Synthesis and Cytotoxicity of 2-Acetyl-4,8-dihydrobenzodithiophene-4,8-dione Derivatives
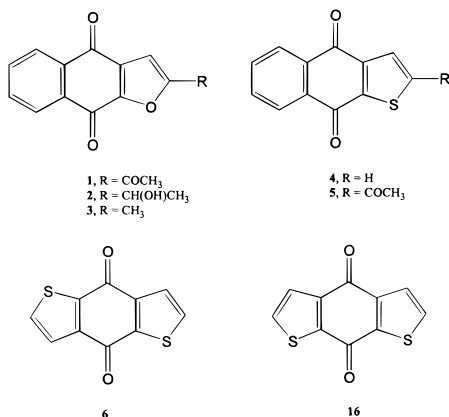
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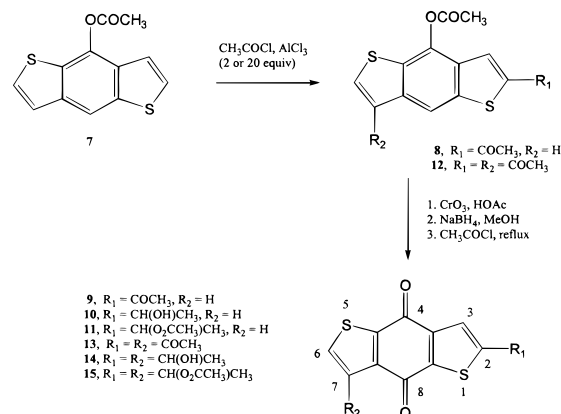
2-Acetyl-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (**9**) and 2-acetyl-4,8-dihydrobenzo-[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (**19**), together with 10 related mono- and disubstituted derivatives, were synthesized and evaluated in vitro by NCI against eight cancer types. All compounds showed significant activity against melanoma, HL-60 leukemia, NCI-H23 non-small-cell lung cancer, OVCAR-3 ovarian cancer, and MDA-MB-435 and MDA-N breast cancer cell lines. Compound **11**, 2-(1′-acetoxyethyl)-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione, showed the highest overall potency (mean GI_{50} = 40 nM).
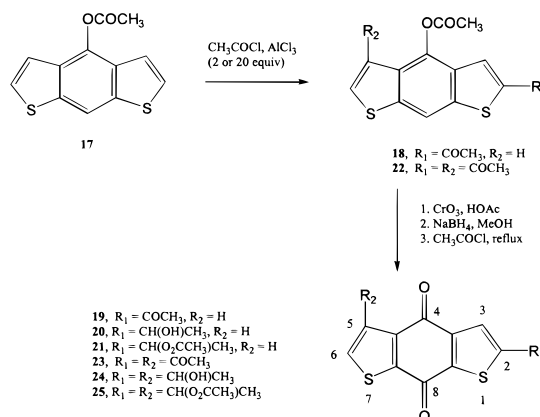
Many naturally occurring substituted anthraquinones[1,2] and naphthoquinones[3] possess cytotoxic antileukemic activities. In addition, the natural furanonaphthoquinones **1**[4] and **2**[4] and their synthetic analogue **3**[3] show potent cytotoxicity against KB cells with ED_{50} values of 4.1, 8.2, and 1.4 µM, respectively. As part of our continuing search for potent and selective cytotoxic antitumor agents, the unsubstituted thiophene derivative naphtho[2,3-*b*]thiophene-4,9-dione (**4**),[5] which is a bioisostere of the furanonaphthoquinone nucleus, also was found to be cytotoxic against KB cells with an ED_{50} value of 6.5 µM.[6] Introduction of a lipophilic acetyl group gave 2-acetylnaphtho[2,3-*b*]thiophene-4,9-dione (**5**) with enhanced cytotoxicity (ED_{50} = 1.6 µM).[6] We have now extended this study to the synthesis and cytotoxic evaluation of two related series containing two thiophene rings: 4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-diones (**6**, **9**−**11**, **13**−**15**) and 4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-diones (**16**, **19**−**21**, **23**−**25**).

