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UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

To Livain

and

To my Family

"Il faut chercher le vrai dans les profondeurs,
le beau sur les sommets."

Paul Marion, *Pensées,*
(1973), p.1

"Ce qu'on appelle créer, n'est parfois qu'une
aptitude à révéler ce qui existe secrètement.
Libérer, c'est déjà créer."

P. Marion, *Pensées,*
(1973), p.12

"La liberté est une source inepuisable d'inventions,
et chaque fois qu'on en favorise l'essor
on enrichit le monde."

Simone de Beauvoir,
La Force de l'Age,
(1960) p.153

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Finally, I wish to thank the University of Ottawa for financial support.

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ABBREVIATIONS AND SYMBOLS

δ	chemical shift (in ppm)
ϵ	extinction coefficient
λ_{max}	wavelength at maximum intensity of absorption
$BF_3 \cdot Et_2O$	boron trifluoride etherate
byp	2,2′-bipyridine
CBr_4	carbon tetrabromide
CCl_4	carbon tetrachloride
CuI	cuprous^I iodide
CSI	chlorosulfonyl isocyanate
d	doublet in ^1H NMR
dd	doublet of doublets in ^1H NMR
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDTA	ethylenediaminetetraacetic acid
E. coli	*erichia coli*
ESR	electron spin resonnance
GC	gas chromatography
G-6P	glucose-6P-dehydrogenase
GSSG	glutathione disulfide
2-halo-BT	2-halo-benzothiazole
LDA	lithium di*iso*propylamine
LPO	lipid peroxidation

m	multiplet in ^{1}H NMR
MCPBA	*meta*-chloroperoxybenzoic acid
min	minute
M	molar
mmole	millimole
m.p.	melting point
β-methoxy-9BBN	β-methoxy-9-borabicyclo-[3.3.1]nonane
MS	mass spectrum
MCMV	murine cytomegalovirus
NBS	*n*-bromosuccinimide
NCS	*n*-chlorosuccinimide
nM	nano molar
NaOH	sodium hydroxide
NiCRA-byp	[NaH-*t*-AmONa-Ni(OAc)$_2$-bipyridine in THF][4:2:1:2]
(dppp)NiCl$_2$	[1,3-*bis*(triphenylphosphino)propane]nickel^{II} dichloride
(dppe)NiCl$_2$	*bis*(diphenylphosphino)ethane]NiCl$_2$
(dppb)NiCl$_2$	*bis*(diphenylphosphino)butane]NiCl$_2$
(dppm)NiCl$_2$	*bis*(diphenylphosphino)methane]NiCl$_2$
NMR	nuclear magnetic resonance
$^1O_2$	singlet oxygen
Pd	palladium
PPh$_3$	triphenylphosphine
(PPh$_3$)$_2$PdCl$_2$	*bis*(diphenylphosphinepalladium) dichloride
PTAM	phenylazotriphenylmethane
SET	single electron-transfer

SV	Sindbis virus
sh	shoulder
SOD	bovine superoxide dismutase
T. erecta	*Tagetes erecta*
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilylchloride
t	triplet in ^{1}H NMR
R_f	substance/solvent front (TLC)
α-T	2,2′:5′,2″-terthienyl or α-terthienyl
α-dithienyl	2,2′-dithienyl
QSAR	quantitative structure-activity relationship
UV	ultraviolet

ABSTRACT

Analogues and derivatives of naturally occurring α-terthienyl <u>3</u> have been synthesized by using the nickel-catalyzed Grignard-Wurtz cross-coupling reaction. This method has proven useful for the introduction of non-polar substituents on 2-bromothiophene which upon subsequent cross-coupling with 5-iodo-α-dithienyl <u>185</u> led to a succesful variety of 5-substituted α-terthienyls. Derivatives of α-terthienyl bearing polar functional groups were synthesized either by:

1) introduction of electron-withdrawing and electron-donating at C-5 and C-5″ or
2) chain extension from an appropriate substituted derivatives

In order to establish structure/activity relationships, various substituent at C-5 on the aromatic ring were made.

Among the derivatives of α-terthienyl, compound <u>165</u> was synthesized by the palladium-catalyzed coupling reaction with CuI. By adapting this methodology on α-dithienyls, the reaction was found to be useful for coupling aryl halides such as 5-iodo-α-dithienyl <u>185</u> with a variety of substituted 1′-alkynes derivatives. A series of functional α-dithienyl acetylene derivatives were made.

The biological activity of α-terthienyl and α-dithienyl derivatives, as determined by feeding trials with the mosquito larvae (*aedes atropalpus*) and brine shrimp, is discussed in light of the relative toxicities of these compounds.

INTRODUCTION

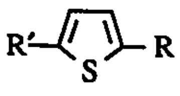
1. Origin and Use of α-Terthienyl and Dithienyl Derivatives

1.1 Occurrence, Structure and Nomenclature.

Plants containing polyacetylenes and thiophenes have played a prominent role world-wide as a naturally occurring pest control agent$^{1-3}$.

In 1947, Zeichmeister and Sease^{4} isolated the first thiophenic product from the petals of the yellow African marigold^{5} *Tagetes erecta*, which was subsequently identified as 2,2′:5′,2″-terthienyl 3 (see below). This biologically active substance was also found to be present in other species including *Flaveria*, *Eclipta*, *Dyssodia*, *Nicolletia* and *Adenophyllum* at concentrations up to 20-440 μg/g weight^{6,7}. Since then, the number of thiophene derivatives isolated from this family of Asteraceae^{8,9} has risen to more than a thousand^{10} and some have also been found in fungi^{11,12}. Interest in this group of compounds intensified when it was discovered that some of them possessed phototoxic and larvicidal activity^{13} against many insects including mosquito larvae, blackfly larvae, some herbivorous insects$^{14-16}$, and certain viruses^{17}.

The term thienyl refers to the monomeric ring system 1, which is included in thiophene 1 (R=R′=H), α-dithienyl 2 (R=H,R′=thienyl in 1), and α-terthienyl 3 (R=R′=thienyl in 1) derivatives.



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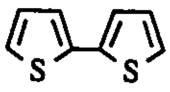

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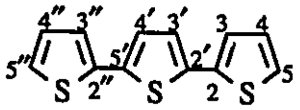

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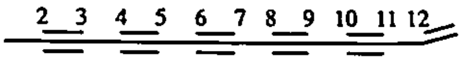
The substituents may occupy the available 2, 3, 4 or 5 positions of each thiophene moiety. Most frequently the substituents are located at the 2- and/or 5-positions which are referred to as the α-positions. Thus, compounds 2 and 3 are named 2,2′-dithienyl and 2,2′:5′,2″-terthienyl respectively. For the sake of simplicity, the term α-terthienyl or α-T will be used to designate 2,2′:5′,2″-terthienyl 3.

1.2 Biosynthesis of α-Terthienyl 3 and α-Dithienyl

Most of the compounds isolated from Asteraceae plant extracts are composed of a mixture of polyacetylenic compounds such as 4, thienyl and substituted



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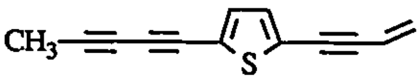
dithienyls with acetylenic functions such as 5 and 6 and substituted α-T 3. The



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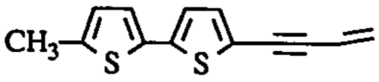
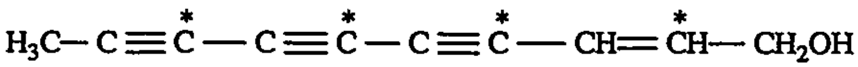


6

occurrence of such compounds points to the possibility of a common precursor[18]. Three research groups led by Sörensen, Bohlmann and Jones respectively have carried out experiments aimed at elucidating the biosynthetic pathway. ^{14}C labelled syntheses of potential precursors as well as biosynthetic feeding experiments, followed by isolation and analysis of the molecules produced, led to the conclusion that the naturally occurring tridecapent-2,4,6,8,10-yn-12-ene 4 could be the precursor for all substituted dithienyls and α-T 3 compounds isolated[11,19]. It is generally accepted that subsequent incorporation of H_2S or its biochemical equivalent ($[H_2S]_{eq.}$) to the conjugated triple bonds of 4 generates the thiophene units in those naturally occurring molecules[20]. A more detailed discussion of the biogenetic pathway for the widespread polyyne hydrocarbon 4 and the incorporation of the biological equivalent of sulfur follows.

1.2.1 Acetylene Biosynthesis

Results obtained by various feeding experiments with ^{14}C acetate with many plants of the Asteraceae family, coupled with the fact that nearly all natural acetylenes have unbranched carbon chains, led to the conclusion that these acetylenes may be derived from fatty acids[21]. In one specific feeding experiment, 2-^{14}C malonate was fed to *Tricholoma grammopodium*[22]. The polyacetylene 7 isolated was shown to have head to tail linkage of labelled carbons except for the two first carbon atoms. This observation supports the hypothesis that acetylenes are formed from fatty acids. In turn, the biogenesis of fatty acids is well established as originating from C_2 units derived from acetyl-CoA[11,22-24] (Scheme 1). Thus acetyl-CoA 8 is first activated by a carboxylation reaction to give malonyl-CoA 9[23-25]. This malonyl-CoA 9 and another acetyl-CoA 8 are transferred to the thiol function of a coenzyme called acyl carrier protein or ACP-SH. The acetyl-S-ACP 11 which results is called the primer. The malonyl-S-ACP 10 then condenses with the acetyl-S-ACP 11 to form acetoacetyl-S-ACP 12 accompanied by a loss of CO_2 and ACP-SH. The next three steps in fatty acid synthesis transform the acetoacetyl group into a butyryl group:

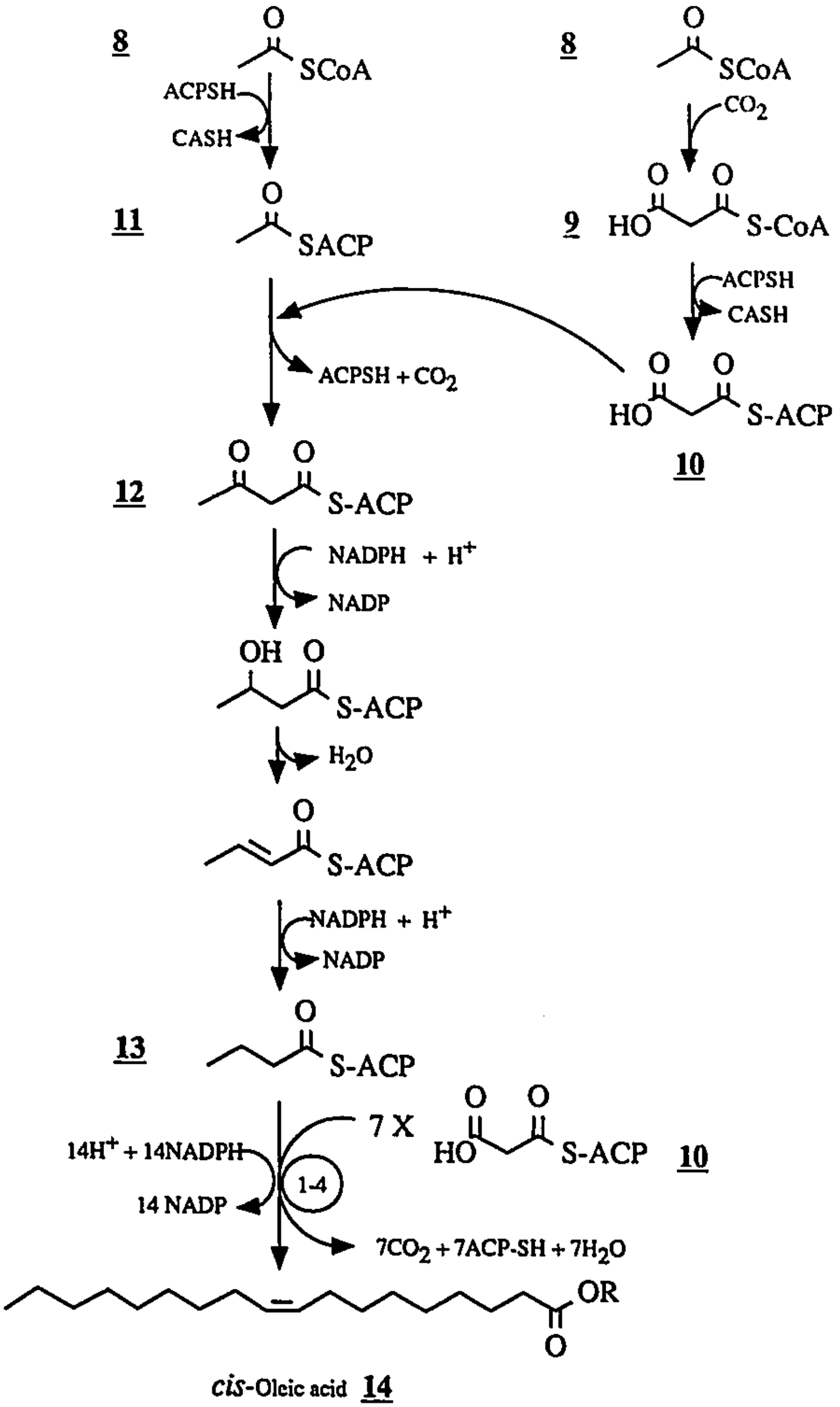


$$H_3C-C\equiv\overset{*}{C}-C\equiv\overset{*}{C}-C\equiv\overset{*}{C}-CH=\overset{*}{C}H-CH_2OH$$

7

1) reduction of the keto group to the corresponding alcohol;
2) dehydratation of the alcohol; and
3) reduction of the α,β-unsaturation.

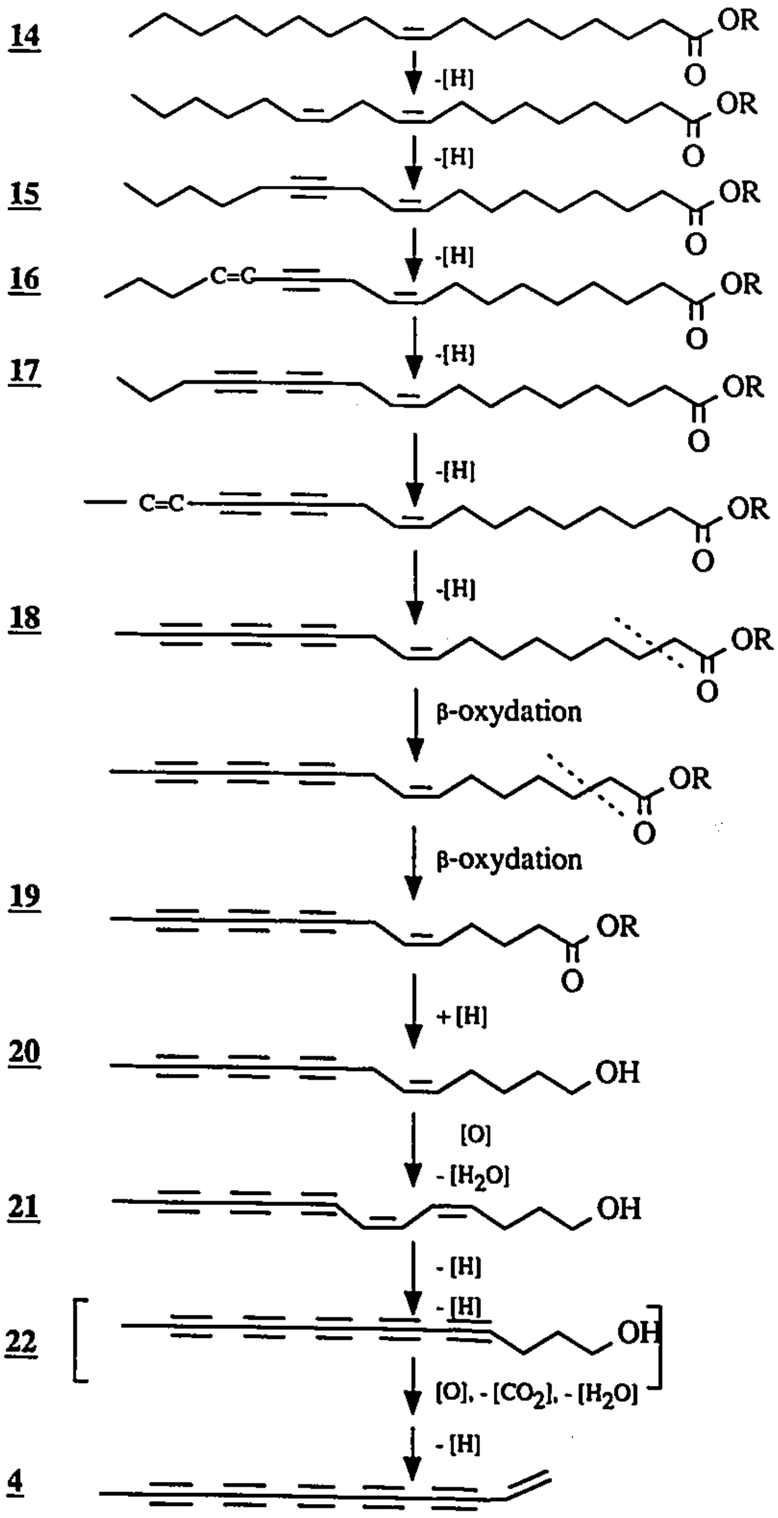
The butyryl-S-ACP 13 formed undergoes nucleophic attack by another malonyl-ACP 10 and, at this point, the chain is lengthened by two more carbon. Seven iterative processes of condensation and steps 1, 2 and 3 lenghten the chain by succesive two carbon units until oleic acid 14 is produced. In order to establish the relationship



Scheme 1. Biogenesis of Oleic Acid 14

between oleic acid and other possible precursors of the natural acetylenes, feeding experiments with ^{14}C and ^{3}H-labelled esters of oleic acid and homologous acid esters with varying numbers of methylene groups were performed. It was found that only the labelled oleic acid is incorporated into the natural acetylenes and not the acids constituted of shorter carbon chain. At this point, different routes are involved in the bio-transformation of oleic acid into naturally occurring acetylenes[11]. In fact, many different pathways are needed to explain the large variety of existing acetylenes. For the sake of simplicity, only the study of the biogenesis of acetylenes leading to the generation of dithienyl and α-terthienyl will be addressed here.

Oleic acid 14 is transformed into the isolable crepenynic acid 15 by two consecutives dehydrogenations (Scheme 2). Further dehydrogenations produce dehydrocrepenynic acid 16, the diyne 17 and the triyne 18. Feeding experiments[11] have shown that the oleic acid 14, crepenynic acid 15, dehydrocrepenynic acid 16 and the diyne acid 17 are all precursors of triyne 18 thus suggesting that this sequence of dehydrogenations is the most likely natural pathway. Double β-oxidation (possibly by known mechanisms of fatty acid chain degradation) of the C_{18}-triyne acid 18 would lead to the C_{14}-acid 19 which then has to be reduced to give the alcohol 20. The latter 20 has been isolated[26] in very minute amounts from *Centaurea moschata L.* The biogenetic transformation sequence of 20 leading to the formation of tridecapentaynene 4 is represented by a pathway analogous to the one established by tracer studies for the formation of tridecatetrayne-diene[27]. Support for the implication of the alcohol 21 came from its isolation from *Chrysanthemum atrum Jaq.*[28]. Further dehydrogenations give the proposed intermediate 22 which, in turn, is converted into the naturally occurring pentaynene[29] 4.

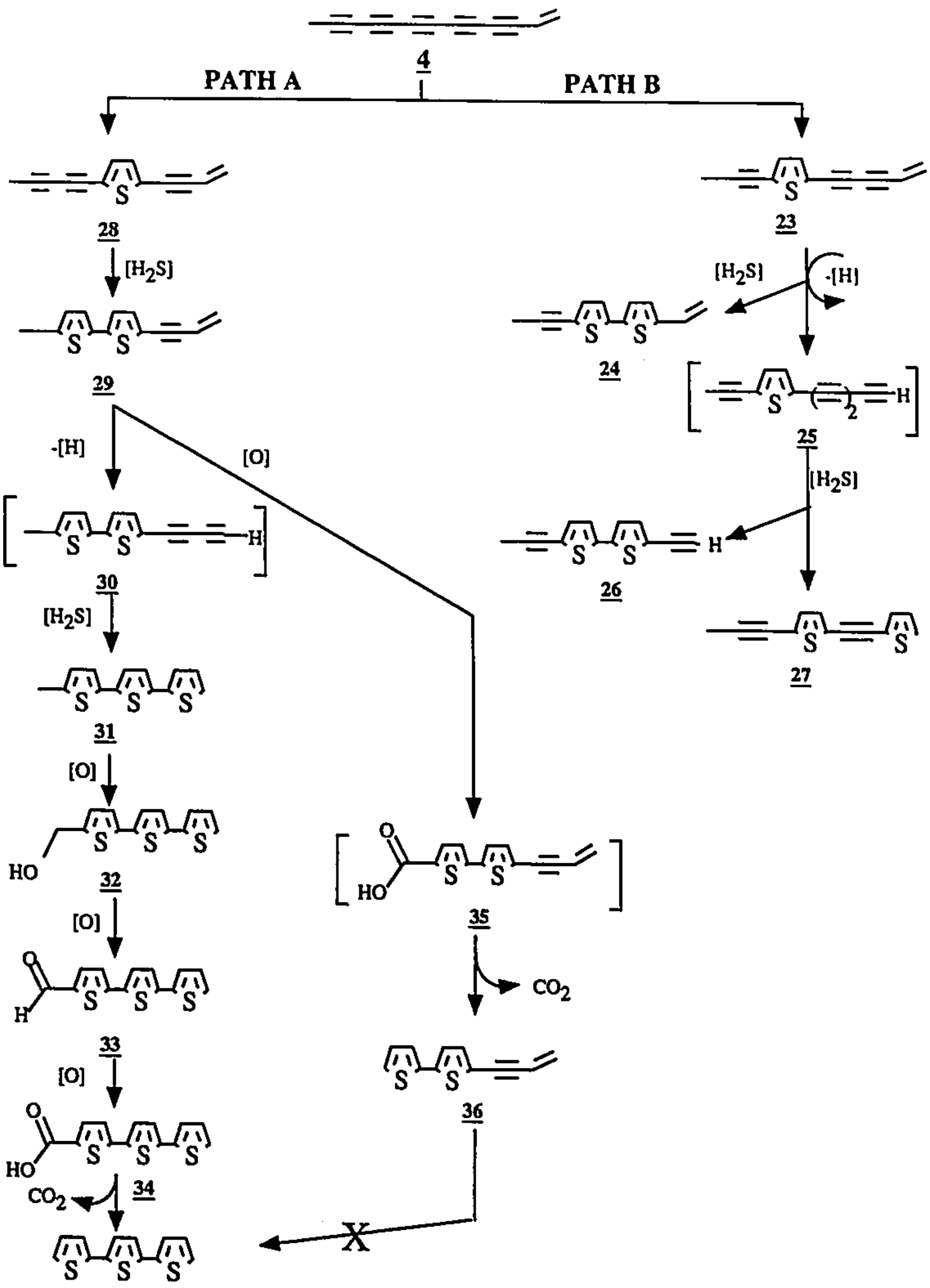


Scheme 2. Biosynthesis of Tridecapentaynene **4**.

1.2.2 Sulfur Incorporation in Tridecapentaynenes 4

Incorporation of sulfur (equivalent of H_2S) into compound 4 (Scheme 3) theoretically gives rise to four possible thiophenes. However, from isolation experiments, only diynes 23[30] and 28[31] have been identified. On formation of the first thiophene ring in 23 and 28, two distinct paths, A and B respectively, are operative. In path B, subsequent incorporation of $[H_2S]_{eq.}$, the biochemical equivalent of H_2S, to 23 gives the α-dithienyl derivatives 24[32]. Alternatively, compound 23 may be dehydrogenated to generate the proposed intermediate 25 which gives, upon incorporation of $[H_2S]_{eq.}$, the 2,5-substituted α-dithienyl 26 and the conjugated thiophene 27. Evidence for this transformation came from the isolation of 26 from *Tagetes erecta L.* flowers[32] and 27 from *Berkheya* species[11].

