7 Hz, $J_{3''\text{-}5''}$ = 1.1 Hz, H-3''), 7.32 (d, 1H, $J_{3'\text{-}4'}$ = 3.8 Hz, H-3'), 7.11 (dd, 1H, $J_{4''\text{-}5''}$ = 5.1 Hz, $J_{4''\text{-}3''}$ = 3.7 Hz, H-4''), 6.24 (d, 1H, $J_{CH\text{-}CH}$ = 15 Hz, =$CHCO_2Me$), 3.71 (s, 3H, CO_2CH_3); ir (potassium bromide): ν max 3090 (=CH), 3080, 2940 (CH), 1700 (CO), 1615 (C=C), 1310 (COC), 1170, 800 (α-T) cm^{-1}; eims: m/z (%), 332 (100), 301 (21), 274 (19), 227 (5).

Anal. Calcd. for $C_{16}H_{12}O_2S_3$: C, 57.84; H, 3.64; S, 28.89. Found: C, 57.80; H, 3.73; S, 28.89.

Methyl 2,2':5',2''-Terthiophene-5-(3'''-propionate) (**13**).

A solution of **12** (794 mg, 2.38 mmoles) in ethyl acetate (350 ml) containing 10% palladium on carbon catalyst (1.0 g) was stirred under hydrogen at 30 psi for 48 hours at room temperature. The mixture was filtered and the filtrate evaporated under reduced pressure to give 575 mg of crude material. The residue was chromatographed on silica gel, eluted with hexane/methylene chloride (1:1) and gave 560 mg (70%) of **13** as a pale yellow solid, mp 113-114°; ^{1}H nmr (deuteriochloroform): δ ppm 7.19 (dd, 1H, $J_{5''\text{-}4''}$ = 5.1 Hz, $J_{5''\text{-}3''}$ = 1.1 Hz, H-5''), 7.14 (dd, 1H, $J_{3''\text{-}4''}$ = 3.7 Hz, $J_{3''\text{-}5''}$ = 1.1 Hz, H-3''), 7.04 (d, 1H, $J_{3'\text{-}4'}$ = 3.8 Hz, H-3'), 6.99 (dd, 1H, $J_{4''\text{-}5''}$ = 5.1 Hz, $J_{4''\text{-}3''}$ = 3.7 Hz, H-4''), 6.98 (d, 1H, $J_{4'\text{-}3'}$ = 3.8 Hz, H-4'), 6.96 (d, 1H, $J_{3\text{-}4}$ = 3.6 Hz, H-3), 6.71 (dt, 1H, $J_{4\text{-}3}$ = 3.6 Hz, $J_{4\text{-}=CH_2}$ = 0.8 Hz, H-4), 3.12 (td, 1H, $J_{CH_2\text{-}CH_2}$ = 7.5 Hz, $J_{CH_2\text{-}4}$ = 0.8 Hz, C$H_2$$CH_2CO_2Me$), 3.69 (s, 3H, CO_2CH_3) 2.67 (t, 2H, $J_{CH_2\text{-}CH_2}$ = 7.5 Hz, CH_2CO_2Me); ir (potassium bromide): ν max 2930 (CH_2), 1730 (CO), 1200 (COC), 800 (α-T) cm^{-1}; eims: m/z (%), 334 (67), 261 (100), 235 (81), 209 (51), 192 (44), 153 (72).

Anal. Calcd. for $C_{16}H_{14}O_2S_3$: C, 57.46; H, 4.22; S, 28.76. Found: C, 57.39; H, 4.34; S, 28.63.

2,2':5',2''-Terthiophene-5-(3'''-propionic Acid) (**14**).