1, R = COCH₃
2, R = CH(OH)CH₃
3, R = CH₃

4, R = H
5, R = COCH₃

6

16

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Scheme 1. Synthesis of Derivatives **9**−**11** and **13**−**15**

8, R₁ = COCH₃, R₂ = H
12, R₁ = R₂ = COCH₃

1. CrO₃, HOAc
2. NaBH₄, MeOH
3. CH₃COCl, reflux

9, R₁ = COCH₃, R₂ = H
10, R₁ = CH(OH)CH₃, R₂ = H
11, R₁ = CH(O₂CCH₃)CH₃, R₂ = H
13, R₁ = R₂ = COCH₃
14, R₁ = R₂ = CH(OH)CH₃
15, R₁ = R₂ = CH(O₂CCH₃)CH₃

Scheme 2. Synthesis of Derivatives **19**−**21** and **23**−**25**

18, R₁ = COCH₃, R₂ = H
22, R₁ = R₂ = COCH₃

1. CrO₃, HOAc
2. NaBH₄, MeOH
3. CH₃COCl, reflux

19, R₁ = COCH₃, R₂ = H
20, R₁ = CH(OH)CH₃, R₂ = H
21, R₁ = CH(O₂CCH₃)CH₃, R₂ = H
23, R₁ = R₂ = COCH₃
24, R₁ = R₂ = CH(OH)CH₃
25, R₁ = R₂ = CH(O₂CCH₃)CH₃

Chemistry

The syntheses of mono- and disubstituted compounds are outlined in Schemes 1 and 2. Syntheses of the starting materials, 4-acetoxybenzo[1,2-*b*:4,5-*b'*]dithiophene (**7**)[7a] and -[1,2-*b*:5,4-*b'*]dithiophene (**17**),[7a] have been previously described. In brief, the former was prepared in four steps from 2,3-dibromothiophene and

Table 1. Cytotoxicity of **6** and **16** against Leukemia Cell Lines

cell line	IC$_{50}$ (μM)	
	6	**16**
KB	0.31	0.27
HCT-8	0.32	0.17
P-388	<0.53	
L-1210	1.7	
A549	0.26	0.17
CAKI-1	1.5	0.59
SK-MEL-2		0.32
MCF-7	0.48	<0.085

thiophenecarboxaldehyde,[7a] and the latter was prepared in three steps from 3-bromothiophene and 2-(chloromethyl)thiophene.[8] Friedel−Crafts acylation of **7** or **17** with 2 equiv of acetyl chloride and AlCl$_3$ gave intermediates **8** and **18**, respectively. CrO$_3$ oxidation in HOAc then gave **9** or **19**. In their ^{1}H NMR spectra, each compound showed one CH$_3$ singlet at ca. 2.67 ppm, AB-type signals at ca. 7.68 and 7.74 ppm, and a singlet at ca. 8.12 ppm. From these data together with the ^{13}C NMR and mass spectral results, both **9** and **19** appeared to be monoacetyl derivatives, with the position of substitution at either C-2 or C-3. X-ray crystallography confirmed both to be the 2-acetyl derivative. Reduction with NaBH$_4$ in MeOH gave the secondary alcohols **10** and **20** in each series, and acetylation of these compounds with acetyl chloride gave the expected **11** and **21**.