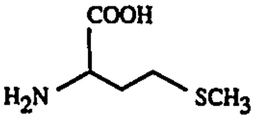
In path A, addition of $[H_2S]_{eq.}$ to 28 would give the well known 2-(3″-buten-1″-ynyl)-5-methyl-2,2′-dithienyl 29 isolated from *Buphthalman salicifolium L.*[33]. The methyl substituent of this α-dithienyl derivatives 29 could be oxidized readily to the proposed intermediate 2-(3″-buten-1″-ynyl)-α-dithienyl-5-carboxylic acid 35. Subsequent loss of CO_2 from 35 gives 36, the first dithienyl derivative isolated[34] from the roots of *Tagetes erecta L.* It was first proposed[35] that compound 36 was a precursor of α-terthienyl 3 but feeding experiments[36] with ^{14}C labelled 36 suggests that this hypothesis is incorrect. Later, several substituted α-terthienyls were isolated and the following generical sequence seems to be acceptable. The α-dithienyl 29 undergoes dehydrogenation to give a proposed dithienyl-diyne intermediate 30 which forms, upon incorporation of $[H_2S]_{eq.}$, 5-methyl-α-terthienyl 31[11]. Lateral oxidation of the methyl group generates successively 5-hydroxymethyl-α-terthienyl 32, 5-formyl-α-terthienyl 33 and α-terthienyl-5-carboxylic acid 34. The latter could undergo enzymatic decarboxylation to produce α-terthienyl 3. The α-terthienyl derivatives 31, 32 and 33 have been isolated from the roots of *Eclipta erecta*[20] while α-terthienyl 3 is found from the roots of *Tagetes erecta L*[4].



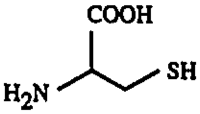
Scheme 3. Sulfur Incorporation to Tridecapentaynene 4

1.2.3 Source of Sulfur and Mechanism of Addition

The manner in which $[H_2S]_{eq.}$ converts two acetylene bonds into thiophene rings in the Asteraceae is still obscure. In the laboratory, the incorporation of H_2S to a diacetylene is performed under basic conditions by refluxing the diyne with $Na_2S{\bullet}9H_2O$ in a polar solvent such as dioxane or tetrahydrofuran (THF)[37]. The search for the biological equivalent of H_2S led to labeling studies with ^{35}S containing substances such as amino acids (see below) and inorganic salts. These experiments showed a low level of incorporation into α-T 3 when *T. erecta* was treated with $[^{35}S]$-sulfate or DL$[^{35}S]$-methionine. Surprisingly, no incorporation into α-T was observed with sodium hydrogen $[^{35}S]$-sulfide[38]. Due to the poor levels of incorporation observed, no major source of sulfur has yet been established. The lack of incorporation of NaH$[^{35}S]$ suggests that the latter is not involved *in vivo*.

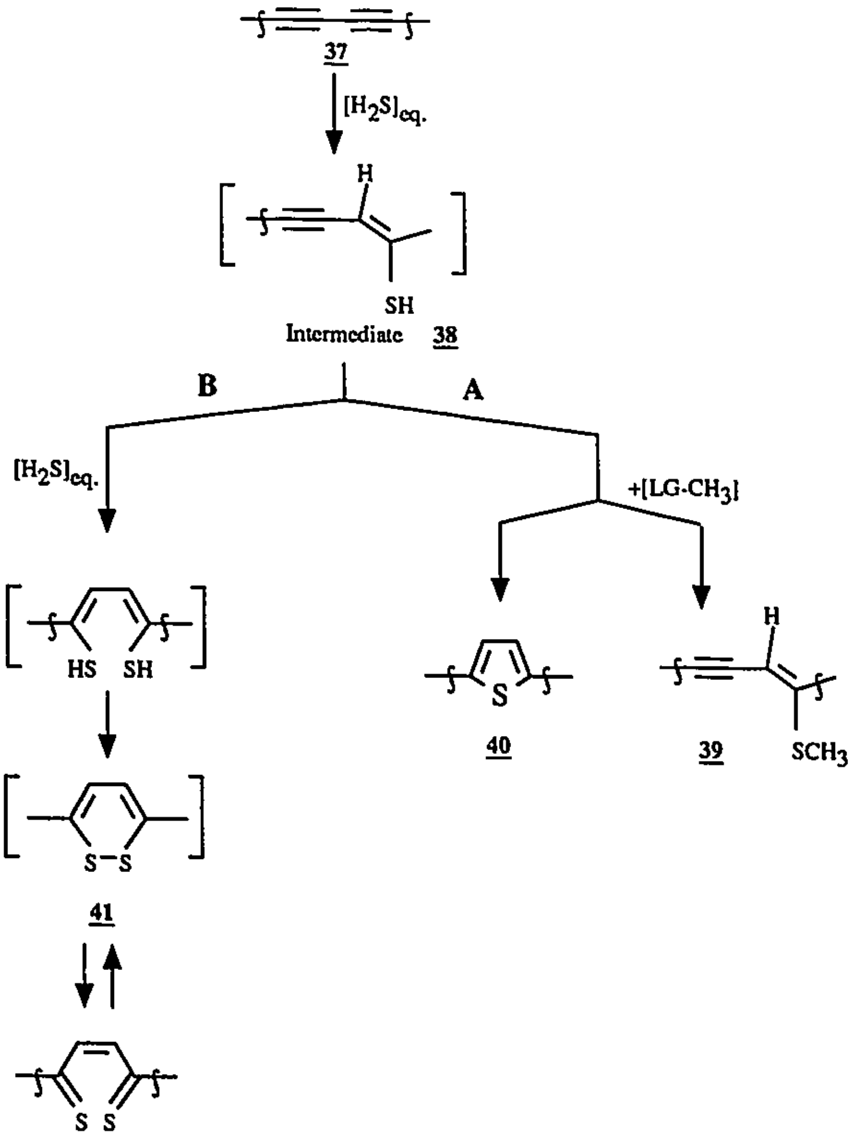


Methionine



Cysteine

A two step reaction has been suggested for incorporation of $[H_2S]_{eq.}$ and support for this stepwise mechanism comes from the fact that many methylthioenolethers (e.g. compound 39), co-exist along with their acetylenic precursors and final cyclized thienyl derivatives[11,39,40]. For instance, tridecapentaynene 4 and the enol derivatives 39 were isolated from *T. erecta*[20]. The following Scheme is proposed[11] (Scheme 4) in which the first step is addition of $[H_2S]_{eq.}$ to the acetylenic precursor 37, generating a thioenol intermediate 38 which may cyclize to the corresponding thiophene 40 or undergo methylation to give the observed methylthioenol ether 39 (Path A). On the other hand, subsequent addition of $[H_2S]_{eq.}$ to the intermediate 38 would give rise to the disulfide



Scheme 4. Incorporation of Sulfur in Thiophene Biosynthesis

derivative 41 (Path B). Evidence for route B comes from the isolation of some of these red colored disulfides from *Eriophyllum caespitosum*[11,39].

1.3 Biological Activity

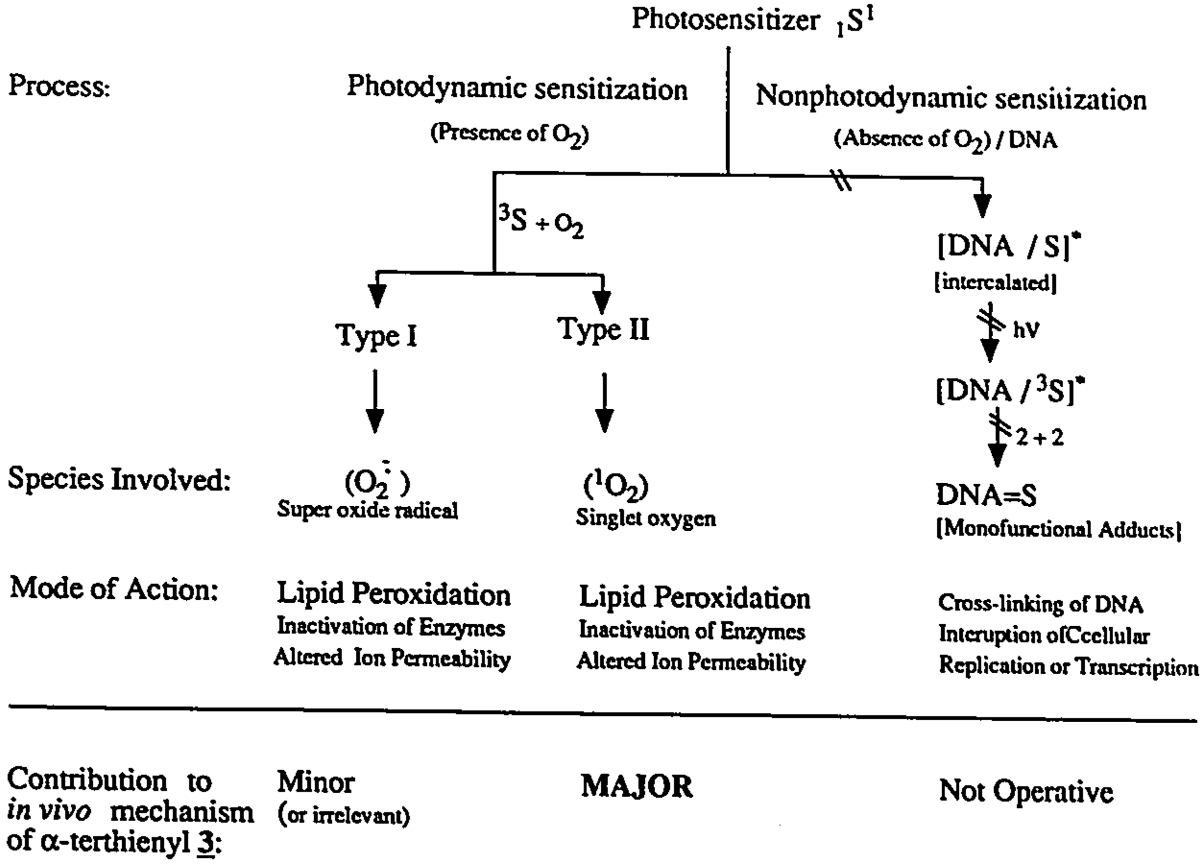
In 1972, it was reported[41] that α-terthienyl 3 and α-dithienyl derivatives, possessed nematicidal activity. In 1975, Chan *et al.*[42] reported that the toxicity of such derivatives was more pronounced on exposure to natural light[41,43] and the term phototoxic activity was used to describe this phenomenon. More recent studies show that α-T 3, on exposure to UV light (350 nm), displays significant antiviral activity against murine cytomegalovirus (MCMV) and Sindbis virus (SV), but possesses no antiviral activity in the dark[3b].

Bakker and Gommers[44] reported on the first mechanistic study with α-terthienyl 3 conducted on glucose-6P-dehydrogenase (G6-P), cholinesterase and malonate dehydrogenase. These enzymes were previously isolated from the plant nematode *Ditylenchus dispsaci*. The enzyme activities were monitored and a significant decrease in activity was observed on treatment with α-terthienyl under UV irradiation. The use of molecular oxygen scavengers such as dithionite and/or mercaptoethanol, created an oxygen free medium which was found to protect G6-P from damage by α-terthienyl 3. This study clearly demonstrated that the phototoxicity of α-T 3 *in vitro* proceeded by a photo oxidative mechanism. These unusual phototoxic properties led several research groups[44,45,46] to undertake studies to evaluate the scope of the toxicity observed and to elucidate the precise mode of action of these α-terthienyl derivatives.

1.3.1 Mode of Action

Photosensitization of a molecule such as α-terthienyl 3 could conceivably take place by two differents processes (nonphotodynamic and photodynamic) as illustrated below (Scheme 5).

(i) Non photodynamic Nonphotodynamic sensitization refers to a process in which the sensitizer does not require O_2 for toxicity. Presensitized molecules may

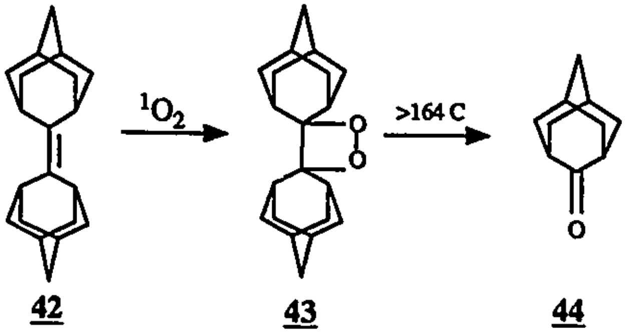


Scheme 5. Relevant Contribution of the Mode and Site of Action of α-T 3.

intercalate into DNA and, upon irradiation, form (2 + 2) photoadducts with DNA bases.[47] This results in cross-linking of the strands of DNA and would disrupt vital cellular functions such as replication and transcription of DNA. Experiments have demonstrated that this is not the case for α-terthienyl[47] 3. As mentioned earlier, Bakker *et al.*[44] reported an oxygen dependent photoactivity for α-T 3 in enzymatic systems *in vitro*. Further studies reported by MacRae *et al.*[45] found no evidence to show that *E. coli* DNA was damaged by α-T 3 upon irradiation with UV light. Moreover, Arnason *et al.*[46], studied the mechanism of α-T 3 *in vivo* with *E. coli* and reported that under anaerobic conditions, α-T 3 displayed no photosensitisizing activity.

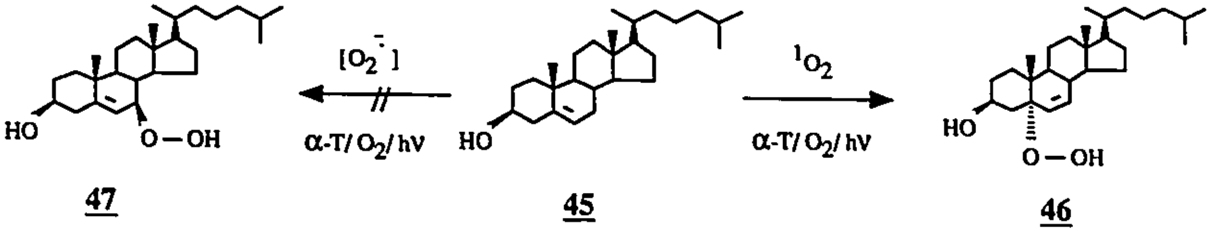
(ii) Photodynamic action The term photodynamic refers to a process in which the molecule is excited in the presence of oxygen. The sensitizer in its excited state can react by two different pathways: Type I and Type II, on contact with a molecule of oxygen. In the Type I pathway (e.g. anthraquinone dyes) production of superoxide radicals ($O_2^{-\cdot}$) arises through a series of electron processes after absorption of a photon by α-T 3. In the Type II process, singlet oxygen ($^1O_2$) is generated by energy transfer from the excited photosensitizer to molecular oxygen. In both types of photodynamic sensitizations, the activated oxygen species may cause serious biological damage[48].

Some chemical trapping experiments suggest that $^1O_2$ is the major product[44] (Scheme 6). When a solution containing the olefin adamantylidene adamantane 42 is exposed to UV light in the presence of α-terthienyl 3 for a short time, dioxetane 43 is formed with no trace left of 42. Upon heating, the ketone 44 results from



Scheme 6.

decomposition of the dioxetane 43. Control experiments without α-terthienyl 3, revealed that the products 43 and 44 were not present. Wat and co-workers[49] found that cholesterol 45 (Scheme 7) was oxidized mainly by singlet oxygen generated *in situ* when an oxygenated solution of α-T 3 and compound 45 were subjected to UV light, to produce 3β-hydroxy-5α-cholest-6-ene-5-hydroperoxide 46. However if $O_2^{-\cdot}$ was involved, the oxidation of cholesterol 45 by this species would produce 7β-hydroperoxyde 47 as the major product[50] but the latter was not observed.



Scheme 7.

Bakker and Gommers[44] have examined the activated oxygen species generated by α-terthienyl 3 when exposed to UV light *in vitro*. Since the lifetime of singlet oxygen is longer in D_2O than in H_2O an enzyme sample, glucose-6-P-dehydrogenase (G6-P), was treated with α-T 3 in D_2O and subjected to UV irradiation for a period of 25 minutes. It was found that the enzyme retained 45% less activity than when the experiment was performed in H_2O, thus suggesting that the production of singlet oxygen is operative. The use of singlet oxygen quenchers containing a sulfide function capable of reducing $^1O_2$ species (e.g. methionine and histidine) protected the enzyme from damage by α-terthienyl 3. Catalase, an enzyme which scavenges peroxide did not have any effect on the G-6P enzyme, nor did the addition of H_2O_2. Bovine superoxide dismutase (SOD) did not affect the enzyme indicating that the Type I process (·O-O⁻) was not involved. Addition of EDTA (ethylenediaminetetraacetic acid) to check for metal-oxygen complexation had no effect. Finally, the radical scavengers mannitol and benzoate had no effect on the system, therefore eliminating the possibility of hydroxyl radical (·OH) as the active oxygen species. These findings suggest that singlet oxygen is the active species *in vitro*.

In 1981, Arnason *et al.*[46] studied the mechanism of α-T <u>3</u> *in vivo*. When the yeast, *S. cerevisiae*, was exposed to α-T and UV irradiation under aerobic conditions, a protective effect was observed upon addition of sodium azide (a singlet oxygen scavenger). In another experiment with *E. coli* in anaerobic environment, protection from α-T <u>3</u> and UV light was observed with bovine SOD (a quencher for the $O_2^{-\cdot}$ radical). It was concluded that the generation of the superoxide radical ($O_2^{-\cdot}$) species cannot be ruled out but these experiments indicate that *in vivo* α-T <u>3</u> activation proceeds mainly by a photodynamic Type II process.

1.3.2 Site of Action

It is now accepted that the site of action of α-T <u>3</u> is the constituents of cell membranes. The lipophilicity of α-T[51] <u>3</u> is very high and is therefore expected to display strong affinity for lipophilic membranes. It is known that membrane components such as unsaturated fatty acids and cholesterol react with $^1O_2$ *in vitro*[52]. In turn, peroxidation of cell membrane phospholipids may lead to various forms of membrane dysfunction such as altered ion permeability and cell lysis. Wat *et al.*[53] reported that exposure of erythrocytes to α-T <u>3</u> under photosensitizing conditions induced potassium ion leakage and hemolysis. Arnason *et al.*[54] observed that α-T <u>3</u> treatment of Mosquito Larvae resulted in increased halide leakage into the external medium and structural damage to anal gill membranes. More recent studies on Mosquito Larvae (*Aedes Atropalpus*) with α-T <u>3</u> on exposure to near UV light, have shown an increase of tissue levels of fluorescent breakdown products resulting from lipid peroxidation (LPO). The reduced form of glutathione is known to be required as a reducing agent equivalent in a number of cellular defence mechanisms which protect against LPO. Analysis of the levels of oxidized glutathione (glutathione disulfide GSSG) after treatment with α-T <u>3</u> and near UV, revealed an increase by almost twofold.

This high level of GSSG has been interpreted as the result of extensive oxidative damage caused by α-T[55] 3.

Other enzymes have been shown to be inactivated by α-T 3 on exposure to UV light. For instance, Yamamoto *et al.*[56] showed that acetylcholinesterase, an enzyme located on the outer membrane of red blood cells, was strongly inactivated while the cytoplasmic enzymes were inactivated only after hemolysis. Confirmation that the membrane was the primary target and that membrane proteins can be damaged came from Downum *et al.*[57] Their studies with *E. coli* showed that, after α-T 3 treatment, the membrane proteins were crosslinked and formed high molecular weight aggregates. Finally, mutagenicity tests confirmed that α-T 3 was not mutagenic and, as mentioned in the discussion of the nonphotodynamic mode of action, there was no evidence to support that the damage caused to micro-organisms is due to intercalation of α-T 3 into DNA[58,59]. A QSAR[159] (Quantitative Structure-Activity Relationship) model is being developed to describe the mode of action of any group of phototoxins. To develop such a model the following factors must be addressed:

a) requirement of a bending angle in the main core of the molecule;
b) effect of substituent(s);
c) importance of $^1O_2$ production; and
d) lipophilicity which should affect the rate at which the substance is absorbed through the cellular membrane.

1.4 Work Described in the Thesis

Part of this thesis will deal with a qualitative analysis of the influence on each of the above factors on the overall biological activity observed.

The major part of this thesis deals with the preparation of analogues and derivatives of α-terthienyl 3. The biological activity studies were carried out by

Dr. R. Marles and F. Duval in Dr. J.T. Arnason's laboratory in the Department of Biology. The results of activity tests as well as the production of singlet oxygen[60-63] are presented in TABLE IX, Section 2.6.

The important physiological activity of α-dithienyl derivatives discovered by Sutfeld[64-66] on enzymological studies in *T. erecta* prompted us to synthesize some of these compounds and this constitutes another part of this thesis. The biological activity tests and the production of singlet oxygen will also be presented (end of Section III).

II ANALOGUES AND DERIVATIVES OF α-TERTHIENYL

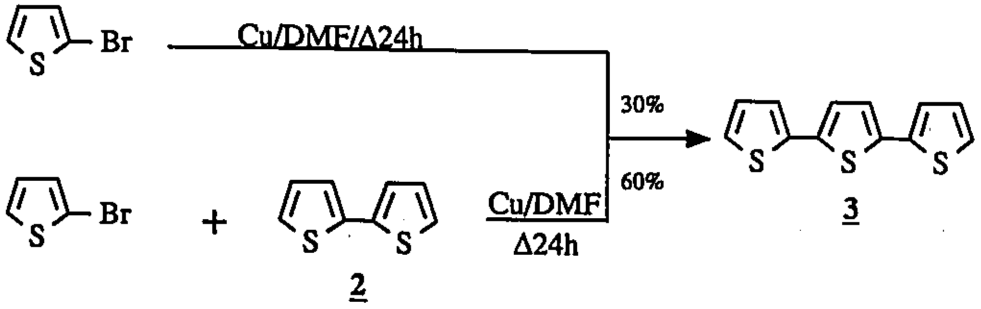
2. RESULTS AND DISCUSSION

2.1 Previous Syntheses of α-Terthienyl 3

Several syntheses of α-terthienyl 3 are reported in the literature[67-70] including the nickel-catalyzed cross-coupling reaction used by Kumada *et al.*[71]. Many of these are described in a review on the preparation of thiophene oligomers[72]. The first synthesis of 3 was reported in 1937, by Steinkopf *et al.*[73]. Zeichmeister and Sease[74] adapted the Ullmann coupling reaction by heating 2-iodothiophene at a high temperature (>200°C) in the presence of copper bronze as catalyst. The reaction gave a mixture of products and three of these were identified as 2,2′-dithienyl 2 (10%), α-quinquethienyl (0.04%, R=H, R′=dithienyls in 3) and α-terthienyl 3 (3%). However, the separation of the mixture was troublesome and yielded only a small amount of the desired α-terthienyl 3.

2.1.1 Kawada Synthesis

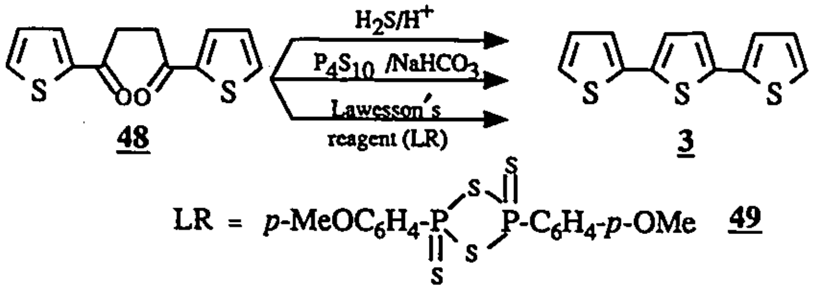
Modification of Steinkopf's method by Kawada[75-77] gave 3 in better yield (60%, Scheme 8).



Scheme 8.

