A Practical Synthesis of Functionalized Alkyl-Oligothiophenes for Molecular Self-Assembly

R. Michalitsch*‡, A. ElKassmi, A. Yassar and F. Garnier

Centre National de la Rechèrche Scientifique (CNRS), Laboratoire des Matériaux Moléculaires, 2, Rue Henry Dunant, 94320 Thiais, France
‡ current address: Dept. of Chemical Engineering, Massachusetts Institute of Technology, 77, Massachusetts Ave., Cambridge, MA 02139
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A synthesis for oligothiophenes that carry an alkyl sidechain with a terminal thiol group is presented. The procedure consists of three basic steps and uses well-known and simple synthetic chemistry. Nevertheless, this strategy for preparing functionalized oligothiophenes provides overall yields that are as high as 25-30% and represents a convenient route towards this interesting class of materials.

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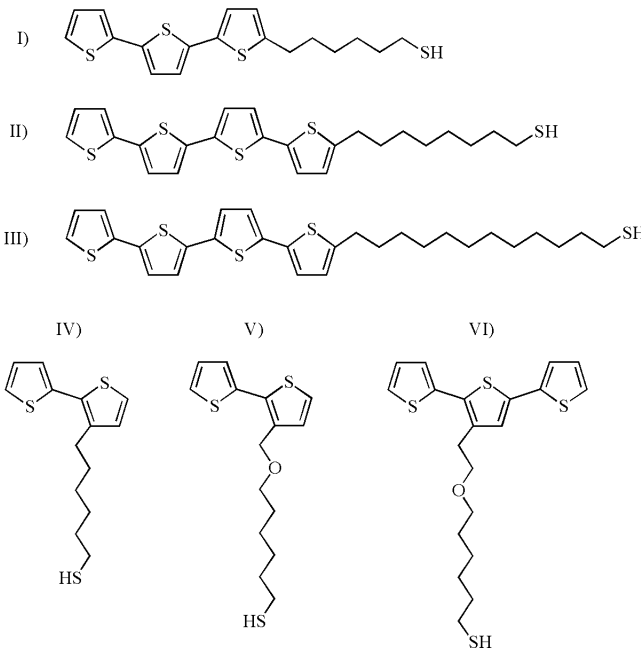
Introduction.

Self-assembly of amphiphilic molecules onto metal surfaces provides the ability for preparing well-ordered and densely packed monolayers of organic compounds [1]. Self-assembled monolayers (SAMs) [2,3] have attracted enormous interest in the past years due to the numerous potential applications of surfaces with controlled molecular architecture in important technologies such as surface patterning [4,5], lithographic techniques [6,7], chemical sensing, molecular recognition [8-10], catalysis [11], and adhesion [12].

Recently, SAMs based on oligomers of aromatic compounds that contain extended systems of conjugated π-electrons gained interest due to their electron-transfer behavior (molecular wires) [13-15] and electrochemical activity [16]. Ordered monolayers of these materials can be used for further developing adhesion promotion, electrical devices and chemical sensors based on SAMs, but require rigorous control of their properties at the molecular level. Oligothiophene derivatives are particularly interesting candidates for molecular self-assembly since their well-known chemistry and structure can provide the desired control over the behavior of SAMs. Recently, bi- and terthiophene derivatives and their synthesis have been presented in the literature [17-20].

In this paper, we report a practical synthesis for 12-(2,2':5',2":5",2"':5"'-quaterthien-5-yl)-dodec-1-ylthiol and 6-(2,2'-bithien-3yl)-hex-1-ylthiol and related compounds (Scheme 1) with linear and t-shaped geometry and the general formula $T_n(CH_2)_m$-SH with T=thiophene.

