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Synthesis of 3,4-*bis*[(Methoxycarbonyl)methyl]thiophene and *bis*-, *ter*- and *penta*Thiophenes with Alternating 3,4-*bis*[(Methoxycarbonyl)methyl]-substituted Rings

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Abstract

The synthesis of 3,4-*bis*[(methoxycarbonyl)methyl]thiophene and *bis*-, *ter*- and *penta*thiophenes, with alternating 3,4-*bis*(methoxycarbonyl)methyl-substituted rings, is reported. These new thiophene derivatives are possible precursors for the preparation of new conducting polymers useful as materials for electronics.

Keywords: *carbonylation; coupling reactions; palladium; thiophenes*

1. Introduction

The synthesis of new 3-substituted or 3,4-disubstituted thiophenes has attracted great interest in the pharmaceutical industry due to the lower toxicity and higher pharmaceutical activity of 3-substituted thiophenes relative to their 2-substituted isomers.[1] More recently, 3- and 3,4-substituted compounds have been used as monomers for the preparation of π-conjugated oligomers and polymers exhibiting interesting electric and electronic properties.[2]

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In particular, polythiophenes containing bulky alkyl groups at the β-position have been employed in the preparation of light-emitting diodes (LEDs), the emission of which ranges from red to blue depending on the extent of conjugation. The conjugation length depends on the amount of main chain distortion due to substituents on the backbone.[3] The regioregularity of the polythiophene chains for monosubstituted polymers in particular, as well as the nature of the substituents play a fundamental role in determining the properties of the materials, such as solubility, conductivity,[4] optical properties,[5] non-linear susceptibility $\chi^{(3)}$ (-3ω,ω,ω,ω) [6] and crystallinity.[7] Furthermore, chirality can be induced in the polymer backbone if the substituents are enantiomerically pure groups. With highly regioregular polymers even stereomutation, depending on the type of cooling after the material melting, can be observed.[8]

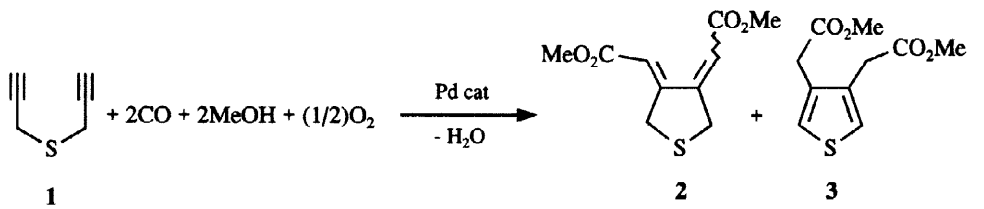
Since thiophenes undergo electrophilic substitution and metallation reactions preferentially at the α-position,[9] β-alkyl substituted molecules are usually prepared from the corresponding halides.[10] Other methods employ ring-closure reactions starting from different noncyclic substrates, but often they lead to products with more than two substitutions in the thiophene ring.[11]

We now wish to report the synthesis of a new symmetrical 3,4-disubtituted thiophene derivative, 3,4-*bis*[(methoxycarbonyl)methyl]thiophene, by a two-step procedure involving an oxidative cyclization-dimethoxycarbonylation of diprop-2-ynyl sulfide, readily available from propynyl bromide and sodium sulfide, followed by base-catalysed aromatization. The synthesis of new *bis*-, *ter*- and *penta*thiophene derivatives in which the thiophene rings are alternately 3,4-substituted with (methoxycarbonyl)methyl chains is also described.

2. Results and discussion

Earlier we reported a new and efficient method for the oxidative carbonylation of a variety of acetylenic substrates catalysed by PdI_2 in conjunction with KI.[12] When the method was applied to diprop-2-ynylsulfide **1**, dialkoxycarbonylation occurred in conjunction with ring

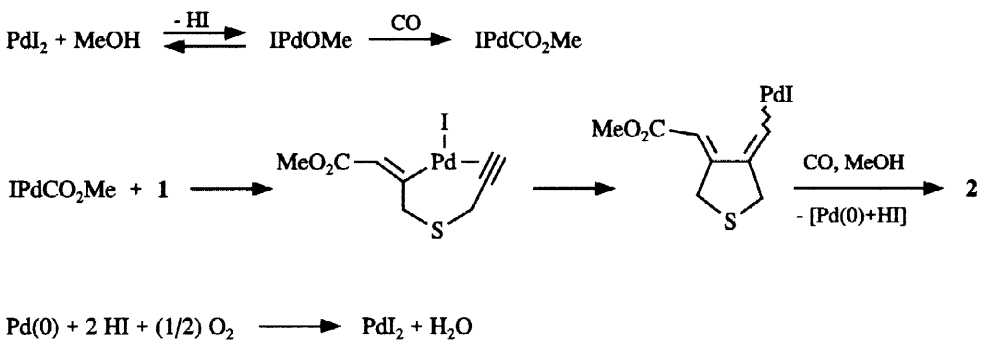
closure in analogy to what was previously reported for 1,6-diynes,[13] 1,7-diynes [14] and dipropynylamines.[15] Thus, by reacting **1** in methanol under 20 atm of a 3:1 mixture of carbon monoxide and air in the presence of PdI_2 + 10 KI at 40 °C, after 4.5 h 3,4-*bis*[(methoxycarbonyl)methylene]tetrahydrothiophene **2** (*Z,Z* : *E,Z* ≅ 1 : 1) and 3,4-*bis*[(methoxycarbonyl)methyl]thiophene **3** (corresponding to isomerization/aromatization of **2**) were obtained in 39 and 3% yield, respectively [eqn. (1)].