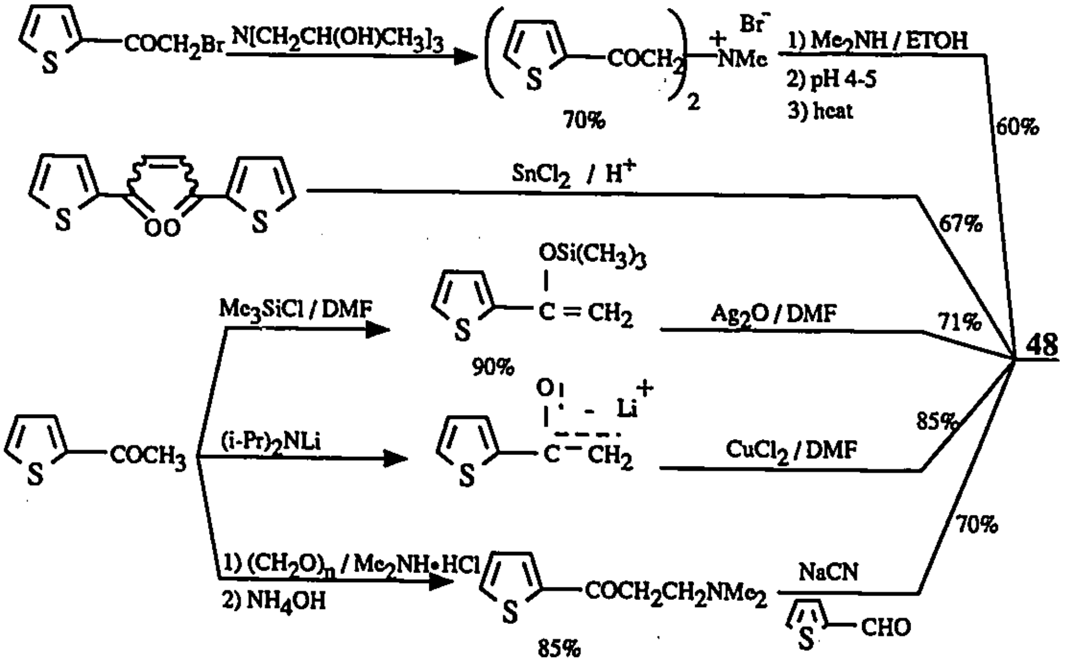
2.1.2 Wynberg Synthesis

Another synthesis for the preparation of α-terthienyl <u>3</u> involves cyclization of 1,4-di-(2′-thienyl)diketone <u>48</u>. This transformation was carried out under acidic conditions in the presence of H_2S[68,78,79] or with phosphorus pentasulfide and sodium hydrogen carbonate[69]. As well, Lawesson's[69] reagent <u>49</u> was found to be effective for this cyclization (Scheme 9).



Scheme 9.

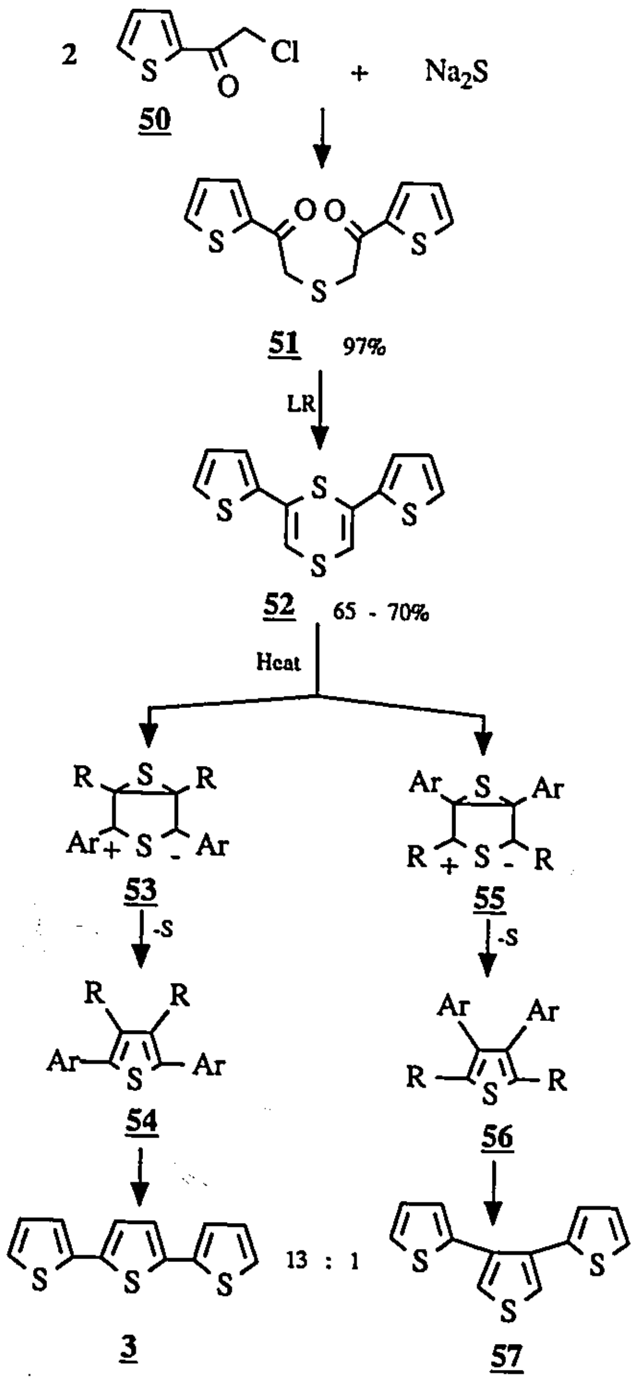
The intermediate <u>48</u> required in the above cyclization can be generated by several methods[68,69,78,79] and these are summarized in Scheme 10.



Scheme 10.

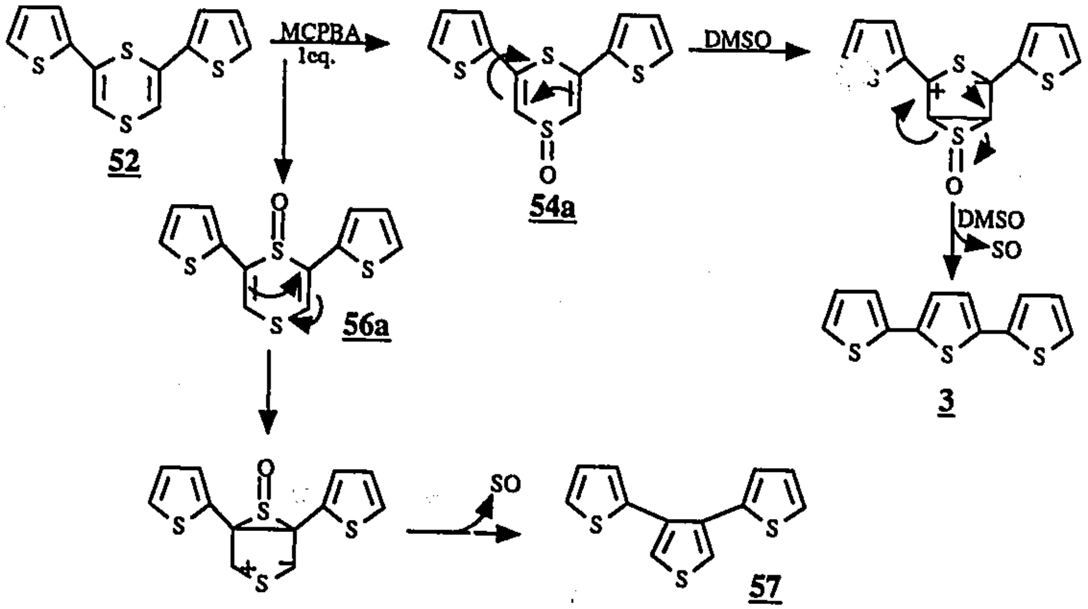
2.1.3 Nakayama Synthesis

A different approach[80] to the synthesis α-terthienyl 3 involves



Scheme 11.

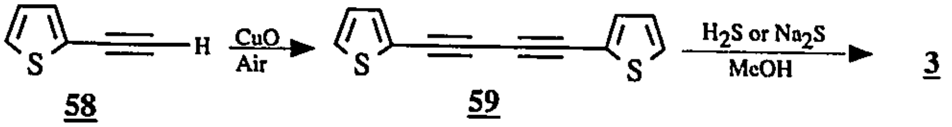
modification of a diketosulfide precursor, obtained in high yield from the condensation of two equivalents of 2-chloroacetylthiophene 50 with sodium sulfide. Thus, the diketosulfide 51 (Scheme 11), on treatment with P_2S_5 or LR 49, was converted *in situ* to the corresponding diketosulfide which in turn afforded the isolable 1,4-dithiin 52[80]. α-Terthienyls 3 and 57 were obtained in 70% yield (in a ratio of 13:1 respectively) by heating the dithiins 52 in *o*-dichlorobenzene under reflux. It is believed that the thiocarbonyl ylides 53 and 55 are involved as intermediates which collapse by extruding sulfur. The predominant formation of α-terthienyl 3 over its isomer 57 is rationalized on the grounds that the ylide 53, has its charges better stabilized by aryl substituents than the isomeric ylide intermediate 55[81]. Improved selectivity (up to 22:1) and a higher yield (90%) could be achieved by oxidation of the dithiin 52 to the sulfoxides 54a and 56a with 1 equivalent of MCPBA, followed by extrusion of sulfur monoxide in the presence of dimethyl sulfoxide[82] (Scheme 12).



Scheme 12.

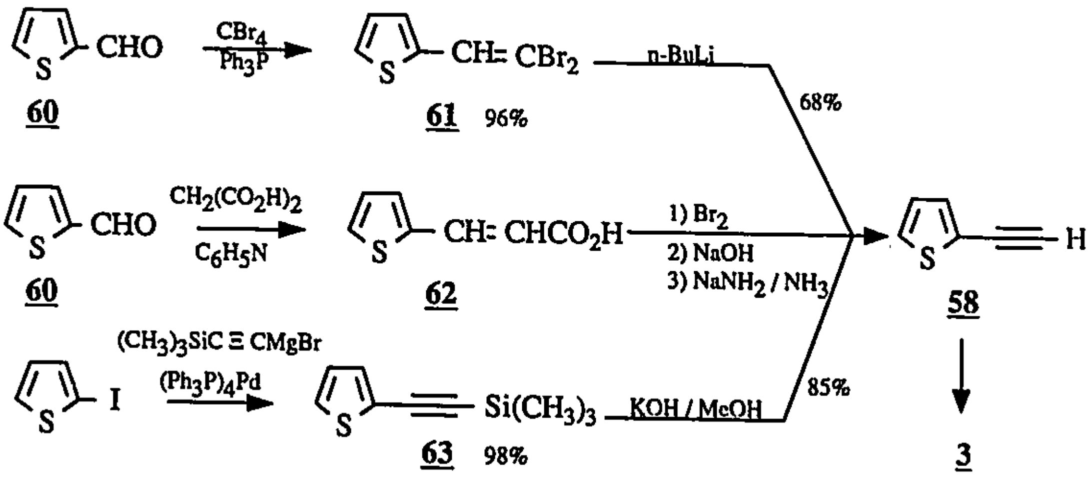
2.1.4 Schulte Synthesis

Alternatively the central ring of α-terthienyl 3 can be introduced by two molecules of 2-thienylacetylene 58 followed by coupling cyclization of the intermediate 59[83-85] with sodium sulfide in methanol (66% yield, Scheme 13). The starting material 58 was prepared according to three different procedures (Scheme 14):



Scheme 13.

a) by a Wittig reaction between 2-formylthiophene 60 and carbon tetrabromide to give the dibromoolefin 62 followed by elimination with *n*-BuLi[83,84] ;

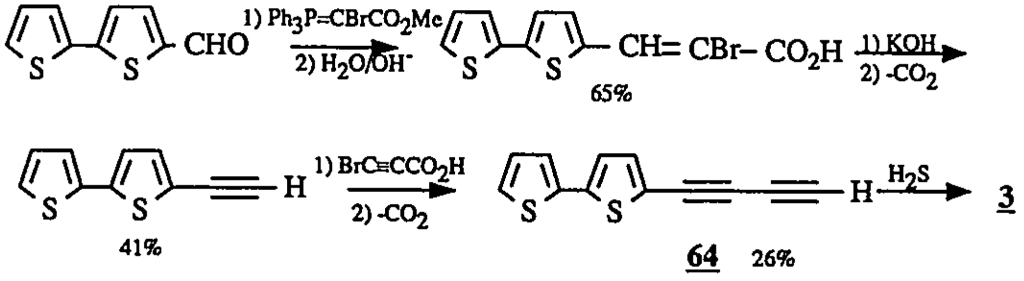


Scheme 14.

b) by the Knoevenagel reaction on 60 followed by bromination to gave the 2-(thienyl)dibromoacrylic acid of 62 which undergoes dehydrobromination and decarboxylation on treatment with base to give the desired 58[86,87]; and

c) by the coupling reaction between 2-iodothiophene and trimethylsilylethynylmagnesium bromide using a catalytic amount of $(Ph_3P)_4Pd$ followed by removal of the silyl group of 63 with KOH[88].

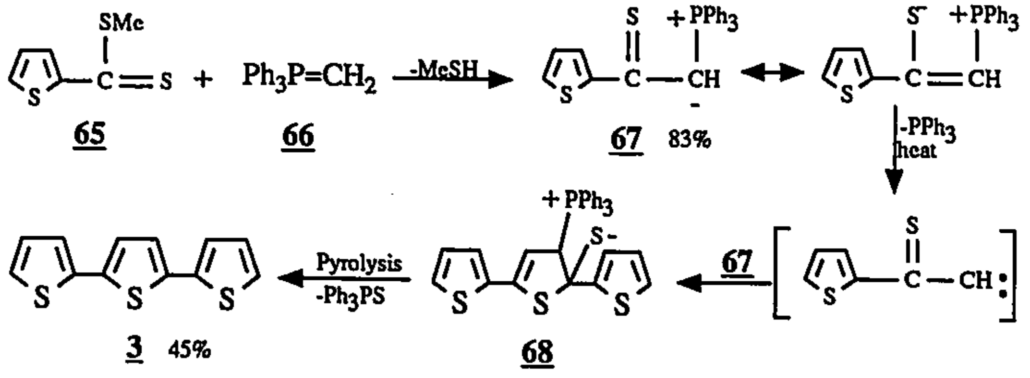
Preparation of the terminal diacetylene 64 and subsequent reaction with hydrogen sulfide is a lengthy and low yield synthesis of 3[85] (Scheme 15).



Scheme 15.

2.1.5 Bestmann and Schaper Synthesis

In the late 70's, Bestmann and Schaper[70] reported a novel and elegant synthesis of α-terthienyl 3 by an essentially one step procedure (Scheme 16). The

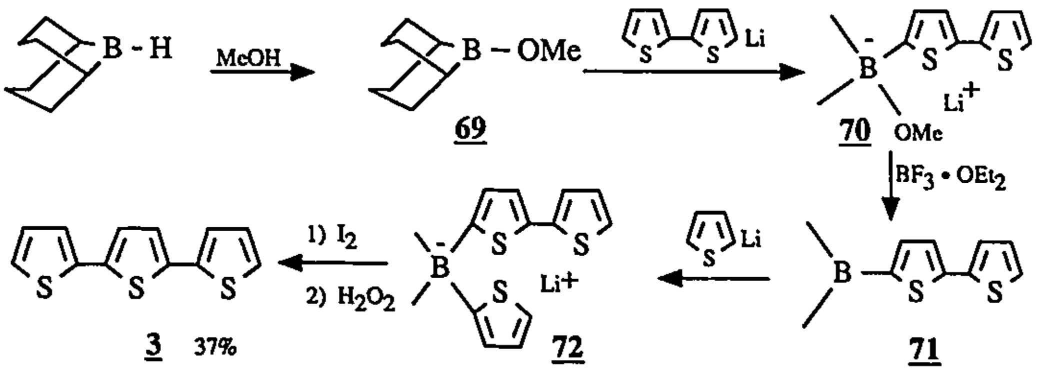


Scheme 16.

stabilized ylide 67 could be obtained by treatment of the dithiomethyl ester of thiophene 65 with methyl phosphorane 66. Pyrolysis of the intermediate 68 gave α-terthienyl 3 in 45% yield. Unfortunately, the unpredictability of the pyrolysis reaction coupled with lower yields in larger scale experiments made this synthesis impractical.

2.1.6 Kagan Synthesis

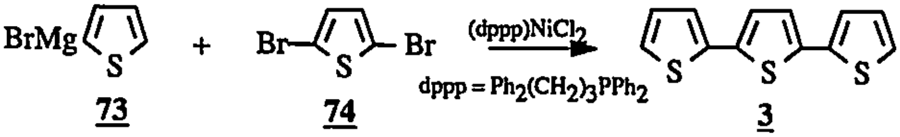
A more recent synthesis of α-terthienyl 3 was carried out *in situ* by exploiting the boran reagent[67] β-methoxy-9-borabicyclo-[3.3.1]nonane (β-methoxy-9BBN) 69. The reagent 69 was treated with 5-dithienyllithium to produce a tetracoordinated species 70 which was hydrolyzed with BF_3 etherate to 71. Treatment of the latter with 2-thienyllithium generated an intermediate 72 which, upon sequential addition of iodine and alkaline hydrogen peroxide, was transformed into α-T 3 in 37% overall yield (Scheme 17).



Scheme 17.

2.1.7 Kumada Synthesis

Kumada *et al.*[71,89-91] developed a general synthetic method utilizing the Grignard-Wurtz reaction in which halogenated compounds such as alkenyl, aryl and heteroaryl bromides or iodides could be efficiently coupled with Grignard reagents such as alkenyl, aryl and heteroaryl magnesium halides in the presence of [1,3-*bis*-(diphenyl-phosphino)-propane]Ni^{II} dichloride and other organometallic catalysts. These authors have reported the preparation of α-terthienyl 3 on a small scale (80% yield, GC analysis) with a cross-coupling reaction between 2-thienyl magnesium bromide 73 and 2,5-dibromothiophene 74 (Scheme 18). This nickel-catalyzed coupling reaction appeared to be the most promising for the large scale preparation of α-terthienyl 3.



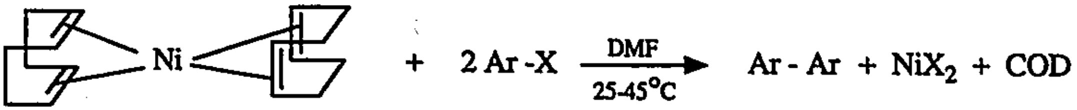
Scheme 18.

2.1.8 Nickel-Complex Catalyzed Grignard-Wurtz Reaction

2.1.8.1 Proposed Mechanisms

The metal promoted coupling reactions of aryl and alkyl halides is one of the mildest and most useful procedures for the formation of the carbon-carbon σ-bonds. Low valent transition metals and transition metal organometallic complexes play an important role as coupling agents for such processes. One of the first examples is the Ullmann coupling reaction of aryl halides in the presence of Cu[92,93]. However, the Ullmann reaction occurs only with reactive halides such as aryl iodides and requires drastic conditions. The successful use of Cu to catalyze aryl coupling reactions has led to the investigation of other transition metal organometallics for this purpose. The homocoupling of aryl and alkenyl halides by the Ni^0 complex catalyzed reaction was discovered by Semmelhack *et al.*[94-96]. Since the pioneering work of Semmelhack *et al.*[94-96], several modifications of the procedure employing zero-valent-nickel catalyst to effect the reductive coupling of aryl halide under homogeneous conditions, have resulted in an efficient methodology (Scheme 19) for the preparation of biaryls. During these developments, several mechanisms have been postulated for similar coupling reactions and this has been the subject of some debate[97]. Nonetheless, there is general agreement on two points in the role played by Ni reagents in the activation of the aromatic carbon-halogen bond. The first is the involvement of aryl Ni$^{\text{II}}$ intermediate[98-103] 75 formed *via* the oxidative addition of the aryl halides (chlorides and bromides) to Ni^0

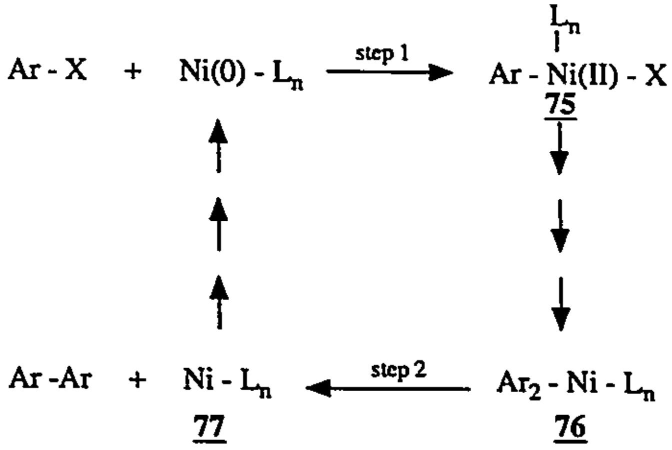
$$2\ \mathrm{ArI} \xrightarrow{\mathrm{Cu}} \mathrm{Ar-Ar}$$



COD=Cyclooctadiene
X=Halides

Scheme 19.

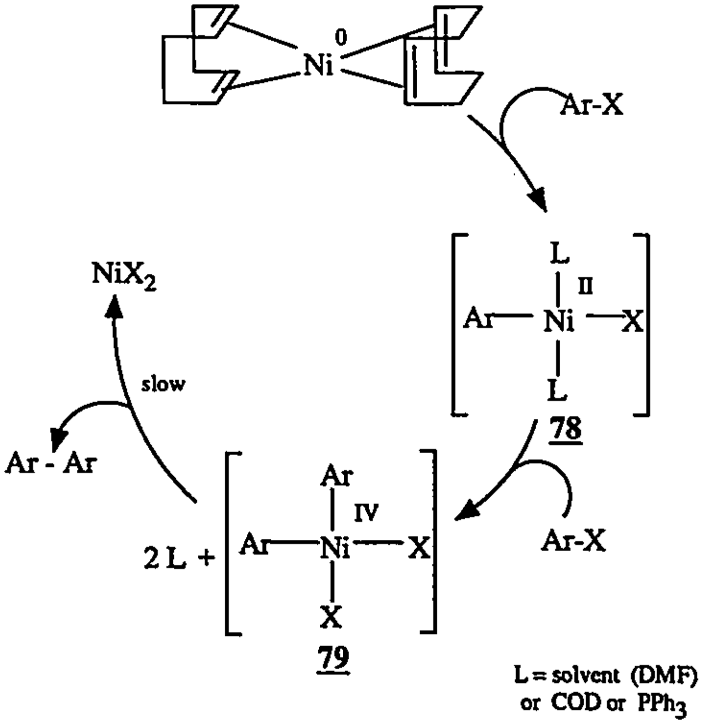
species[104-106] (step 1, Scheme 20). The second is biaryl formation which occurs by reductive elimination from a biaryl Ni intermediate 76 (step 2, Scheme 20). The exact



Scheme 20.

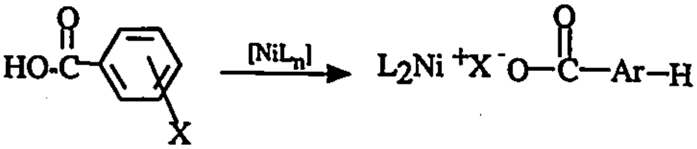
sequence of steps from the aryl Ni^{II} 75 to the biaryl Ni species 76 and the oxidation states of the latter intermediate 77 is still controversial[107]. This is partly due to the fact that the mechanism of catalysis by Ni seems to be dependent on many variables such as the nature of the aryl halides, solvent, phosphine ligand, choice of reducing metal (e.g. Zn, Mg, Mn) and electrolysis. The following discussion summarizes some of the pertinent details of the main mechanistic sequences reported in the literature.

Semmelhack *et al.*[94] proposed the sequence shown in Scheme 21 for the use of $Ni^0(COD)_2$ in the preparation of biaryls[108,109]. The oxidative addition of the aryl halide to Ni^0 would generate the proposed aryl Ni^{II} complex 78. This intermediate reacts with a second equivalent of aryl halides to form the biaryl Ni^{IV} species 79, which undergoes reductive elimination as the slow step. This rationalization was consistent with the observation that formation of biphenyl was slower than the disappearance of iodobenzene in the presence of $Ni^0(COD)_2$. Reinvestigation of the effects of various solvents and added ligands revealed that in toluene and THF, no coupling is observed and $Ni^0(COD)_2$ decomposes to Ni metal. However, the presence of a few mole equivalents of



Scheme 21. Preparation of Biaryls Proposed by Semmelhack[94].

DMF or with PPh_3 as ligand promotes efficient biaryl formation. Also, the pure complex *bis*(triphenylphosphine)phenylNi bromide 78 was prepared and was found to undergo slow decomposition (even at 25°C in DMF) and biphenyl was obtained in almost quantitative yield after 12 hours at 50°C. Similar results were reported for the decomposition of the above complex in toluene at 80°C[110]. This method for biaryl coupling requires only mild conditions and is compatible with common polar functional groups on the aryl halides such as ketone, aldehyde or ester. However, this method does not extend to aryl halides bearing acidic protons such as alcohols, carboxylic acids (Scheme 22) and amides. Reduction of the aryl halides to free arene with Ni^0 then becomes the primary process.