Scheme 1

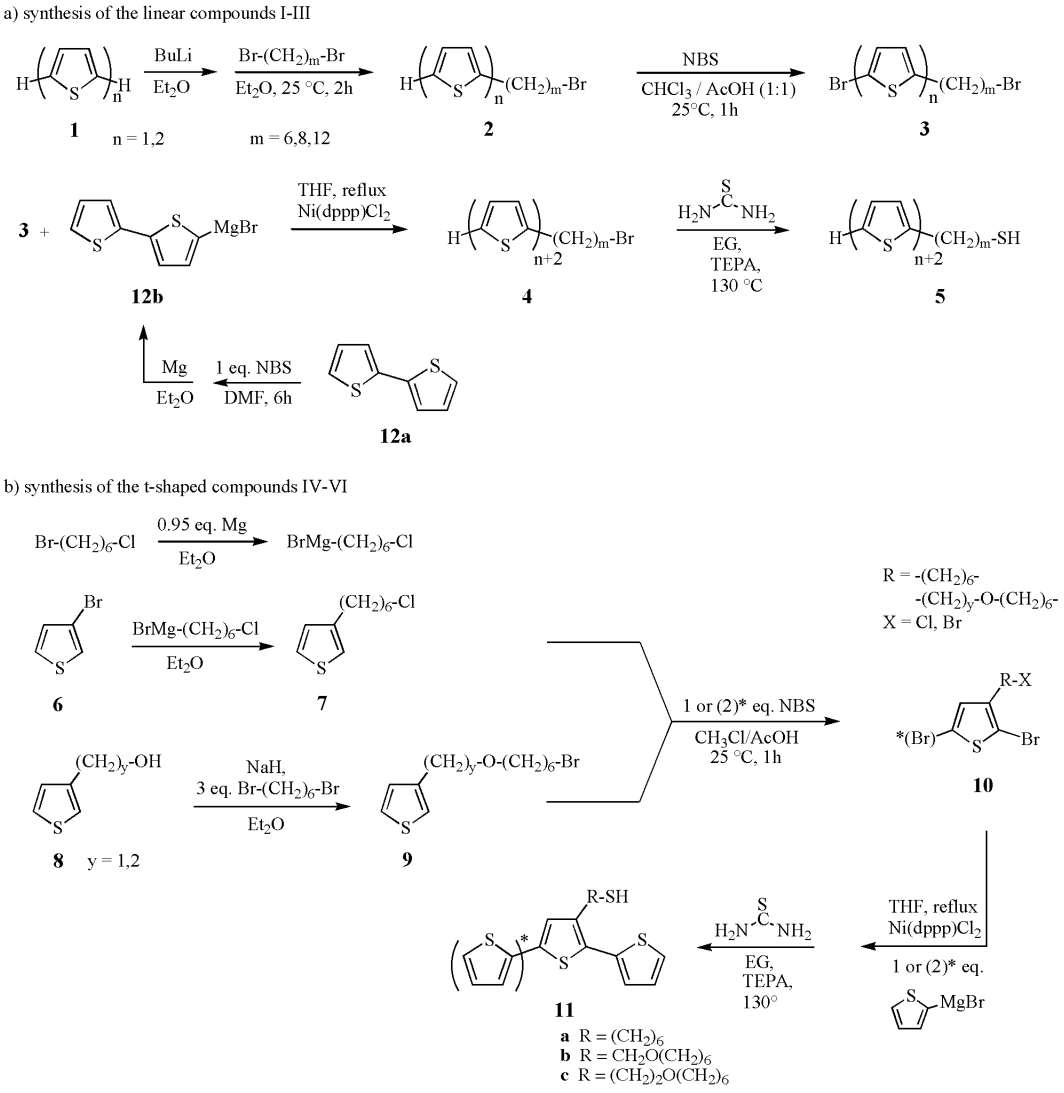


Results and Discussion.

Functionalized oligothiophenes with linear geometry. Thiophene and 2,2'-bithiophene **1** were lithiated to 2-lithiothiophene and 5-lithio-2,2'-bithiophene, respectively, and alkylated with a 3 to 5 fold excess of 1,12-dibromododecane or related dibromoalkanes with shorter alkylchains. The alkylation gave 52-58% of the desired alkyl-substituted thiophene **2** with a terminal bromide group (Scheme 2.a). In recent studies [19,20], similar alkyl-derivatized thiophenes were obtained by a two or even four step procedure that involved the acylation of the thiophene moiety and the subsequent reduction of the obtained ketone with BH_3 or N_2H_4 (the latter requiring temporary replacement of the bromide with a hydroquinone ether). The alkylated thiophene derivative was then brominated in the free α-position using *N*-bromosuccinimide (NBS) in a mixture of acetic acid and chloroform [21] at room temperature and gave the regioselectively brominated thiophene derivative **3** (84-92% yield).

