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SELECTIVE AND EFFICIENT SYNTHESES OF PHOTOTOXIC 2,2':5',2''-TERTHIOPHENE DERIVATIVES BEARING A FUNCTIONAL SUBSTITUENT IN THE 3'- OR THE 5-POSITION

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Abstract: Efficient and selective procedures have been developed to prepare on a medium scale several phototoxic 2,2':5',2''-terthiophene derivatives of general formula ***2*** and ***3***, which are characterized by a functional substituent in the 3'- or the 5-position. Most of these procedures, which are based on the construction of the 2,2':5',2''-terthiophene moiety and involve palladium-mediated carbon-carbon bond forming reactions, allow to overcome synthetic difficulties that may be found in the synthesis of compounds ***2*** and ***3*** starting from 2,2':5',2''-terthiophene ***(1a)***.

Over the past few years thiophenes isolated from plants in the family *Compositae* have stimulated much interest because their wide range of photobiological effects[1,2]. The most scrutinized member of this group of secondary metabolites is 2,2':5',2''-terthiophene ***(1a)***. Chemical, biochemical and photophysical studies have thoroughly substantiated that compound ***1a*** is a photodynamic sensitizer which efficiently generates singlet oxygen[2a,3a], but which can also give rise to the production of superoxide radical anion in an aqueous medium[3]. On the other hand, the oxygen dependent phototoxicity of ***1a*** has been described in nematodes, microorganisms, fish and plants, fungi as well as in eggs and larvae of insects[4]. Interestingly, this substance has been also patented as a promising pesticide[5]. However, its lack of selectivity raises challenging questions about the risks to handlers and to non-target organisms.

In the course of a study aimed to investigate the effect of substituents and structural variations on the light-dependent toxicity and the photophysical properties of ***1a***, recently we developed convenient procedures to synthesize on a medium scale (5 - 10 g) several derivatives of ***1a*** of general formula ***1***, which include some naturally-occurring substances, *i.e.* compounds ***1b***, ***1e***, ***1f***, ***1g*** and ***1h***[6].

Interestingly, during a preliminary investigation on the insecticidal and acaricidal properties of compounds ***1*** it was found that : *i*) in the presence of daylight, the order of toxicity of the substances tested against larvae and eggs of *Aedes aegypti*, larvae and adults of *Tetranichus urticae* was ***1e*** > ***1b*** >***1a*** > ***1c*** > ***1f*** > ***1d***; *ii*) compound ***1e*** displayed significant selectivity[7]. In fact, although it resulted to be extremely active against adults of *T. urticae*, it exhibited low phototoxicity against larvae of *A. aegypti* and

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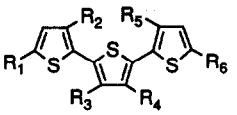
#In partial fulfilment of his Ph.D. work

Leptinotarsa decemlineata[7] and its activity against these insect species was comparable to that of the most effective compound among the terthiophenes tested , *i.e.* ***1a***.



1

1a : $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$

1b : $R_1 = CH_3$; $R_2 = R_3 = R_4 = R_5 = R_6 = H$

1c : $R_1 = R_3 = R_4 = R_6 = H$; $R_2 = R_3 = CH_3$

1d : $R_1 = R_6 = H$; $R_2 = R_3 = R_4 = R_5 = CH_3$

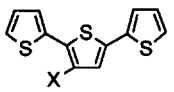
1e : $R_1 = R_2 = R_4 = R_5 = R_6 = H$; $R_3 = OCH_3$

1f : $R_1 = CH_2OAc$; $R_2 = R_3 = R_4 = R_5 = R_6 = H$

1g : $R_1 = CH_2OH$; $R_2 = R_3 = R_4 = R_5 = R_6 = H$

1h : $R_1 = CH_2OCOCH{=}C(CH_3)_2$; $R_2 = R_3 = R_4 = R_5 = R_6 = H$

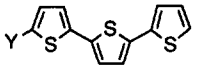
More recently, as a part of our research effort to discover new phototoxic 2,2':5',2"-terthiophene derivatives useful for agricoltural applications which are more potent and selective than naturally-occurring compounds ***1a***, ***1b***, ***1e***, ***1f***, ***1g*** and ***1h***, we have disclosed efficient and selective routes for the preparation of two structural analogues of ***1e***, *i.e.* compounds ***2a*** and ***2b***, as well as of 2,2':5',2"-terthiophene derivatives of general formula ***3***, which bear a functional group or a stereodefined and functionalized aliphatic carbon chain in the 5-position of their polyheteroarene units.



2

2a : $X = OC_2H_5$

2b : $X = SCH_3$



3

3a : $Y = CHF_2$

3b : $Y = OCH_3$

3c : $Y = CH\overset{E}{=}CH\text{-}COOEt$

3d : $Y = CH\overset{E}{=}CH\text{-}CONH\text{-}i\text{-}Bu$

3e : $Y = Br$

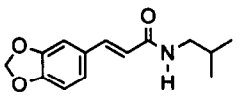
3f : $Y = COOEt$

3g : $Y = CONH\text{-}i\text{-}Bu$

3h : $Y = C{\equiv}C\text{-}(CH_2)_2\text{-}CH\overset{E}{=}CH\text{-}CONH\text{-}i\text{-}Bu$

Compounds ***3*** include 5-difluoromethyl-2,2':5',2"-terthiophene ***(3a)***, a structural analogue of ***1b***, and the terthiophenes ***3d***, ***3g*** and ***3h*** which are characterized by structural elements identical to those present in some natural or synthetic insecticidal *N*-(2-methylpropyl)carboxyamides[8]. In particular, compound ***3d*** represents an analogue of *(E)*-fagaramide ***(4)***, a substance isolated from *Fagara macrophylla*[9], which inhibits the growth of larvae of *Pectinophora gossypiella, Heliothis virescens, H. zea* and *Spodoptera frugiperda*[10] and exhibits lethal toxicity for larvae of *Culex pipiens* and *Biomphalaria glabratus*[10]. On the

other hand, compound ***3g*** contains the *N*-(2-methylpropyl)carboxyamide group, typical for several insecticidal lipophilic amides[8], as well as the 5-substituted 2,2':5',2"-terthiophene unit which is responsible for the phototoxic properties of several natural and synthetic terthiophenes, and compound ***3h*** contains an *(E)*-*N*-(2-methylpropyl)-2-hepten-6-ynamide group, which is also present in the synthetic carboxyamide ***5*** endowed with high insecticidal and acaricidal activities[11].



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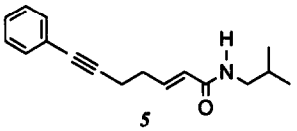
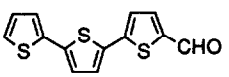
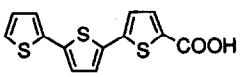


5

We now describe the efficient and selective procedures developed to prepare on a medium scale (1 - 10 g) these terthiophenes of general formula ***2*** and ***3***. These procedures allow to overcome synthetic difficulties that may be found in the synthesis of ***2*** and ***3*** starting from easily available 2,2':5',2"-terthiophene ***(1a)***. In fact, the functionalization of ***1a*** gives rise essentially to 5 and 5,5" substituted derivatives[12,13,14]. On the other hand, to the best of our knowledge, only two reactions which involve the efficient and selective introduction of a functional group into the 5-position of ***1a*** have been reported in the literature so far. These are the Vilsmeier reaction of ***1a*** with $POCl_3$ and dimethylformamide[13] or *N*-methylformanilide[12], and the metallation of ***1a*** with LDA followed by carboxylation with solid carbon dioxide[14], respectively. Moreover, the so obtained 5-substituted 2,2':5',2"-terthiophenes, *i.e.* compounds ***3i*** and ***3l***, are not much soluble in the most common organic solvents, chlorinated aliphatic hydrocarbon excluded, and, therefore, generally appear unsuitable as starting materials for the preparation on a medium scale of other 5-substituted terthiophene derivatives.