1 **2** **3** (1)

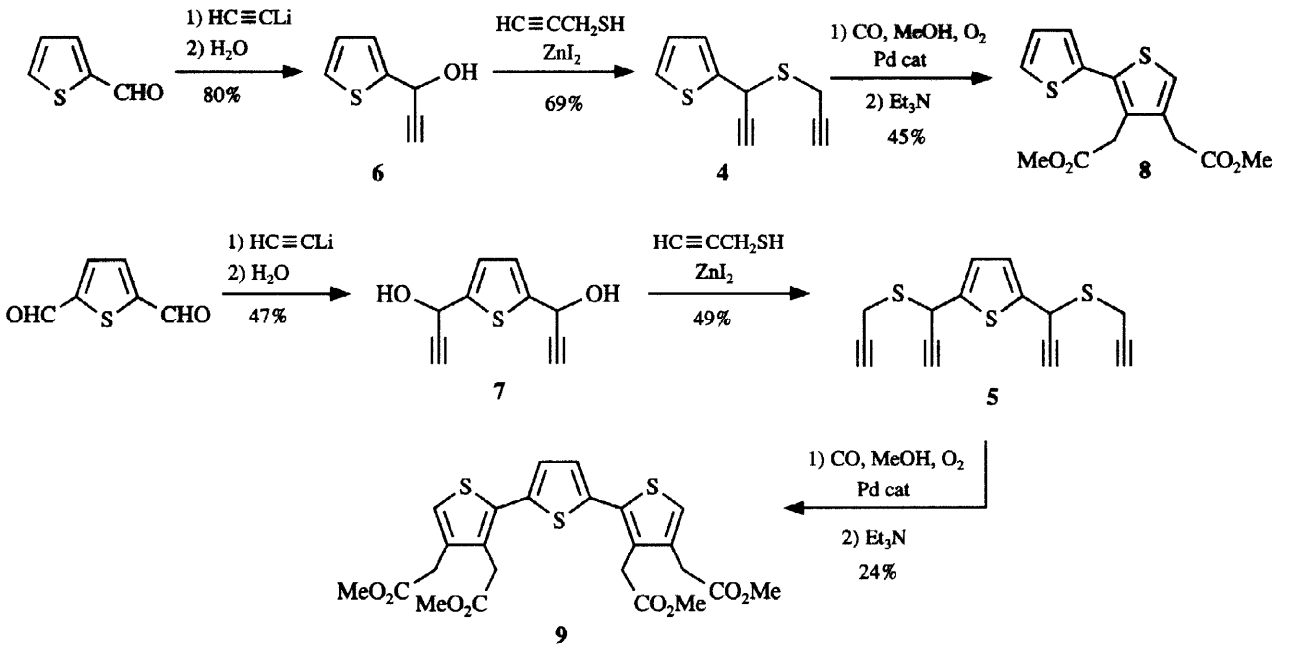
Products **2** could be readily isomerized into **3** without previous separation by treating the crude carbonylation mixture with Et_3N at 60 °C for 3 h (40% overall isolated yield based on starting **1**).

According to what has been previously reported,[13] a reasonable mechanism for formation of **2** involves insertion of the triple bond into the methoxycarbonylpalladium bond followed by cyclization and methoxycarbonylation, as depicted in Scheme 1 (anionic iodide ligands are omitted for simplicity).



Scheme 1

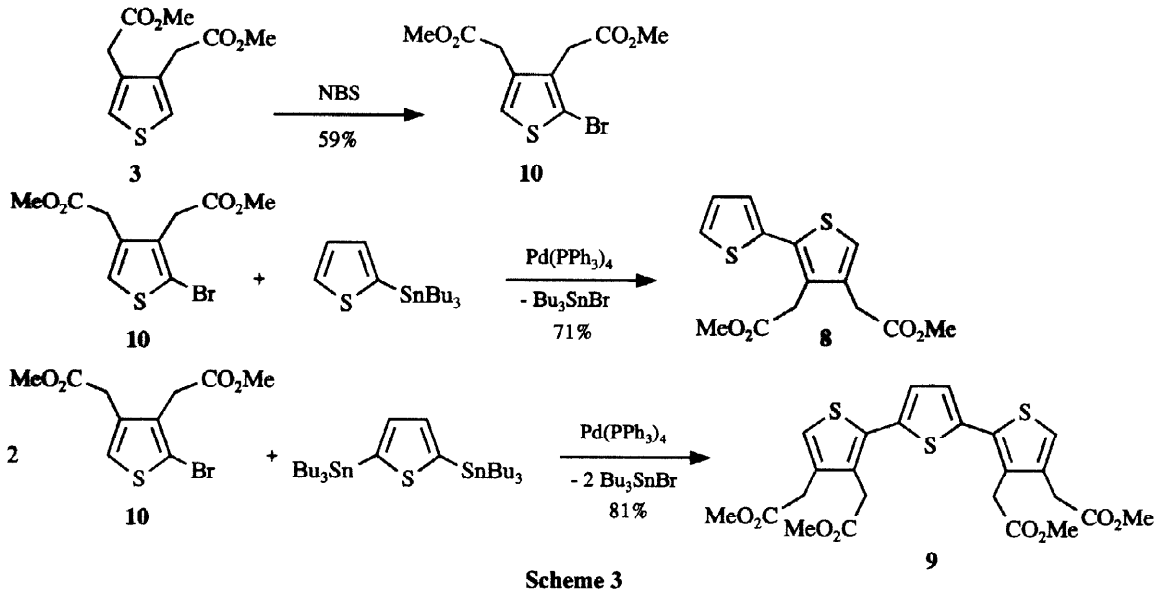
The same sequence of oxidative dicarbonylation-isomerization was applied to 2-[1-(prop-2-ynylthio)prop-2-ynyl]thiophene **4** and 2,5-*bis*[1-(prop-2-ynylthio)prop-2-ynyl]thiophene **5** (readily available from ZnI_2-promoted condensation [16] of prop-2-yn-1-thiol and propynyl alcohols **6** and **7**, respectively) to give the new *bis*- and *ter*thiophene derivatives **8** and **9** in moderate yields (45% and 24%, Scheme 2).



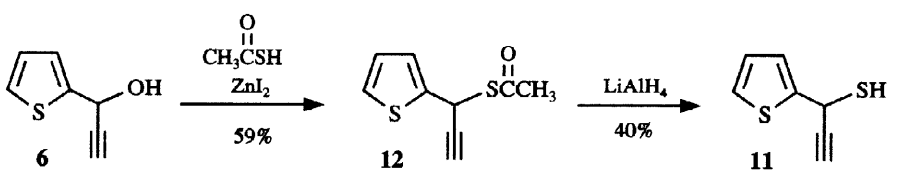
Scheme 2

Stille coupling [17] between 2-(tributylstannyl)thiophene or 2,5-*bis*(tributylstannyl)thiophene and 2-bromo-3,4-*bis*[(methoxycarbonyl)methylthiophene **10**, easily prepared by monobromination of **3**, provided an alternative method for making oligothiophenes such as **8** and **9** (Scheme 3).