A solution of **13** (558 mg, 1.67 mmoles) in methanol/THF (1:1) (50 ml) and 4*M* sodium hydroxide solution (4.0 ml, 13 mmoles) was stirred at room temperature for 48 hours, then evaporated to dryness at room temperature. The residue was suspended in water (400 ml) and acidified with 2*M* hydrochloric acid solution until the *p*H of the reaction mixture was 2. The yellow solid that formed was filtered, washed with water (10 ml) and dried under vacuum to afford 445 mg (85%) of **14** as a yellow solid, mp 186-187°; ^{1}H nmr (acetone-d_6): δ ppm 7.52 (dd, 1H, $J_{5''\text{-}4''}$ = 5.1 Hz, $J_{5''\text{-}3''}$ = 1.2 Hz, H-5''), 7.32 (dd, 1H, $J_{3''\text{-}4''}$ = 3.6 Hz, $J_{3''\text{-}5''}$ = 1.2 Hz, H-3''), 7.25 (d, 1H, $J_{3'\text{-}4'}$ = 3.8 Hz, H-3'), 7.17 (d, 1H, $J_{4'\text{-}3'}$ = 3.8 Hz, H-4'), 7.14 (d, 1H, $J_{3\text{-}4}$ = 3.6 Hz, H-3), 7.09 (dd, 1H, $J_{4''\text{-}5''}$ = 5.1 Hz, $J_{4''\text{-}3''}$ = 3.6 Hz, H-4''), 6.85 (d, 1H, $J_{4\text{-}3}$ = 3.6 Hz, H-4), 3.34 (br s, 1H, CO_2H), 3.01 (t, 2H, $J_{CH_2\text{-}CH_2}$ = 7.2 Hz, CH_2-CH_2CO_2H), 2.59 (t, 2H, $J_{CH_2\text{-}CH_2}$ = 7.3 Hz, CH_2CO_2H); uv (ethanol): λ max 350 nm (ε 31670); ir (potassium bromide): ν max 3200-2500 (COOH), 2920 (CH_2), 1700 (CO), 1220 (COC), 800 (α-T) cm^{-1}; eims m/z (%), 320 (57), 261 (100), 251 (11).

Anal. Calcd. for $C_{15}H_{12}O_2S_3$: C, 57.81; H, 3.64; S, 28.93. Found: C, 58.08; H, 3.72; S, 28.79.

2-Bromo-5-(3'-methyl-2'-butenyl)thiophene.

A solution of LDA [1.6 *M* *n*-BuLi in hexane (2.0 ml) and diisopropylamine (310 mg, 3.06 mmoles)] generated *in situ* was stirred at −40° for 30 minutes in THF (15 ml), then cooled to −70° and 2-bromothiophene (500 mg, 3.06 mmoles) was added dropwise. The mixture was stirred for 30 minutes at −70°, 4-bromo-2-methyl-2-butene (457 mg, 3.06 mmoles) was added and stirring was continued overnight while the solution was allowed to warm slowly to rt. The reaction mixture was hydrolyzed by addition of 2*M* hydrochloric acid until *p*H ≈ 2 was reached and the THF was removed under reduced pressure. The residue was extracted with chloroform (3 x 25 ml), dried over magnesium sulfate, filtered and concentrated to dryness. The residual oil was distilled under vacuum (bp 90°/1.3 mmHg) to yield 357 mg (45%) of the desired compound as a colorless oil; ^{1}H nmr (deuteriochloroform): δ ppm 6.82 (d, 1H, $J_{3\text{-}4}$ = 3.7 Hz, H-3), 6.51 (d, 1H, $J_{4\text{-}3}$ = 3.7 Hz, $J_{4\text{-}CH_2}$ = 1.2 Hz, H-4), 5.30 (tq, 1H, $J_{CH\text{-}CH_2}$ = 7.3 Hz, $J_{CH\text{-}CH_3}$ = 1.5 Hz, =CH), 3.41 (d, 2H, $J_{CH_2\text{-}CH}$ = 6.8 Hz, CH_2), 1.73 (d, 3H, $J_{CH_3\text{-}CH}$ = 1.1 Hz, CH_3), 1.67 (s, 3H, CH_3); eims: m/z (%), 230 (59), 217 (33), 215 (33), 151 (31), 136 (100), 135 (27).

Anal. Calcd. for $C_9H_{11}SBr$: C, 46.76; H, 4.79; S, 13.86. Found: C, 46.77; H, 4.96; S, 13.69.