3i



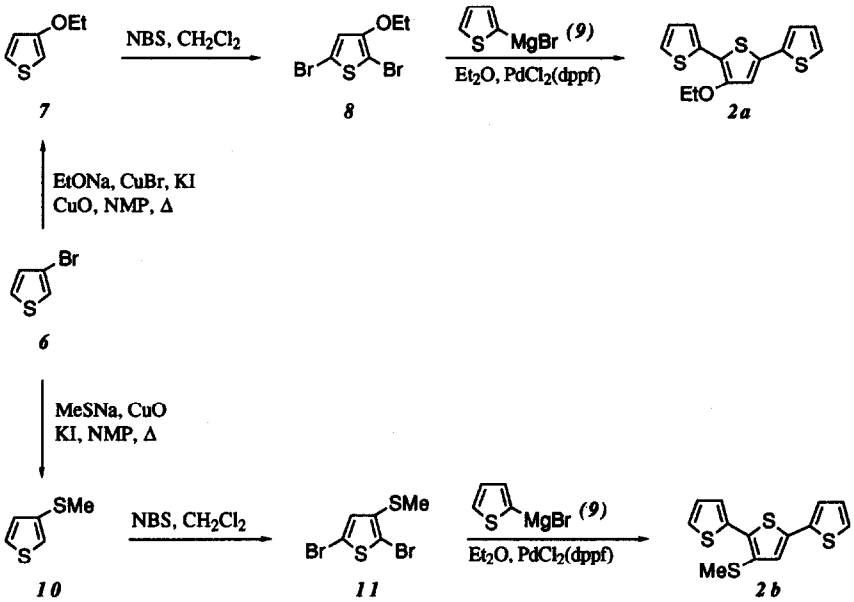
3l

The reaction sequences which we used to prepare compounds ***2a*** and ***2b*** are reported in Scheme 1. Thus, according to a modification of the procedure described for the synthesis of 3-methoxythiophene[15], 3-ethoxythiophene ***(7)*** was prepared in 82% yield by treatment of commercially available 3-bromothiophene ***(6)*** with sodium ethoxide and *N*-methyl-2-pyrrolidinone (NMP), in the presence of *ca.* 0.5 equiv of CuO and catalytic amounts of CuBr and KI. Bromination of ***7*** with 2 equiv of NBS gave compound ***8*** in 82% yield. Finally, treatment of ***8*** with 3 equiv of an Et_2O solution of 2-thienylmagnesium bromide ***(9)***, in the presence of a catalytic amount of $PdCl_2$(dppf) [dppf = 1,1'-bis(diphenylphosphino)ferrocene] afforded 3'-ethoxy-2,2':5',2"-terthiophene ***(2a)*** in 91% yield.

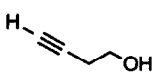
In a similar way, 3-(methylthio)thiophene ***(10)***, which was obtained in 41% yield by reactions of ***6*** with a solution of sodium thiomethoxide in NMP, in the presence of CuO and a small amount of KI, was reacted with NBS in CH_2Cl_2 to give 2,5-dibromo-3-(methylthio)thiophene ***(11)*** in 83% yield[16]. Then, the cross-coupling reaction between ***11*** and 3 equiv of an Et_2O solution of ***9***, in the presence of $PdCl_2$(dppf), provided 3'-

methylthio-2,2':5',2"-terthiophene ***(2b)*** in 86% yield.

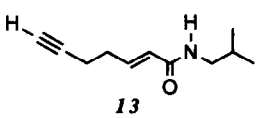
Scheme 1



The synthesis of the 2,2':5',2"-terthiophenes of general formula ***3*** was carried out according to three different strategies. In particular, taking into account that 5-formyl-2,2':5',2"-terthiophene ***(3i)*** is quite soluble in CH_2Cl_2, 5-difluoromethyl-2,2':5',2"-terthiophene ***(3a)*** was prepared by elaboration of the formyl group of ***3i*** which involved treatment of a CH_2Cl_2 solution of this aldehyde with a suitable fluorinating agent. The second strategy, which was followed to prepare 5-methoxy-2,2':5',2"-terthiophene ***(3b)***, ethyl ***(E)***-3-(2,2':5',2"-terthien-5-yl)propenoate ***(3c)*** and 5-bromo-2,2':5',2"-terthiophene (***3e***), involved the construction of the 2,2':5',2"-terthiophene moities of these substances by Pd-catalyzed cross-coupling reactions between a 5-halo-2,2'-bithiophene and a suitable 5-substituted 2-thienylmetal derivative or between a 2,2'-bithien-5-ylmetal derivative and a suitable 5-substituted 2-bromothiophene. By elaboration of the functional groups of compounds ***3c*** and ***3e*** it was then possible to synthesize (***E***)-*N*-(2-methylpropyl)-3-(2,2':5',2"-terthien-5-yl)-propenamide ***(3d)*** and 5-ethoxycarbonyl-2,2':5',2"-terthiophene (***3f***) and *N*-(2-methylpropyl)-2,2':5',2"-terthien-5-ylcarboxyamide (***3g***), respectively. Finally, ***(E)***-*N*-(2-methylpropyl)-7-(2,2':5',2"-terthien-5-yl)-2-hepten-6-ynamide ***(3h)*** was synthesized using a strategy which involved as final key step a Pd(0)-CuI mediated cross-coupling reaction between ***3e*** and ***(E)***-*N*-(2-methylpropyl)-2-hepten-6-ynamide ***(13)***, easily available starting from 3-butyn-1-ol ***(12)***.



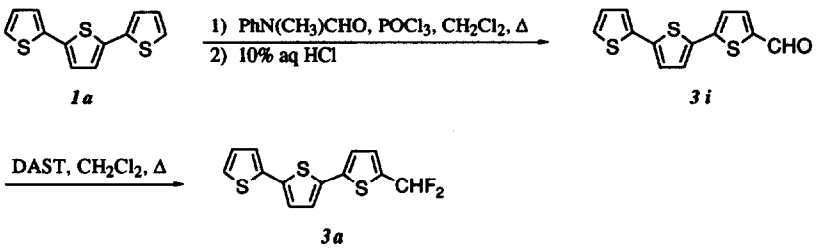
12



13

Thus, according to a general method for fluorination of carbonyl compounds[17], 5-formyl-2,2':5',2"-terthiophene *(3i)*, which was obtained in 78% yield by the Vilsmeier reaction of *1a* with $POCl_3$ and *N*-methylformanilide[12], was reacted with an equivalent amount of diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 solution at room temperature for 96 h to give in 38% yield compound *3a* having chemical purity higher than 98.5% (Scheme 2).

Scheme 2

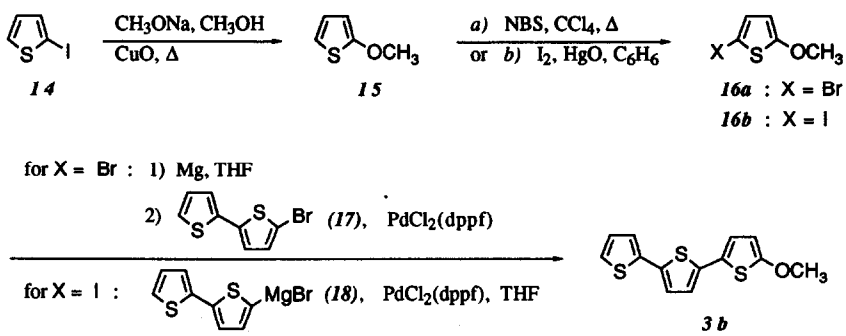


1a *3i* *3a*

Interestingly, *3a* resulted to be quite instable and in the presence of water was easily converted into its precursor, *i.e.* *3i*.

Compound *3b* was synthesized according to the reaction sequence reported in Scheme 3.

Scheme 3



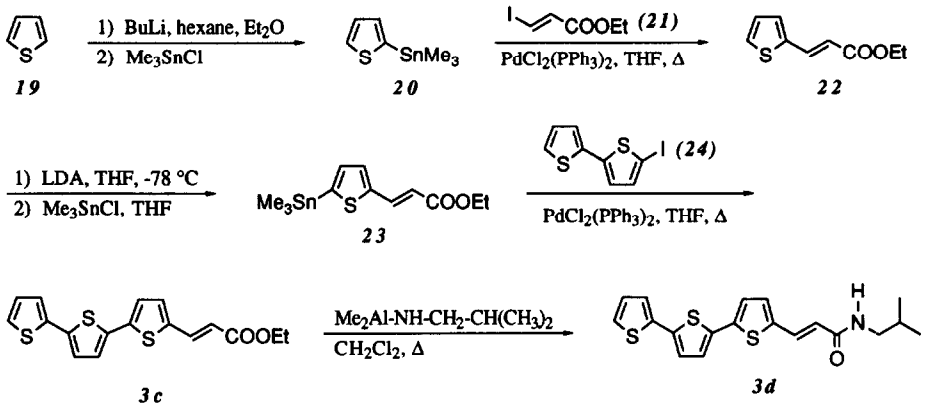
14 *15* *16a* : X = Br *16b* : X = I *3b*

In particular, 2-methoxythiophene *(15)*, which was prepared in 92% yield by treatment of 2-iodothiophene *(14)* with CuO and a solution of sodium methoxide in methanol[18], was reacted with 0.49 equiv of NBS in CCl_4[18,19] to give 2-bromo-5-methoxythiophene *(16a)* in 64% yield. The cross-coupling reaction between a THF solution of the Grignard reagent derived from *16a* and 5-bromo-2,2'-bithiophene *(17)*[20], in the presence of a catalytic amount of $PdCl_2$(dppf), gave compound *3b* in 80% yield. This result was better than that obtained when 2-iodo-5-methoxythiophene *(16b)*, which was obtained in 81% yield by iodination of *15* with iodine in the presence of yellow HgO, was reacted with a THF solution of 2,2'-bithien-5-ylmagnesium bromide *(18)*, in the

presence of a catalytic amount of $PdCl_2$(dppf). In fact, this coupling reaction afforded a complex reaction mixture from which it was possible to isolate 97% chemically pure ***3b*** in 24% yield.