Dipropynylsulfides analogous to **4** and **5** but containing additional thienyl substituent(s) at the methylene group(s), possible precursors of new interesting *ter*- and *penta*thiophene derivatives, could not be prepared by direct condensation between **6** or **7** and 1-(2-thienyl)prop-2-yn-1-thiol **11** (readily available by reduction of the corresponding thiolacetate **12** as shown in Scheme 4). In fact, neither the ZnI_2-catalysed reaction nor a possible alternative such as the Mitsunobu reaction [18] worked with this thiol.

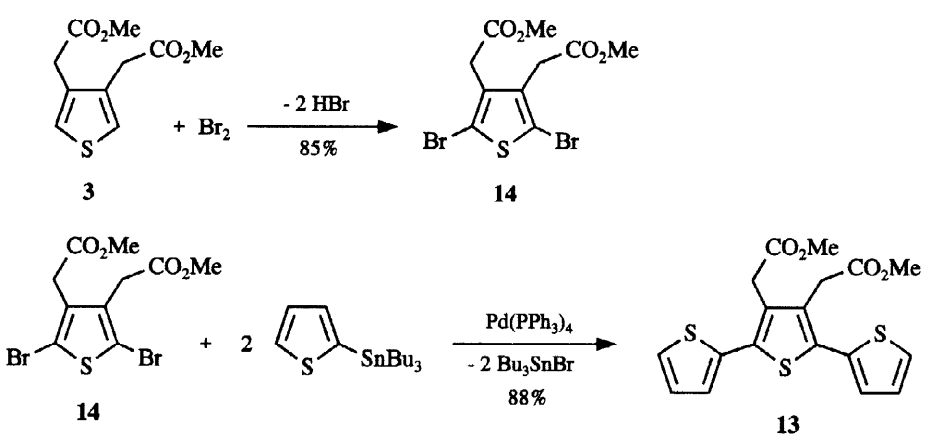


Scheme 3



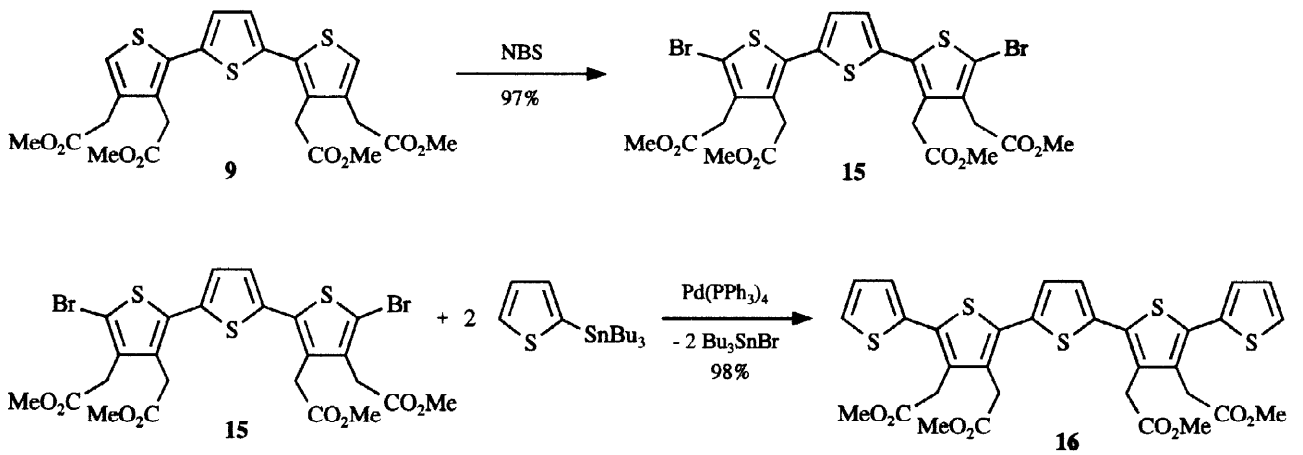
Scheme 4

However, the desired *ter*thiophene **13** was successfully prepared by Stille coupling between 2-(tributylstannyl)thiophene and 2,5-dibromo-3,4-*bis*[(methoxycarbonyl)methyl]thiophene **14** (75% overall yield from **3**, Scheme 5).



Scheme 5

Analogously, the coupling reaction between 2-(tributylstannyl)thiophene and 5,5^{II}-dibromo-3,4,3^{II},4^{II}*tetra*[(methoxycarbonyl)methyl]-2,2^{I},2^{II}-*ter*thiophene **15** afforded the *penta*thiophene **16** in 95% overall yield based on **9** (Scheme 6).



Scheme 6

In conclusion, we have described synthetic routes to new *mono-*, *bis-*, *ter-* and *penta*thiophenes containing alternating 3,4-bis[(methoxycarbonyl)methyl]substituted rings. Our synthetic methodology is based on the oxidative dicarbonylation method, applied to dipropynyl sulfides **1**, **5** and **8**, and the Stille coupling between 2-(tributylstannyl)thiophene or 2,5-*bis*(tributylstannyl)thiophene and bromo derivatives **10**, **14** and **15**.

The use of these new thiophene derivatives as monomers for the synthesis of polythiophenic materials is in progress.

3. Experimental

Mps were determined on a Reichert Thermovar melting point apparatus and are uncorrected. Elemental analyses were carried out with a Carlo Erba Elemental Analyser Mod. 1106. IR spectra were recorded on a Perkin-Elmer Paragon 1000 PC FT-IR spectrometer. Mass spectra were obtained using an HP 5972A spectrometer at 70 eV ionizing voltage and a VG Analytical

ZAB-2F. UV spectra were taken in MeOH with a Hitachi U-2000 spectrophotometer. ^1H NMR spectra were taken on a Bruker AC300 spectrometer and run on $CDCl_3$ solutions with Me_4Si as internal standard. Chemical shifts and coupling constants (J) are given as δ values (ppm) and in Hz, respectively.

The reaction mixtures were analysed by TLC (SiO_2 or Al_2O_3) or by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone (HP-5) as the stationary phase. Products were separated by conventional extraction techniques, followed by chromatographic procedures on silica or alumina with suitable eluents. Merck silica gel 60 (60-230 mesh) and neutral alumina 90 (70-230 mesh) were used for column chromatography. Analytical TLC plates and silica gel 60F254 for PTLC were purchased from Merck.