A diacetyl derivative in each dithiophene series was prepared by Friedel−Crafts acetylation (20 equiv) of **7** and **17** to give **12** and **22**, followed by CrO$_3$ oxidation to give **13** and **23**. Three structures are possible for each product: two symmetric (for **13**, 3,7- or 2,6-disubstituted; for **23**, 3,5- or 2,6-disubstituted) and one asymmetric (for **13**, 2,7-disubstituted; for **23**, 2,5-disubstituted). In each case (data given only for **13**), because the IR spectrum showed three carbonyl absorptions (1670, 1675, and 1695 cm^{-1}), the ^{1}H NMR spectrum showed two methyl singlets (2.66 and 2.67 ppm) and nonequivalent aromatic signals (7.91 and 8.11 ppm), and the ^{13}C NMR spectrum showed four carbonyl signals (173.8, 174.0, 190.6, and 196.9 ppm), the two symmetric structures were ruled out. Thus, in both dithiophene series, acetylation occurred first at C-2 and then at the carbon β to the second sulfur atom giving, after oxidation, 2,7-diacetyl-4,8-dihydrobenzo[1,2-*b*:4,5-*b′*]dithiophene-4,8-dione (**13**) and 2,5-diacetyl-4,8-dihydrobenzo-[1,2-*b*:5,4-*b′*]dithiophene-4,8-dione (**23**). Reduction followed by acetylation of **13** and **23** then gave **14** and **24**, respectively, followed by acetylation to **15** and **25**, respectively.

Results and Discussion

In preliminary testing, the unsubstituted parent compounds **6** and **16** showed significant activity against several leukemia cell lines (see Table 1). Therefore, the substituted compounds **9**−**11**, **13**−**15**, **19**−**21**, and **23**−**25** were submitted to NCI for in vitro testing[9−11] against 58 human tumor cell lines derived from leukemia, small- and non-small-cell lung cancers, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, and breast cancer. All compounds were active against all cell lines with GI$_{50}$ values ranging from 1.2 μM (com-

pound **15**) to 0.040 μM (compound **11**). (Activity is defined as GI$_{50}$ < 100 μM, where GI$_{50}$ is the molar concentration causing 50% cell growth inhibition). Table 2 shows the biological data in melanoma, HL-60 leukemia, non-small-cell lung cancer, ovarian cancer, and breast cancer cell lines; these cell lines, in general, showed increased sensitivity to this compound class (see discussion below).

In the 4,8-dihydrobenzo[1,2-*b*:4,5-*b′*]dithiophene-4,8-dione series, the monosubstituted 2-(1′-acetoxyethyl) compound **11** showed the highest overall potency (mean GI$_{50}$ = 40 nM); however, the analogous compound **21** was among the least active in the 4,8-dihydrobenzo[1,2-*b*:5,4-*b′*]dithiophene-4,8-dione series. In the latter series, the monosubstituted 2-acetyl compound **19** was the most active with a mean GI$_{50}$ value of 47 nM. In both series, compounds with one hydroxyethyl group (**10** and **20**) also showed excellent overall cytotoxicity. Only one disubstituted compound [**14**, 2,7-bis(1′-hydroxyethyl)-4,8-dihydrobenzo[1,2-*b*:4,5-*b′*]dithiophene-4,8-dione] showed overall cytotoxicity comparable to that of the monosubstituted compounds.

Compounds **13** and **15**, which are disubstituted with acetyl and 1-acetoxyethyl groups, were not selective toward melanoma cell lines and, in general, were less active in all cell lines. The remaining 10 compounds showed striking potency toward all melanoma cell lines. Compounds **11** and **19** were the most sensitive with GI$_{50}$ values ranging from 33 to <10 nM in these cell lines. All compounds including **13** and **15** showed high activity against HL-60(TB) leukemia, OVCAR-3 ovarian cancer, and MDA-MB-435 and MDA-N breast cancers.

COMPARE computations[9] were performed on the NCI screening data for these 12 compounds, and all were negative (Pearson correlation coefficients < 0.6) against the NCI "Standard Agent" database. These compounds therefore probably act by a mechanism differing from those of the Standard Agents.

Conclusions

In summary, in a direct comparison, the monosubstituted compounds, in general, displayed stronger selectivity than the corresponding disubstituted compounds. 2-(1′-Acetoxyethyl)-4,8-dihydrobenzo[1,2-*b*:4,5-*b′*]dithiophene-4,8-dione (**11**) and 2-acetyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b′*]dithiophene-4,8-dione (**19**) were the most active compounds tested and are candidates for further in vivo testing.