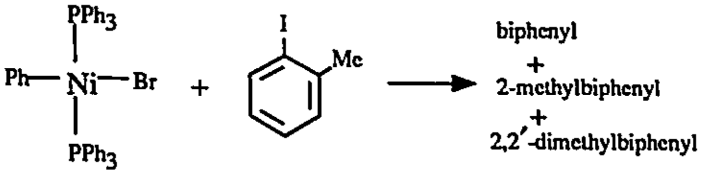


Scheme 22.

Aryl nitro compounds completely inhibit the reaction, perhaps by the formation of a nitrosoNi^0 complex[111] (see below). Another limitation of the Semmelhack method is that it requires stoichiometric amounts of expensive and air sensitive Ni^0 reagents. Also, aryl chlorides give poor yields. All attempts in cross-coupling unsymmetrical aryl halides with Ni^0 failed to give a high degree of selectivity and an equimolar mixture (see Example below) of the three possible biaryls[96] was obtained.

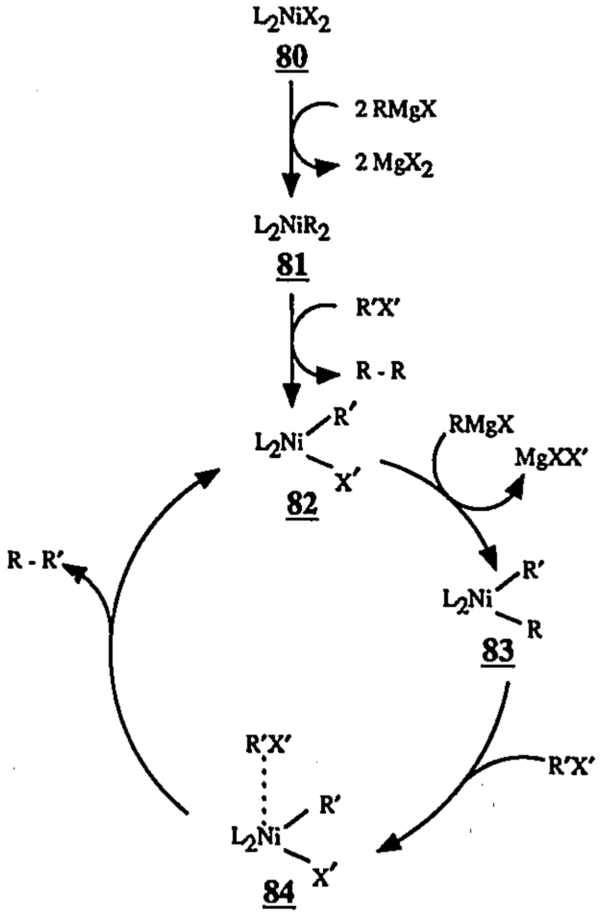
$$RNO_2 + (Et_3P)_4Ni \xrightarrow{-PEt_3} Et_3PO + (RNO)Ni(PEt_3)_2$$

Example



Several research groups have recognized these limitations and have sought alternate methods or modifications of the method. Organometallic reagents (Grignard) are unable to undergo nucleophilic substitution reactions with organic halides. Fortunately this limitation was alleviated with the discovery that addition of transition metal salts allowed for formation of the C-C bond. Among the transition metal salts used were Cu^I, Cu^{II}, Ag^I and various group VIII metals. In spite of the fact that this methodology was successful in making C-C bonds; these reactions still suffer from the disadvantage of requiring at least stoichiometric amounts of transition metal.

Two independent research groups, Kumada *et al.*[112] and Corriu *et al.*[113], discovered almost simultaneously that cross-coupling reactions involving alkenyl and aryl halides with various Grignard reagents could be achieved using a small amount of phosphine Ni^{II} complex as modified catalyst for Kharash type reactions[114]. This methodology offers high yields of cross-coupling products under mild conditions and is truly catalytic with respect to the Ni^{II}. The reactions work equally well with primary and secondary alkyl, aryl, alkenyl and allylic Grignard reagents. Reactive halide substrates work well, except for simple alkyl halides which fail to react. With simple aryl and alkyl Grignard reagents, diphosphine [$Ph_2(CH_2)_3Ph_2$] complexes of Ni^{II} chloride were found to be the most effective catalysts. $Me_2P(CH_2)_2PMe_2$ complexes are most suitable for alkenyl and allylic Grignard reactions whereas the *bis*(triphenylphosphine) complexes are the most effective catalysts for reactions involving sterically hindered Grignard reagents. In studies of the cross-coupling reaction with organic halides, Kumada *et al.*[115] proposed a catalytic cycle (Scheme 23), in which the dihalodiphosphine-Ni 80 reacts with a Grignard reagent to form the intermediate diorgano-Ni complex 81. The two organic groups on



Scheme 23. Nickel - Catalyzed Coupling of Grignard Reagents with Halides Proposed by Kumada[115]. This figure is reproduced from Reference 115.

L_2NiR_2 81 are released by the action of an aryl halides R′X′ to undergo coupling along with the formation of $L_2Ni^{II}R'X'$ 82. Metathesis of the Grignard reagent replaces the halide-Ni bond in the intermediate 82 to produce the corresponding unsymmetrical organo-Ni complex $L_2Ni(R')R$[116] 83, from which the cross-coupling product R-R is released by the attack of the organic halides, possibly *via* the pentacoordinated intermediate 84, and regenerates the $L_2Ni^{II}R'X'$ species 82 to complete the catalytic cycle. Bidentate phosphine ligands seem to exhibit much higher catalytic activity than unidentate ones. The catalytic activity also depends on the length of the methylene bridge between the two diphenylphosphino groups with maximum activity observed when the three methylene unit is present. For instance, the efficiency of the bidentate ligand decreases roughly in the sequence: Ni(dppp) (Ph_2P-$CH_2CH_2CH_2PPh_2$) > dppe (Ph_2P-$CH_2CH_2PPh_2$) > dppb ($Ph_2PCH_2CH_2CH_2CH_2PPh_2$) > cis-dpen,  >>> dppm ($Ph_2PCH_2PPh_2$) (practically inactive). This strong phosphine dependence for catalytic activity suggests that catalytically active Ni complexes must contain phosphine ligands.

Important solvent effects were observed for these Ni^{II} promoted cross-coupling reactions. Thus, reactions performed in diethyl ether proceed considerably faster compared with those performed in THF[115]. It was suggested that the more basic THF binds more tightly with the Ni centre to prevent the approach of the halides and/or the Grignard reagent.

Florio *et al.*[117] showed that coupling reactions are also dependent on the nature of the aryl substrate, especially if the aryl moiety contains functional groups capable of acting as ligands. Thus, aryl halides could serve simultaneously as ligands and oxidizing agents. Elegant examples of this class of aryl halides are the 2-halogenobenzothiazoles. In contrast to Kumada's results, cross-coupling reactions involving Ni^{II} complex catalysts containing unidentate phosphine ligands displayed superior activity than catalysts containing bidentate phosphines. Furthermore, the catalytic activity of the Ni^{II}

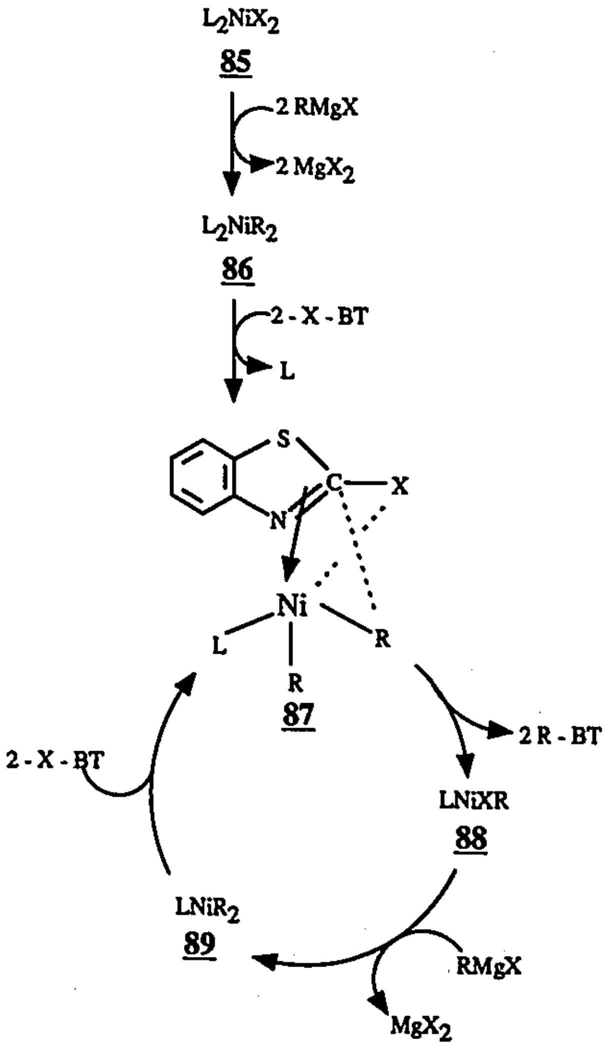
catalysts decreases with increasing basicity:

Most Active Least Active

$Cl_2Ni(PPh_3)_2 > Cl_2Ni(PPh_2Et)_2 > Cl_2Ni(PPhEt_2)_2 > Cl_2Ni(PEt_3)_2$

Least Basic Most Basic

This trend suggests that a less basic phosphine ligand eases its replacement by 2-halo-BT (benzothiazole) in Ni^{II} complex, to form a catalytically active species Ni^{II} (2-halo-BT) and Scheme 24 was proposed[117] for the mechanism involved.

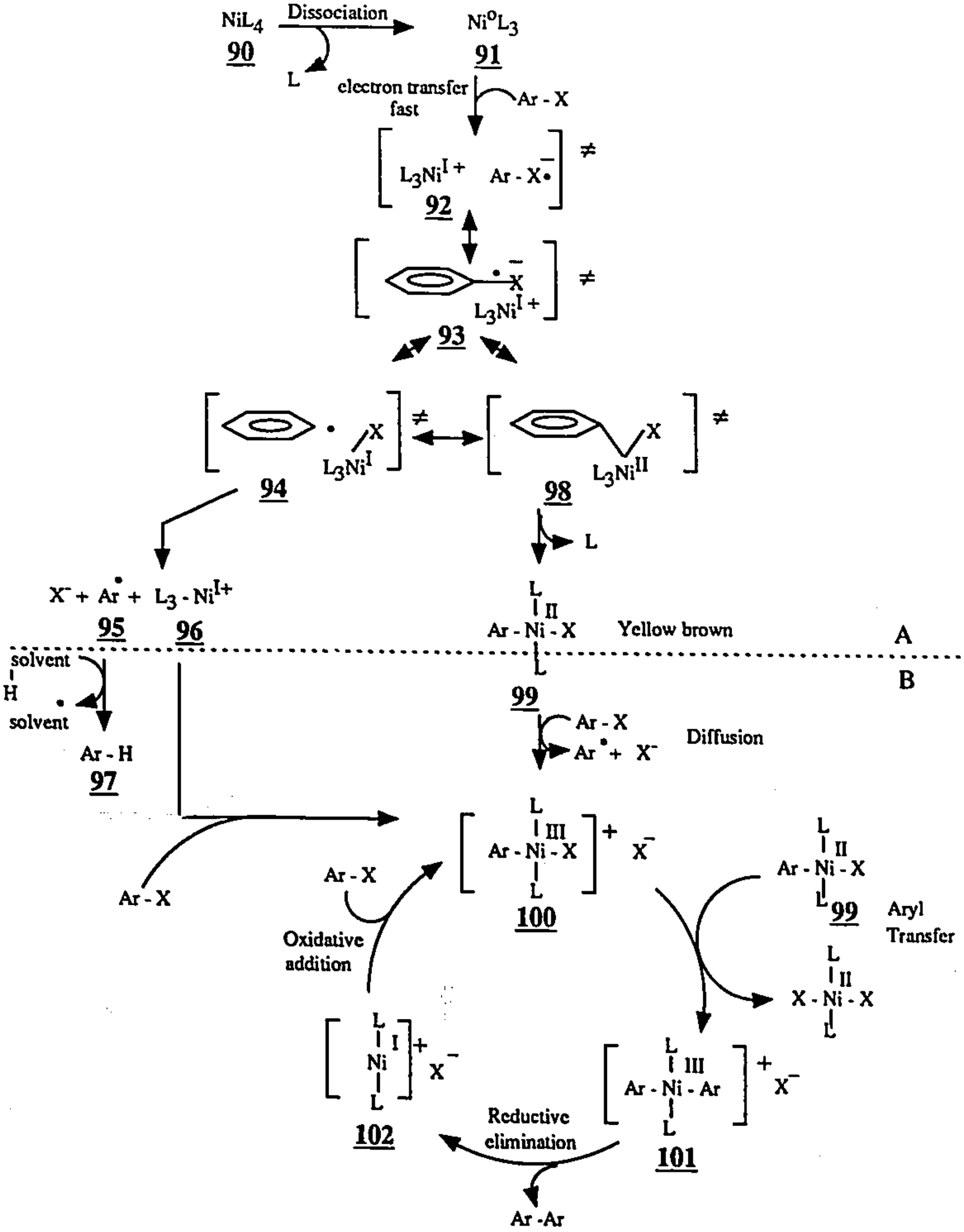


Scheme 24. Proposed Mechanism for the Cross-Coupling Reaction of 2-Halo-Benzothiazoles with Ni^{II} Complex (Activated Grignard Reagent)[117].

According to this mechanism, the Ni^{II} phosphine-complex 85 undergoes metathesis with the Grignard reagent to form the intermediate 86. Replacement of one phosphine ligand "L" in NiL_2R_2 86 with 2-halo-BT generates the NiR_2L(2-halo-BT) complex 87. It is worth mentioning that coordination of the benzothiazole moiety on Ni can occur *via* the double bond (N=C), the N atom or the sulfur atom. This catalytically active species 87 leads to the complex 88 by release of the cross-coupled product, 2R-BT[118]. Reaction of the complex 88, first with RMgX, gives the intermediate 89 and subsequently with 2-halo-BT regenerates the catalyst 87.

The essential coordination of 2-halo-BT to Ni as well as the role played by the phosphine ligand on the active complex have been documented by the synthesis of complexes containing either a 2-halogenobenzothiazole or a phosphine ligand. Thus, the study of catalytic activity in the cross-coupling reaction of 2-Cl-BT with Grignard reagents using diamagnetic $NiBr(H_2O)$(2-Cl-BT) complex, reveals that it was somewhat active on its own. However, addition of PMe_3 to the complex enhanced the catalytic activity of the complex and optimum catalytic activity was observed at a phosphine:Ni ratio of 1. Another study was carried out on the $Br_2Ni(DMSO)PMe_3$ complex. This Ni^{II} complex has a non phosphorus ligand, DMSO, that can be replaced by 2-halo-BT. Indeed it has been observed that the complex Br_2Ni(2-Cl-BT)PMe_3 was formed upon reaction of 2-Cl-BT with $Br_2Ni(DMSO)PMe_3$. A similar or slightly higher catalytic activity for the C-C cross-coupling process of 2-halobenzothiazole was observed for the Br_2Ni(2-Cl-BT)PMe_3 complex as compared with the complex $Br_2Ni(H_2O)$(2-Cl-BT) + 1 equivalent of PMe_3. This consistent optimum catalytic activity at a P:Ni ratio of 1 supports the proposition that the coordination of 2-halo-BT is a relevant step in the cross-coupling process and that the presence of one phosphine ligand is also an important factor. This mechanism is consistent with the observed reverse halogen reactivity order of F > Cl > I. The small steric requirement of the fluorine atom coupled with its high metal affinity enables it to coordinate better with the Ni atom. One problem associated with both the catalytic cycle of Kumada[115] (Scheme 23) and that of Florio *et al.*[117] (Scheme 24), is that it is not clear how the action of an aryl halides promotes the release of the homocoupled products R-R and the cross-coupled products R-R′ from the respective intermediates **81** and **84**, (Scheme 23) and **87** in Scheme 24. The choice of Ni^0 as active intermediate originates intuitively from the evidence that intermediates **81** and **83** (Scheme 23) may undergo prior reductive elimination to produce biaryl and Ni^0 species which could readily undergo oxidative addition with aryl halides to generate the intermediate Ni^{II} species **82**.

In order to shed more light on the mechanism by which the aryl halides interacts with the organo Ni species **91** and **99**, Tsou and Kochi[103] undertook thorough mechanistic studies of the oxidative addition of aryl halides to Ni^0 complexes and to aryl Ni^{II} complexes. In considering the possible involvement of Ni^0, Ni^I, NI^{II}, Ni^{III} and Ni^{IV} species, elegant mechanistic work by Kochi *et al.*[119,120] led to the conclusion that biaryl formation involves a radical chain process in which the Ni^I and aryl Ni^{II} were reactive intermediates. An overall summary[103] of the mechanism of oxidative addition to Ni^0 and the proposed biaryl synthesis from aryl-Ni^{II} complexes are summarized in Scheme 25 in which the study on the Ni^0 species is indicated by "A" and is separated by a dotted line from the study performed with Ar-Ni^{II} which is indicated by "B". The overall process is triggered by the initial formation of the Ni^0 species. In studies with Ni^0 complexes and aromatic halides, it was found that when NiL_4 **90** was dissolved in either hydrocarbon or ethereal solvents, dissociation into coordinatively unsaturated Ni^0L_3 species **91** readily occurs and is accompanied by a color change to purple-red. The rate of disappearence of the complex **91** has been found to be sensitive to the nature of the solvent and increases in the order: hexane<THF<toluene. When an aryl iodide was employed instead of bromide or chloride, electron transfer occurs more rapidly. This was also observed with an



Scheme 25. Summary of the Mechanism Proposed by Kochi[103].
A - Refers to Ni^0 Studies.
B - Refers to Ni^{II} and Ni^{III} Studies.

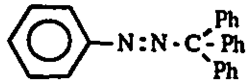
electron-withdrawing substituent on the aryl moiety, in comparison to an unsubstituted aryl and/or with an electron-donating group. Moreover, steric effects did not play a dominant role in the reaction of Ni^0 with an aryl halides, e.g. even (2,4,6-tri-*t*--butyl)bromobenzene reacted. A kinetic experiment[103] on the rate of reaction between various aryl halides and $Ni^0(PEt_3)_4$ was carried out by monitoring the disappearance of $Ni^0(PEt_3)_3$ by following the change in absorbance at 500 nm from which it was established that the reaction was first order in each reagent (see below).

$$\frac{-d[Ni^0L_3]}{dt} = K_{obs}[NiL_3][Ar-X]$$

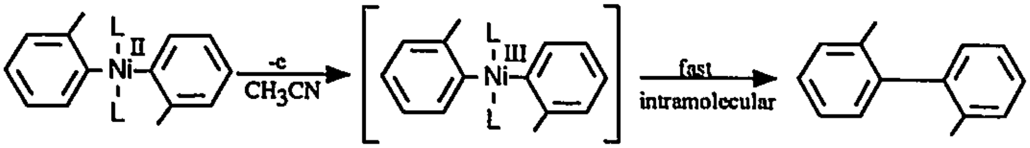
Kinetic studies have shown that, upon adding a triethylphosphine ligand, the rate of disappearance of Ni^0 was retarded suggesting the involvement of the unsaturated species $Ni^0(PEt_3)_3$ in the oxidative addition. Upon addition of an aryl halide to the Ni^0 complex **91**, a reaction readily occurred when $L=(PEt_3)_3$ was employed. As a result, the yellow-brown solutions contained two principal species: the Ni^{II} oxidative adduct **99** and the paramagnetic Ni^I species $XNiL_3$ **96**, which is possibly derived from the proposed transition state **92**. The presence of the paramagnetic Ni^I species **96** has been detected by ESR (electron spin resonance) spectroscopy and the lines characterized by comparison with authentic samples. The ESR technique was also used to quantify the amount of the Ni^I formed. The adduct **99** is formed with the loss of one phosphine ligand whereas the three phosphine ligand remains on the Ni^I product **96**. The intermediate **99** could be isolated from aryl chlorides and bromides in good yield[121] and characterized[122,123] as the *trans* isomer.

The relative amounts of complexes **96** and **99** vary depending on several factors. For instance, compound **96** is favored by polar solvents, use of aryl iodide and the presence of Ni^I (autocatalyst) while **99** is favored by non polar solvents and use of substituted aromatics having electron-donating functional groups. The presence of Ni^{II} complex **99** exerts no effect on the ratio of **96** and **99** formed. Support for a common intermediate 93 was based on the observation that the change in the rate of the reaction was not accompanied with a corresponding change in product distribution. Thus, the rate-limiting activation process cannot lead directly to $Ni^{(I,II)}$ products. Since no significant change in the reaction rate (disappearance of Ni^0) was observed upon addition of Ni^I complex 96 to the reaction and that this led to increased yields, suggest that Ni^I and the Ni^{II} products are formed subsequent to the rate-limiting step. Cyclic voltammetric measurements show that the Ni^0 species 91 undergoes facile oxidation to Ni^I. The fact that aryl halides can easily be reduced electrochemically suggests that they can participate as electron aceptors in electron-transfer processes from the Ni^0 donor, which would give the ion pair 92. It was suggested that Ni^I lies below the plane of the aromatic ring (as in 93), and is displaced toward the halide (as shown in transition state 94), or inserted following the collapse of the ion pair (98). The partitionning of the ion pair between 99 and 96 can be represented by the competition between cage collapse and spontaneous fragmentation of the $ArX^{\cdot-}$ moiety and the relevance of the aryl radical 95 by diffusion out of the solvent cage. However, it is also possible that phosphine loss precedes the collapse of the ion pair (92 to 99). The very short-lived aryl radical 95 abstracts a proton from the solvent to give the observed arene product 97. When the Ni^0 species 91 is mostly converted to Ni^I 96, the organic product derived from the aryl halide, consisted mainly of the corresponding arene 97 thus suggesting the formation of an aryl radical. Further evidence for the aryl radical 95, came from the observed ESR spectrum for (2,4,6-tri-*t*-butyl)bromobenzene which was observed directly from the reaction mixture.

Ni^{II} studies[119] (bottom of Scheme 25, "B") indicate that the catalytic reaction begins with an electron transfer from the aryl organo Ni^{II} complex 99 to the aryl halide to give the Ni^{III} complex 100 (presumably *via* a process similar to 91 → 96) and the aryl halide ion radical which can dissociate to release an aryl radical along with its corresponding halide anion. It is noteworthy that the aryl Ni^{II} complex 99 gives high yields of homocoupled products in a polar solvent (e.g. CH_3NO_2) without consuming the aryl halide. Thus, the presence of aryl halide is important in nonpolar solvents but is not important in polar solvents which implies a different mechanism. Since investigation was performed in nonpolar solvents, it was found that formation of biaryls was very low in the absence of aryl halides but quantitative in the presence of aryl halides. Although an induction period was observed initially there is an abrupt rate enhancement in the presence of aryl halides. The induction period was shown to be extremely sensitive to the presence of free ligand. Thus, when 0.1 equivalent of PPh_3 was added, the induction period increased fourfold. On the other hand, addition of $NiBr_2$ or methyl triflate drastically decreased or eliminated the induction period, presumably by sequestering the phosphine ligand. The dual observation of aryl scrambling and an induction period suggested two processes: (1) a radical chain process and (2) free aryl radicals as reactive intermediates.

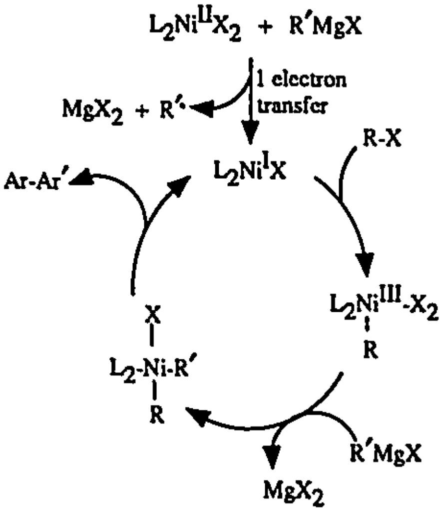
The second option is unlikely since the free aryl radical **95** derived from the oxidation of Ni^0 complex **91**, could not be trapped by 1,4-dihydrobenzene. Furthermore, independent generation of a free phenyl radical from phenylazotriphenylmethane (PTAM)  had no effect on the production of cross-coupled product and there were no incorporation of this free Ar$\cdot$ in the biaryl products. Therefore free aryl radicals cannot contribute in the process which leads to biaryl coupling or to aryl scrambling. The first alternative, i.e. involving a nickel radical chain process, would imply an electron transfer from Ni^{II} to Ar-X to produce an $ArNi^{III}$ species **100**. (See Scheme 25) Support for this electron transfer limiting step comes from the addition of 0.1 equivalent of duroquinone, a good electron acceptor, which causes a fourfold increase in the induction period. Additional support for the involvement of an aryl Ni^{III} intermediate came from the observed spectral changes of the Ni^{II} species **99** upon oxidation. Thus, the direct chemical oxidation of the analoguous o-$CH_3C_6H_4Ni^{II}Br(PEt_3)_2$ with several oxidants such as hexachloroiridate^{IV}, cerium^{IV} and cobalt^{II} trifluoroacetate at -50°C, showed the formation of a new species with an absorption spectrum band at λ_{max} 410 nm. This unstable intermediate also displayed an intense ESR spectrum attributed to the paramagnetic intermediate ArNi^{III} **100**.