2-(Tributylstannyl)thiophene, 2-formylthiophene, *tetrakis*(triphenylphosphine)palladium(0), PdI_2 and ZnI_2 were commercial products. Prop-2-ynyl-1-thiol,[19] diprop-2-ynylsulfide **1**,[20] 2,5-diformylthiophene[21] and 2,5-*bis*(tributylstannyl)thiophene[22] were prepared according to literature procedures.

3.1. *Oxidative carbonylation of diprop-2-ynyl sulfide* **1**.

A 300 mL stainless steel autoclave (Parr) with magnetic stirring was charged in the presence of air with 20.0 mg of PdI_2 (0.056 mmol), 92.2 mg of KI (0.56 mmol) and 1.22 g (11.1 mmol) of **1** dissolved in 22 mL of methanol. The autoclave was pressurized with CO (15 atm) and air (up to 20 atm of total pressure) and stirred and heated at 40 °C. After 5 h, the reaction mixture was cooled, methanol removed *in vacuo* and the residue extracted with CH_2Cl_2. Carbonylation products were separated by column chromatography [SiO_2, hexane-ethyl acetate 98:2; order of elution: **2** (*Z,Z* isomer), **2** (*E,Z* isomer), **3**].

3.2. *3,4-Bis[(methoxycarbonyl)methylene]tetrahydrothiophene* **2**

3.2.1. *Z,Z isomer*

Pale yellow solid, mp 85-88 °C. Found: C, 52.7%; H, 5.2; S, 13.9. Calcd for $C_{10}H_{12}O_4S$: C, 52.6; H, 5.3; S, 14.0. IR (film): ν/cm^{-1} 2946 (vw), 1710 (s), 1636 (m), 1463 (m), 1359 (m),

1259 (m), 1228 (m), 1198 (m), 1176 (s), 995 (w) and 860 (w); ^{1}H NMR: δ/ppm 3.77 (s, 6 H, 2 CO_2Me), 4.10 (d, 4 H, ^4J = 2.1, 2 CH_2) and 6.32 (t, 2 H, ^4J = 2.1, 2 =CH); MS: m/z 228 (M^+, 3), 197 (23), 196 (89), 169 (13), 168 (50), 167 (10), 165 (17), 164 (76), 153 (16), 138 (17), 137 (100), 125 (36), 111 (29), 110 (18), 109 (31), 97 (16), 69 (14), 65 (16), 63 (14) and 59 (19).

3.2.2. E,Z isomer

Pale yellow solid, mp 79-82 °C. Found: C, 52.6%; H, 5.3; S, 14.0. Calcd for $C_{10}H_{12}O_4S$: C, 52.6; H, 5.3; S, 14.0. IR (film): ν/cm^{-1} 2919 (vw), 2850 (vw), 1724 (s), 1699 (s), 1637 (w), 1432 (w), 1380 (w), 1201 (s), 1179 (w), 1149 (m), 894 (w) and 880 (w); ^{1}H NMR: δ/ppm 3.53 (d, 2 H, ^4J = 1.6, CH_2), 3.74 (s, 3 H, CO_2Me), 3.75 (s, 3 H, CO_2Me), 4.14 (d, 2 H, ^4J = 2.3, CH_2), 6.03 (t, 1 H, ^4J = 1.6, =CH); and 6.86 (t, 2 H, ^4J = 2.3, =CH); MS: m/z 228 (M^+, 1), 197 (16), 196 (98), 169 (43), 168 (45), 165 (21), 164 (65), 153 (16), 138 (16), 137 (100), 136 (82), 125 (31), 111 (26), 110 (18), 109 (32), 108 (10), 97 (18), 69 (14), 65 (17), 63 (16), 59 (21) and 51 (11).

3.3. 3,4-Bis[(methoxycarbonyl)methyl]thiophene 3.

The crude reaction mixture from oxidative carbonylation of **1** was added to Et_3N (450 mg, 4.44 mmol) and stirred at 60°C for 3 h. Column chromatography (SiO_2, hexane-ethyl acetate 1 : 1) afforded 1.0 g (40% based on starting **1**) of pure **3** as a colourless oil. Found: C, 52.6%; H, 5.3; S, 14.1 Calcd for $C_{10}H_{12}O_4S$: C, 52.6; H, 5.3; S, 14.0. IR (film): ν/cm^{-1} 3101 (w), 2999 (w), 2953 (m), 2844 (w), 1731 (s), 1435 (s), 1414 (m), 1336 (s), 1264 (s), 1201 (s), 1167 (s), 1012 (s), 933 (w), 893 (w), 867 (w), 803 (m), 735 (w) and 659 (w); UV: λ_{max} (MeOH) = 238 nm ; ^{1}H NMR: δ/ppm 3.64 (s, 4 H, 2 CH_2), 3.69 (s, 6 H, 2 CO_2Me), and 7.17 (s, 2 H, aromatic); MS: m/z 228 (M^+, 10), 196 (53), 169 (39), 168 (28), 164 (31), 137 (38), 136 (32), 111 (100), 110 (22), 109 (23) and 59 (15).

3.4. *2-[1-(Prop-2-ynylthio)prop-2-ynyl]thiophene* **4.**

The method of Guindon [16] was employed. To a solution of **6** (5.65 g, 41 mmol) in dry 1,2-dichloroethane (85 mL) dried ZnI_2 (6.54 g, 20.5 mmol) was added under nitrogen. The resulting yellow suspension was stirred for 15 min, then prop-2-yn-1-thiol (3.56 g, 49.4 mmol) was added and the mixture was stirred for 30 min at room temperature. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 to give, after purification through column chromatography (SiO_2, hexane-chloroform 9:1), pure **4** as a yellow oil (5.42 g, 69%). Found: C, 62.6%, H, 4.3, S, 33.2. Calcd for $C_{10}H_8S_2$: C, 62.5, H, 4.2, S, 33.3. IR (film): ν/cm^{-1} 3290 (s), 3103 (vw), 2948 (w), 2912 (w), 2117 (w), 1601 (w), 1427 (w), 1406 (w), 1312 (vw), 1283 (w), 1233 (m), 1175 (vw), 1040 (vw), 945 (vw), 880 (vw), 852 (w), 835 (w), 707 (s) and 651 (s); ^1H NMR (300 MHz, $CDCl_3$): δ/ppm 2.28-2.31 (m, 1 H, $CH_2C{\equiv}CH$), 2.64 (d, 1 H, ^4J = 2.5, $CHC{\equiv}CH$), 3.25 (distorted dd, 1 H, ^2J = 16.7, ^4J = 2.7, CHH), 3.53 (distorted dd, 1 H, ^2J = 16.7, ^4J = 2.5, CHH), 5.25 (dd, 1 H, $^4J_1$ = 2.5, $^4J_2$ = 0.7, CH), 6.93 (dd, 1 H, $^3J_1$ = 5.1, $^3J_2$ = 3.6, H-4), 7.16 (distorted ddd, 1 H, ^3J = 3.6, $^4J_1$ = 1.2, $^4J_2$ = 0.7, H-3), 7.25 (dd, 1 H, ^3J = 5.1, ^4J = 1.2, H-5); MS: m/z 192 (M^+, 3), 121 (100), 77 (14) and 69 (12).