Experimental Section

All melting points were determined on a Yanaco MP-500D apparatus and are uncorrected. IR spectra were recorded on Shimadzu IR-440 and Nicolet Impact 400 FT-IR spectrophotometers as KBr pellets. NMR spectra were obtained on Bruker ARX3OO FT-NMR and Varian VXR-300 FT-NMR spectrometers with tetramethylsilane (TMS) as an internal standard. The chemical shift values are expressed in δ values (parts per million). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra (MS) were measured with HP 5995 GC-MS and JEOL JMS-Hx 110 spectrometers. Ultraviolet spectra were recorded on a Shimadzu UV-160A spectrophotometer. Elemental analyses were performed by National Cheng Kung University and National Chung Hsing University, Taiwan. Flash column chromatography was per-

Table 2. Inhibition of in Vitro Cancer Cell Lines by Disubstituted Dihydrobenzothiophenediones

	cytotoxicity GI$_{50}$ (μM)^{a,b}											
cell line	**9**	**10**	**11**	**13**	**14**	**15**	**19**	**20**	**21**	**23**	**24**	**25**
Melanoma												
LOX IMVI	0.025	0.010	<0.010	1.1	0.055	1.6	<0.010	0.024	0.21	0.022	0.12	0.12
MALME-3M	0.117	0.016	<0.010	0.13	0.028	0.19	0.016	0.019	0.12	0.22	0.15	0.13
M14	0.13	0.015	0.013	1.5	0.058	0.51	0.017	0.015	0.16	0.44	0.16	0.12
SK-MEL-2	0.20	0.091	0.026	1.7	0.11	1.6	0.033	0.031	0.42	0.16	0.20	0.15
SK-MEL-28	0.16	0.017	0.019	1.8	0.19	1.7	<0.010	0.039	0.65	0.20	0.23	0.21
SK-MEL-5	0.023	<0.010	0.014	1.2	0.013	0.63	<0.010	0.014	0.11	0.32	0.14	0.034
UACC-257	0.13	0.015	0.025	0.56	0.062	0.63	0.014	0.018	0.21	0.17	0.16	0.17
UACC-62	0.21	0.016	0.017	2.0	0.032	1.1	0.017	0.022	1.4	0.23	0.25	0.20
Leukemia												
HL-60(TB)	0.045	0.015	<0.010	0.053	0.011	0.068	<0.010	0.069	1.7	<0.010	0.44	0.65
Non-Small-Cell Lung Cancer												
NCI-H23	0.15	0.015	0.011	1.3	0.034	0.87	0.018	0.016	0.22	0.29	0.19	0.16
NCI-H522	0.16	0.12	0.15	0.53	0.30	<0.010	0.017	0.12	0.87	0.38	0.40	0.20
Ovarian Cancer												
OVCAR-3	0.16	0 0.024	<0.010	0.23	0.012	0.28	<0.010	0.12	0.49	0.030	0.36	0.27
OVCAR-8	0.30	0.20	0.036	1.5	0.22	0.46	0.031	0.16	1.4	0.23	0.26	0.23
Breast Cancer												
HS 578T	0.16	0.11	0.16	2.4	0.32	2.1	0.036	0.058	0.51	0.28	0.32	0.25
MDA-MB-435	0.037	<0.010	<0.010	0.18	0.018	0.19	<0.010	0.016	0.18	0.23	0.16	0.021
MDA-N	0.037	0.013	<0.010	0.17	0.021	0.21	<0.010	0.019	0.019	0.20	0.15	0.059
BT-549	0.18	0.078	0.046	1.7	0.16	2.1	0.018	0.035	0.28	0.91	0.20	0.20
mean value^{c,d}	0.42	0.11	0.040	1.2	0.15	1.2	0.047	0.14	0.79	0.34	0.48	0.23

^{a} Data obtained from NCI's in vitro disease-oriented tumor cells screen. ^{b} Data are an average of at least two testings. ^{c} Mean values over all cell lines tested. ^{d} The variance between the least and the most sensitive cell lines ranged from 100- to 600-fold.

formed on silica gel (mesh 25–150 μm). Precoated silica gel plates (Kieselgel 60 F$_{254}$, 0.25 mm; Merck) were used for TLC analysis.