The paramagnetic intermediate **100** undergoes aryl transfer with ArNi^{II}X **99** to give the diaryl Ni^{III}halo intermediate **101**. Reductive elimination of the diaryl ligand as a biaryl product gives rise to the Ni^{I}X species **102**. Tsou and Kochi[119] have shown that the rate of reductive elimination of biaryl involving Ni^{III} species generated by anodic oxidation of a parent Ni^{II} complex (o-$CH_3C_6H_4)_2Ni(PEt_3)_2$ is fast. Moreover, crossover experiments performed on the slow thermolysis of Ni^{II} revealed no aryl scrambling. The authors[119] concluded that the elimination process is intramolecular (Scheme 26).



Scheme 26.

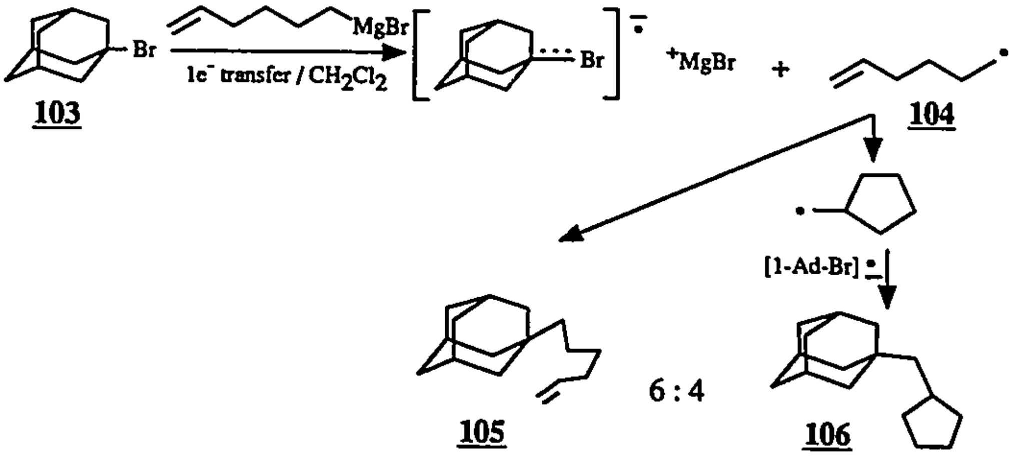
Oxidative addition of Ar-X to the Ni^{I} species **102** regenerating the active Ni^{III} species **100**, completes the catalytic cycle. The study was performed using large amounts of Ni catalyst which favors the bimolecular aryl transfer step between **100** and **99**. Collmann[125]



Scheme 27.[126]

suggested that similar steps may be involved in the nickel-catalyzed cross-coupling reaction in which the Grignard reagent served both as a reducing agent and aryl transfer agent (Scheme 27).

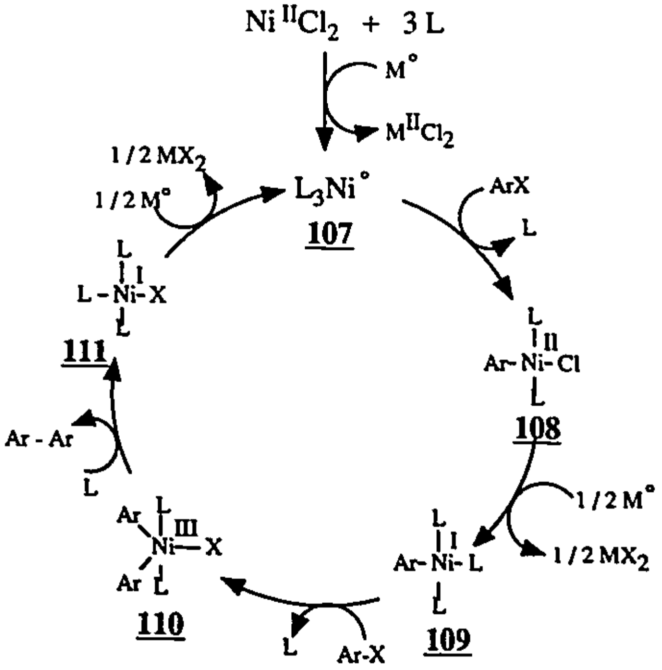
It is now recognized that Grignard reagents may serve as electron donors in a single electron transfer (SET) process. Recent studies by Equichi *et al.*[126] on cross-coupling reactions of *t*-alkyl halides with Grignard reagents (Scheme 28) indicate that 5-hexenylmagnesium bromide reacts with adamantyl bromide 103 by a SET mechanism



Scheme 28.

generating the 5-hexenyl radical intermediate 104 which gives rise to 1-(5′-hexenyl)adamantane 105 and 1-(cyclopentylmethyl)adamantane 106 in a 6:4 ratio. Product 106 comes from the cyclization of the 5-hexenyl radical prior to the chain termination reaction with adamantyl bromide ion radical. However, as pointed out by Colon and Kelsey[127], the proposed mechanism (see Scheme 29) is also incomplete since it fails to account for the lack of reactivity of organolithium reagent (e.g. the role of Mg in these coupling reactions remains to be clarified).

The Ni^{II} promoted coupling of aryl halides with Grignard reagent can be achieved using catalytic amount of Ni^{II} catalysts. One of the disavantages of this method



Scheme 29. Summary of the Mechanism for the Biaryl Synthesis Catalyzed by Ni Complex in the Presence of a Reducing Driving Force (Metal) Proposed by Colon *et al.*[127] and Refined by Amatore *et al.*[107]

is that it does not allow for the presence of polar functional groups (e.g. carbonyl) which react with the organomagnesium reagent present. In this context, Kende *et al.*[128] reported a modification of Semmelhack's original method (see p. 27) for homo-biaryl coupling compatible with carbonyl functionalities. They prepared the active Ni^0 reagent *in situ* from the reduction of $(PPh_3)_2Ni^{II}Cl_2$ with Zn dust in DMF. However, they still used the Ni complex in stoichiometric amounts. Kumada and co-workers[129] confirmed that

$$1\ L_2Ni^{II}X_2 + 1\ Zn \longrightarrow 1\ L_nNi^0 + ZnX_2$$

$$1\ L_nNi^0 + 2\ RX \longrightarrow R\text{-}R + L_2NiX_2$$

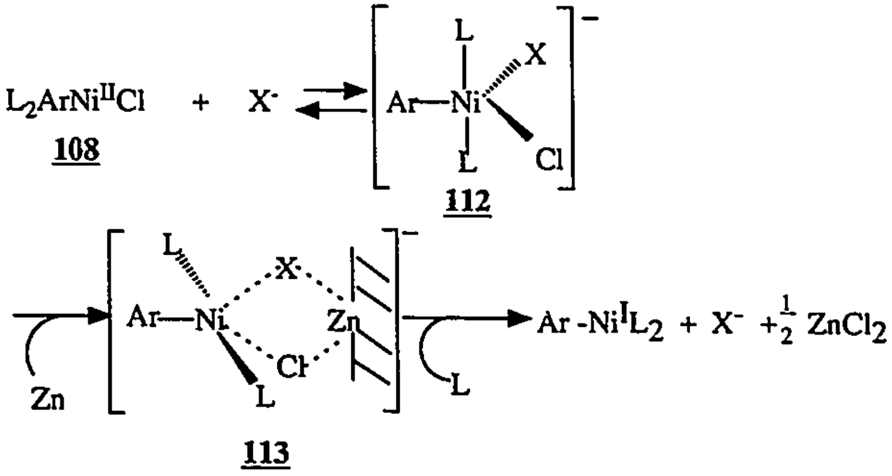
Kende's procedure could be made catalytic in Ni by using a stoichiometric amount of Zn. A similar catalytic system involving the *in situ* reduction of different *bis*(trialkylphosphine)Ni^{II} chlorides with Zn was also reported[130]. Meanwhile Colon *et al.*[131] discovered an efficient synthesis of biaryls from aryl chlorides using a catalytic mixture of simple anhydrous Ni salt and PPh_3 in the presence of a reducing metal (Zn, Mg or Mn).

The reaction occurs rapidly (within minutes in certain cases) under mild conditions and a wider variety of functional groups such as ester, ketone, aldehyde, nitrile, amine and alcohol can be accommodated.

Recent mechanistic studies carried out by Colon and Kelsey[127] also suggest the intermediacy of Ni^{I} and Ni^{III} (Scheme 29). The cycle is initiated by the reduction of Ni^{II} salts to Ni^{0} by Zn with the coordination of three phosphine ligands. The propagation steps include the fast oxidative addition of Ar-X to L_3Ni^{0} species **107** to form an Ar-$Ni^{II}L_2$ intermediate **108**. This complex, under the reducing conditions of excess Zn, is reduced to the Ni^{I} species **109** *via* a single electron uptake. The latter oxidatively adds aryl halides to afford the diaryl Ni^{III} complex **110** which undergoes rapid reductive elimination of Ar-Ar and Ni^{I} complex **111**. The cycle is completed by a further single electron transfer to the $L_3Ni^{I}X$ complex **111** which regenerates the initial L_3Ni^{0} species **107**.

Kinetic studies[127] have shown that the reaction rate is *pseudo* zero order in Ar-X which means that Ar-X is not involved in the rate limiting step. These studies also revealed that the reaction rate is first order in Ni and bromide ion and autocatalytic in halide ion but only in the co-presence of Zn. Halides and other anions decrease the reaction rate in the order (i.e. decreasing catalytic activity): $I^- > Br^- >> Cl^- > SO_4^{2-} > F^- >$ none. The reaction rate is also dependent on the triphenylphosphine to Ni ratio but is asymptotic at a ratio of 6 and higher. Rate inhibition at high Ph_3P:Ni ratios was not observed. Finally, excess zinc (greater overall active surface) also influenced the reaction rate.

These observations suggest that the rate-determining step is an intramolecular electron transfer from the Zn metal and Ni species. The authors[127] also postulate the role of halides ion in this reduction process leading to the generation of the key intermediate Ar-$Ni^{I}L_3$ **109**. Thus the reduction of the Ni^{II} species **108** by zinc may involve the formation of a five-coordinate nickelate intermediate **112** (Scheme 30). The latter could form a bridged Zn complex **113** on the surface which would facilitate electron transfer. The effects of halide on the reaction rate correlate with their ability to act as bridging ligands and decrease in the same order $I^- > Br^- >> Cl^- > SO_4^{2-} > F^-$.



Scheme 30.

Recently, Amatore and Jutand[107] carried out a parallel study by performing the reaction in the presence of a cathode and the results support the involvement of Ni^0, Ni^I, Ni^{II} and Ni^{III} (*c.f.* Scheme 29), along with a few refinements. First, the chain initiation involves two distinct sequential transfers of one electron to the Ni^{II} species to generate an unsaturated Ni^0 complex **107**. Second, in the absence of Zn, the rate limiting step is the reductive elimination.

Although catalytic, this biaryl synthesis was unsuitable for selective cross-coupling of aryl halides and resulted in a mixture of biaryl products (Ar-Ar + Ar-Ar′ + Ar′-Ar′). Very recently Caubère and co-workers[132] found that homo-coupling of aryl bromides and chlorides was efficiently achieved with a Ni-containing complex reducing agent NiCRA-byp[4:2:1:2]. The latter was prepared from NaH, *t*-AmONa (*t*-amyl alcohol over Na), and $Ni(OAc)_2$ in the presence of 2,2′-bipyridine (byp) in the molar ratio of

4:2:1:2 respectively. The NiCRA-bpy[132] system allows coupling of substituted phenols and was also efficient in promoting cross-coupling of aryl halides. Indeed, the normal statistical distribution for the biaryl products (Ar-Ar:Ar-Ar′:Ar′-Ar′ = 25:50:25) was superceded by a ratio of 10:81:9 respectively (Example below). Results indicated that cross-coupling was favored by reaction between an easily reduced aryl halides substituted by an electron-donating group with a second aryl halides which contained a halogen less reactive toward low valent Ni species and substituted with an electron-withdrawing group.

Example

	Ar-Ar	Ar-Ar′	Ar′-Ar′
p - MeO-Ar-Br + p - CF_3-Ar′-Cl $\longrightarrow$	10.0	81	9
p - Me_2N-Ar-Br + p - F-Ar′-Cl $\longrightarrow$	13.7	71	15.3

Although not supported by a full mechanistic analysis, Caubère *et al.*[132] suggested that the first step must be an oxidative addition of the most reactive aryl halides with Ni^0 species present in NiCRA. Then the successive steps completing the catalytic cycle could be analogous to those proposed by Colon and Kelsey[127]. Although this reactions has been demonstrated to be catalytic in Ni^0, it remains that for synthetic purposes, stoichiometric amounts of $Ni(OAc)_2$ must be employed, otherwise side reactions such as reduction producing arene predominate.

In conclusion, the different catalytic cycles discussed are not to be viewed as opposite or contradictory but rather as mechanistic sequences whose relative importance vary as a function of the exact experimental conditions. For instance, in the Tsou and Kochi[103] proposal (Scheme 25) the Ni^{II} is oxidized to Ni^{III} by Ar-X; this is favored under a non-reducing environment. On the other hand Colon and Kelsey[127] (Scheme 29) proposed that Ni^{II} is reduced to Ni^{I} by Zn and this is favored under excess of homogenous reductant.

Based on the elegant and thorough mechanistic studies by Tsou and

Kochi[103], the paramagnetic Ni^{I} and Ni^{III} species are recognized as relevant intermediates in the catalyzed synthesis of biaryl from aryl halides. Further research may provide refinements of this mechanistic model, but it is suspected that the crucial role played by Ni^{I} and Ni^{III} will remain a central feature for the coupling of aryl halides.

2.1.8.2 Effect of the Solvent

It was found from previous studies[133] in our laboratory that the choice of solvent may have an effect on the Grignard-Wurtz reaction. Different kinds of solvents have been employed in order to find out the effect in terms of yield. A desired solvent would readily generate the Grignard reagent to give a high yield of cross-coupled product, preferably in the absence of heat. For example, in the Grignard-Wurtz reaction for the preparation of α-terthienyl 3, GC analysis has shown the presence of many side products.

TABLE I. Study of the Yields of α-Terthienyl 3 Obtained using Various Ether Solvents.[133]

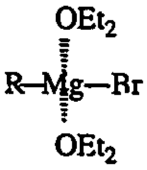
Solvents	Isolated Yield % of α-Terthienyl 3
Diethyl ether	73
n-Propyl ether	70
n-Butyl ether	55
Di*iso*propyl ether	*
Dimethoxyethane	16
Tetrahydrofuran	47
Tetrahydrofuran and Diethyl ether	45
1,4-Dioxane	*

* No reaction

Results obtained for the preparation of α-terthienyl 3 in various ethers as solvent are presented in TABLE I[133].

As shown in TABLE I, the solvent diethyl ether and *n*-propyl ether seem to be the solvents of choice for the synthesis of α-terthienyl 3. However, a large scale preparation of α-terthienyl 3 performed in *n*-propyl ether resulted in rather low yield. For instance, THF appeared to decrease the reaction yield considerably (47%), giving rise to a large amount of homo-coupled Grignard product and a small quantity of unreacted starting material. It was shown from NMR studies that aryl Grignard reagents decrease the formation of ArMgX in THF compared to diethyl ether.

$$2\,RMgX \rightleftarrows R_2Mg + MgX_2$$



$$R{-}\underset{\underset{OEt_2}{\vdots}}{\overset{\overset{OEt_2}{\vdots}}{Mg}}{-}Br$$

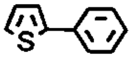
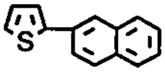
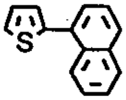
Kumada *et al.*[115] had found diethyl ether to be superior to THF although the reaction occurs more rapidly and without difficulty. THF may bind with the Ni catalyst, therefore inhibiting the approach of the organic halides[115] and preventing the formation of the organo-Ni complex. Among other solvents employed, *n*-butyl ether gave a modest yield (55%), whereas di*iso*propyl ether and dioxane gave unsuccessful results. DME was found to give poor results as well. These results are in agreement with previous findings in the literature[134].

2.1.9 Analogues and Derivatives of α-Terthienyl 3 Previously Synthesized.

For the past few years, our laboratory has embarked on a program to prepare both analogues and derivatives of α-T 3 and related compounds (e.g. α-dithienyl derivatives). Many analogues of α-T 3 have been prepared in our laboratory[133] and elsewhere. A list of these appears in TABLE II. Several derivatives of α-T 3 were previously synthesized in our laboratory[133,135] and are shown in TABLE III. Because of the demonstrated phototoxicity of α-T 3 toward certain insect pests, efforts have been made to elucidate the mechanism of action and to establish what structural features may enhance the biological activity of these potent phototoxins.

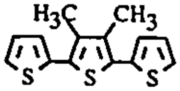
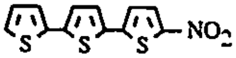
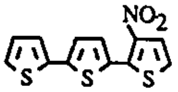
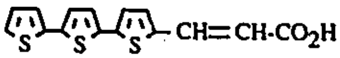
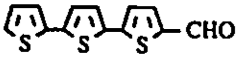
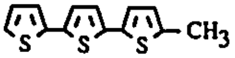
A discussion of the biological activity of some of these compounds is found in Section 2.6.

TABLE II. Analogues of α-Terthienyl 3 Previously Synthesized.[133]

No.	Compounds	References
114*		71
115*		71
116*		136[a]
117*		136[b]
118*		95, 135
119*		96, 138, 104
120		94, 136
121		94, 136
122		94, 136
3*		95, 135
123		137

* Synthesized in our laboratory.[133]

TABLE III. Derivatives of α-Terthienyl <u>3</u> Previously Prepared in our Laboratory.[133,135]

No.	Compounds	Yield %
<u>3</u>		75
<u>124</u>		*
<u>125</u>		82
<u>126</u>		17
<u>127</u>		*
<u>128</u>		43
<u>129</u>		47
<u>130</u>		85
<u>131</u>		30
<u>132</u>		70
<u>133</u>		71
<u>134</u>		45
<u>135</u>		24
<u>136</u>		57
<u>137</u>		26
<u>138</u>		16
<u>139</u>		82

* Obtained as an unseparable mixture of (<u>3</u> & <u>124</u>) and (<u>3</u> & <u>127</u>) isomers.

2.2 ANALOGUES AND DERIVATIVES OF α-TERTHIENYL

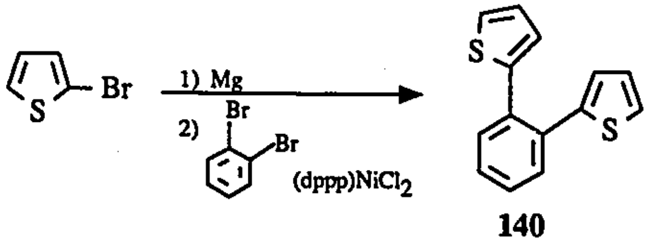
In this section, the synthesis of analogues and derivatives of α-terthienyl 3 will be described and a list of these compounds is given in TABLE IV.

2.2.1 Analogues of α-Terthienyl 140 and 141

In order to determine if the activity of α-T 3 is related to the type of aromatic unit involved, three geometrical isomers were prepared, *para* [1,4-(di-2′-thienyl)-benzene] 117, *meta* [1,3-(di-2′-thienyl)-benzene] 118 and *ortho* [1,2-(di-2′-thienyl)-benzene] 140. A fourth compound 141 in which the phenyl unit is attached at one end of the molecule was also prepared (TABLE IV). All the compounds listed in TABLE II, including 140 and 141 in TABLE IV, were synthesized by the Kumada procedure[91].

1,2-(Di-2′-thienyl)-benzene 140

By adaptation of the Kumada procedure, two equivalents of 2-thienyl magnesium bromide generated *in situ*, were coupled with the readily available 1,2-dibromobenzene in the presence of (dppp)$NiCl_2$ as catalyst (Scheme 31) yielding 1,2-(di-2′-thienyl)-benzene 140 in low yield (3%). Repeating the experiment with longer reaction and reflux time did not improve the yield.



140

Scheme 31.

TABLE IV. Derivatives and Analogues of α-Terthienyl **3**.

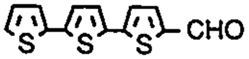
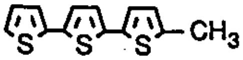
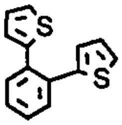
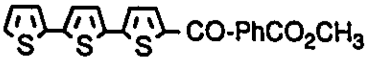
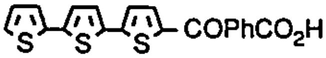
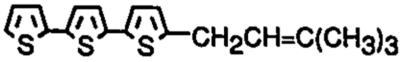
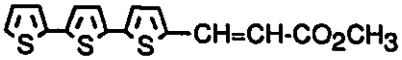
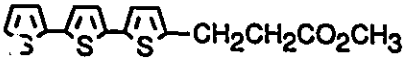
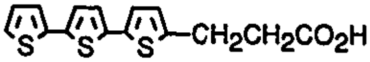
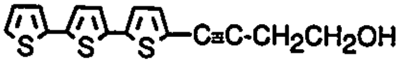
No.	Compounds	Yield %
3		75
130		75
131		75
132		56
133		71
134		*
135		*
136		*
137		*
138		65
140		3
141		30
142		56
143		44
144		67
145		14
146		35
147		44

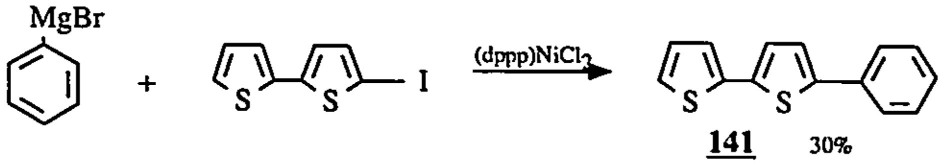
TABLE IV (continued)

No.	Compounds	Yield %
148		92
149		*
150		80
151		45
152		*
153		60
154		75
155		100
156		15
157		92
158		70
159		80
160		94
161		15
162		15
163		15
164		15
165		70

* Obtained as an inseparable mixture of 5- and 5,5″- isomers.

5-(2,2′-Dithienyl)-benzene 141

Using similar coupling methodology, phenyl magnesium bromide was treated with 5-iodo-2,2′-dithienyl (Scheme 32) to afford 5-(2,2′-dithienyl)-benzene 141 in reasonable yield (30%). The preparation 5-iodo-α-dithienyl is described in Part III.



Scheme 32.