3.5. *2,5-Bis(prop-2-ynylthio)prop-2-ynyl]thiophene* **5.**

The procedure described for **4** was followed using 5.07 g (26.4 mmol) of **7**, 210 mL of dry 1,2-dichloroethane, 8.7 g (27.3 mmol) of dried ZnI_2 and 4.56 g (63.4 mmol) of prop-2-yn-1-thiol. Owing to the low solubility of **7** in 1,2-dichloroetane, heating of the mixture at 45 °C before the addition of ZnI_2 was needed. Flash chromatography (hexane-ethyl acetate 85 : 15) afforded 3.88 g (49%) of **5** as a yellow oil. Found: C, 64.1%, H, 3.9, S, 32.1. Calcd for $C_{16}H_{12}S_3$: C, 64.0, H, 4.0, S, 32.0. IR (film): ν/cm^{-1} 3289 (s), 2944 (vw), 2908 (vw), 2117 (vw), 1605 (vw), 1469 (vw), 1403 (w), 1235 (m), 1181 (w), 1040 (w), 954 (w), 815 (w), 731 (w), and 648 (s); ^1H NMR: δ/ppm 2.29-2.31 (m, 2 H, 2 $CH_2C{\equiv}CH$), 2.65 (d, 2 H, ^4J = 2.5, 2 $CHC{\equiv}CH$), 3.28 (distorted dd, 2 H, ^2J = 16.7, ^4J = 2.6, 2 CHH), 3.53 (distorted dd, 2 H, ^2J =

16.7, ^4J = 2.6, 2 CH*H*), 5.19 (d, 2 H, ^4J = 2.5, 2 CH), 7.00 (s, 2 H, aromatic); FAB-MS (v^+, NBA): m/z 301 [$(M+1)^+$, 4], 300 [$M^{+\cdot}$, 4], 261 (6), 229 (93), 189 (100) and 158 (91).

3.6. 1-(2-Thienyl)prop-2-yn-1-ol 6.

This alkynol, prepared by ethynylation [23] of 2-formylthiophene, was a colourless liquid, bp 42 °C/0.01 mmHg (yield = 80%). Found: C, 61.0%; H, 4.2; S, 23.2. Calcd for C_7H_6OS: C, 60.9; H, 4.3; S, 23.2. IR (film): ν/cm^{-1} 3374 (m, br), 3290 (s), 3107 (w), 2875 (w), 2119 (w), 1434 (m), 1291 (m), 1267 (m), 1229 (m), 1170 (w), 1019 (s), 934 (m), 919 (m), 853 (m), 841 (m) and 757 (w); ^1H NMR: δ/ppm 2.68 (d, 1 H, ^4J = 2.2, C≡CH), 5.63 (s br, 1 H, C*H*OH), 6.97 (dd, 1 H, $^3J_1$ = 5.1, $^3J_2$ = 3.5, H-4), 7.16-7.19 (m, 1 H, H-3) and 7.30 (dd, 1 H, ^3J = 5.1, ^4J = 1.4, H-5); MS: m/z 140 (M^++2, 5), 139 (M^++1, 10), 138 (M^+, 100), 137 (46), 121 (51), 111 (20), 110 (11), 109 (27), 105 (24), 85 (79), 84 (26), 77 (24), 69 (21), 66 (17), 65 (13), 63 (13), 58 (17), 57 (14), 53 (57) and 51 (17).

3.7. 2,5-Bis[1-(1-hydroxyprop-2-ynyl)]thiophene 7.

This alkynol, prepared by ethynylation [23] of 2,5-diformylthiophene,[21] was a pale yellow solid, mp 120-125 °C (dec.) (yield = 47%). Found: C, 62.6%; H, 4.2; S, 16.8. Calcd for $C_{10}H_8O_2S$: C, 62.5; H, 4.2; S, 16.7. IR (KBr): ν/cm^{-1} 3340 (m), 3280 (s), 2119 (w), 1655 (w), 1475 (w), 1304 (w), 1273 (w), 1217 (w), 1131 (w), 1018 (s), 920 (w), 823 (w), 771 (m), 696 (m) and 671 (m); ^1H NMR: δ/ppm 3.12 (d, 2 H, ^4J = 2.3 C≡CH), 5.65 (s br, 2 C*H*OH), 6.99 (s, 2 H, aromatic); MS: m/z 194 (M^++2, 1), 193 (M^++1, 3), 192 (M^+, 23), 175 (10), 139 (12), 138 (9), 137 (100), 121 (44), 109 (18), 102 (6), 93 (5), 85 (11), 77 (14), 69 (21), 65 (16) and 53 (51).

3.8. *3,4-Bis[(methoxycarbonyl)methyl]-2,2'-bithiophene* **8**.

3.8.1. *Method A: oxidative carbonylation of* **4**.