2-Acetyl-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (9). To a stirring mixture of acetyl chloride (5.1 g, 65 mmol) and AlCl$_3$ (8.7 g, 65 mmol) in 1,2-dichloroethane (200 mL) under N$_2$ was added dropwise a solution of 4-acetoxy-benzo[1,2-*b*:4,5-*b'*]dithiophene (7)^{7a} (8 g, 32.3 mmol) in 1,2-dichloroethane (90 mL). After stirring for 4 h, this solution was poured into dilute HCl and the aqueous layer was extracted with CHCl$_3$ three times. The combined extracts were washed with saturated NaHCO$_3$ and water, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to give 7.5 g of the crude intermediate 4-acetoxy-2-acetylbenzo-[l,2-*b*:4,5-*b'*]dithiophene (8).

To a suspension of crude **8** (7.5 g) in HOAc (30 mL) was added CrO$_3$ (5.7 g, 57 mmol). After the mixture stirred for 1 h, *i*-PrOH (20 mL) and CHCl$_3$ (300 mL) were added and stirred for 30 min. The resulting solution was poured into ice water, and the aqueous layer was extracted with CHCl$_3$ three times. The combined extracts were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, CHCl$_3$) to give **9** (mp 223–225 °C) in 45% yield: IR (KBr) 1650, 1670 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.67 (s, 3H, CH$_3$), 7.68 (d, $J = 5.1$ Hz, 1H, H-7), 7.74 (d, $J = 5.1$ Hz, 1H, H-6), 8.12 (s, 1H, H-3); ^{13}C NMR (CDCl$_3$) δ 26.9 (C-2-CH$_3$), 126.9 (C-7), 129.4 (C-3), 134.3 (C-6), 170.0 (C-4), 174.4 (C-8), 190.7 (C-2-C=O); MS *m/z* 262 (M$^+$). Anal. (C$_{12}$H$_6$O$_3$S$_2$) C, H.

2-Acetyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (19). This compound was prepared in an analogous manner from 4-acetoxybenzo[1,2-*b*:5,4-*b'*]dithiophene (18): yield 35%; mp 173–175 °C; UV (CH$_2$Cl$_2$) λ_{max} 277 (log ϵ 4.44); IR (KBr) 1663 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.66 (s, 3H, CH$_3$), 7.67 (d, $J = 5.1$ Hz, 1H, H-5), 7.76 (d, $J = 5.1$ Hz, 1H, H-6), 8.11 (s, 1H, H-3); ^{13}C NMR (CDCl$_3$) δ 26.8 (C-2-CH$_3$), 126.9 (C-5), 129.4 (C-3), 134.6 (C-6), 150.1 (C-2), 172.9 (C-4), 125 (C-8), 190.4 (C-2-C=O); MS *m/z* 262 (M$^+$). Anal. (C$_{12}$H$_6$O$_3$S$_2$) C, H.

2-(1'-Hydroxyethyl)-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]-dithiophene-4,8-dione (10). To a suspension of **9** (3.0 g, 11.2 mmol) in MeOH (200 mL) was added NaBH$_4$ (1.5 g, 39.7 mmol), and stirring continued for 2 h. After acidification with