2.2.2 DIRECT SUBSTITUTION OF α-TERTHIENYL 3

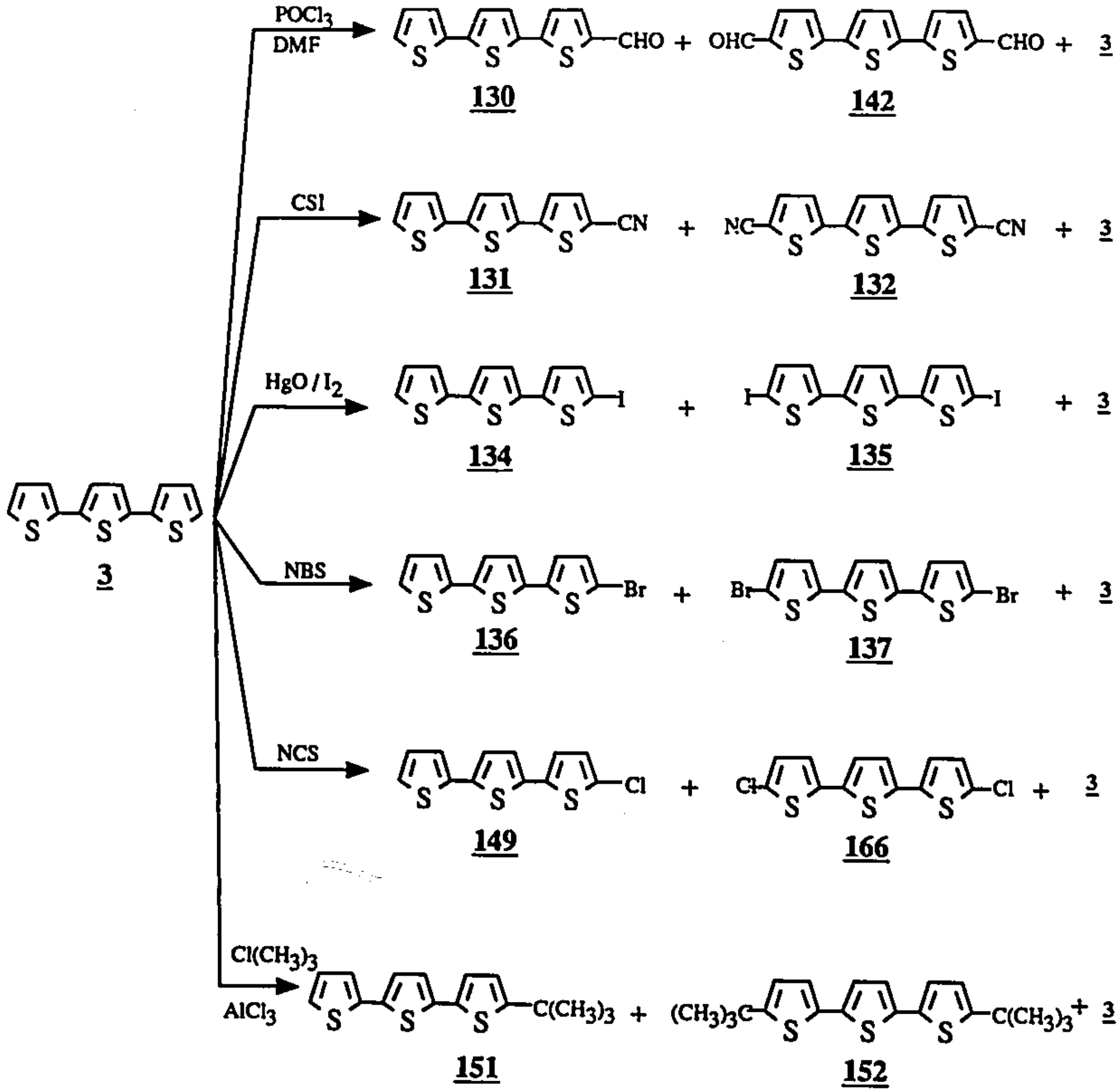
Having developed a reproducible and large scale synthesis of α-terthienyl 3, the latter proved a useful substrate[136] for the introduction of substituents. TABLE III summarizes the derivatives previously prepared and yields reported are from unoptimized reactions conditions. The synthesis of additional derivatives of α-T 3 enabled us to expand the potential insecticidal activity profile of α-terthienyl 3. TABLE IV shows several compounds which were synthesized subsequently.

Investigation of the effect of substituents on the activity of α-T 3 began with the introduction of polar functions on α-terthienyl 3. This was accomplished in two ways.

Method 1. α-Terthienyl 3 was subjected to classical electrophilic aromatic substitution. Scheme 33 summarizes all the compounds prepared from α-terthienyl 3 by this method.

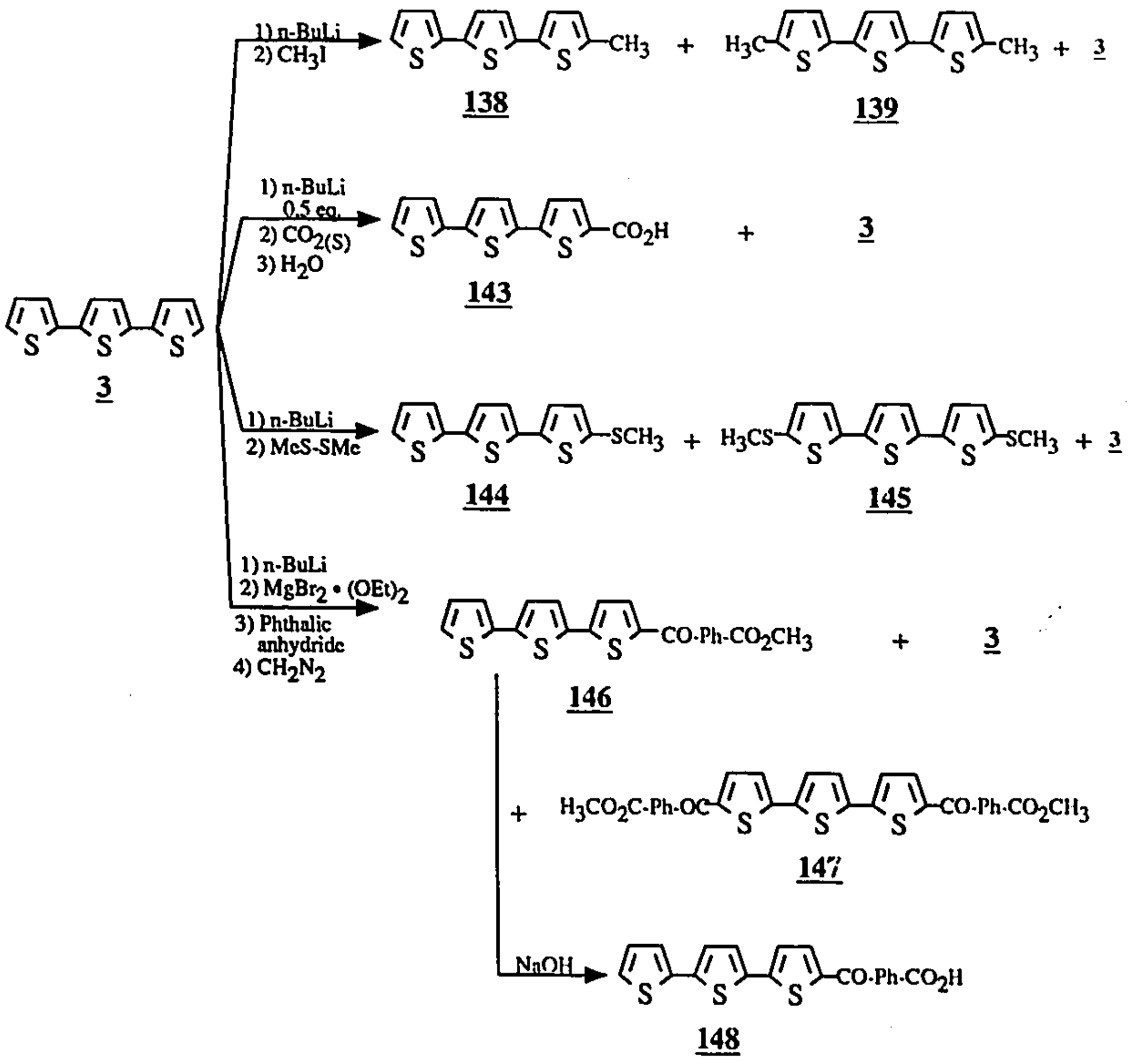
Method 2. α-Terthienyl 3 was lithiated by treatment with *n*-BuLi at -30°C and the resulting anion was quenched with various electrophiles. Scheme 34 summarizes the compounds obtained from α-terthienyl 3 using this methodology.

Method 1



Scheme 33. Electrophilic Aromatic Substitution of α-Terthienyl 3.

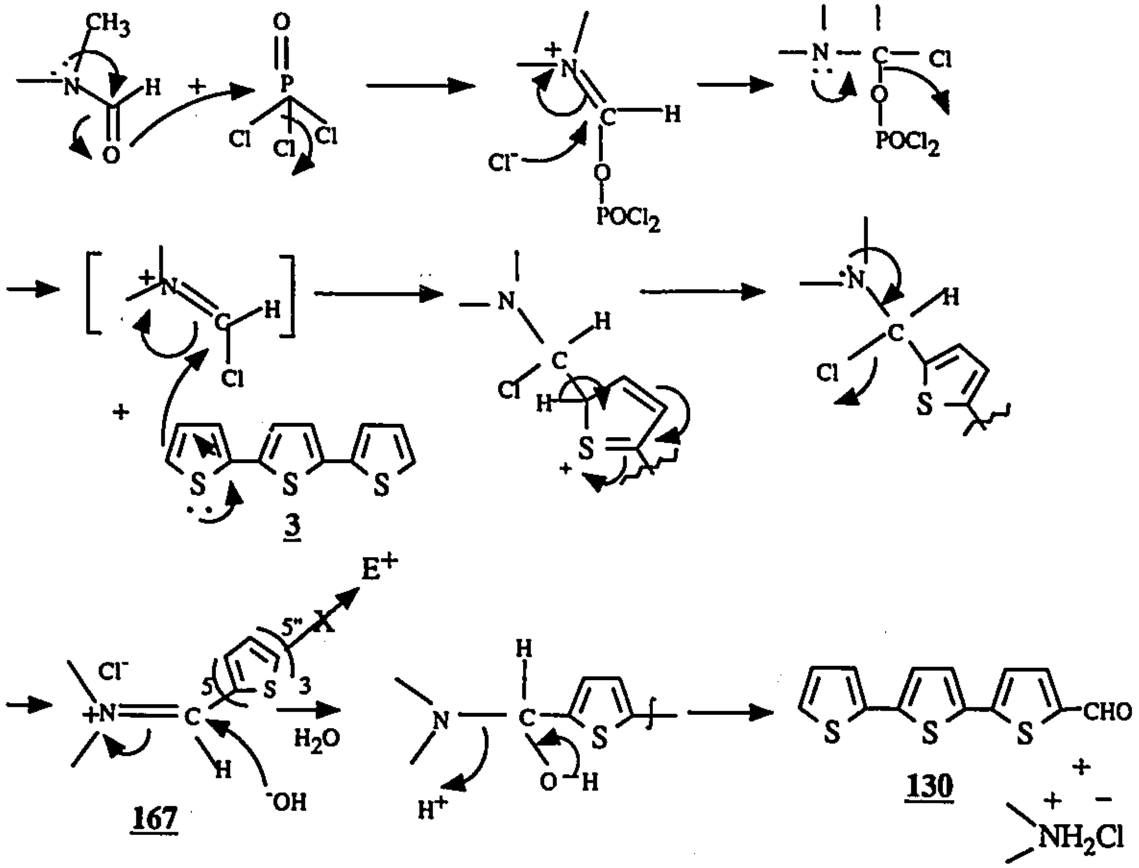
Method 2



Scheme 34. Lithiation of α-Terthienyl 3 Followed by Addition of an Electrophile.

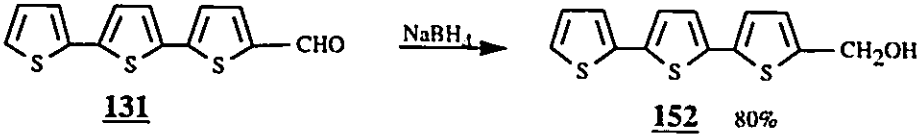
2.2.2.1 Mono and Diformyl-α-terthienyl 130, 142

Following the Nakayama procedure[137], 5-formyl-2,2′:5′,2″-terthienyl 130 was prepared[135] from α-T 3 in 75% yield by modification of the Vilsmeier formylation[138,139] reaction using phosphorus oxychloride (3 equivalents) and dimethylformamide and heating at 70°C for 1 hour. Identical treatment of the 5-formyl-α-T 130 gave 5,5″-diformyl-α-terthienyl 142, in 56% yield. The addition of more $POCl_3$ and DMF did not improve the yield of the mono formyl-α-T. A plausible explanation for this is that the formation of the 5-mono iminium salt 167 (Scheme 35) deactivates the 5″-position of α-terthienyl 3 toward subsequent electrophilic aromatic substitution.



Scheme 35.

Sodium borohydride reduction (Scheme 36) of 5-formyl-α-terthienyl 130,

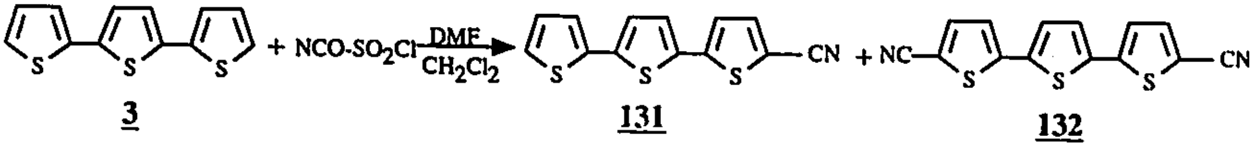


Scheme 36.

previously obtained by formylation of α-terthienyl 3, gave 5-hydroxymethyl-α-terthienyl 150 in 80% yield.

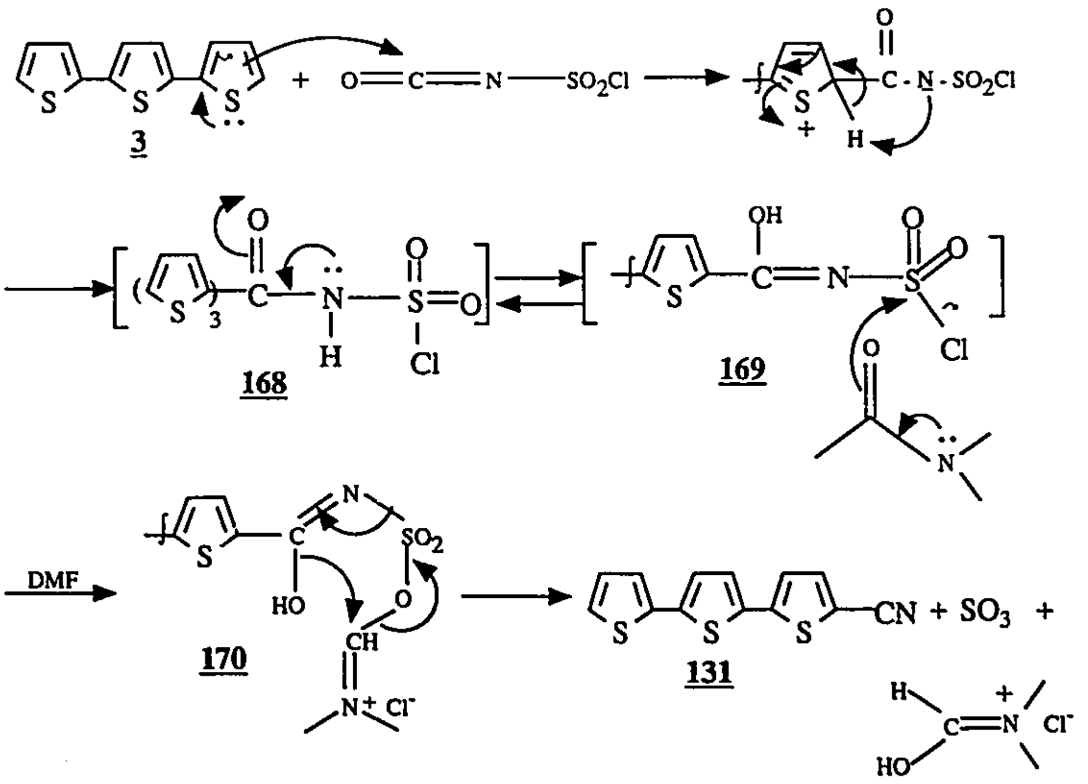
2.2.2.2 Preparation of Mono and Dicyano-α-terthienyl 131, 132

5-Cyano-2,2′:5′,2″-terthienyl 131 was obtained by adapting the cyanation procedure of Lohaus[140,141] to α-T 3. In previous work[133] the title compound 131 was obtained by treating α-T 3 with 2 eq. of chlorosulfonyl isocyanate (CSI) in dichloromethane at room temperature (Scheme 37). The 5-amide N-sulfonyl chloride of α-terthienyl 168 (Scheme 38) generated *in situ* gave, upon addition of dimethylformamide, a mixture of 5-cyano-α-T 131 (58%) and 5,5″-dicyano-α-terthienyl 132 (31%). Careful



Scheme 37.

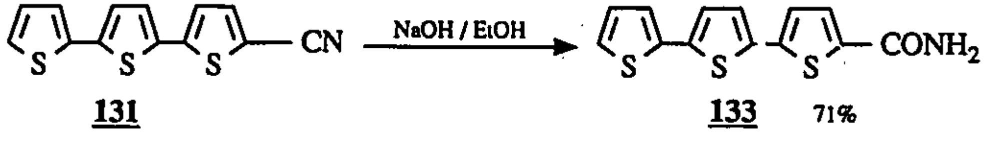
analysis of the experimental conditions revealed that the same reaction at lower temperature (-30°C) with 1.2 eq. of CSI resulted in the formation of the monocyano product 131 in greater yield (75%). The mechanism of this reaction proposed by Lohaus[140] involves displacement of the chloride ion (Scheme 38) on the tautomer 169 of the chlorosulfonyl intermediate 168 forming a six-membered transition state 170 which decomposes to liberate the cyanated compound 131.



Scheme 38.

2.2.2.3 Preparation of α-Terthienyl-5-carboxamide 133

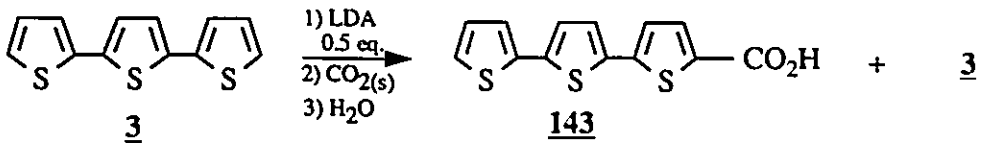
α-Terthienyl-5-carboxamide 133 was prepared by treating the 5-cyano-α-T derivatives 131 (Scheme 39) with NaOH in ethanol. Column chromatography of the crude product gave a yellow solid (71% yield) identified as α-terthienyl-5-carboxamide 133.



Scheme 39.

2.2.2.4 Preparation of α-Terthienyl-5-carboxylic Acid 143

This derivative was first prepared by Kagan[142] (Scheme 40) using lithiation (LDA 0.5 eq.) methodology on α-terthienyl 3[143]. Generation of the anion followed by treatment with $CO_{2(s)}$ resulted, after chromatographic separation, in a mixture of 143 (44%) and unreacted α-T 3 (50% yield).

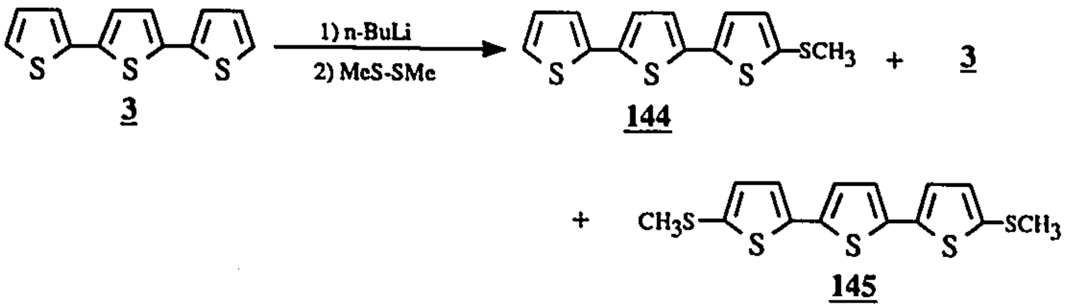


Scheme 40.

Using more than 0.5 eq. of LDA produced a mixture of mono- and dicarboxylic acids along with some α-terthienyl 3.

2.2.2.5 Mono- and Dithiomethyl-α-terthienyl 144 and 145

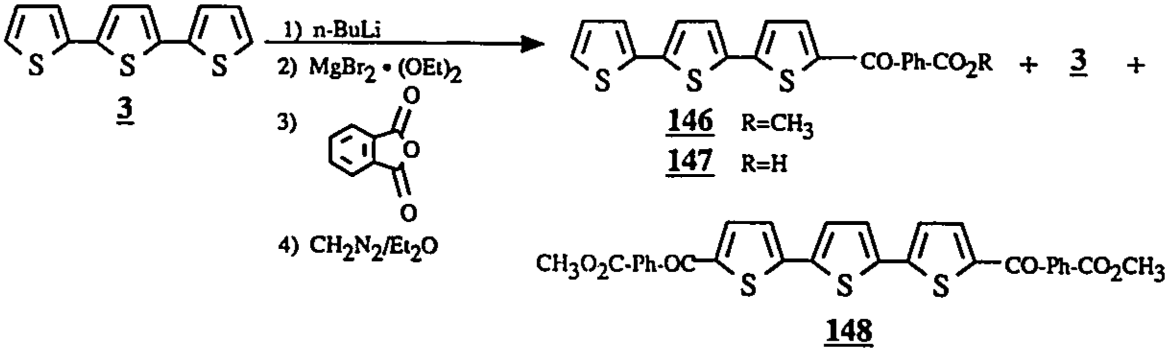
In this case, α-T 3 was lithiated with *n*-BuLi, and quenched with dimethyl disulfide (Scheme 41) to gave a mixture of 5-thiomethyl-α-T 144 (67%) and 5,5″-dithiomethyl-α-terthienyl 145 (14%)[144]. Both compounds 144 and 145 were separated adequately on silica since the substituents were sufficiently polar.



Scheme 41.

2.2.2.6 Methyl Ester of Mono- and Dicarboxybenzoyl-α-terthienyl 146 and 148

A mixture of mono and disubstituted derivatives was obtained by nucleophilic attack of α-T 3 (Scheme 42) on an equivalent amount of phthalic anhydride. Since the mixture could not be easily separated on silica, the crude product was methylated with an ethereal diazomethane solution. Separation of the methylated mixture on silica gave two major products, the methyl monosubstituted ester derivative 146 (35%) and the disubstituted ester derivative 148 (44%) along with a small amount of α-terthienyl 3 (12%). Compound 146 was hydrolyzed to yield 5-(2‴-carboxybenzoyl)-α-terthienyl 147 as a pure product in almost quantitative yield.



Scheme 42.

2.2.2.8 Halogenated Derivatives of α-Terthienyl: I, Br, Cl.

Early attempts to prepare halogenated derivatives of α-terthienyl 3 in our laboratory[133] were based on adaptations[145] of a published literature[146] procedure for the introduction of substituents on thiophene.

Mono- and Diiodo-α-terthienyl 134 and 135

Utilizing the method of Minnis[145b], of α-T 3 was treated with HgO and I_2 in $CHCl_3$ to give a mixture of 5-iodo 134 and 5,5″-diiodo-α-terthienyl 135 along with unreacted starting material[133]. After several silica chromatographic column separations, 5-iodo-α-T 134 was obtained in 45% yield. An alternative procedure was to treat α-T 3 with a saturated solution of mercuric chloride and the mercuric chloride salt of α-T 3 thus obtained was treated with iodine for 24 hours. Soxhlet extraction of the reaction mixture with CH_2Cl_2 and evaporation of the solvent gave a mixture consisting of 5-iodo-α-T 134 and unreacted α-T 3, but the former could not be separated from the latter[133].

Mono- and Dibromo-α-terthienyl 136 and 137

Bromination[147,148] of α-T 3 by treatment with N-bromosuccinimide (NBS) led to a mixture of 5-bromo-α-T 136 and 5,5″-dibromo-α-T 137 with unreacted α-T 3[133]. This mixture was extremely difficult to separate into its components on silica gel and only partial purification could be achieved.

Mono- and Dichloro-α-terthienyl 139 and 166

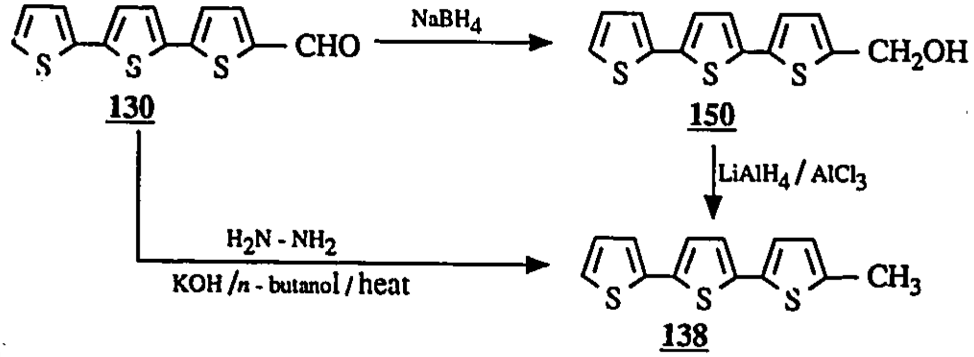
Similar to the bromination of α-T 3, a mixture of mono 139 and dichlorinated-α-T 166 was obtained when α-T 3 was treated with N-chlorosuccinimide. Although the chlorinated products could be detected by TLC and GC, they could not be sufficiently purified to be used in further studies[133].