The method described for **3** was employed, using 70 mg of PdI_2 (0.194 mmol), 323 mg of KI (1.95 mmol) and 1.12 g (5.8 mmol) of **4** dissolved in 58 mL of methanol. The autoclave was pressurized with CO (15 atm) and air (up to 20 atm of total pressure) and stirred and heated at 70 °C for 2 h. The reaction mixture was cooled and methanol removed *in vacuo*. The residue was extracted with CH_2Cl_2, added of Et_3N (235 mg, 2.32 mmol) and stirred at 25°C for 2 h. Column chromatography (SiO_2, hexane-ethyl acetate 7 : 3) afforded 810 mg (45%) of **8** as a colourless oil. Found: C, 54.3%; H, 4.4; S, 20.6 Calcd for $C_{14}H_{14}O_4S_2$: C, 54.2; H, 4.5; S, 20.7. IR (film): ν/cm^{-1} 3110 (vw), 3074 (vw), 2998 (vw), 2949 (w), 2840 (vw), 1714 (s), 1640 (m), 1434 (m), 1351 (m), 1253 (m), 1201 (s), 1174 (s), 993 (vw), 868 (w), 834 (w), 735 (w) and 704 (m); UV: λ_{max} (MeOH) = 288 nm; ^1H NMR (300 MHz, $CDCl_3$): δ/ppm 3.66 (s, 2 H, CH_2), 3.70 (s, 3 H, CO_2Me), 3.71 (s, 3 H, CO_2Me), 3.75 (s, 2 H, CH_2), 7.08 (dd, 1 H, $^3J_1$ = 5.1, $^3J_2$ = 3.6, H-4'), 7.16 (s, 1 H, H-5), 7.19 (dd, 1 H, ^3J = 3.6, ^4J = 1.2, H-3') and 7.34 (dd, 1 H, ^3J = 5.1, ^4J = 1.2, H-5'); MS: m/z 312 (M^++2, 11), 311 (M^++1, 19), 310 (M^+, 97), 278 (52), 252 (13), 251 (75), 250 (26), 246 (11), 223 (11), 220 (17), 219 (51), 218 (100), 207 (11), 194 (11), 193 (79), 192 (22), 191 (69), 190 (29), 178 (11), 177 (10), 147 (34), 121 (16), 115 (12), 95 (13), 77 (11), 69 (18) and 59 (33).

3.8.2. *Method B: Stille coupling between* **10** *and 2-(tributylstannyl)thiophene.*

A mixture of **10** (0.74 g, 2.42 mmol), 2-(tributylstannyl)thiophene (1.07 g , 2.87 mmol), $Pd(PPh_3)_4$ (0.11 g, 0.096 mmol) in dry *N,N*-dimethylformamide (DMF) (9 mL) was heated (oil bath temperature = 105 °C) with stirring for 1 h in nitrogen atmosphere. The reaction was quenched with water and extracted with CH_2Cl_2. After drying over $CaCl_2$, column chromatography (SiO_2, hexane-ethyl acetate 7:3) afforded pure **8** (0.53 g, 71%).

3.9. *3,4,3^{II},4^{II}-Tetra[(methoxycarbonyl)methyl]-2,2^{I},2^{II}-terthiophene* **9**.

3.9.1. *Method A: oxidative carbonylation of* **5**.

The method described for **3** was employed, using 180 mg of PdI_2 (0.50 mmol), 830 mg of KI (5.0 mmol) and 0.75 g (2.5 mmol) of **5** dissolved in 50 mL of a 1:1 mixture of methanol and 1,2-dimethoxyethane. The autoclave was pressurized with CO (15 atm) and air (up to 20 atm of total pressure) and stirred and heated at 70 °C for 15 h. The reaction mixture was cooled and methanol removed *in vacuo*. The residue was extracted with CH_2Cl_2, added of Et_3N (253 mg, 2.5 mmol) and stirred at 25 °C for 5 h. Column chromatography (SiO_2, hexane-ethyl acetate 7:3) afforded 322 mg (24%) of **9** as a pale yellow solid, mp 101-102 °C. Found: C, 53.6%; H, 4.5; S, 18.0 Calcd for $C_{24}H_{24}O_8S_3$: C, 53.7; H, 4.5; S, 17.9. IR (KBr): ν/cm^{-1} 3006 (vw), 2953 (w), 2922 (vw), 1735 (s), 1437 (m), 1341 (m), 1198 (s), 1168 (s), 982 (m), 890 (w) and 721 (m); UV: λ_{max} (MeOH) = 326 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 3.66 (d, 4 H, ^4J = 0.9, 2 CH_2), 3.71 (s, 6 H, 2 CO_2Me), 3.72 (s, 6 H, 2 CO_2Me), 3.78 (s, 4 H, 2 CH_2), 7.16 (s, 2 H, H-3^{I}, H-4^{I}), 7.18 (t, 2 H, ^4J = 0.9, H-5, H-5^{II}); FAB-MS (ν^+, NBA): m/z 538 [$(M+2)^+$, 24], 537 [$(M+1)^+$, 40], 536 ($M^{+\cdot}$, 100), 505 (9), 477 (9), 445 (13), 417 (41) and 389 (20).

3.9.2. *Method B: Stille coupling between* **10** *and 2,5-bis(tributylstannyl)thiophene.*

A mixture of **10** (1.3 g, 4.25 mmol), 2,5-bis(tributylstannyl)thiophene (1.27 g , 1.92 mmol), $Pd(PPh_3)_4$ (0.087 g, 0.075 mmol) in dry DMF (11 mL) was heated (oil bath temperature = 105 °C) with stirring for 1 h under nitrogen. The reaction was quenched with water and extracted with CH_2Cl_2. After drying over $CaCl_2$, column chromatography (SiO_2, hexane-ethyl acetate 8:2) afforded crude **9** as a pale yellow solid (0.92 g, 81% based on **10**). Recrystallization from MeOH gave pure **9** as a pale yellow crystals (mp 101-102 °C) (0.72 g, 63%). Additional crystals were obtained by repeated crystallization from the mother liquors yielding an additional 10%.

3.10. 2-Bromo-3,4-bis[(methoxycarbonyl)methylthiophene **10**.