Compounds ***3c*** and ***3d***, which are characterized by functional group sensitive to Grignard reagents, could not be prepared using a procedure similar to that employed to prepare ***3b***. Therefore, their synthesis was performed (Scheme 4) using a reaction sequence which involved as key step a palladium mediated cross-coupling reaction between a suitable 5-substituted 2-thienyltrimethylstannane and a 5-halo-2,2'-bithiophene. Thus, 2-thienyltrimethylstannane ***(20)***, which was obtained in 89% yield by metallation of thiophene ***(19)*** with butyllithium, followed by treatment with trimethyltin chloride, was reacted with a THF solution of ethyl *(E)*-3-iodoacrylate ***(21)***, in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, to give ethyl *(E)*-3-(2-thienyl)propenoate ***(22)*** in 74% yield. Metallation of ***22*** by treatment with a THF solution of LDA at -78 °C, followed by reaction with trimethyltin chloride, gave stereoisomerically pure ethyl *(E)*-3-(5-trimethylstannyl-2-thienyl)propenoate ***(23)*** in *ca.* 88% yield. A THF solution of this compound was successively reacted with 0.83 equiv of 5-iodo-2,2'-bithiophene ***(24)***[21], in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, to produce compound ***3c*** in 51% yield.

Scheme 4



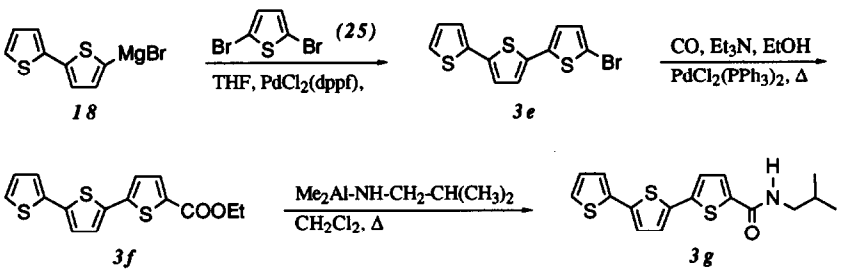
19 ***20*** ***22*** ***23*** ***3c*** ***3d***

Then, according to a general method developed for direct conversion of esters to amides[22], compound ***3c*** was reacted with a CH_2Cl_2 solution of the dimethylaluminum amide which was prepared *in situ* by treatment of trimethylalane with an equimolar amount of 2-methylpropylamine. Compound ***3d*** was so obtained in 96% yield (Scheme 4).

5-Bromo-2,2':5',2"-terthiophene ***(3e)***, which we used as a precursor to compounds ***3f***, ***3g*** (Scheme 5) and ***3h*** (Scheme 6), could not be efficiently synthesized using a procedure reported in the literature[12] which involves bromination of 2,2':5',2"-terthiophene ***(1a)*** with *N*-bromosuccinimide (NBS). In fact, this reaction afforded a mixture of 5 and 5,5" brominated derivatives from which we were unable to isolate, on a preparative scale, chemically pure ***3e***. However, we succeeded in the synthesis of ***3e*** on a preparative scale using the

following simple procedure. A THF solution of 2,2'-bithien-5-ylmagnesium bromide ***(18)*** was reacted with 1.2 equiv of 2,5-dibromothiophene ***(25)***, in the presence of a catalytic amount of $PdCl_2$(dppf) (Scheme 5). Purification by crystallization of the crude reaction product gave ***3e*** having chemical purity higher than 98% in 38% yield.

Scheme 5



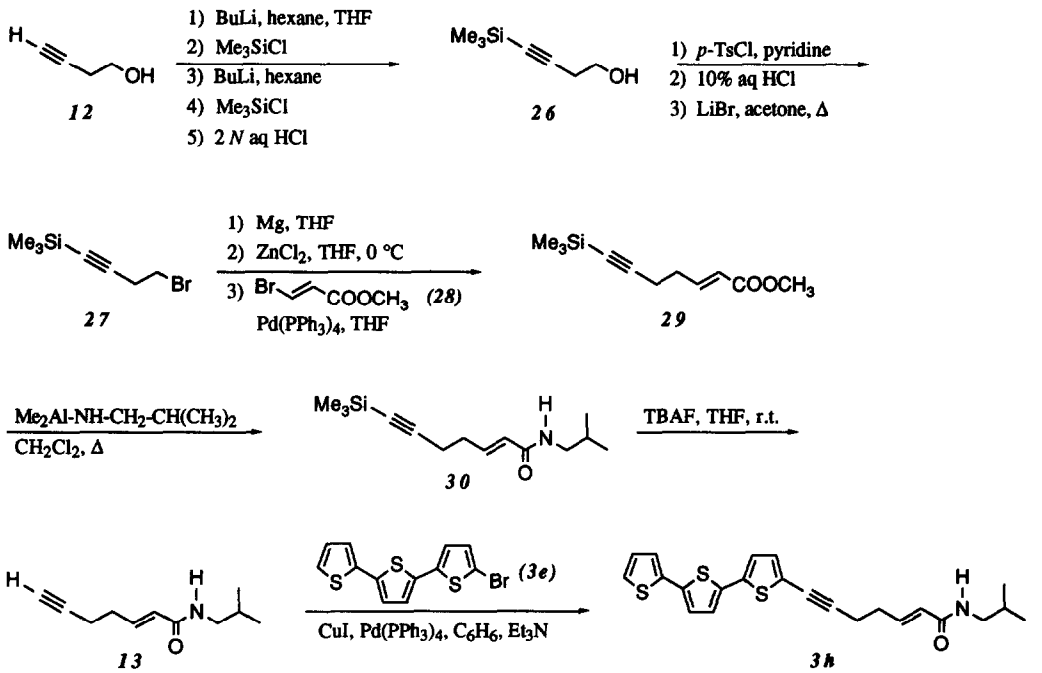
18 *3e* *3f* *3g*

This compound was converted in 94% yield into 5-ethoxycarbonyl-2,2':5',2"-terthiophene ***(3f)*** by a procedure previously employed for ethoxycarbonylation of some thienyl and bithienyl bromides[20] which consisted of charging a mixture of 1 equiv of heteroaryl bromide, 2.8 equiv of triethylamine, a large excess of ethanol and a catalytic amount of $PdCl_2(PPh_3)_2$ into an autoclave. After sealing, the autoclave was pressurized to 20 atm with carbon monoxide and maintained at 100 °C for 22 h (Scheme 5). Interestingly, no precautions were necessary to exlude air. According to the same procedure used to prepare ***3d*** from ***3c***, compound ***3f*** was then reacted with dimethylaluminum-*N*-(2-methylpropyl)amide to give *N*-(2-methylproyl)-2,2':5',2"-terthien-5-ylcarboxyamide ***(3g)*** in 85% yield (Scheme 5).

Finally, the synthesis of the most structurally complex among the terthiophene derivatives of general formula ***3***, *i.e.* *(E)*-*N*-(2-methylpropyl)-7-(2,2':5',2"-terthien-5-yl)-2-hepten-6-ynamide ***(3h)***, was accomplished using the reaction sequence reported in Scheme 6.

In particular, 4-trimethylsilyl-3-butyn-1-ol ***(26)***, which was prepared in 75% yield starting from 3-butyn-1-ol ***(12)*** according to a procedure reported in the literature[23], was converted in 67% yield into bromide ***27*** *via* the corresponding *p*-toluensulfonyl ester. Cross-coupling reaction between the organozinc reagent derived from ***27*** and methyl *(E)*-3-bromoacrylate ***(28)***, in the presence of a catalytic amount of $Pd(PPh_3)_4$, gave chemically and stereoisomerically pure methyl *(E)*-7-trimethylsilyl-2-hepten-6-ynoate ***(29)*** in *ca.* 67% yield. This ester was converted in 96% yield into the corresponding *N*-(2-methylpropyl)carboxyamide, ***30***, by reaction with a CH_2Cl_2 solution of dimethylaluminum-*N*-(2-methylpropyl)amide. Reaction of ***30*** with a THF solution of TBAF then provided *(E)*-*N*-(2-methylpropyl)-2-hepten-6-ynamide ***(13)*** in quantitative yield. Finally, cross-coupling reaction between ***13*** and a benzene solution of compound ***3e*** which contained 1.3 equiv of triethylamine, in the presence of 3.9 mole % of $Pd(PPh_3)_4$ and 13.4 mole % of CuI, gave chemically and stereoisomerically pure ***3h*** in 47% yield.

Scheme 6



Studies aimed to investigate the phototoxic and photophysical properties of compounds **2** and **3** are actually under way.