2.2.3 ALKYL DERIVATIVES OF α-TERTHIENYL 3

2.2.3.1 Preparation of 5-Methyl-α-terthienyl 138

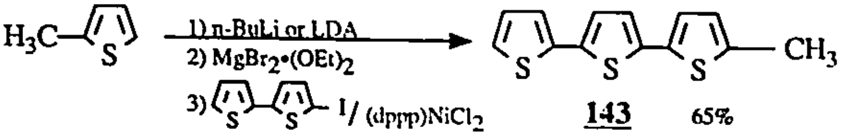
Since the 5-methyl derivative of α-T 3 is a naturally occurring compound in *T. erecta*[11] and contains an electron-donating group, it was of interest to prepare this compound for biological evaluation. Two syntheses of 5-methyl-α-T 138 had been attempted previously[133]. The first synthesis of 5-methyl-α-T 138 made use of the Grignard-Wurtz cross-coupling reaction between 5-iodo-α-T 134 and methyl magnesium iodide in the presence of (dppp)NiCl_2 as catalyst. On work up, only a small amount of 5-methyl-α-T 138 was detected along with other polymeric components by GC analysis. In the second synthesis, the methyl group was introduced *via* lithiation of α-T 3 to yield, after stirring at r.t. for 24 hours, a mixture of 5-methyl-α-T 138, 5,5″-dimethyl-α-T 139 and unreacted α-T 3 as determined by HPLC. Attempts to separate this mixture by silica column chromatography were not successful. Although small amounts of 5-methyl-α-T 138 and 5,5″-dimethyl-α-T 139 could be isolated in pure forms by HPLC using a reverse phase column, this procedure was unsuitable for the preparation of larger quantities of pure 5-methyl-α-T <u>138</u> required for biological screening. A solution to this problem was to start from an easily available pure monosubstituted α-T whose functional group could be transformed into a methyl substituent. 5-Formyl-α-T <u>130</u> was selected as a potential candidate to fulfill these requirements.

5-Formyl-α-terthienyl <u>130</u> prepared as described in Section 2.4.2.1, was subjected to a Huang-Minlon modification[145a] of the Wolff-Kishner reduction[146,149b] to give the corresponding hydrazone (Scheme 43) which, on heating with alkali, gave 5-methyl-α-terthienyl <u>138</u>. While the yield was as high as 93% on small scale (100 mg), it could not be reproduced for larger scale preparation. However, it was found that stepwise reduction of the formyl group to the methyl substituent was more suitable for large scale production. Thus, 5-hydroxymethyl-α-terthienyl <u>150</u> obtained by sodium borohydride reduction of the aldehyde <u>130</u> was further reduced with lithium aluminum hydride in the presence of aluminum chloride[148] to afford the methyl derivative <u>138</u> in 91% yield.



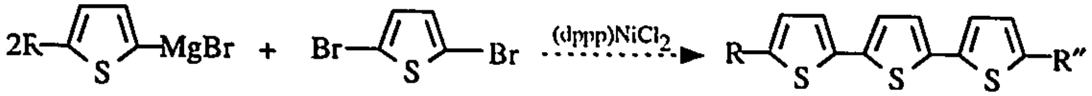
Scheme 43.

Although 5-methyl-α-T <u>138</u> could be prepared by stepwise reduction of 5-formyl-α-T <u>130</u>, the fact that the biological activity of 5-methyl-α-T was higher than that of α-T <u>3</u> prompted the investigation of more efficient syntheses for this compound. A convergent synthesis was developed and found to be suitable for multigram production of **138**. Lithiation of the readily available 2-methylthiophene with LDA (Scheme 44) at -30°C, conversion to the Grignard reagent and coupling *in situ* with 5-iodo-α-dithienyl gave the desired compound 138 (65%).



Scheme 44.

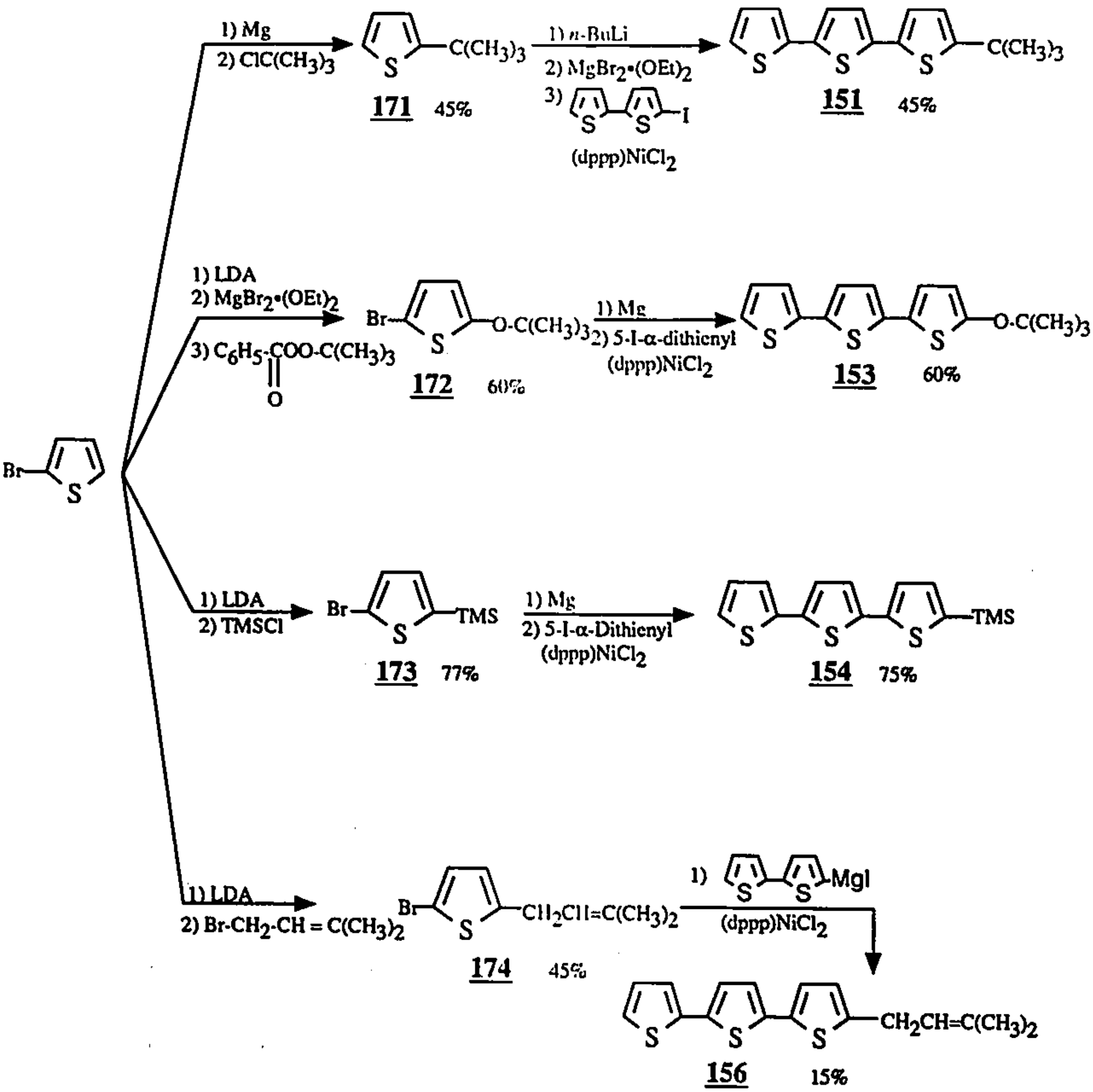
This method offers the possibility of preparing 5,5″-disubstituted derivatives of α-terthienyl 3 by simply coupling two equivalent of the Grignard reagent of monosubstituted thiophene (Scheme 45) with 2,5-dibromothiophene. However, this



Scheme 45.

methodology was not exploited since the disubstituted derivatives of α-T 3 generally tend to be less active (see Section 2.6) than the monosubstituted analogues.

Using the methodology[150] shown in Scheme 44 for the large scale preparation of 5-methyl-α-terthienyl 138, other non-polar substituents, including *t*-butyl, *t*-butoxy, trimethylsilyl, and 3-methyl-2-butenyl could now be introduced. Thus, the desired non polar groups were first introduced on thiophene or 2-bromo-thiophene and subsequent reaction with 5-iodo-α-dithienyl under the Grignard-Wurtz coupling conditions gave, after chromatographic separation or simple crystallization, the pure monosubstituted derivatives of α-terthienyl 3. The success of this methodology relies on the ease of purification of the 2-substituted-thiophene and the 2-bromo-5-substituted-thiophene (Scheme 46).


1) Mg
2) ClC(CH3)3
C(CH3)3
171 45%
1) n-BuLi
2) MgBr2•(OEt)2
3)
I
(dppp)NiCl2
C(CH3)3
151 45%
1) LDA
2) MgBr2•(OEt)2
3) C6H5-COO-C(CH3)3
O
Br
O-C(CH3)3
172 60%
1) Mg
2) 5-I-α-dithienyl
(dppp)NiCl2
O-C(CH3)3
153 60%
Br
S
1) LDA
2) TMSCl
TMS
173 77%
1) Mg
2) 5-I-α-Dithienyl
(dppp)NiCl2
TMS
154 75%
1) LDA
2) Br-CH2-CH = C(CH3)2
CH2CH=C(CH3)2
174 45%
1)
MgI
(dppp)NiCl2
CH2CH=C(CH3)2
156 15%

Scheme 46.

2.2.3.2 Preparation of 5-*t*-Butyl-α-terthienyl 151

The synthesis of 5-*t*-butyl-α-terthienyl 151 had been attempted[133] previously by a Friedel-Craft alkylation of α-terthienyl 3 with the use of $AlCl_3$ as Lewis-acid catalyst[151]. This reaction yielded a mixture of mono-151 and disubstituted α-T 152 (Scheme 33) along with unreacted α-terthienyl 3. Pure 5,5″-*t*-dibutyl-α-terthienyl 152 was obtained after several separations on a silica column. The remaining material, including 5-*t*-butyl-α-T 151 and α-T 3, could not be separated further[133].

Alternatively, 151 was obtained using the approach used for the preparation of 5-methyl-α-T 138. 2-*t*-Butylthiophene 171, prepared according to a literature procedure[152], was treated with *n*-BuLi followed by $MgBr_2{\cdot}OEt_2$. Coupling of the resulting Grignard reagent with 5-iodo-lithiodithienyl (Scheme 46) *in situ* afforded 5-*t*-butyl-α-terthienyl 151 in 45% yield.

2.2.3.3 5-*t*-Butoxy-α-terthienyl 153

Using the methodology described earlier (Scheme 46), 2-bromothiophene was treated with LDA to form the 2-bromo-5-lithiothiophene which was transformed to the Grignard reagent and then treated *in situ* with *t*-butylperoxybenzoate to produce 2-bromo-5-*t*-butoxythiophene[151] 172 (60% yield). Compound 172 was coupled with 5-iodo-α-dithienyl to produce the desired 5-*t*-butoxy-α-terthienyl 153 in good yield (60%). This compound requires storage at low temperature (-10°C) in the dark, otherwise polymerization occurs readily at room temperature and on exposure to natural light.

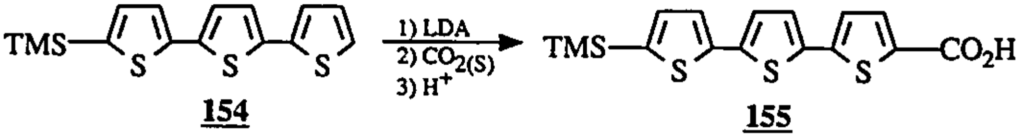
2.2.3.4 5-Trimethylsilyl-α-terthienyl 154

Similarly, 2-bromo-5-trimethylsilylthiophene 173 was prepared starting with 2-bromothiophene, which was lithiated with LDA and subsequently treated *in situ* with trimethylsilylchloride to give 173 in 77% yield[151]. The Grignard reagent of the monomer 173 was coupled with 5-iodo-α-dithienyl yielding 5-trimethylsilyl-α-terthienyl

154 in 75% yield.

2.2.3.5 5-Carboxyl-5″-trimethylsilyl-α-terthienyl 155

With compound 154 in hand, it was possible to introduce a carboxylic acid function at the 5-position. Lithiation of compound 154 (Scheme 47) with one equivalent of LDA followed by treatment with $CO_{2(s)}$ gave, after acidification, the 5-carboxyl-5″-trimethylsilyl-α-terthienyl 155 in quantitative yield.



Scheme 47.

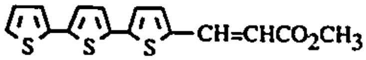
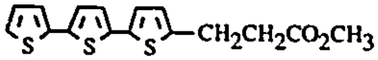
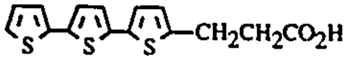
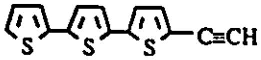
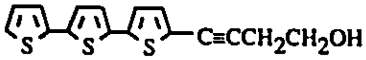
2.2.3.6 5-(3‴-Methyl-2‴-butenyl)-α-terthienyl 156

2-Bromo-5-lithiothiophene was generated *in situ* and treated with 4-bromo-2-methyl-2-butene to give the 2-bromo-5-(3′-methyl-2′-butenyl)thiophene 174 (45% yield). The latter was coupled with the Grignard reagent of 5-iodo-α-dithienyl to provide 5-(3‴-methyl-2‴-butenyl)-α-terthienyl 156 in low yield (15%). Attempts to prepare the Grignard reagent of 174 for further coupling with 5-iodo-α-dithienyl failed. Longer reaction time did not enhance formation of the Grignard reagent of 174 and no product could be isolated on attempts to couple with 5-iodo-α-dithienyl.

2.2.4 ALKENYL DERIVATIVES OF α-TERTHIENYL 3

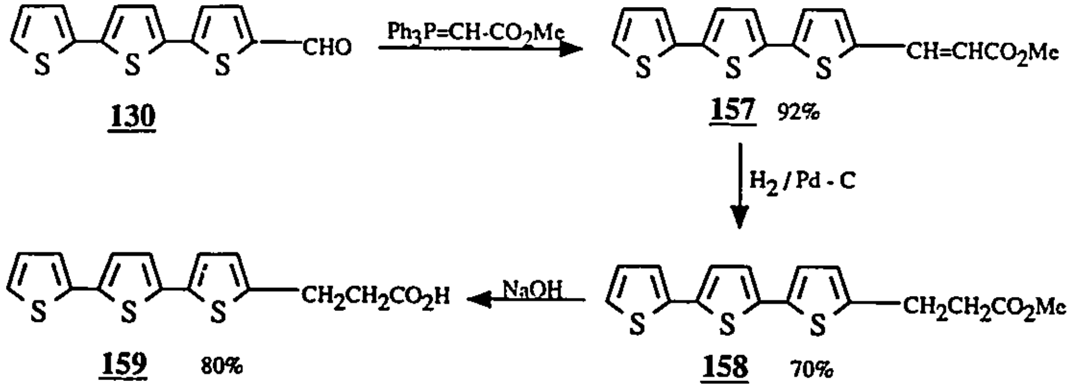
Another feature that we decided to study was the extension of conjugation to the thiophene and/or a combination of both extra conjugation and having linear pyrethrin-type[153a] substituents. Such substituents are found in a class of pesticides which are not phototoxic. The following compounds were prepared: methyl α-terthienyl-5-[(E)-3‴-acrylate] 157, methyl α-terthienyl-5-(3‴-propionate) 158, α-terthienyl-5-(3‴-propionic acid) 159, 5-(2‴-dibromoethenyl)-α-terthienyl 160, 5-(2‴-dichloroethenyl)-α-terthienyl 161 and 5-(2‴-difluoroethenyl)-α-terthienyl 162. A second set of compounds in which the linearity of the substituent is addressed were prepared: 5-ethynyl-α-terthienyl 163, 5-(2‴-prop-1‴-ynyl)-α-terthienyl 164 and 5-(4‴-hydroxybut-1‴-ynyl)-α-terthienyl 165 (TABLE V).

TABLE V. Derivatives of α-Terthienyl 3 with 5-Substituted 1-Alkenyl or 1-Alkynyl.

157	
158	
159	
160	
161	
162	
163	
164	
165	

2.2.4.1 Methyl α-Terthienyl-5[(E)-3‴-acrylate] 157

The well known advantage of the reaction of aldehydes with stabilized phosphorus ylides is that a high degree of selectivity in the geometry of the resulting olefin can be achieved by using the appropriate reaction conditions[153b]. As anticipated, the olefination reaction of 5-formyl-α-terthienyl 130 with the Wittig reagent methyl-(triphenylphosphoranylidene)acetate[153b] in THF (Scheme 48) under reflux for 13 hours, provided methyl-α-terthienyl-5-[(E)-3‴-acrylate] 157 in 92% yield and none of the Z-olefin was detected.



Scheme 48.

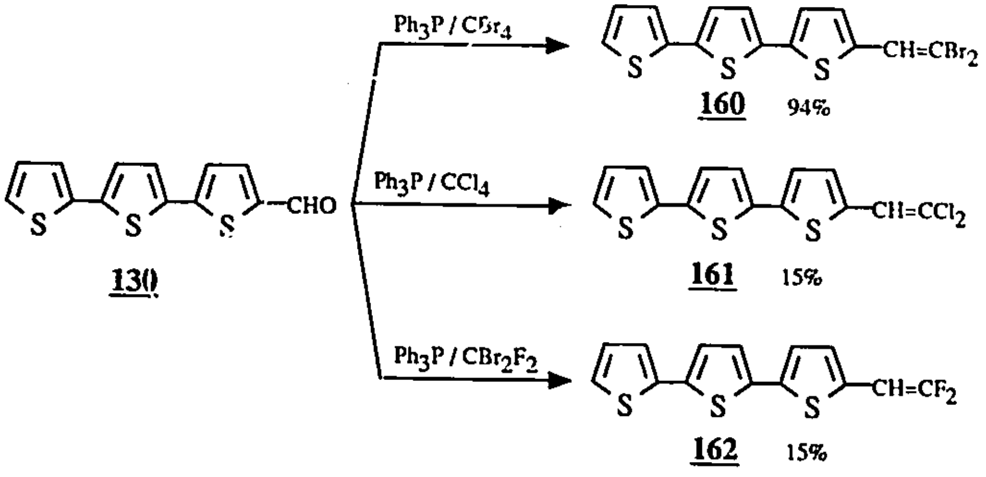
2.2.4.2 Methyl α-Terthienyl-5-propionate 158 and Propionic Acid 159

Methyl α-terthienyl-5-[(E)-3‴-acrylate] 157 was hydrogenated with 10% palladium on carbon (Scheme 48) to afford methyl α-terthienyl-5-(3‴-propionate) 158 in 70% yield. Hydrolysis of 158 with sodium hydroxide in methanol/THF (1:1), yielded α-terthienyl-5-(3‴-propionic acid) 159 in good yield (80%).

2.2.5 GEMDIHALOGENATED 5-ETHENYL-α-TERTHIENYL 160, 161 and 162.

Corey and Fuchs[154] reported the sucessful application of an unstabilized Wittig reagent using triphenylphosphine in the presence of CBr_4 or CCl_4. The phophorus ylide generated, when treated *in situ* with various aldehydes, gave 1,2-addition products as an ylidenedibromide substituent in reasonable yield (60-90%).

This methodology was applied for the preparation of 160 by Kagan and Arora[37]. When triphenylphosphine was treated with CBr_4 in the presence of 5-formyl-α-terthienyl 130, 5-(2‴-dibromoethenyl)-α-terthienyl 160 was obtained in 94% yield. It is crucial that the aldehyde 130 be added within five minutes to the ylid generated *in situ*, otherwise decreased yields were observed, or more likely, the reaction failed completely (Scheme 49). 5-(2‴-Dichloroethenyl)-α-terthienyl 161 was prepared *via* the above procedure using CCl_4 instead of CBr_4 to give a low yield (15%) of 161. Similarly, dibromodifluoromethane was employed with triphenylphosphine in the Wittig reaction with 130 to yield the 5-(2‴-difluoroethenyl)-α-terthienyl 162 (15%).

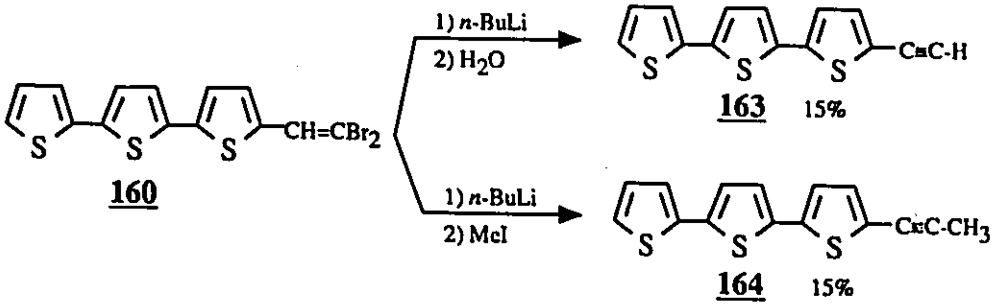


Scheme 49.

2.2.6 5-ETHYNYL α-TERTHIENYL DERIVATIVES 163, 164 and 165

5-Ethynyl-α-terthienyl 163 and 5-(2‴-Prop-1‴-ynyl)-α-terthienyl 164

The aldehyde 130 can transformed into a terminal acetylene by following a known procedure[37]. The dibromoolefin 160 was treated with two equivalents of *n*-BuLi solution in THF (-78°C/1h → 25°C/1h) to generate the lithio derivative of 163 (Scheme 50). Hydrolysis of the latter with water produced 5-ethynyl-α-terthienyl 163 in 15% yield. Generation of the lithioderivative 163 and treatment with methyl iodide gave

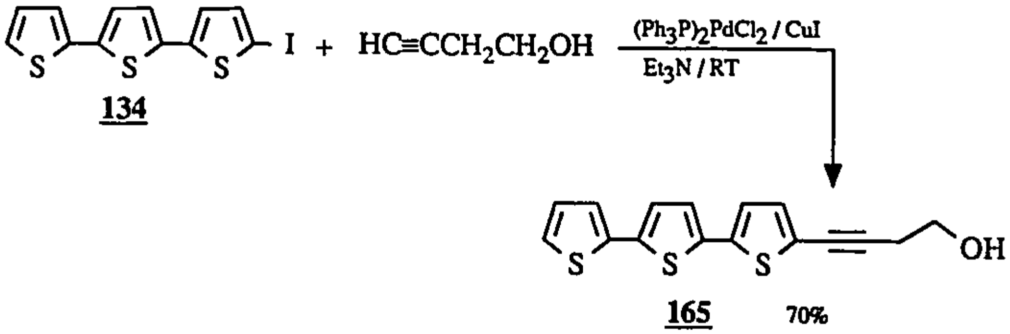


Scheme 50.

5-(2‴-prop-1‴-ynyl)-α-terthienyl 164 in rather low yield.

5-(4‴-Hydroxybut-1‴-ynyl)-α-terthienyl 165

In order to extend the chain on the acetylene functional group, the readily available 1-butyn-3-ol (propargyl alcohol) was coupled with 5-iodo-α-terthienyl 134 in the presence of *bis*(triphenylphosphine)Pd^{II} dichloride as catalyst with copper^{I} iodide to give the 5-(4‴-hydroxybut-1‴-ynyl)-α-terthienyl 165 (Scheme 51) in 70% yield. This coupling reaction is discussed in more detail in Part III.



Scheme 51.