In a separate procedure the second building block for the thiophene oligomer was prepared by brominating 2,2'-bithiophene **12a** with NBS in dimethylformamide (DMF) and converting the brominated intermediate to the related Grignard compound **12b**. A regioselective Grignard cross coupling reaction (Kumada coupling) of **3** with **12b**, catalyzed by Ni(dppp)Cl_2 (Nickel-diphenylphosphinopropane) [22,23], yielded 65-71% of the oligothiophene **4** and maintained the terminal bromide group on the sidechain. Under these conditions, the alkylbromide did not react with the Grignard intermediate and produced no other side reactions.

Scheme 2



In the last step, the halogen in the terminal position of the alkylchain was converted into a thiol function [24] *via* formation of an isothioronium salt that was subsequently cleaved by tetraethylene-pentamine (TEPA). The products (Table 1.) were the desired thiol **5** (73-88% yield) and a nonvolatile guanidine salt.

Table 1

Compound	Overall Yield
6-(2,2':5',2'-terthien-5yl)-hex-1-ylthiol, I	23%
8-(2,2':5',2":5",2"':5"'-quaterthien-5-yl)-oct-1-ylthiol, II	25%
12-(2,2':5',2":5",2"':5"'-quaterthien-5-yl)-dodec-1-ylthiol, III	21%

Functionalized Oligothiophenes with t-Shaped Geometry.

3-Alkylthiophenes that contain a terminal leaving group on the chain were used as intermediates for preparing functionalized 3-alkyloligothiophenes [25,26]. However, these intermediates are not accessible by simple alkylation with Grignard compounds due to the side reactions of dihaloalkanes in the Grignard coupling reactions that are usually used in the preparation of alkylthiophene building blocks. On the other hand, the use of organolithium compounds is also largely limited. Although thiophene can be lithiated in position 3 (*i.e.* β-position) under kinetic conditions (-80 °C) by a halogen-metal exchange on 3-bromothiophene, the subsequent alkylation with dihaloalkanes proceeds slowly at low temperatures and gives poor yields. Higher temperatures accelerate the reaction, but produce an isomerization of the lithiated intermediate to the thermodynamically more stable 2-lithiothiophene and yields a mixture of different products that are difficult to separate. A procedure for an alkylation of thiophene with a dihaloalkane in position 3 has been proposed by Bäuerle *et*

al. [26] and involves the protection of one of the terminal halogen groups with a hydroquinoneether that is cleaved with HBr in acetic anhydride after the Grignard coupling with 3-bromothiophene. However, this procedure involves 3 steps and requires substantial amounts of time.

We have been looking for an alternative procedure for alkylating thiophene in its β-position in order to accelerate the synthesis of 3-alkylthiophene building blocks with terminal leaving groups on the alkyl chain. A simple strategy for preparing such thiophene intermediates involves the use of a Grignard compound that is prepared from 1-bromo-6-chlorohexane (Scheme 2.b). The Grignard reagent can be formed selectively on the bromide group and shows no intramolecular cyclization, but reacts readily with 3-bromothiophene under ambient conditions. Using this strategy we prepared 1-chloro-6-(thien-3-yl)hexane **7** in 55% yield.

For the t-shaped molecules V and VI (Scheme 1) we circumvented the alkylation of the thiophene ring by using thiophen-3-yl-methanol or -ethanol as starting material and introducing an ether functional group in the alkylchain. The presence of the ether group in the sidechain had no influence on the properties of the SAMs, which showed identical behavior for both bithiophene derivatives (IV and V).

The ether containing side chain was prepared by converting the alcohol group on 3-thiophenemethanol into its alcoholate, which was added to a three-fold excess of 1,6-dibromohexane (Scheme 2.b) in THF at 60 °C. The yield of the corresponding ether **9** was 60-63%. Subsequently, the positions 2 and 5 (α-positions) on the 3-substituted thiophene were brominated with NBS in acetic acid and chloroform. The use of one equivalent of the brominating agent allows to regioselectively brominate thiophene in the α-position next to the sidechain, while the use of two equivalents of NBS (indicated with an asterisk in Scheme 2) produces the α,α' brominated compound **10** (68-73% yield). The remaining steps for preparing the oligothiophene moiety *via* Grignard cross couplings and the terminal thiol group on the sidechain were identical to those described above.