EXPERIMENTAL

GLC analyses were performed on a Dani 6500 gas-chromatograph equipped with a Perkin Elmer LCI-100 integrator. Two types of capillary columns were used: a SRL-300 bonded FSOT column (30 m x 0.25 mm i.d.) and a SRL-150 bonded FSOT column (30 m x 0.25 mm i.d.). TLC analyses were performed using Merck plastic sheets coated with silica gel F_{254}. Purification by MPLC were performed on a Jobin-Yvon Chromatospac Prep 10 instrument, using a Knauer differential refractometer as detector, or on a Büchi 681 instrument, using a Bischoff 8100 differential refractometer as detector. ^1H NMR spectra were recorded on a Varian Gemini 200 MHz or on a Varian VXR 300 MHz spectrometer using TMS as an internal standard. Electron impact mass spectra were recorded on a VG 70-70E mass spectrometer interfaced with a Dani 3800 gas-chromatograph. The absorption data were obtained using a Jasco 7800 spectrophotometer and were registered in 95% EtOH at 25 °C using concentrations of *ca.* 6-7 10^{-4} mol/l.

All reactions of air and water sensitive materials were performed in flame dried glassware under an

atmosphere of nitrogen or argon. Air and water sensitive solutions were transfered with hypodermic syringes or double-ended needles.

The following compounds were prepared according to the literature: $PdCl_2(dppf)$[24], $PdCl_2(PPh_3)_2$[25], $Pd(PPh_3)_4$[26], 2,2':5',2"-terthiophene ***(1a)***[6], 2-methoxythiophene ***(15)***[18], 2-bromo-5-methoxythiophene ***(16a)***[18,19], ethyl ***(E)***-3-iodoacrylate ***(21)***[27], 5-iodo-2,2'-bithiophene ***(24)***[21], 4-trimethylsilyl-3-butyn-1-ol ***(26)***[23] and methyl ***(E)***-3-bromoacrylate ***(28)***[28].

3-Ethoxythiophene *(7)*

NMP (50 ml) was added to a solution of sodium ethoxide in ethanol which was prepared by dissolution of sodium (6.9 g, 300 mmol) in ethanol (90 ml). The mixture was heated to 150 °C and ethanol was distilled off at 150 Torr. Subsequently 3-bromothiophene ***(6)*** (32.6 g, 200 mmol) and copper(I) bromide (2.92 g, 20.3 mmol) were added and the mixture was maintained at 115 °C for *ca.* 1 h. A GLC analysis revealed that no reaction had occured. Copper(II) oxide (8.13 g, 102 mmol) and potassium iodide (0.59 g, 3 mmol) were then added and the resulting mixture was maintained for 8 h at 110-115 °C. It was then cooled to room temperature, diluted with Et_2O and filtered on Celite. The filtrate was washed with a saturated aqueous NH_4Cl solution, dried and fractionally distilled to give compound **7** (21.0 g, 82% yield): b.p. 88-89 °C/37 Torr. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.16 (dd, 1H, J = 5.2 and 3.1 Hz, H-5), 6.75 (dd, 1H, J = 5.2 and 1.5 Hz, H-4), 6.22 (dd, 1H, J = 3.1 and 1.5 Hz, H-2), 4.00 (q, 2H, J = 7.0 Hz, OCH_2), 1.39 (t, 3H, J = 7.0 Hz, CH_3). EIMS, *m/z* (%): 128 (M^+, 23), 100 (75), 99 (11), 72 (27), 71 (22), 55 (14), 45 (100), 39 (34), 38 (11).

2,5-Dibromo-3-(ethoxy)thiophene *(8)*

A solution of **7** (6.4 g, 50 mmol) in CH_2Cl_2 (65 ml) was stirred at room temperature while *N*-bromosuccinimide (18.0 g, 101 mmol) was added portionwise and the mixture was allowed to stir for 14.5 h. The mixture was diluted with Et_2O and filtered. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution and water, dried, concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using hexane as eluant, to give 98% chemically pure ***8*** (11.7 g, 82% yield). This compound was distilled to give 99.6% chemically pure ***8*** (10.6 g, 74% yield): b.p. 68-69 °C/0.1 Torr. ^1H NMR ($CDCl_3$, 200 MHz): δ 6.76 (s, 1H, H-4), 4.06 (q, 2H, J = 7.0 Hz, OCH_2), 1.38 (t, 3H, J = 7.0 Hz, CH_3). EIMS, *m/z* (%): 288 (M^++2, 25), 286 (M^+, 45), 284 (M^+-2, 25), 260 (52), 258 (100), 256 (51), 229 (6), 151 (21), 149 (21), 125 (17), 123 (16), 97 (6), 81 (8), 69 (26), 54 (9), 45 (10). Anal. Calcd. for $C_6H_6Br_2OS$: C, 25.20; H, 2.11. Found: C, 25.44; H, 1.99.

3'-Ethoxy-2,2':5',2"-terthiophene *(2a)*

A 0.8 *M* Et_2O solution of 2-thienylmagnesium bromide ***(9)*** (60 mmol) was added during 0.5 h to a stirred mixture of ***8*** (5.76 g, 20.1 mmol) and $PdCl_2$(dppf) (0.29 g, 0.40 mmol) in Et_2O (30 ml) cooled at -20 °C. The resulting mixture was maintained for 2 h at 0 °C and for 15.5 h at room temperature and then it was refluxed for 1.5 h. It was cooled to 0 °C, poured into a large excess of saturated aqueous NH_4Cl solution and extracted with Et_2O. The dried organic extract was filtered through Celite, concentrated *in vacuo* and purified by MPLC on silica gel, using hexane as eluant, to give 99% pure ***2a*** (5.38 g, 91% yield): m.p. 48.5-49 °C (hexane). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.21 (dd, 1H, J = 3.5 and 1.2 Hz, H-3"), 7.20 (dd, 1H, J = 5.1 and 1.2 Hz, H-5" or H-5), 7.19 (dd, 1H, J = 5.1 and 1.2 Hz, H-5 or H-5"), 7.15 (dd, 1H, J = 3.7 and 1.2 Hz, H-3), 7.00 (dd, 2H, J = 5.1 and 3.7 Hz, H-4 and H-4"), 6.91 (s, 1H, H-4'), 4.18 (q, 2H, J = 7.0 Hz, OCH_2), 1.47 (t, 3H, J = 7.0 Hz, CH_3). EIMS, *m/z* (%): 294 (M^++2, 15), 293 (M^++1, 20), 292 (M^+, 100), 291 (M^+-1, 38), 265 (13), 264 (27), 263 (79), 262 (27), 235 (8), 219 (6), 129 (7), 128 (10), 127 (67), 126 (30), 108 (7), 69 (8), 45 (6). UV (95% EtOH): λ_{max} (ε/$M^{-1}cm^{-1}$) 370 (21500), 263 nm (8600). Anal. Calcd. for $C_{14}H_{12}OS_3$: C, 57.50; H, 4.14. Found: C, 57.71; H, 4.27.

3-(Methylthio)thiophene *(10)*

Copper(II) oxide (8.26 g, 104 mmol) and potassium iodide (1.33 g, 8 mmol) were added to a mixture of 3-bromothiophene ***(6)*** (32.6 g, 200 mmol), sodium thiomethoxide (24.4 g, 353 mmol) and NMP (250 ml). The resulting mixture was maintained at 115-120 °C under stirring for 77 h. It was then cooled to room temperature, poured into a large excess of aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was filtered, dried and fractionally distilled by using a Fischer Spaltrohr system to give compound ***10*** (10.7 g, 41% yield): b.p. 95.6-95.7 °C/20 Torr. (lit.[29] b.p. 93-94 °C/30 Torr).

2,5-Dibromo-3-(methylthio)thiophene *(11)*

According to the literature[30], a solution of ***10*** (10.65 g, 81.9 mmol) in CH_2Cl_2 (110 ml) was stirred at room temperature while NBS (29.6 g, 166 mmol) was added portionwise. The mixture was stirred for 15.5 h, then filtered and concentrated *in vacuo*. The residue was diluted with Et_2O and filtered. The filtrate was washed with a saturated aqueous $NaHCO_3$ solution and water, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel using hexane as eluant to give compound ***11*** (19.7 g, 83% yield). The spectral properties of this compound were in good agreement with those previously reported[30].

3'-Methylthio-2,2':5',2''-terthiophene *(2b)*

This compound which was prepared in 86% yield and 99.5% chemical purity by reaction of 2-thienylmagnesium bromide ***(9)*** with ***11***, in the presence of a catalytic amount of $PdCl_2$(dppf), according to the same procedure followed to synthesize ***2a*** had: m.p. 31-34 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34 (dd, 1H, J = 3.6 and 1.0 Hz, H-3'' or H-3), 7.30 (dd, 1H, J = 5.2 and 1.0 Hz, H-5 or H-5''), 7.22 (dd, 1H, J = 5.2 and 1.0 Hz, H-5'' or H-5), 7.16 (dd, 1H, J = 3.6 and 1.0 Hz, H-3 or H-3''), 7.08 (s, 1H, H-4'), 7.04 (dd, 1H, J = 5.2 and 3.6 Hz, H-4 or H-4''), 7.01 (dd, 1H, J = 5.2 and 3.6 Hz, H-4'' or H-4), 2.47 (s, 1H, SCH_3). EIMS, *m/z* (%): 296 (M^++2, 20), 295 (M^++1, 18), 294 (M^+, 100), 282 (6), 281 (6), 280 (29), 279 (5), 247 (5), 246 (20), 238 (10), 127 (13), 69 (8), 45 (16). UV (95% EtOH): λ_{max} (ε/$M^{-1}cm^{-1}$) 365 (18600), 286 (8400), 256 nm (8100). Anal. Calcd. for $C_{13}H_{10}S_4$: C, 53.02; H, 3.42. Found: C, 53.17; H, 3.46.