5-(3'''-Methyl-2'''-butenyl)-2,2':5',2''-terthiophene (**15**).

A solution of the Grignard reagent prepared from boiling under reflux 5-iodo-2,2'-dithienyl [5] (397 mg, 1.35 mmoles) with magnesium turnings (33 mg, 1.35 mmoles) in diethyl ether (10 ml) for 2 hours was added dropwise to a solution of 2-bromo-5-(3'-methyl-2'-butenyl)thiophene (314 mg, 1.35 mmoles) in diethyl ether (2 ml) and 10 mg of Ni[dppp]Cl_2 [6] catalyst and the reaction mixture was stirred overnight at room temperature. The reaction mixture was acidified with 2*M* hydrochloric acid until *p*H ≈ 2 was reached, extracted with dichloromethane (4 x 25 ml), dried over calcium chloride, filtered and concentrated under vacuum. Purification of the residue on silica gel using *n*-pentane as eluent afforded 48 mg (11%) of product **15** as a pale yellow solid, mp 71-72°; ^{1}H nmr (deuteriochloroform): δ ppm 7.18 (dd, 1H, $J_{5''\text{-}4''}$ = 5.1 Hz, $J_{5''\text{-}3''}$ = 1.2 Hz, H-5''), 7.13 (dd, 1H, $J_{3''\text{-}4''}$ = 3.6 Hz, $J_{3''\text{-}5''}$ = 1.2 Hz, H-3''), 7.03 (d, 1H, $J_{3'\text{-}4'}$ = 3.8 Hz, H-3'), 6.99 (dd, 1H, $J_{4''\text{-}5''}$ = 5.1 Hz, $J_{4''\text{-}3''}$ = 3.6 Hz, H-4''), 6.97 (d, 1H, $J_{4'\text{-}3'}$ = 3.8 Hz, H-4'), 6.96 (d, 1H, $J_{3\text{-}4}$ = 3.6 Hz, H-3), 6.67 (dt, 1H, $J_{4\text{-}3}$ = 3.6 Hz, $J_{4\text{-}CH_2}$ = 1.1 Hz, H-4), 5.35 (tq, 1H, $J_{CH\text{-}CH_2}$ = 7.3 Hz, $J_{CH\text{-}CMe_2}$ = 1.4 Hz, CH=CMe_2), 3.48 (d, 2H, $J_{CH_2\text{-}CH}$ = 7.1 Hz, Ar-CH_2), 1.75 (d, 3H, $J_{CH_3\text{-}CH}$ = 1.0 Hz, CH_3), 1.70 (d, 3H, $J_{CH_3\text{-}CH}$ = 1.0 Hz, CH_3); ir (potassium bromide): ν max 2920 (CH_2), 1735 (CH), 800 (α-t) cm^{-1}; eims: m/z (%), 231 (7), 230 (60), 136 (100), 135 (27), 39 (27).

Anal. Calcd. for $C_{17}H_{16}S_3$: C, 64.51; H, 5.09; S, 30.39. Found: C, 64.26; H, 5.09; S, 30.47.

5-(2'''-Carbomethoxybenzoyl)-2,2':5',2''-terthiophene (**16**).