dilute HCl, the solution was extracted with CHCl$_3$. The organic fraction was washed with water, dried, and condensed. The residue was purified by column chromatography (silica gel, CHCl$_3$) to give **10** as a yellow solid (mp 166–168 °C) in 93% yield: IR (KBr) 1650, 1680 (C=O), 3200–3600 (OH) cm^{-1}; ^{1}H NMR (DMSO-*d$_6$*) δ 1.48 (d, $J = 6.3$ Hz, 3H, CH$_3$), 5.02–5.07 (m, 1H, CH), 6.10 (d, $J = 4.8$ Hz, 1H, OH), 7.45 (s, 1H, H-3), 7.62 (d, $J = 5.1$ Hz, 1H, H-7), 8.15 (d, $J = 5.1$ Hz, 1H, H-6); ^{13}C NMR (DMSO-*d$_6$*) δ 25.3 (C-2-CH$_3$), 64.6 (C-2-CH), 120.7 (C-3), 126.1 (C-7), 135.5 (C-6), 163.0 (C-2), 174.0, 174.4 (C-4, C-8); MS *m/z* 264 (M$^+$). Anal. (C$_{12}$H$_8$O$_3$S$_2$) C, H.

2-(1'-Hydroxyethyl)-4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]-dithiophene-4,8-dione (20). Compound **19** was reduced in a similar manner to give compound **20**: yield 85%; mp 170–172 °C; UV (CHCl$_3$) λ_{max} 238 (log ϵ 4.35), 294 (log ϵ 4.21); IR (KBr) 1655, 1663 (C=O), 3100–3500 (OH) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.65 (d, $J = 6.5$ Hz, 3H, CH$_3$), 5.16–5.21 (m, 1H, CH), 7.43 (s, 1H, H-3), 7.60 (d, $J = 5.1$ Hz, 1H, H-5), 7.66 (d, $J = 5.1$ Hz, 1H, H-6); ^{13}C NMR (CDCl$_3$) δ 25.3 (C-2-CH$_3$), 66.5 (C-2-CH), 121.8 (C-3), 126.6 (C-5), 133.4 (C-6), 160.0 (C-2), 173.1 (C-4), 176.0 (C-8); MS *m/z* 264 (M$^+$). Anal. (C$_{12}$H$_8$O$_3$S$_2$) C, H.

2-(1'-Acetoxyethyl)-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]-dithiophene-4,8-dione (11). Acetyl chloride (1.1 g, 13.6 mmol) was added to a solution of **10** (2.0 g, 7.4 mmol) in 1,2-dichloroethane (100 mL), and the mixture was refluxed for 4 h. After this time, the solution was poured into ice water. The organic layer was separated, washed with saturated NaHCO$_3$ and water, dried, and evaporated. The residue was subjected to column chromatography (silica gel, C$_6$H$_6$) to give **11** as a yellow solid (mp 174–176 °C) in 74% yield: IR (KBr) 1645, 1655, 1724 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.68 (d, $J = 6.6$ Hz, 3H, CHC*H$_3$*), 2.13 (s, 3H, COC*H$_3$*), 6.10–6.17 (q, $J = 6.6$ Hz, 1H, CH), 7.53 (s, 1H, H-3), 7.63 (d, $J = 5.1$ Hz, 1H, H-7), 7.68 (d, $J = 5.1$ Hz, 1H, H-6); ^{13}C NMR (CDCl$_3$) δ 21.0 (C-2-CO*C$_3$*), 22.0 (C-2-CH*C*H$_3$), 67.4 (C-2-CH), 123.4 (C-3), 126.6 (C-7), 133.6 (C-6), 154.0 (C-2), 169.8 (C-2-C=O), 174.4 × 2 (C-4, C-8); MS *m/z* 306 (M$^+$). Anal. (C$_{14}$H$_{10}$O$_4$S$_2$) C, H.