5-Formyl-2,2':5',2''-terthiophene *(3i)*

N-methylformanilide (6.05 g, 44.8 mmol) and $POCl_3$ (6.23 g, 40.7 mmol) were mixed at room temperature and the resulting mixture was stirred for 15 min. A solution of 2,2':5',2''-terthiophene ***(1a)*** (10.1 g, 40.7 mmol) in CH_2Cl_2 (100 ml) was added and the mixture was stirred under reflux for 40 h. It was then cooled to room temperature and poured into a large excess of 10% aqueous HCl. The mixture was stirred for 1 h and extracted with CH_2Cl_2. The organic extract was washed with brine, dried and concentrated *in vacuo*. The residue was purified by MPLC on a silica gel column, using benzene as eluant, to give 98% chemically pure ***3i*** (8.77 g, 78% yield): m.p. 137-138 °C (lit.[12] m.p. 135-136 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 9.85 (s, 1H, CHO), 7.65 (d, 1H, J = 3.9 Hz, H-4), 7.26 (dd, 1H, J = 5.1 and 1.1 Hz, H-5''), 7.25 (d, 1H, J = 3.9 Hz, H-3' or H-4' or H-3), 7.21 (d, 2H, J = 3.9 Hz, H-3 or H-4' or H-3' and H-3''), 7.11 (d, 1H, J = 3.9 Hz, H-4' or H-3' or H-3), 7.03 (dd, 1H, J = 5.1 and 3.7 Hz, H-4''). EIMS, *m/z* (%): 278 (M^++2, 15), 277 (M^++1, 19), 276 (M^+, 100), 275 (18), 248 (5), 247 (8), 203 (17), 124 (5), 69 (6). UV (95% EtOH): λ_{max} (ε/$M^{-1}cm^{-1}$) 398 (27700), 268 (7200), 240 nm (8300).

5-Difluoromethyl-2,2':5',2''-terthiophene *(3a)*

Diethylaminosulfur trifluoride (2.64 ml, 20 mmol) was added to a solution of ***3i*** (2.76 g, 10 mmol) in

CH_2Cl_2 (65 ml) and the resulting mixture was stirred under reflux for 96 h. After this period a GLC analysis showed that a new compound, ***3a***, was present and that the molar ratio between ***3i*** and ***3a*** was *ca.* 38/62. The reaction mixture was cooled to room temperature, poured into water and extracted with CH_2Cl_2. The organic extract was washed with water dried and concentrated *in vacuo*. The residue was dissolved in benzene and filtered. The filtrate was concentrated *in vacuo* and purified by MPLC on silica gel, using a mixture of benzene and hexane (2/3 *v/v*) as eluant to give 95% chemically pure ***3a*** (1.12 g, 38% yield). This substance was crystallized from hexane to give 98.4% pure ***3a***: m.p. 139-140 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.24 (dd, 1H, J = 5.0 and 1.1 Hz, H-5"), 7.21-7.15 (m, 2H, H-3" and H-4), 7.05 (m, 3H, H-3, H-3' and H-4'), 7.03 (dd, 1H, J = 5.0 and 3.6 Hz, H-4"), 6.81 (t, 1H, J = 56.1 Hz, CHF_2). EIMS, *m/z* (%): 300 (M^++2, 17), 299 (M^++1, 20), 298 (M^+, 100), 297 (M^+-1, 7), 279 (7), 128 (6), 124 (9), 69 (8), 45 (7). UV (95% EtOH) λ_{max} ($\varepsilon/M^{-1}cm^{-1}$) 355 (23200), 254 nm (8400). Anal. Calcd. for $C_{13}H_8F_2S_3$: C, 52.32; H, 2.70. Found: C, 52.23; H, 2.72.

2-Iodo-5-methoxythiophene *(16b)*

A stirred solution of 2-methoxythiophene ***(15)***[18] (6.91 g, 60.6 mmol) in benzene (60 ml) was treated with alternate portions of yellow HgO (15.6 g, 72 mmol) and iodine (18.3 g, 72 mmol) during 45 min. The mixture was filtered and the filtrate was washed with a saturated aqueous $Na_2S_2O_3$ solution and water, dried, and concentred *in vacuo*. The residue was purified by MPLC on silica gel, using hexane as eluant, to give 92% chemically pure ***16b*** (11.7 g, 81% yield) as a viscous oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 6.90 (d, 1H, J = 4.0 Hz, H-4 or H-3), 5.92 (d, 1H, J = 4.0, H-3 or H-4), 3.85 (s, 3H, OCH_3). EIMS, *m/z* (%): 242 (M^++2, 8), 241 (M^++1, 11), 249 (M^+, 100), 225 (78), 197 (40), 127 (10), 98 (97), 82 (7), 70 (48), 69 (39), 57 (7), 45 (9), 38 (11). Anal. Calcd. for C_5H_5IOS: C, 25.02; H, 2.10. Found: C, 24.53; H, 1.97.

5-Methoxy-2,2':5',2"-terthiophene *(3b)*

A 0.58 *M* THF solution of the Grignard reagent prepared from 2-bromo-5-methoxythiophene ***(16a)***[18,19] (5.60 g, 29.0 mmol) was added during 15 min to a stirred mixture of 5-bromo-2,2'-bithiophene ***(17)*** (5.88 g, 24.0 mmol) and $PdCl_2$(dppf) (350mg, 0.48 mmol) in THF (70 ml) maintained at 0 °C. The resulting mixture was stirred for 24 h at room temperature, poured into a large excess of saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was filtered, dried and concentrated *in vacuo*. The residue was refluxed in hot benzene containing charcoal, filtered through Celite and concentrated *in vacuo*. The residue was crystallized from hexane to give 98.8% pure ***3b*** (5.34 g, 80% yield): m.p. 104.5-105.5 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.19 (dd, 1H, J = 5.0 and 1.1 Hz, H-5"), 7.14 (dd, 1H, J = 3.6 and 1.1 Hz, H-3"), 7.03 (d, 1H, J = 3.8 Hz, H-3' or H-4'), 7.00 (dd, 1H, J = 5.0 and 3.6 Hz, H-4"), 6.89 (d, 1H, J = 3.8 Hz, H-4' or H-3'), 6.80 (d, 1H, J = 3.9 Hz, H-3), 6.12 (d, 1H, J = 3.9 Hz, H-4), 3.90 (s, 3H, OCH_3). EIMS, *m/z* (%): 280 (M^++2, 13), 279 (M^++1, 14), 278 (M^+, 83), 265 (15), 264 (17), 263 (M^+-CH_3, 100), 235 (19), 230 (17), 191 (8), 190 (11), 139 (7), 69 (13), 45 (12). UV (95% EtOH): λ_{max} ($\varepsilon/M^{-1}cm^{-1}$) 366 (24700), 248 nm (7800). Anal. Calcd. for $C_{13}H_{10}OS_3$: C, 56.08; H, 3.62. Found: C, 56.54; H, 3.63.

It must be noted that, using a procedure very similar to that described above, the cross-coupling reaction between 2-iodo-5-methoxythiophene ***(16b)*** (5.52 g, 23.0 mmol) and a 0.5 *M* THF solution of Grignard reagent derivated from 5-bromo-2,2'-bithiophene ***(17)*** (6.77 g, 27.6 mmol), in the presence of $PdCl_2$(dppf) (0.74 g, 1.0 mmol), gave 97% chemically pure compound ***3b*** (1.52 g) in 24% yield.

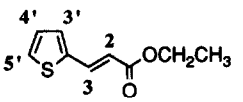
2-Thienyltrimethylstannane *(20)*

A 2.85 *M* hexane solution of butyllithium (70 ml) was added during 0.5 h to a solution of thiophene ***(19)*** (19.3 g, 230 mmol) in Et_2O (500 ml), maintained at 0 °C and the mixture was stirred for 5 h at room

temperature. A solution of trimethyltin chloride (36.6 g, 184 mmol) in Et_2O (150 ml) was then added during 0.5 h and the resulting mixture was stirred for 17 h. It was then poured into water (400 ml) containing acetic acid (6 ml) and extracted with Et_2O. The organic extract was washed with an aqueous $NaHCO_3$ solution and water, dried, concentrated and distilled to give compound ***20*** (40.2 g, 89% yield): b.p. 86-87 °C/11 Torr (lit.[31] b.p. 97-99 °C/33 Torr).