Table 2

Molecule	Overall Yield
6-(2,2'-bithien-3yl)-hex-1-ylthiol, IV	19%
6-[(2,2'-bithien-3yl)-methoxy]-hex-1-ylthiol, V	26%
6-[2-(2,2':5',2''-terthien-3'-yl)-ethoxy]-hex-1-ylthiol , VI	21%

NMR spectra of the raw materials suggested that the exposure of the compounds to air effected an oxidative coupling of ~30-40% of the thiol groups to disulfides. The thiol–disulfide mixtures were treated with a dispersion of Zn powder in HCl (H_2O/EtOH = 1:1) to regenerate the thiol groups by reductive cleavage of the disulfide-bridge.

EXPERIMENTAL

5-(12-Bromododecyl)-2,2'-bithiophene (**2**).

2,2'-Bithiophene 5.32g (20 mmol) and 2.55g (22 mmol) of TMDEA (tetramethyldiethylamine) were stirred with 100 ml of dry THF under inert atmosphere, to which 8.8 ml (22 mmol) of *n*-BuLi solution (2.5 *M* in hexane) were slowly added through a dropping funnel. The reaction mixture was stirred for about 1 hour at 25 °C and then transferred under inert conditions to another dropping funnel and added to a solution of 9.84g (30 mmol) of 1,12-dibromododecane in refluxing anhydrous THF. The mixture was refluxed for 8 hours, hydrolyzed with a minimum of water, filtered over silica gel, diluted in 100 ml of water, extracted with chloroform, and dried over $MgSO_4$. The crude product was purified by distillation under vacuum and gave 5.13g (62% **2**; $bp_{(\sim 0.1mm)}$= 154 °C ^{1}H-NMR (250 MHz $CDCl_3$): δ 7.18 (1H, dd, J = 1.0 and 5.0 Hz, 5'-H), 7.12 (1H, dd, J = 3.5 and 0.9 Hz, 3'-H), 6.98 (1H, dd, J = 3.5 and 5.2 Hz, 4'-H), 6.92 (1H, d, J = 3.6 Hz, 4-H), 6.66 (1H, d, J = 3.6 Hz, 3-H), 3.4 (2H, t, J = 6.9, 1a-H, -CH_2-T), 2.8 (2H, t, J = 7.6 Hz, 12a-H, CH_2-Br), 1.92 ppm (2H, m , 2a-H, -CH_2-), 1.82 ppm (2H, m, 11a-H), 1.25 ppm (16H, m, 3a to10a-H).

5-Bromo-5'-(12-bromodocecyl)-2,2'-bithiophene (**3**).

5-(12-Bromododecyl)-2,2'-bithiophene, 3g (7.2 mmol), were solubilized in 80 ml of a mixture (1:1) of acetic acid and chloroform, to which 1.41g of NBS (7.92 mmol) were added in small amounts under continuous stirring and ambient conditions. When the reaction was finished (checked by thin layer chromatography, TLC), the mixture was poured in 100 ml of water and the organic phase was separated; the aqueous solution was extracted with several portions of chloroform. The organic phases were combined and washed with $NaHCO_3$ and dried over $MgSO_4$. The chloroform was finally evaporated and the product purified by column chromatography over silica gel (70-200 mesh). Elution with hexane gave 2.45 g (71%) of **3** as a white powder, Mp: 58°C; ^{1}H-NMR (250 MHz $CDCl_3$): δ 7.14 (1H, dd, J = 3.5 and 0.9 Hz, 3'-H), 7.05 (1H, dd, J = 3.5 and 5.2 Hz, 4'-H), 6.94 (1H, d, J = 3.6 Hz, 4-H), 6.60 (1H, d, J = 3.6 Hz, 3-H), 3.4 (2H, t, J = 6.9, 1a-H, CH_2-T), 2.80 (2H, t, J = 7.6 Hz, 12a-H, CH_2-Br), 1.92 (2H, m, 2a-H, -CH_2-), 1.82 (2H, m, 11a-H), 1.25 (16H, m, 3a to 10a-H, -CH_2-).

Anal. Calcd. for $C_{20}H_{28}Br_2S_2$: C, 48.79; H,5.73; Br,32.46; S,13.03. Found: C, 48.63; H, 5.78; Br, 32.14; S, 12.83.

5-(12-Bromodedecyl)-2,2';5',2";5",2'"-quaterthiophene (**4**).