To a solution of α-terthiophene **1** (347 mg, 1.39 mmoles) in diethyl ether (25 ml) was added 1.6 *M* *n*-BuLi (0.86 ml) at −40° and the reaction mixture was stirred for 30 minutes. Magnesium bromide-diethyl ether (370 mg, 1.40 mmoles) was then added at −40° and stirring was continued for 30 minutes while the solution was allowed to warm to 0°. The mixture was cooled to −70° and phthalic anhydride (207 mg, 1.39 mmoles) was added. The temperature was increased to 25° and the mixture stirred for 1 hour. After acidification of the reaction mixture with 2*M* hydrochloric acid until *p*H ≈ 2 was reached, the solvent was removed under reduced pressure and extracted with chloroform (6 x 25 ml), dried over calcium chloride and concentrated under vacuum to afford a mixture of mono and diacid (610 mg). Methylation with an etheral diazomethane solution at 0° followed by purification on silica gel using chloroform as eluent gave the methyl monosubstituted ester **16**, 200 mg (35%), mp 105-106°; ^{1}H nmr (deuteriochloroform): δ ppm 8.03 (ddd, 1H, $J_{3'''\text{-}4'''}$ = 7.4 Hz, $J_{3'''\text{-}5'''}$ = 1.6 Hz, $J_{3'''\text{-}6'''}$ = 0.7 Hz, H-3'''), 7.63 (ddd, 1H, $J_{4'''\text{-}3'''}$ = 7.4 Hz, $J_{4'''\text{-}5'''}$ = 7.5 Hz, $J_{4'''\text{-}6'''}$ = 1.5 Hz, H-4'''), 7.56 (ddd, 1H, $J_{5'''\text{-}4'''}$ = 7.5 Hz, $J_{5'''\text{-}6'''}$ = 7.4 Hz, $J_{5'''\text{-}3'''}$ = 1.6 Hz, H-5'''), 7.48 (ddd, 1H, $J_{6'''\text{-}5'''}$ = 7.4 Hz, $J_{6'''\text{-}4'''}$ = 1.5 Hz, $J_{6'''\text{-}3'''}$ = 0.7 Hz, H-6'''), 7.25 (dd, 1H, $J_{5''\text{-}4''}$ = 5.2 Hz, $J_{5''\text{-}3''}$ = 1.2 Hz, H-5''), 7.23 (d, 1H, $J_{4\text{-}3}$ = 3.9 Hz, H-4), 7.19 (dd, 1H, $J_{3''\text{-}4''}$ = 3.6 Hz, $J_{3''\text{-}5''}$ = 1.2 Hz, H-3''), 7.14 (d, 1H, $J_{4'\text{-}3'}$ = 4.0 Hz, H-4'), 7.10 (d, 1H, $J_{3\text{-}4}$ = 3.9 Hz, H-3), 7.08 (d, 1H, $J_{3'\text{-}4'}$ = 4.0 Hz, H-3'), 7.02 (dd, 1H, $J_{4''\text{-}5''}$ = 5.2 Hz, $J_{4''\text{-}3''}$ 3.6 Hz, H-4''), 3.73 (s, 3H, CO_2CH_3); ir (potassium bromide): ν max 3080 (CH), 2960 (CH_2), 1690 (ketone CO), 1645 (ester CO), 1300 (C-O-C), 800 (α-t) cm^{-1}; eims: m/z (%), 410 (100), 149 (41), 129 (100), 57 (87).

Anal. Calcd. for $C_{21}H_{14}O_3S_3$: C, 61.44; H, 3.43; S, 23.43. Found: C, 61.52; H, 3.31; S, 23.18.

5,5''-bis(2'''-Carbomethoxybenzoyl)-2,2':5',2''-terthienyl (**17**).

Compound **17** was also obtained (347 mg, 44%), mp 215-216°; ^{1}H nmr (deuteriochloroform): δ ppm 8.03 (ddd, 1H, $J_{6'''\text{-}5'''}$ = 7.3 Hz, $J_{6'''\text{-}4'''}$ = 1.4 Hz, $J_{6'''\text{-}3'''}$ = 0.6 Hz, H-6'''), 7.62 (ddd, 1H, $J_{5'''\text{-}4'''}$ = 7.3 Hz, $J_{5'''\text{-}6'''}$ = 7.3 Hz, $J_{5'''\text{-}3'''}$ = 1.5 Hz, H-5'''), 7.56 (ddd, 1H, $J_{4'''\text{-}5'''}$ = 7.3 Hz, $J_{4'''\text{-}3'''}$ = 7.2 Hz, $J_{4'''\text{-}6'''}$ = 1.4 Hz, H-4'''), 7.47 (ddd, 1H, $J_{3'''\text{-}4'''}$ = 7.2 Hz, $J_{3'''\text{-}5'''}$ = 1.5 Hz, $J_{3'''\text{-}6'''}$ = 0.6 Hz, H-3'''), 7.26 (s, 2H, H-3',4'), 7.15 (d, 2H, $J_{3\text{-}4\ =\ 3''\text{-}4''}$ = 3.9 Hz, H-3,3''), 7.12 (d, 2H, $J_{4\text{-}3\ =\ 4''\text{-}3''}$ = 3.9 Hz, H-4,4''), 3.73 (s, 6H, 2 x CO_2CH_3); ir (potassium bromide): ν max 3080 (CH), 2950 (CH_2), 1730 (ketone CO), 1640 (ester CO), 1300 (C-O-C), 800 (α-t) cm^{-1}; fabms: m/z (%), 572 (0.2), 461 (31), 369 (93), 277 (100), 186 (100), 185 (100), 149 (94), 94 (100), 93 (100).