Ethyl *(E)*-3-(2-thienyl)propenoate *(22)*

A mixture of ***20*** (23 g, 93.2 mmol) and ethyl *(E)*-3-iodoacrylate ***(21)***[27] (18.0 g, 79.7 mmol) in THF (130 ml) was added to a suspension of $PdCl_2(PPh_3)_2$ (2.93 g, 3.98 mmol) in THF (200 ml) and the resulting mixture was maintained under reflux for 6 h. After this period a GLC analysis showed that the reaction had gone to completion. The reaction mixture was cooled to room temperature, poured into an aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was washed with water, dried, concentrated *in vacuo* and purified by MPLC on silica gel using benzene as eluant. The chromatographic fractions which contained the desired product were concentrated and distilled. The distillate was again purified by MPLC on silica gel, using benzene as eluant, to give chemically and stereoisomerically pure ***22*** (10.7 g, 74% yield): b.p. 80-81 °C/0.15 Torr (lit.[32] 118-120 °C/3 Torr). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.78 (dd, 1H, J = 15.7 and 0.6 Hz, H-3), 7.36 (dd, 1H, J = 5.0 and 1.0 Hz, H-5'), 7.24 (ddd, 1H, J = 3.6, 1.0 and 0.6 Hz, H-3'), 7.04 (dd, 1H, J = 5.0 and 3.6 Hz, H-4'), 6.24 (d, 1H, J = 15.7 Hz, H-2), 4.25 (q, 2H, J = 7.1 Hz, OCH_2), 1.23 (t, 3H, J = 7.1 Hz, CH_3). EIMS, *m/z* (%): 183 (M^++1, 5), 182 (M^+, 39), 154 (14), 139 (6), 138 (11), 137 (100); 121 (8), 111 (8), 110 (47), 109 (60), 108 (19), 97 (9), 83 (6), 82 (9), 69 (20), 65 (41), 63 (12), 62 (6), 59 (8), 58 (9), 51 (13), 50 (11), 45 (19), 39 (24), 38 (17).



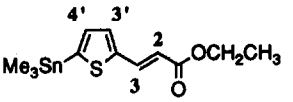
22

Ethyl *(E)*-3-(5-trimethylstannyl-2-thienyl)propenoate *(23)*

A solution of compound ***22*** (10.2 g, 56.1 mmol) in THF (40 ml) was added during 1 h to a solution of LDA (6.9 g, 64.4 mmol) in THF (200 ml) cooled to -78 °C and the resulting mixture was stirred for 0.5 h at this temperature. A solution of trimethyltin chloride (25.6 g, 128.7 mmol) in THF (80 ml) was then added and the mixture, after stirring for 0.5 h at -78 °C, was allowed to warm to room temperature. After stirring for 21 h the reaction mixture was warmed up to 50 °C for 0.5 h, cooled to 0 °C, poured into a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was washed with water until neutrality, dried and concentrated *in vacuo*. The residue was diluted with benzene and hexane in a 3/7 *v/v* ratio and filtered. The filtrate was concentrated *in vacuo* to give a residue (17.3 g). GLC and ^1H NMR analysis of this residue showed that it was constituted of ***22*** and the desired compound, ***23***, in a 1/9 molar ratio. Fractional distillation of a small portion of this mixture allowed to isolate 96% chemically pure ***23***: b.p. 116 °C/0.04 Torr. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.81 (d, 1H, J = 15.6 Hz, H-3), 7.33 (d, 1H, J = 3.2 Hz, H-3'), 7.13 (d, 1H, J = 3.2 Hz, H-4'), 6.23 (d, 1H, J = 15.6 Hz, H-2), 4.24 (q, 2H, J = 7.1 Hz, OCH_2), 1.32 (t, 3H, J = 7.1 Hz, CH_3), 0.39 (s, 9H, $Sn(CH_3)_3$). EIMS, *m/z* (%): 346 (M^++1, 12), 345 (M^+, 5), 335 (18), 333 (20), 332 (16), 331 (100), 330 (36), 329 (74), 328 (29), 327 (43), 303 (9), 301 (21), 299 (17), 297 (9), 165 (14), 163 (9), 137 (20), 136 (13), 134 (9), 108 (6), 76 (6). Anal. Calcd. for $C_{12}H_{18}O_2SSn$: C, 41.77; H, 5.26. Found: C, 42.00; H, 5.40.

In an attempt to purify the mixture of ***22*** and ***23*** by MPLC on silica gel, using a mixture of benzene and hexane in a 3/7 *v/v* ratio, it was observed that compound ***23*** underwent partial destannylation. Therefore

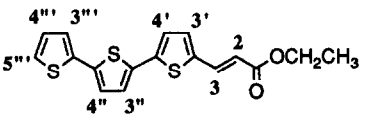
this mixture of ***22*** and ***23*** was used in the next step without any further purification.



23

Ethyl *(E)*-3-(2,2':5',*2"*-terthien-5-yl)propenoate *(3c)*

The mixture of compounds ***22*** and ***23*** obtained as above described (8.51 g, 23.3 mmol of ***23***) was added to a stirred mixture of 5-iodo-2,2'-bithiophene ***(24)***[21] (5.66 g, 19.4 mmol) and $PdCl_2(PPh_3)_2$ (0.68 g, 0.97 mmol) in THF (70 ml). The resulting mixture was maintained under reflux for 6 h. After this period a GLC analysis showed that the reaction had gone to completion. The reaction mixture was cooled to 20 °C, poured into a large excess of water and extracted with $CHCl_3$. The organic extract was washed with water, dried, filtered and concentrated *in vacuo*. The residue was diluted with benzene, filtered and concentrated. The residue was purified by MPLC on silica gel using benzene as eluant. The chromatographic fractions which contained the desired product were concentrated and the residue so obtained was crystallized from a mixture of benzene and hexane to give chemically and stereoisomerically pure ***3c*** (3.45 g, 51.4% yield): m.p. 132-132.5 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.70 (d, 1H, J = 15.7 Hz, H-3), 7.22 (dd, 1H, J = 5.0 and 1.1 Hz, H-5'"), 7.17 (dd, 1H, J = 3.6 and 1.1 Hz, H-3'"), 7.13-7.05 (m, 4H, H-4', H-3', H-4" and H-3"), 7.01 (dd, 1H, J = 5.0 and 3.6 Hz, H-4'"), 6.13 (d, 1H, J = 15.7 Hz, H-2), 4.25 (q, 2H, J = 7.1 Hz, OCH_2), 1.32 (t, 3H, J = 7.1 Hz, CH_3). EIMS, *m/z* (%): 348 (M^++2, 9), 347 (M^++1, 11), 346 (M^+, 50), 318 (13), 302 (11), 274 (20), 272 (9), 137 (16), 135 (9), 123 (9), 121 (10), 109 (9), 97 (9), 95 (16), 93 (10), 85 (7), 83 (12), 82 (9), 81 (47), 71 (13), 70 (11), 69 (100), 68 (19), 67 (17), 57 (21), 55 (28), 43 (26), 41 (46), 39 (9). UV (95% EtOH): λ_{max} (ε/$M^{-1}cm^{-1}$) 408 (35200), 318 (5300), 250 nm (13200). Anal. Calcd. for $C_{17}H_{14}O_2S_3$: C, 58.93; H, 4.07. Found: C, 59.14; H, 4.00.

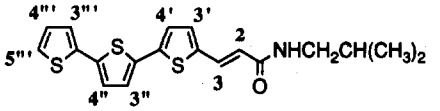


3c

(E)*-*N*-(2-Methylpropyl)-3-(2,2':5',*2"*-terthien-5-yl)propenamide *(3d)

A 2 *M* hexane solution of trimethylalane (7.8 mmol) was slowly added to a solution of 2-methylpropylamine (0.78 ml, 7.8 mmol) in CH_2Cl_2 (12 ml) and the mixture was stirred for 10 min at room temperature. A solution of ***3c*** (1.35 g, 3.9 mmol) in CH_2Cl_2 (70 ml) was added and the resulting mixture was maintained under reflux (for 26 h) until a TLC analysis of a sample of this mixture, after quenching with 10% aqueous HCl, showed that the reaction had gone to completion. The reaction mixture was carefully quenched at 0 °C with 10% aqueous HCl and extracted with CH_2Cl_2. The organic extract was washed with water until neutrality, dried and concentrated *in vacuo*. The residue was diluted with a mixture of benzene and Et_2O (150 ml) in a 9/1 *v/v* ratio and filtered. The filtrate was concentrated *in vacuo* and the residue was crystallized from a mixture of benzene and THF. The solid crystalline compound so obtained was purified by MPLC on silica gel, using a mixture of benzene and THF (9/1 *v/v*) as eluant, to give chemically and stereoisomerically pure ***3d*** (1.39 g, 96% yield): m.p. 188 °C (from $CHCl_3$/hexane). ^1H NMR ($CDCl_3$, 200 MHz, 51 °C): δ 7.68 (d, 1H, J = 15.1 Hz, H-3), 7.22 (dd, 1H, J = 5.1 and 1.1 Hz, H-5'"), 7.17 (dd, 1H, J = 3.6 and 1.1 Hz, H-3'"), 7.20-7.10 (m, 4H, H-4', H-3', H-4" and H-3"), 7.01 (dd, 1H, J = 5.1 and 3.6 Hz, H-4'"), 6.16 (d, 1H, J =

15.1 Hz, H-2), 5.58 (br s, 1H, NH), 3.21 (t, 2H, J = 6.4 Hz, NCH_2), 1.91-1.17 (m, 1H, N-C-CH), 0.95 (d, 6H, J = 6.7 Hz, $C(CH_3)_2$). EIMS, *m/z* (%): 375 (M^++2, 18), 374 (M^++1, 25), 373 (M^+, 100), 319 (6), 317 (26), 303 (14), 302 (23), 301 (70), 276 (6), 275 (11), 274 (41), 273 (26), 272 (22), 260 (19), 248 (6), 240 (18), 230 (9), 227 (9), 203 (9), 151 (11), 136 (7), 127 (8), 121 (8), 69 (9), 55 (8), 45 (9). UV (95% EtOH): λ_{max} (ε/$M^{-1}cm^{-1}$) 401 (36000), 315 (5600), 249 nm (16000). Anal. Calcd. for $C_{19}H_{19}NOS_3$: C, 61.09; H, 5.13. Found: C, 61.31; H, 5.32.