5-Bromo-2,2'-bithienyl, 2.4g (10 mmol), in 30 ml of anhydrous THF were added dropwise under inert atmosphere to 0.24 g (10 mmol) of magnesium turnings in 10 ml of THF. The reaction mixture was refluxed until the disappearance of magnesium and the resulting Grignard solution transferred to another experimental setup. There it was slowly dropped into a mixture of 3.8g (9.5 mmol) of **3** with (1 mol%) Ni(dppp)Cl_2 [(1,3-bis(diphenylphosphino)-propanedichloro-nickel(II)) in 40 ml anhydrous THF. Refluxing overnight produced a Grignard cross coupling reaction to give **4**. The workup consisted of hydrolyzing with several ml of 1 *N* HCl, extraction with chloroform, drying the solution with $MgSO_4$ and evaporation of the solvent. The product was purified by a silica gel-chromatography (70-200 mesh) with heptane until the elution of bithiophene **2** and quaterthiophene; afterwards, ethyl acetate was progressively added to the heptane to elute the desired product, giving 3.3 g (59 %) of **4** as a red-brown powder; mp: 122 °C; ^{1}H-NMR (250

MHz $CDCl_3$): δ 7.2-6.80 (8H, m), 6.68 (1H, d, J = 3.6 Hz, 3-H), 3.4 (2H, t, J = 6.9, 1a-H, CH_2-T), 2.80 (2H, t, J = 7.6 Hz, 12a-H, CH_2-Br), 1.92 (2H, m, H-2a, -CH_2-), 1.82 (2H, m, 11a-H), 1.25 (16 H, m, H-3a to 10a).

Anal. Calcd. for $C_{28}H_{33}BrS_4$: C, 58.20; H, 5.76; Br, 13.84; S, 22.21. Found: C, 57.80; H, 5.93; Br, 13.31; S, 22.32.

12-(2,2':5',2":5",2"':5"'-Quaterthien-5-yl)dodecane-1-thiol III (**5**).

A mixture of 3 ml of ethyleneglycol (EG) and 0.83 g (11 mmol = 1.1 equivalents) of thiourea was stirred at 80 °C under inert atmosphere until the solution became homogenous, at which time 5.6g (10 mmol) **4** were added in one portion and the reaction temperature was raised to 130 to 140 °C. These conditions were kept for about 2 hours until the isothioronium salt was formed and the reaction solution became homogenous. The isothioronium intermediat was finally cleaved by the addition of 0.9 g (5 mmol, 0.5 equivalents) of tetraethylenepentamine (TEPA). After additional 3 hours the mixture was subjected to work up. The reaction solution was diluted with ether and 1 *N* HCl. The following extraction procedure was carried out under inert atmosphere to avoid oxidative coupling of the thiolfunctions to disulfides. The gathered organic fractions were washed to neutral and dried with $MgSO_4$. The residual solvent was evaporated under vacuum and the product recrystallized from hexane to isolate 3.7g (70 %) of **5**; mp = 112-116° C, UV absorption maximum 404 nm, IR (CCl_4) 3112, 3069 aromatic CH, 2953, 2921, 2858 aliphatic CH, 2458 SH, 1508 aromatic CC, 788, 694 cm^{-1} aromatic CH, out of plane; ^{1}H-NMR (250 MHz $CDCl_3$): δ 7.2-6.80 (8H, m), 6.68 ppm (1H, d, J = 3.6 Hz, 3-H), 2.72 (2H, t, J = 7.6 Hz, 1a-H, CH_2-T), 2.48 (2H, q, J = 7.4 and 7.1 Hz, 12a-H, CH_2-S), 1.92 (2H, m, 2a-H), 1.82 (2H, m, 11a-H), 1.33 (1H, t, J = 7.7 Hz, S-H), 1.25 (16H, m, 3a to10a-H, -CH_2-).

Anal. Calcd. for $C_{28}H_{34}S_5$: C, 63.33; H, 6.46; S, 30.21. Found: C, 62.91; H, 6.72; S, 29.85.