2-(1'-Acetoxyethyl)-4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]-dithiophene-4,8-dione (21). Compound **21** was prepared by acetylation of **20** in an analogous manner: yield 68%; mp 165–166 °C; UV (CH$_2$Cl$_2$) λ_{max} 239 (log ϵ 4.33), 294 (log ϵ 4.23); IR (KBr) 1670, 1750 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.69 (d, $J =$

6.6 Hz, 3H, CHCH_3), 2.11 (s, 3H, COCH_3), 6.08–6.15 (q, J = 6.6 Hz, 1H, CH), 7.49 (s, 1H, H-3), 7.58 (d, J = 5.1 Hz, 1H, H-5), 7.67 (d, J = 5.1 Hz, 1H, H-6); ^{13}C NMR (CDCl$_3$) δ 21.0 (C-2-COCH$_3$), 21.9 (C-2-CHCH$_3$), 67.3 (C-2-CH), 123.6 (C-3), 126.7 (C-5), 133.6 (C-6), 154.0 (C-2), 169.8 (C-2-C=O), 172.9 (C-4), 175.6 (C-8); MS m/z 324 (M + NH$_4^+$). Anal. (C$_{14}$H$_{10}$O$_4$S$_2$) C, H.

2,7-Diacetyl-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (13). Compound **7** was converted first to **12** and then to **13** using similar reaction conditions as for the synthesis of **9** from **7**. The molar equivalents of acetyl chloride and AlCl$_3$ was increased to 20. Column chromatography on silica gel eluting with CHCl$_3$–EtOH (100:1) gave **13** (mp 207–208 °C) in 41% yield: UV λ_{max} (CHCl$_3$) 279 (log ϵ 3.43); IR (KBr) 1670, 1675, 1695 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.66 (s, 3H, C-7-CH$_3$), 2.67 (s, 3H, C-2-CH$_3$), 7.91 (s, 1H, H-3), 8.11 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6) δ 26.7 (C-2-CH$_3$), 30.4 (C-7-CH$_3$), 130.0 (C-3), 135.4 (C-6), 173.5 (C-4), 173.8 (C-8), 191.4 (C-7-C=O), 196.7 (C-7-C=O); MS m/z 304 (M$^+$). Anal. (C$_{14}$H$_8$O$_4$S$_2$) C, H.

2,7-Diacetyl-4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (23). Compound **17** was converted in two steps to **23** as detailed in the above procedure: yield 32%; mp 190–192 °C; UV (CH$_2$Cl$_2$) λ_{max} 226 (log ϵ 3.99), 275 (log ϵ 3.96); IR (KBr) 1650, 1676, 1689 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.66 (s, 3H, C-5-CH$_3$), 2.67 (s, 3H, C-2-CH$_3$), 7.81 (s, 1H, H-6), 8.07 (s, 1H, H-3); ^{13}C NMR (CDCl$_3$) δ 26.9 (C-2-CH$_3$), 30.6 (C-5-CH$_3$), 129.7 (C-3), 135.0 (C-6), 147.9 (C-5), 150.7 (C-2), 172.8 (C-4), 175.0 (C-8), 190.6 (C-2-C=O); MS m/z 304 (M$^+$). Anal. (C$_{14}$H$_8$O$_4$S$_2$) C, H.

2,7-Bis(1′-hydroxyethyl)-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (14). Compound **13** was reduced with NaBH$_4$ as in the preparation of **10**. Column chromatography on silica gel eluting with CHCl$_3$–MeOH (100:1) gave **14** as a yellow solid (mp 218–219 °C) in 90% yield: IR (KBr) 1650, 1670 (C=O), 3100–3500 (OH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.36 (d, J = 6.0 Hz, 3H, C-7-CH$_3$), 1.48 (d, J = 6.0 Hz, 3H, C-2-CH$_3$), 5.05 (s, 1H, C-2-OH), 5.33 (s, 1H, C-7-OH), 5.52 (m, 1H, C-7-CH), 6.17 (m, 1H, C-2-CH), 7.41 (s, 1H, H-3), 7.97 (s, 1H, H-6); ^{13}C NMR (DMSO-d_6) δ 24.8 (C-7-CH$_3$), 25.5 (C-2-CH$_3$), 64.1 (C-7-CH), 64.9 (C-2-CH), 120.7 (C-3), 130.1 (C-6), 174.7 (C-4), 175.3 (C-8); MS m/z 308 (M$^+$). Anal. (C$_{14}$H$_{12}$O$_4$S$_2$) C, H.