3d

5-Bromo-2,2':5',2''-terthiophene *(3e)*

A 0.49 *M* THF solution of the Grignard reagent derived from 5-bromo-2,2'-bithiophene ***(17)*** (68.6 mmol) was added during 3 h to a mixture of 2,5-dibromothiophene ***(25)*** (19.3 g, 82.3 mmol) and $PdCl_2$(dppf) (0.54 g, 0.74 mmol) in THF (85 ml) maintained at 0 °C. The resulting mixture was stirred for 20.5 h at 0 °C and for 2 h at room temperature, poured into a large excess of diluted aqueous HCl and extracted with $CHCl_3$. The organic extract was washed with water until neutrality, dried, filtered and concentrated *in vacuo*. The residue was dissolved in hot $CHCl_3$ containing charcoal, filtered through Celite and concentrated *in vacuo*. This operation was repeated twice. The final residue was purified by crystallization from a mixture of THF and hexane to give 98% chemically pure ***3e*** (8.42 g, 37.5% yield): m.p. 138.5 °C (lit.[33] 135-136 °C). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.22 (dd, 1H, J = 5.1 and 1.0 Hz, H-5''), 7.16 (dd, 1H, J = 3.7 and 1.2 Hz, H-3''), 7.05 (d, 1H, J = 3.9 Hz, H-4' or H-3'), 7.01 (dd, 1H, J = 5.1 and 3.7 Hz, H-4''), 6.99 (d, 1H, J = 3.9 Hz, H-3' or H-4'), 6.96 (d, 1H, J = 3.9 Hz, H-3), 6.89 (d, 1H, J = 3.9 Hz, H-4). EIMS, *m/z* (%): 330 (21), 329 (22), 328 (M^+, 100), 327 (21), 326 (M^+, 100), 248 (7), 247 (29), 246 (9), 214 (10), 205 (9), 204 (11), 203 (71), 189 (7), 164 (9), 163 (7), 158 (7), 145 (9), 127 (9), 102 (9), 82 (6), 69 (20), 63 (9), 45 (16).

5-Ethoxycarbonyl-2,2':5',2''-terthiophene *(3f)*

A mixture of compound ***3e*** (2.0 g, 6.10 mmol), ethanol (16 ml), triethylamine (2 ml, 14.4 mmol) and $PdCl_2(PPh_3)_2$ (0.2 g, 0.28 mmol) was charged into a open glass vial which was introduced into a stainless steel 200 ml autoclave. No precaution were taken to exclude air. After sealing, the autoclave was pressurized to 20 atm with carbon monoxide and heated to 100 °C for 22 h. Upon cooling and venting the excess of carbon monoxide, the contents of the autoclave were removed and volatiles evaporated. The crude product was dissolved in $CHCl_3$, washed with diluted aqueous HCl and water, and, after drying, filtered and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of benzene and hexane (1/1 *v/v*), as eluant. The chromatographic fractions which contained the desired product were concentrated and crystallized from a mixture of benzene and hexane to give 99% pure ***3f*** (1.71 g, 87% yield): m.p. 86.5-87 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.68 (d, 1H, J = 3.9 Hz, H-4), 7.23 (br d, 1H, J = 5.1 Hz, H-5''), 7.18 (br d, 1H, J = 3.7 Hz, H-3''), 7.16 (d, 1H, J = 3.9 Hz, H-3 or H-3' or H-4'), 7.10 (d, 1H, J = 3.9 Hz, H-4' or H-3' or H-3), 7.07 (d, 1H, J = 3.9 Hz, H-3 or H-4' or H-3'), 7.01 (dd, 1H, J = 5.1 and 3.7 Hz, H-4''), 4.35 (q, 2H, J = 7.1 Hz, OCH_2), 1.38 (t, 3H, J = 7.1 Hz, CH_3). EIMS, *m/z* (%): 322 (M^++2, 15), 321 (M^++1, 22), 320 (M^+, 100), 294 (10), 293 (9), 292 (58), 275 (13), 248 (8), 203 (19), 97 (9), 85 (12), 71 (10), 57 (14), 43 (18). UV (95% EtOH): λ_{max} (ε/$M^{-1}cm^{-1}$) 380 (29100), 262 (8200), 231 nm (9300). Anal. Calcd. for $C_{15}H_{12}O_2S_3$: C, 56.22; H, 3.77. Found: C, 56.47; H, 3.71.

N*-(2-methylpropyl)-2,2':5',5''-terthien-5-ylcarboxyamide *(3g)

According to the procedure followed to prepare compound ***3d***, a solution of ***3f*** (0.73 g, 2.3 mmol) in CH_2Cl_2 (20 ml) was reacted for 92 h with a solution of the dimethylaluminum amide prepared *in situ* by treatment of a solution of 2-methylpropylamine (0.46 ml, 4.6 mmol) in CH_2Cl_2 (15 ml) with a 2 *M* hexane solution of trimethylalane (2.3 ml, 4.6 mmol). The reaction mixture was worked up as in the case of ***3d*** to give a residue which was purified by MPLC on silica gel, using a mixture of benzene and THF (95/5 *v/v*), as eluant. The chromatographic fractions which contained the desired compound were concentrated and the residue so obtained (0.67 g, 99% pure, 85% yield) was crystallized from a mixture of benzene and hexane to give 99.8% pure ***3g*** (0.60 g, 76% yield): m.p. 166.5-168 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.38 (d, 1H, J = 3.9 Hz, H-4), 7.23 (dd, 1H, J = 5.1 and 1.1 Hz, H-5"), 7.18 (dd, 1H, J = 3.7 and 1.1 Hz, H-3"), 7.13 (d, 1H, J = 3.9 Hz, H-3 or H-3' or H-4'), 7.09 (d, 1H, J = 3.9 Hz, H-3' or H-4' or H-3), 7.08 (d, 1H, J = 3.9 Hz, H-4' or H-3' or H-3), 7.01 (dd, 1H, J = 5.1 and 3.7 Hz, H-4"), 5.98 (br s, 1H, NH), 3.27 (t, 2H, J = 6.7 Hz, NCH_2), 1.90 (n, 1H, J = 6.7 Hz, N-C-CH), 0.98 (d, 6H, J = 6.7 Hz, $C(CH_3)_2$). EIMS, *m/z* (%): 349 (M^++2, 17), 348 (M^++1, 23), 347 (M^+, 100), 293 (11), 292 (13), 291 (64), 277 (15), 276 (16), 275 (93), 248 (14), 247 (17), 204 (8), 203 (51), 137 (11), 101 (9), 43 (6), 41 (7). UV (95% EtOH): λ_{max} (ε/$M^{-1}cm^{-1}$) 372 (28300), 254 (8300), 233 nm (9400). Anal. Calcd. for $C_{17}H_{17}NOS_3$: C, 58.75; H, 4.93. Found: C, 58.58; H, 4.72.

4-Bromo-1-trimethylsilyl-1-butyne *(27)*

p-Toluensulfonyl chloride (59.7 g, 313 mmol) was portionwise added to a stirred solution of 4-trimethylsilyl-3-butyn-1-ol ***(26)***[23] (35.4 g, 249 mmol) in pyridine (260 ml) maintained at 0 °C. After stirring for 1 h at 0 °C and 15 h at room temperature the mixture was poured into cold 10% aqueous HCl and extracted with Et_2O. The organic extract was washed with 10% aqueous HCl, an aqueous $NaHCO_3$ solution and water, dried and concentrated *in vacuo*. LiBr (41.4 g, 476 mmol) was added during 15 min to a solution of the residue so obtained in acetone (300 ml) and the mixture was stirred for 13.5 h at room temperature and for 6.5 h under reflux. It was then poured into water (1400 ml) and extracted with pentane. The organic extract was washed with an aqueous $NaHCO_3$ solution and water, dried and distilled to give compound ***27*** (34.0 g, 67% yield): b.p. 72-73 °C/10.5 Torr (lit.[34] b.p. 70-75 °C/5 Torr). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.43 (t, 2H, J = 7.6 Hz, H-1), 2.78 (t, 2H, J = 7.6 Hz, H-2), 0.16 (s, 9H, $SiMe_3$).