A solution of *N*-bromosuccinimide (NBS) (3 g, 16.9 mmol) in dry DMF (50 mL) was added dropwise (*ca.* 20 min) under nitrogen to a cooled solution (-20 °C) of **3** (3.85 g, 16.9 mmol) in dry DMF (150 mL). The mixture was warmed up to room temperature and let stir overnight. After DMF was evaporated *in vacuo*, the residue was extracted with CH_2Cl_2 (100 mL) and added of ice. The organic phase was separated and washed with brine. After drying over $CaCl_2$, column chromatography (SiO_2, hexane-ethyl acetate 8:2) afforded pure **10** as a colourless oil (3.7 g, 71%). Found: C, 39.2%, H, 3.5, S, 10.5. Calcd for $C_{10}H_{11}BrO_4S$: C, 39.1, H, 3.6, S, 10.4. IR (film): ν/cm^{-1} 3095 (w), 2999 (w), 2950 (m), 2842 (w), 1731 (s), 1435 (s), 1412 (m), 1386 (m), 1335 (s), 1265 (s), 1198 (s), 1162 (s), 1109 (w), 1014 (m), 951 (m) and 720 (w); ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 3.63 (s, 2 H, CH_2), 3.67 (s, 2 H, CH_2), 3.69 (s, 3 H, CO_2Me), 3.70 (s, 3 H, CO_2Me) and 7.16 (s, 1 H, aromatic); MS: m/z 308 [(M^++2), 13], 306 (M^+, 13), 276 (59), 274 (58), 249 (34), 248(30), 247 (35), 246 (28), 217 (35), 216 (41), 215 (35), 214 (37), 191 (90), 189 (100), 167 (23), 110 (27), 109 (43), 108 (19), 69 (49), 65 (36) and 59 (33).

3.11. 1-(2-Thienyl)prop-2-yn-1-thiol **11**.

The method of Volante [24] was employed. A solution of **12** (5.3 g, 27.0 mmol) in dry ether (50 mL) was added dropwise to a suspension of $LiAlH_4$ (560 mg, 14.7 mmol) in 20 mL of dry ether under nitrogen at -5 °C - 0 °C. After the reaction mixture was warmed up to room temperature and stirred for 3 h, the excess hydride was destroyed by careful addition of 10% HCl, and the layers were separated. The aqueous phase was extracted with ether, and the combined organic phases dried over Na_2SO_4. Distillation under reduced pressure (42 °C, 0.9 mmHg) afforded pure **11** as a yellow oil (1.65 g, 40%). Found: C, 54.4%, H, 4.0, S, 41.6. Calcd for $C_7H_6S_2$: C, 54.5, H, 3.9, S, 41.6. IR (film): ν/cm^{-1} 3288 (s), 3105 (vw), 2912 (vw), 1433 (w), 1279 (m), 1232 (w), 1041 (w), 851 (w), 834 (w), 705 (s) and 658 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 2.64 (d, 1 H, J = 2.5, ≡CH), 2.88 (d, 1 H, J = 6.8, SH), 5.12 (ddd, 1 H, ^{3}J

= 6.8, $^4J_1$ = 2.5, $^4J_2$ = 0.8, CH), 6.92 (dd, 1 H, $^3J_1$ = 5.0, $^3J_2$ = 3.5, H-4), 7.12-7.16 (m, 1 H, H-3), 7.24 (dd, 1 H, ^3J = 5.0, ^4J = 1.4, H-5); MS: m/z 154 (M^+, 3), 121 (100), 77 (14), 69 (12), 63 (6) and 51 (5).

*3.12. 1-(2-Thienyl)prop-2-ynyl-1-thiolacetate **12**.*

The method of Gauthier [25] was employed. To a solution of 7.32 g (53.0 mmol) of **6** in dry 1,2-dichloroethane (110 mL), dried ZnI_2 (8.8 g, 27.6 mmol) was added under nitrogen. The resulting yellow suspension was stirred for 15 min, then prop-2-yn-1-thiol (4.79 g, 63 mmol) was added and the stirring was continued for additional 30 min. The reaction was quenched with water (110 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases dried over $CaCl_2$. Distillation under reduced pressure (55 °C, 0.01 mmHg) afforded pure **12** as a colourless oil (6.1 g, 59%). Found: C, 55.0%, H, 4.2, S, 32.7. Calcd for $C_9H_8OS_2$: C, 55.1, H, 4.1, S, 32.7. IR (film): ν/cm^{-1} 3288 (s), 3107 (vw), 3074 (vw), 2915 (vw), 2120 (vw), 1695 (s), 1431 (w), 1353 (w), 1272 (w), 1231 (w), 1131 (s), 1109 (m), 951 (m), 853 (w), 705 (s) and 627 (s); ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 2.36 (s, 3 H, CH_3CO), 2.56 (d, 1 H, ^4J = 2.5, ≡CH), 5.78 (dd, 1 H, $^4J_1$ = 2.5, $^4J_2$ = 0.7, CH), 6.92 (dd, 1 H, $^3J_1$ = 5.2, $^3J_2$ = 3.5, H-4), 7.15-718 (m, 1 H, H-3), 7.23 (dd, 1 H, ^3J = 5.2, ^4J = 1.3, H-5); MS: m/z 196 (M^+, 14), 154 (14), 153 (14), 121 (100), 77 (20) and 69 (16).

*3.13. 3^{I},4^{I}-Bis[(methoxycarbonyl)methyl]-2,2^{I},2^{II}-terthiophene **13**.*

A mixture of **14** (2.5 g, 6.5 mmol), 2-(tributylstannyl)thiophene (5.6 g , 15 mmol), $Pd(PPh_3)_4$ (0.3 g, 0.26 mmol) in dry DMF (33 mL) was heated (oil bath temperature = 105 °C) with stirring for 1.5 h in nitrogen atmosphere. The reaction was quenched with water and extracted with CH_2Cl_2. After drying over $CaCl_2$, flash chromatography (hexane-ethyl acetate 6:4) afforded crude **13** as a pale yellow solid (2.24 g, 88%). Repeated crystallization from CH_2Cl_2-hexane gave pure **13** as colourless crystals (mp 119-120 °C) (2.04 g, 80%). Found: C, 55.2%, H, 4.1, S, 24.4. Calcd for $C_{18}H_{16}O_4S_3$: C, 55.1, H, 4.1, S, 24.5. IR (KBr): ν/cm^{-1} 2997 (vw),

2949 (vw), 1731 (s), 1432 (w), 1343 (w), 1330(w), 1201 (m), 1175 (s) and 717 (m);); UV: λ_{max} (MeOH) = 320 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 3.73 (s, 6 H, 2 CO_2Me), 3.78 (s, 4 H, 2 CH_2), 7.09 (dd, 2 H, $^3J_1$ = 5.3, $^3J_2$ = 3.6, H-4, H-4^{II}), 7.23 (dd, 2 H, ^3J = 3.6, ^4J = 1.1, H-3, H-3^{II}) and 7.36 (dd, 2 H, ^3J = 5.3, ^4J = 1.1, H-5, H-5^{II}); MS: m/z 394 (M^++2, 17), 393 (M^++1, 22), 392 (M^+, 100), 360 (13), 333 (37), 332 (12), 302 (13), 301 (25), 300 (65), 275 (30), 274 (10), 273 (36), 272 (10), 241 (13), 240 (24), 227 (16), 208 (13), 207 (35), 136 (11), 127 (18), 121 (10), 69 (11) and 59 (16).