6-(2,2'-Bithiophen-3-yl)hexane-1-thiol IV, (**11a**).

mixture of 3 ml of ethyleneglycol (EG) and 0.42 g (5.5 mmol = 1.1 eq) of thiourea was stirred at 80°C under inert atmosphere until the solution became homogenous, at which time 1.43g (5 mmol) 3-(6-chlorohexyl)-2,2'-bethiophene were added in one portion and the reaction temperature was raised to 130 to 140 °C. Finally 0.5 g tetraethylenepentamine were added to cleave the formed isothioronium salt. After the reaction was complete and cooled to room temperature at which time 20 ml ether were added to the reaction mixture and extracted several times with water. The collected ether phase was then extracted three times with 100 ml 10% HCl (aqueous) and brought to pH 7 with 10% $NaHCO_3$. The crude product was filtered over silica that was pretreated with triethylamine. After evaporating the solvent, we obtained 0.99g (78% yield) of **11** as a colorless oil; $b.p._{\cdot(1mm)}$ = 134 °C, UV abs. λ max. = 296 nm,

^{1}H-NMR (250 MHz $CDCl_3$): δ 7.21 (1H, d, J = 5.0 Hz, 5'-H), 7.06-7.10 (1H, dd, J = 5.0 Hz and 1.3, 5-H), 6.93 - 6.99 (2H, m, 3´-H and 4´-H), 6.83 (1H, d, J = 5.0 Hz, 4-H), 2.62 (2H, t, J = 7.1, 1a-H, CH_2-T), 2.42 (2H, q, J = 7.25 Hz, 6a-H, CH_2-S), 1.45 (4H, m, 2a-H and 5a-H),1.32 (1H, t, 7.7 Hz, S-H) 1.25 (4H, m, 3a and 4a-H); IR (CCl_4), 3110, 3070, CH aromat. weaker than in III, 2460 cm^{-1} SH.

Anal. Calcd. for $C_{14}H_{18}S_3$: C, 59.52; H, 6.42; S, 34.06. Found: C, 59.44; H, 6.51; S, 33.88.

6-[(2,2´-bithien-3-yl)methoxy]-hexane-1-thiol, V (**11b**).

Compound **11b** was obtained as a colorless oil; $b.p._{\cdot(\sim1mm)}$ = 138 °C, IR (CCl_4): 2454 SH, 1152 cm^{-1} O-CH_2 asym., UV abs. λ max. 368 nm; ^{1}H-NMR (250 MHz $CDCl_3$): δ 7.23 (1H, d, J = 5.0 Hz, 5'-H), 7.08 (1H, dd, J = 5.0 and 1.3 Hz, 5-H), 6.95 – 7.00 (2H, m, 3'-H and 4'-H), 6.83 (1H, d, J = 5.0 Hz, 4-H), 3.81 (2H, s, 1a-H, CH_2-T), 3.42 (2H, t, 2a-H, CH_2-O), 2.4 (2H, q, J = 7.25 Hz, 7a-H, CH_2-S), 1.45 (4H, m, 3a and 6a-H, CH_2-), 1.31 (1H, t, 7.7 Hz, S-H), 1.25 (4H, m, 4a and 5a H).

Anal. Calcd. for $C_{15}H_{20}OS_3$: C, 57.65; H, 6.45; O, 5.12; S, 30.78. Found: C, 57.44; H, 5.21; S, 30.83.

6-[2-(2,2':5',2"-Terthien-3'-yl)-ethoxy]-hexane-1-thiol , VI (**11c**).

Compound **11c** was obtained as an oil $b.p._{\cdot(\sim1mm)}$ = 168 °C, IR (CCl_4): 2455 SH, 1142 cm^{-1} O-CH_2 asym., UV abs.: λ max. 368 nm; ^{1}H-NMR (250 MHz $CDCl_3$): δ 7.19 ppm (2H, dd, J = 5.0 Hz and 1.3 Hz, 5 and 5"-H), 6.93-6.99 (4H, m, 3 and 3"-H, 4 and 4"H), 6.81 (1H, 3'-H), 3.50 (2H, t, 2a-H, O-CH_2-CH_2-T), 3.42 (2H, t, 3a-H, O-CH_2-CH_2-) 2.76 (2H, t, J = 7.1, 1a-H, CH_2-T), 2.41 (2H, q, J = 7.25 Hz, 8a-H, H_2C-S), 1.43-1.67 (4H, m, 4a and 7a H,) 1.31 (1H, t, 7.7 Hz, S-H), 1.25 (4H, m, 5a and 6a H).

Anal. Calcd. for $C_{20}H_{24}OS_4$: C, 58.78; H, 5.92; O, 3.92; S, 31,39. Found: C, 58.4; H, 6.28; S, 30.83.

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