2,7-Bis(1′-hydroxyethyl)-4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (24). Compound **23** was reacted in a similar manner as for **14** to give **24**: yield 85%; mp 218–220 °C; UV (CH$_2$Cl$_2$) λ_{max} 241 (log ϵ 4.51); IR (KBr) 1650, 1670 (C=O), 3100–3500 (OH) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.65 (d, J = 6.6 Hz, 3H, C-2-CH$_3$), 1.98 (d, J = 6.6 Hz, 3H, C-5-CH$_3$), 5.16–5.21 (m, 1H, C-2-CH), 5.30–5.35 (m, 1H, C-5-CH), 7.43 (s, 1H, H-3), 7.56 (s, 1H, H-6); ^{13}C NMR (CDCl$_3$) δ 25.6 (C-2-CH$_3$), 26.6 (C-5-CH$_3$), 52.2 (C-5-CH), 65.0 (C-2-CH), 122.0 (C-3), 155.8 (C-6), 155.8 (C-5), 160.0 (C-2), 173.0 (C-4), 175.6 (C-8); MS m/z 308 (M$^+$). Anal. (C$_{14}$H$_{12}$O$_4$S$_2$) C, H.

2,7-Bis(1′-acetoxyethyl)-4,8-dihydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione (15). Compound **15** was prepared from **14** in an identical manner to that of compound **11**: yield 72%; yellow solid; mp 180–182 °C; UV (CHCl$_3$) λ_{max} 245 (log ϵ 4.32); IR (KBr) 1640, 1720 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.58 (d, J = 6.6 Hz, 3H, C-7-CHCH_3), 1.67 (d, J = 6.6 Hz, 3H, C-2-CHCH_3), 2.12 (s, 6H, COCH$_3$ × 2), 6.10–6.16 (q, J = 6.6 Hz, 1H, C-2-CH), 6.50–6.56 (q, J = 6.6 Hz, 1H, C-7-CH), 7.50 (s, 1H, H-3), 7.62 (s, 1H, H-6); ^{13}C NMR (CDCl$_3$) δ 21.0, 21.1, 21.3, 22.0 (CH$_3$ × 4), 67.4, 67.8 (CH × 2), 123.2 (C-3), 128.6 (C-6), 154.0 (C-7), 154.1 (C-2), 169.6, 169.7 (C-2-C=O, C-7-C=O), 174.3, 174.8 (C-4, C-8); MS m/z 392 (M$^+$). Anal. (C$_{18}$H$_{16}$O$_6$S$_2$) C, H.

2,7-Bis(1′-acetoxyethyl)-4,8-dihydrobenzo[1,2-*b*:5,4-*b'*]dithiophene-4,8-dione (25). Compound **24** was acetylated in a similar manner as given above to produce **25**: yield 68%; mp 172–174 °C; UV (CH$_2$Cl$_2$) λ_{max} 226 (log ϵ 4.10); IR (KBr) 1663, 1655 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.58 (d, J = 6.6 Hz, 3H, C-5-CHCH_3), 1.68 (d, J = 6.6 Hz, 3H, C-2-CHCH_3), 2.12 (s, 6H, COCH$_3$ × 2), 6.10–6.17 (q, J = 6.6 Hz, 1H, C-2-CH), 6.50–6.57 (q, J = 6.6 Hz, 1H, C-5-CH), 7.51 (s, 1H, H-3), 7.63 (s, 1H, H-6); ^{13}C NMR (CDCl$_3$) δ 21.0, 21.2, 21.3, 22.0 (CH$_3$ × 4), 67.4 (C-2-CH), 67.8 (C-5-CH), 123.8 (C-3), 128.7 (C-6), 146.5 (C-5), 154.3 (C-2), 169.8 × 2 (C-2-C=O, C-5-C=O), 172.9 (C-4), 176.2 (C-8); MS m/z 391 (M$^+$ − 1). Anal. (C$_{18}$H$_{16}$O$_6$S$_2$) C, H.

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JM980394T