3.14. 2,5-Dibromo-3,4-bis[(methoxycarbonyl)methylthiophene ***14****.*

A solution of Br_2 (6.2 g, 38.8 mmol) in glacial acetic acid (6 mL) was added dropwise to a solution of **3** (1.78 g, 7.81 mmol) in glacial acetic acid (20 mL). The mixture was heated with stirring at 60 °C for 1 h, then poured into 40 ml of cold water added of $Na_2S_2O_5$ to destroy the excess of bromine and extracted with CH_2Cl_2. After drying over $CaCl_2$, the solvent was evaporated *in vacuo*. The crude product was recrystallized from CH_2Cl_2-pentane to give pure **14** as pale yellow crystals (mp 88-89 °C) (2.55 g, 85%). Found: C, 31.2%, H, 2.7, S, 8.2. Calcd for $C_{10}H_{10}Br_2O_4S$: C, 31.1, H, 2.6, S, 8.3 IR (KBr): ν/cm^{-1} 3023 (vw), 3000 (vw), 2950 (w), 2845 (vw), 1732 (s), 1439 (s), 1277 (s), 1165 (s), 1122 (m), 1010 (s), 987 (m), 935 (m), 839 (m), 722 (w), and 643 (w); ^{1}H NMR: δ/ppm 3.67 (s, 4 H, 2 CH_2), 3.70 (s, 6 H, 2 CO_2Me); MS: m/z 388 [(M^++4), 10], 386 [(M^++2), 21], 384 (M^+, 10), 356 (41), 354 (69), 352(38), 327 (36), 324 (33), 322 (53), 296 (30), 295 (29), 294 (53), 271 (51), 269 (100), 267 (60), 247 (19), 189 (13), 188 (10), 108 (17), 69 (13) and 59 (24).

3.15. 5,5^{II}-Dibromo-3,4,3^{II},4^{II}tetra[(methoxycarbonyl)methyl]-2,2^{I},2^{II}-terthiophene ***15****.*

A solution of NBS (0.66 g, 3.72 mmol) in dry DMF (20 mL) was added dropwise (*ca.* 20 min) under nitrogen to a cooled solution (-20 °C) of **9** (1.0 g, 1.86 mmol) in dry DMF (50 mL). The mixture was warmed up to room temperature and let stir overnight. After DMF was evaporated *in vacuo*, CH_2Cl_2 (40 mL) and ice were added to the residue. The organic phase

was separated, washed with brine and dried over $CaCl_2$. Solvent evaporation afforded crude **15** as a yellow solid (1.25 g, 97%). Repeated crystallization from MeOH gave pure **15** as pale yellow crystals (mp 141-142 °C) (1.13 g, 88 %). Found: C, 41.5%, H, 3.1, S, 14.0. Calcd for $C_{24}H_{22}Br_2O_8S_3$: C, 41.5, H, 3.2, S, 13.9. IR (KBr): ν/cm^{-1} 2994 (vw), 2952 (vw), 1741 (s), 1437 (w), 1273 (m)and 1007(w); ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 3.71 (s, 4 H, 2 CH_2), 3.72 (s, 6 H, 2 CO_2Me), 3.73 (s, 6 H, 2 CO_2Me), 3.76 (s, 4 H, 2 CH_2) and 7.15 (s, 2 H, H-3^{I}, H-4^{I}); FAB-MS (ν$^+$, NBA): m/z 696 [(M+4)$^{\cdot+}$, 66], 694 [(M+2)$^{\cdot+}$, 100], 692 (M$^{\cdot+}$, 45), 616 (16), 614 (15), 584 (14), 582 (12), 556 (18), 554 (15), 528 (7) and 526 (6).

3.16. 3^{I},4^{I},3^{II},4^{III}-Tetra[(methoxycarbonyl)methyl]-2,2^{I},2^{II},2^{III},2^{IIII}-pentathiophene **16**

A mixture of **15** (1,0 g, 1.44 mmol), 2-(tributylstannyl)thiophene (1.3 g , 3.47 mmol), $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol) in dry DMF (40 mL) was heated (oil bath temperature = 105 °C) with stirring for 1 h under nitrogen. The reaction was quenched with water and extracted with CH_2Cl_2. After drying over $CaCl_2$, column chromatography (hexane-ethyl acetate 1:1) afforded crude **16** as an orange solid (0.96 g, 95%). Repeated crystallization from MeOH gave pure **16** as orange crystals (mp 170-171 °C) (0.91 g, 90%). Found: C, 54.9%, H, 4.1, S, 22.8. Calcd for $C_{32}H_{28}O_8S_5$: C, 54.8, H, 4.0, S, 22.9. IR (KBr): ν/cm^{-1} 3102 (vw), 3068 (vw),2996 (vw), 2954 (w), 1733 (s), 1436 (m), 1266 (m), 1246(m), 1190 (m), 1013 (m), 830 (w), and 708 (w); UV: λ_{max} (MeOH) = 360 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm 3.73 (s, 6 H, 2 CO_2Me), 3.74 (s, 6 H, 2 CO_2Me), 3.79 (s, 4 H, 2 CH_2), 3.82 (s, 4 H, 2 CH_2), 7.10 (dd, 2 H, $^3J_1$ = 5.1, $^3J_2$ = 3.7, H-4, H-4^{IIII}), 7.21 (s, 2 H, H-3^{II}, H-4^{II}), 7.23 (dd, 2 H, ^{3}J = 3.7, ^{4}J = 1.2, H-3, H-3^{IIII}) and 7.34 (dd, 2 H, ^{3}J = 5.1, ^{4}J = 1.2, H-5, H-5^{IIII}); FAB-MS (ν$^+$, NBA): m/z 702 [(M+2)$^+$, 37], 701 [(M+1)$^+$, 50], 700 (M$^{\cdot+}$, 100), 669 (5), 641 (16), 609 (7), 581 (17) and 553 (6).

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