Methyl *(E)*-7-trimethylsilyl-2-hepten-6-ynoate *(29)*

A 0.70 *M* THF solution of the Grignard reagent prepared from ***27*** (29 g, 141 mmol) was added to a solution of $ZnCl_2$ (21.1 g, 156 mmol) in THF (100 ml) maintained at 0 °C and the resulting mixture was stirred for 15 min. A solution of methyl *(E)*-3-bromoacrylate ***(28)***[28] (25.7 g, 156 mmol) and $Pd(PPh_3)_4$ (9.6 g, 8.27 mmol) in THF (200 ml) was subsequently added to this mixture maintained at -20 °C. After stirring for 20 min at -20 °C, 17 h at 0 °C, 24 h at room temperature and 3 h at 35 °C the reaction mixture was poured into a saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic extract was washed until neutrality, dried, filtered and concentrated *in vacuo*. The residue was diluted with hexane, filtered and concentrated *in vacuo*. The residue obtained from this last operation, which was repeated thrice, was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (9/1 *v/v*) as eluant, to give chemically and stereoisomerically pure ***29*** (19.7 g, 66.3% yield). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.02 (dt, 1H, J = 15.6 and 5.5 Hz, H-3), 5.89 (dt, 1H, J = 15.6 and 1.5 Hz, H-2), 3.74 (s, 3H, OCH_3), 2.47-2.34 (m, 4H, H-4 and H-5), 0.14 (s, 9H, $SiMe_3$). EIMS, *m/z* (%): 210 (M^+, 9), 197 (8), 196 (22), 195 (100), 180 (9), 179 (56), 167 (16), 165 (20), 163 (13), 137 (24), 136 (8), 135 (21), 109 (17), 107 (8), 106 (24), 105 (12), 97 (13), 96 (12), 91 (32), 90 (18), 89 (100), 83 (36), 82 (16), 81 (16), 78 (11), 75 (75), 73 (54), 68 (9), 67 (13), 65 (9), 59 (59), 55 (25), 53 (13), 45 (14), 43 (33), 39 (13). Anal. Calcd. for $C_{11}H_{18}O_2Si$: C, 62.80; H, 8.62. Found C, 62.97; H, 8.52.

(E)-N*-(2-Methylpropyl)-7-trimethylsilyl-2-hepten-6-ynamide *(30)

According to the procedure followed to prepare ***3d***, a solution of ***29*** (4.5 g, 21.4 mmol) in CH_2Cl_2 (50 ml) was reacted at 45 °C for 9.5 h and at room temperature for 12.5 h with a solution of the dimethylaluminum amide prepared *in situ* by treatment of a solution of 2-methylpropylamine (4.29 ml, 42.9 mmol) in CH_2Cl_2 (105 ml) with a 2 *M* hexane solution of trimethylalane (21.4 g, 42.9 mmol). The cooled reaction mixture was carefully treated at 0 °C with an excess of 10% aqueous HCl and extracted with CH_2Cl_2. The organic extract was washed with water until neutrality, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of hexane and Et_2O (1/1 *v/v*) as eluant, to give 99% chemically and stereoisomerically pure ***30*** (5.1 g, 95.6% yield): m.p. 83.5-85 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 6.81 (br d, 1H, J = 15.3 Hz, H-3), 5.85 (d, 1H, J = 15.3 Hz, H-2), 5.79 (br s, 1H, NH), 3.15 (t, 2H, J = 6.5 Hz, NCH_2), 2.55-2.25 (m, 4H, CH_2-CH_2), 1.95-1.70 (m, 1H, N-C-CH), 0.92 (d, 6H, J = 6.7 Hz, $C(CH_3)_2$), 0.15 (s, 9H, $SiMe_3$). EIMS, *m/z* (%): 252 (M^++1, 8), 251 (M^+, 34), 237 (14), 236 (66), 208 (8), 195 (7), 180 (25), 179 (100), 110 (8), 107 (9), 105 (7), 96 (9), 83 (20), 82 (17), 75 (29), 74 (12), 73 (46), 59 (19), 55 (10), 43 (11), 41 (14). Anal. Calcd. for $C_{14}H_{25}NOSi$: C, 66.87; H, 10.02; N, 5.57. Found: C, 66.82; H, 10.26; N, 5.42.

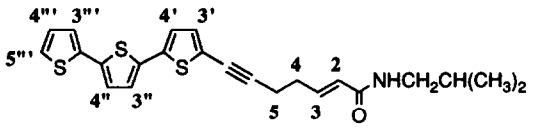
(E)-N*-(2-Methylpropyl)-2-hepten-6-ynamide *(13)

A solution of ***30*** (5.05 g, 20.1 mmol) and tetrabutylammonium fluoride trihydrate (12.7 g, 40.2 mmol) in THF was stirred for 5 h at room temperature. After this period a GLC analysis showed that the reaction had gone to completion. The reaction mixture was then poured into diluted aqueous HCl and extracted with Et_2O. The organic extract was washed with an aqueous $NaHCO_3$ solution and water, dried and concentrated *in vacuo*. The residue was purified by MPLC on silica gel, using a mixture of benzene and Et_2O (8/2 *v/v*) as eluant, to give chemically and stereoisomerically pure ***13*** (3.55 g, quantitative yield): m.p. 60.5-61.5 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 6.80 (dt, 1H, J = 15.3 and 6.6 Hz, H-3), 5.91 (br s, 1H, NH), 5.90 (dt, 1H, J = 15.3 and 1.4 Hz, H-2), 3.15 (t, 1H, J = 6.5 Hz, NCH_2), 2.50-2.25 (m, 4H, CH_2-CH_2), 1.99 (t, 1H, J = 2.4 Hz, H-7), 1.90-1.70 (m, 1H, N-C-CH), 0.93 (d, 6H, J = 6.7 Hz, $C(CH_3)_2$). EIMS, *m/z* (%): 180 (M^++1, 9), 179 (M^+, 14), 164 (12), 136 (14), 124 (11), 108 (10), 107 (100), 79 (11), 77 (26), 68 (10), 55 (15), 42 (12), 39 (16). Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 74.19; H, 9.81; N, 7.97.

(E)-N*-(2-Methylpropyl)-7-(2,2':5',2''-terthien-5-yl)-2-hepten-6-ynamide *(3h)

A solution of ***13*** (1.2 g, 70 mmol) in benzene (15 ml) was added to a stirred mixture of $Pd(PPh_3)_4$ (0.30 g, 0.26 mmol), CuI (0.17 g, 0.90 mmol), triethylamine (1.2 ml, 8.87 mmol) and 5-bromo-2,2':5',2''-terthiophene ***(3e)*** (1.86 g, 5.68 mmol) in benzene (75 ml). The reaction mixture was stirred for 46.5 h at room temperature and then poured into a large excess of an aqueous NH_4Cl solution and extracted repeatedly with a mixture of benzene and THF (1/1 *v/v*). The organic extract was washed with a saturated aqueous NH_4Cl solution and water, dried and concentrated *in vacuo*. The residue was dissolved in hot THF containing charcoal and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by MPLC on silica gel, using a mixture of CH_2Cl_2 and THF (97/3 *v/v*) as eluant, to give 99% chemically and stereoisomerically pure ***3h*** (1.12 g, 46.5% yield): m.p. 194-196 °C. ^1H NMR ($CDCl_3$, 200 MHz, 55 °C): δ 7.20 (dd, 1H, J = 5.2 and 1.3 Hz, H-5'''), 7.16 (dd, 1H, J = 3.5 and 1.3 Hz, H-3'''), 7.09-6.93 (m, 5H, H-4''', H-4'', H-3'', H-4' and H-3'), 6.85 (dt, 1H, J = 15.2 and 6.5 Hz, H-3), 5.88 (d, 1H, J = 15.2 Hz, H-2), 5.45 (br s, 1H, NH), 3.16 (t, 2H, J = 6.4 Hz, NCH_2), 2.64-2.54 (m, 2H, H-4), 2.49 (t, 2H, J = 6.5 Hz, H-5), 1.90-1.70 (m, 1H, N-C-CH), 0.93 (d, 6H, J = 6.8 Hz, $C(CH_3)_2$). EIMS, *m/z* (%): 425 (M^+, 24), 325 (14), 285 (45), 277 (27), 263 (19), 262 (96), 261

(14), 183 (63), 149 (100), 116 (25), 108 (29), 107 (42), 80 (19), 79 (20), 77 (37), 69 (41), 57 (46), 55 (30), 52 (20), 43 (48), 41 (42). UV (95% EtOH): λ_{max} (ε/$M^{-1}cm^{-1}$) 374 (30900), 255 (shoulder, 9500), 233 nm (shoulder, 16000). Anal. Calcd. for $C_{23}H_{23}NOS_3$: C, 64.90; H, 5.45. Found: C, 65.10; H, 5.51.



3h

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