Anal. Calcd. for $C_{30}H_{20}O_6S_3$: C, 62.92; H, 3.51; S, 16.79. Found: C, 63.13; H, 3.76. S, 16.66.

4,5-(1'''-Carboxy-2'''-benzoic acid)-2,2':5',2''-terthiophene (**18**).

Hydrolysis of the methyl monoester **16** was performed by treating it with 2*M* sodium hydroxide solution (2 ml) in methanol (10 ml) with stirring overnight. The methanol was removed under vacuum at room temperature, and water (10 ml) was added. The solution was then acidified with diluted hydrochloric acid followed by extraction with dichloromethane (3 x 25 ml). After removal of the solvent, the pure monoacid **20** was obtained as a yellow solid 179 mg (93%), mp 238-239°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ ppm 7.98 (ddd, 1H, $J_{3'''\text{-}4'''}$ = 7.5 Hz, $J_{3'''\text{-}5'''}$ = 1.8 Hz, $J_{3'''\text{-}6'''}$ = 0.7 Hz, H-3'''), 7.72 (ddd, 1H, $J_{4'''\text{-}3'''}$ = 7.5 Hz, $J_{4'''\text{-}5'''}$ = 7.4 Hz, $J_{4'''\text{-}6'''}$ = 1.5 Hz, H-4'''), 7.68 (ddd, 1H, $J_{5'''\text{-}4'''}$ = 7.4 Hz, $J_{5'''\text{-}6'''}$ = 7.3 Hz, $J_{5'''\text{-}3'''}$ = 1.8 Hz, H-5'''), 7.59 (dd, 1H, $J_{5''\text{-}4''}$ = 5.1 Hz, $J_{5''\text{-}3''}$ = 1.2 Hz, H-5''), 7.54 (d, 1H, $J_{4\text{-}3}$ = 3.8 Hz, H-4), 7.52 (ddd, 1H, $J_{6'''\text{-}5'''}$ = 78.3 Hz, $J_{6'''\text{-}4'''}$ = 1.5 Hz, $J_{6'''\text{-}3'''}$ = 0.7 Hz, H-6'''), 7.42 (dd, 1H, $J_{3''\text{-}4''}$ = 3.6 Hz, $J_{3''\text{-}5''}$ = 1.2 Hz, H-3''), 7.38 (d, 1H, $J_{4'\text{-}3'}$ = 4.0 Hz, H-4'), 7.36 (d, 1H, $J_{3\text{-}4}$ = 3.8 Hz, H-3), 7.19 (d, 1H, $J_{3'\text{-}4'}$ =

4.0 Hz, H-3'), 7.13 (dd, 1H, $J_{4''-5''}$ = 5.1 Hz, $J_{4''-3''}$ = 3.6 Hz, H-4''); ir (potassium bromide): ν max 3090-2500 (COOH), 1690 (ketone CO), 1650 (acid CO), 1280 (C-O-C), 800 (α-t) cm^{-1}; eims: m/z (%), 396 (100), 203 (43), 275 (32), 69 (60), 43 (71).

Anal. Calcd. for $C_{20}H_{12}O_3S_3$: C, 60.59; H, 3.04; S, 24.26. Found: C, 60.76; H, 3.05; S, 24.19.

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