2.3 STRUCTURE DETERMINATION OF α-TERTHIENYL DERIVATIVES

^{1}H NMR spectroscopy was used for structure elucidation of the mono and disubstituted derivatives of α-terthienyl 3. The effect of a substituent on the chemical shift of the monosubstituted thiophene ring protons (TABLE VI) follows a pattern similar to that observed for α-terthienyl 3 (see TABLE VII). The monosubstituted derivatives of α-T 3 (see *Figures 1, 2, 3, 4* and TABLE VII) are easily characterized by the presence of three doublets of doublets for the three protons present on the unsubstituted thiophene ring. Typical J values for these proton-proton couplings are as follow: $J_{5''\text{-}4''} = 5.1 - 5.5$ Hz, $J_{4''\text{-}3''} = 3.5 - 3.7$ Hz and $J_{5''\text{-}3''} = 1.0 - 1.2$ Hz. The remaining four protons exhibit signals with doublets in the $J = 3.4 - 4.0$ Hz range. The C-4′ and C-3′ protons are readily recognized by the close proximity of their chemical shifts, which occur downfield as a

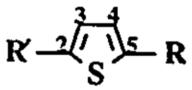


TABLE VI. ^{1}H-Chemical Shifts[155] (δ in ppm relative to TMS) and Coupling Constants (J in Hz) in Substituted Thiophenes.

2- or 5- Substituent	C-2	C-3	C-4	C-5	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{2,5}$
R′=R=H	7.20	6.96	6.96	7.20	4.8	1.0	3.5	2.8
R=CH_3	-0.36	-0.24	-0.29	*	-	-	-	-
R=C≡CH	+0.15	-0.16	-0.12	*	-	-	-	*
R=Br	-0.05	-0.27	-0.11	*	-	-	-	*
R=SCH_3	0.03	-0.18	-0.05	*	-	-	-	*
R=CN	+0.47	0.00	+0.28	*	-	-	-	*
R=CHO	+0.65	+0.10	+0.45	*	-	-	-	*
R=COOH	+0.80	+0.80	+0.40	*	-	-	-	*

* Substituent at C-5

result of the substituent, (deshielded in the case of an electron-withdrawing group and shielded in the presence of electron-donating groups). As predicted, the proton at C-4 is the most affected by the substituent. The substituent has little or no effect on the chemical shifts of protons located on the 2nd and 3rd thiophene rings (see *Figures 1* and *2*). The NMR data for some monosubstituted derivatives of α-T 3 are summarized in TABLE VII.

The ^{1}H NMR spectrum for the 5,5″-disubstituted derivatives are greatly simplified when the substituent are identical. The overall spectrum is reduced to the presence of two doublets for the C-4 and 4″ protons and for the C-3 and 3″protons, and a singlet for the C-3′ and 4′ protons (see *Figures 5* and *6*). The ^{1}H NMR data for some 5,5″-disubstituted-α-terthienyl are summarized in TABLE VIII.

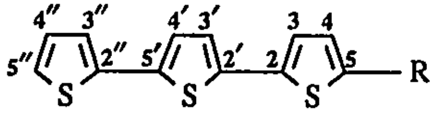


TABLE VII. ^{1}H NMR Data[a] for 5-Substituted Derivatives of α-Tethienyls.

No.	Substituent	H-5″	H-4″	H-3″	H-4′	H-3′	H-3	H-4	Coupling Constants (Hz)					Substituent
	R	(dd, 1H)	(dd,1H)	(dd, 1H)	(d, 1H)	(d, 1H)	(d, 1H)	(d, 1H)	$J_{4''5''}$	$J_{3''5''}$	$J_{3''4''}$	$J_{3'4'}$	$J_{3,4}$	at C-5
3[a]	H	7.43	7.08	7.29	(7.22)	(7.22)	7.29	7.08	5.4	1.0	3.6	3.8	3.8	H
130	CHO	7.50	7.12	7.38	(7.49)	(7.30)	7.47	7.93	5.0	1.0	3.7	3.8	4.0	δ9.9 (s, 1H)
131	CN	7.50	7.12	7.38	(7.42)	(7.46)	7.30	7.81	5.5	1.0	3.5	3.7	3.5	CN
138	CH_3	7.19	6.70	7.13	(6.97)	(7.02)	6.94	6.65	5.1	1.1	3.5	3.6	3.4	δ2.47 (s, 3H)
144[b]	SCH_3	7.44	7.08	7.30	(7.22)	(7.17)	7.17	7.05	5.1	1.1	3.6	3.8	3.7	δ2.5 (s, 3H)
163	C≡CH	7.22	7.01	7.17	(6.99)	(7.06)	7.06	7.16	5.1	1.1	3.6	3.8	3.8	δ3.39 (d, 1H)
164	$C{\equiv}CCH_3$	7.21	7.01	7.16	(7.04)	(7.06)	6.99	6.97	5.1	1.2	3.6	3.8	3.8	δ2.08 (s, 3H)

[a] 300 or 200 MHz ^{1}H NMR.
[b] Acetone-d^6 as solvent, for all other compounds $CDCl_3$ was used.
Numbers in parentheses are tentative assignments.

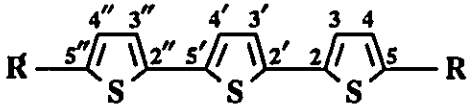


TABLE VIII. ^{1}H NMR Data[a] for 5,5″-Disubstituted Derivatives of α-Tethienyl.

No.	Substituent R=R′	H-4″, 4 (d, 2H)	H-3″, 3 (d, 2H)	H-3′, 4′ (s, 2H)	Coupling Constants (Hz) $J_{3'',4''} = J_{3,4}$	Substituent at C-5″,5
<u>131</u>	CN	7.53	7.15	7.21	3.9	CN
<u>142</u>	CHO	7.68	7.28	7.30	3.5	δ9.86 (s, 2H, C$\underline{H}$O)
<u>145</u>	SCH_3	6.98	6.95	6.99	3.7	δ2.50 (s, 6H, $SC\underline{H}_3$)
<u>152</u>	$C(CH_3)_3$	6.70	6.93	6.95	4.0	δ1.37 (s, 18H, $C(C\underline{H}_3)_3$)
<u>155</u>[b]	R=$Si(CH_3)_3$ R″= COOH	7.26	7.40	7.41	*	δ0.33 (s, 9H, $Si(C\underline{H}_3)_3$) δ2.82 (s, 1H, COO$\underline{H}$)

[a] $CDCl_3$ solvent, 300 or 200 MHz ^{1}H NMR.

[b] ^{1}H NMR for compound <u>155</u>, δ7.26(d, 1H, $J_{4''-3''}$=3.5Hz, H-4″), 7.40(dd, 1H, $J_{3''-4''}$=3.5Hz, H-3″), 7.41(d, 1H, H-4′), 7.72(d, 1H, J_{4-3}=3.9Hz, H-4), 7.29(d, 1H, $J_{3'-4'}$=3.8Hz, H-3′), 7.35(d, 1H, J_{3-4}=3.9Hz, H-3).

* Different Coupling Constants.

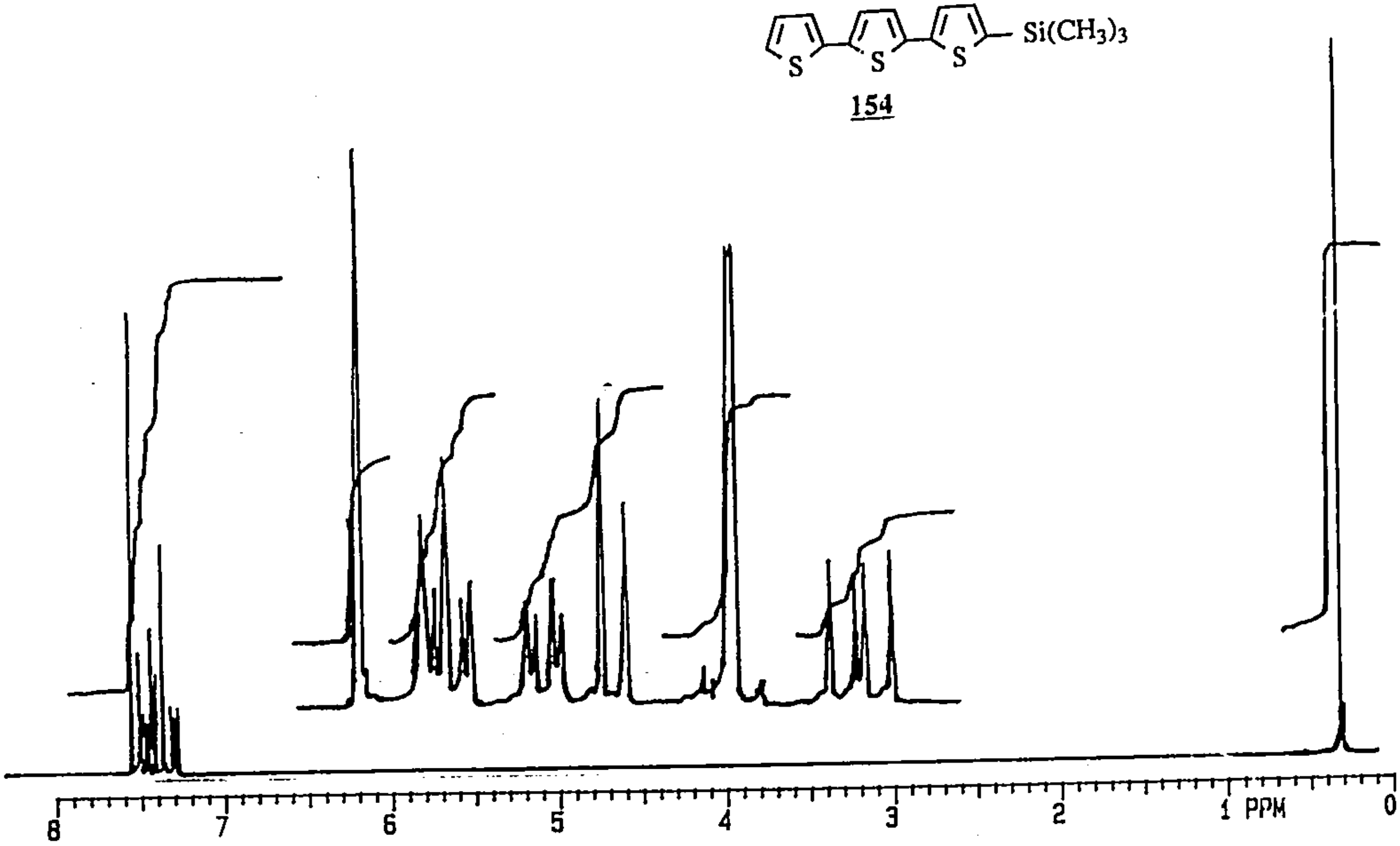


Figure 1. ^{1}H NMR Spectrum of 5-Trimethylsilyl-α-terthienyl <u>154</u>.

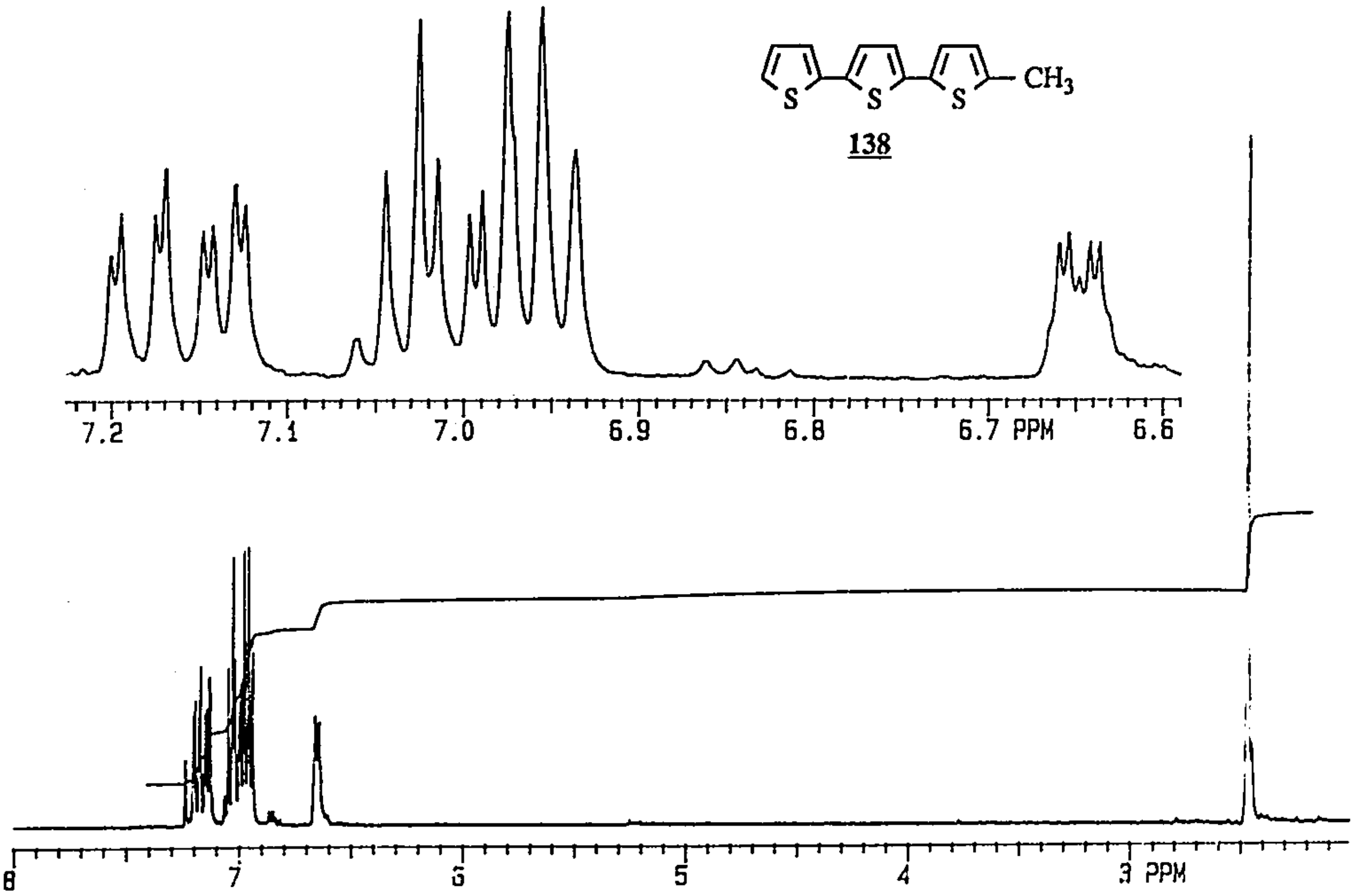
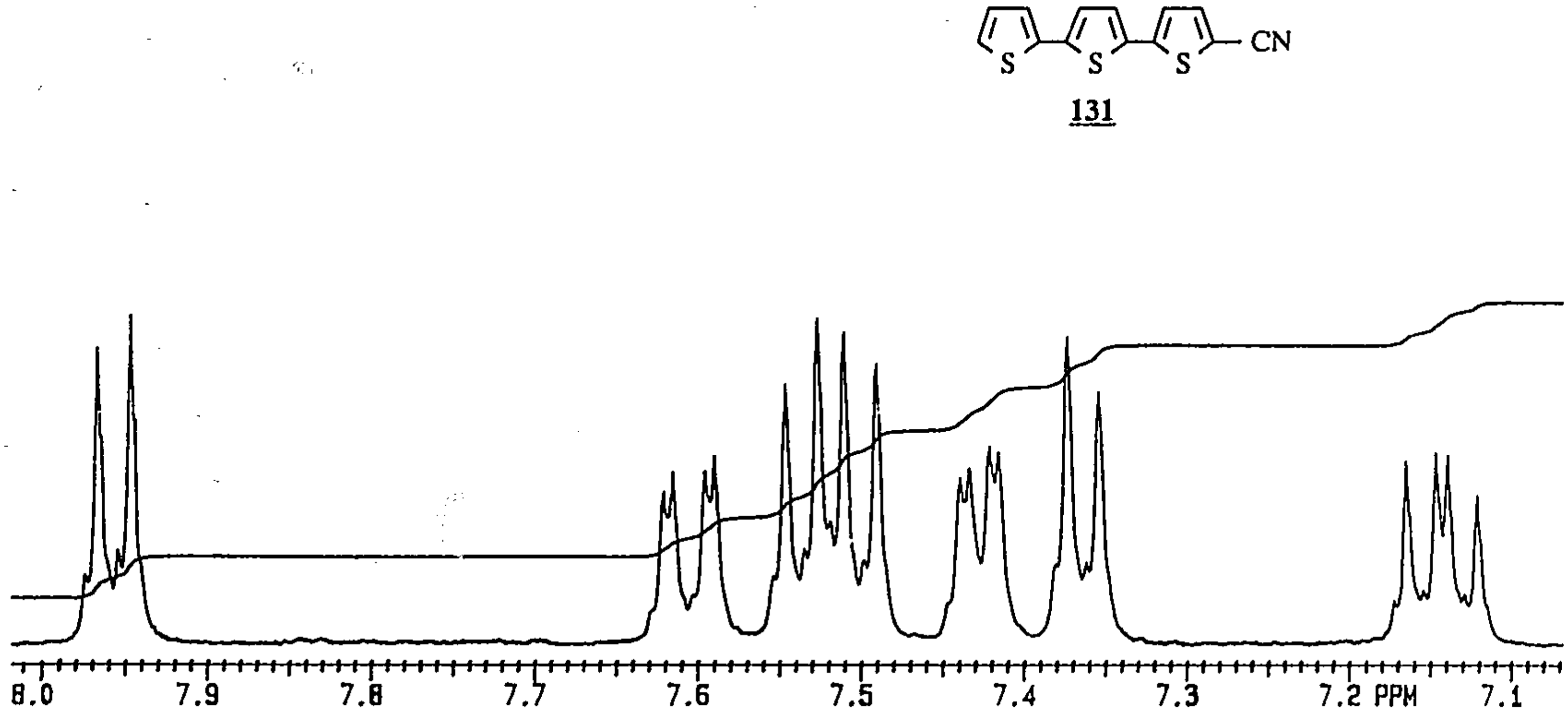


Figure 2. ^{1}H NMR Spectrum of 5-Methyl-α-terthienyl 138, (upper: Expansion of the aromatic terthienyl).



131

Figure 3. ¹H NMR Spectrum of 5-Cyano-α-terthienyl 131.

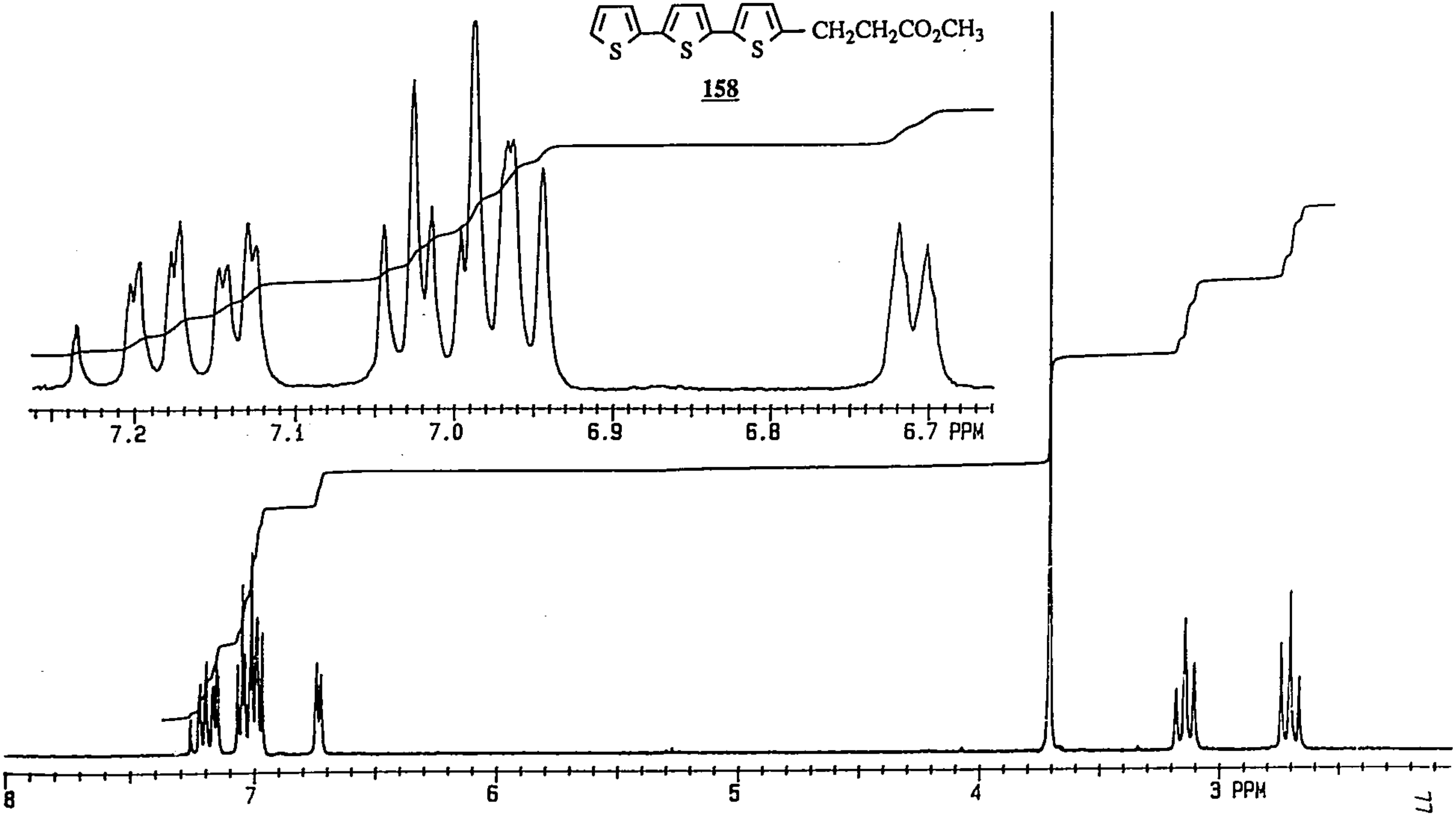
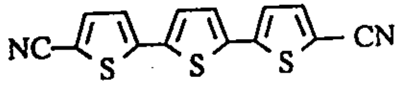


Figure 4. ^{1}H NMR Spectrum of Methyl α-Terthienyl-5-propionate 158.



132

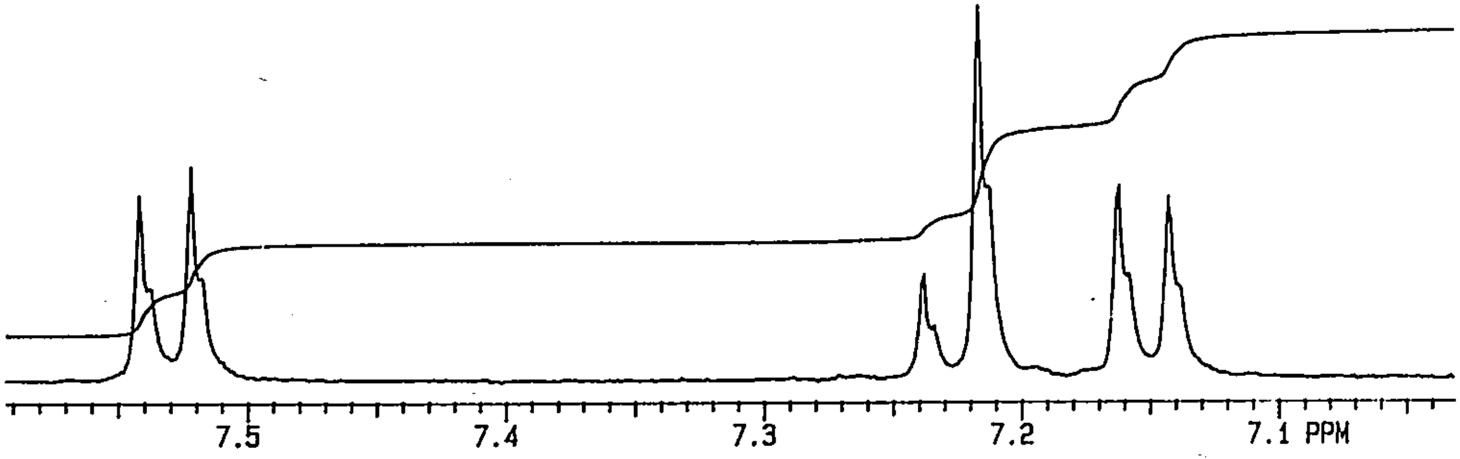


Figure 5. **^{1}H NMR Spectrum of 5,5″-Dicyano-α-terthienyl <u>132</u>.**

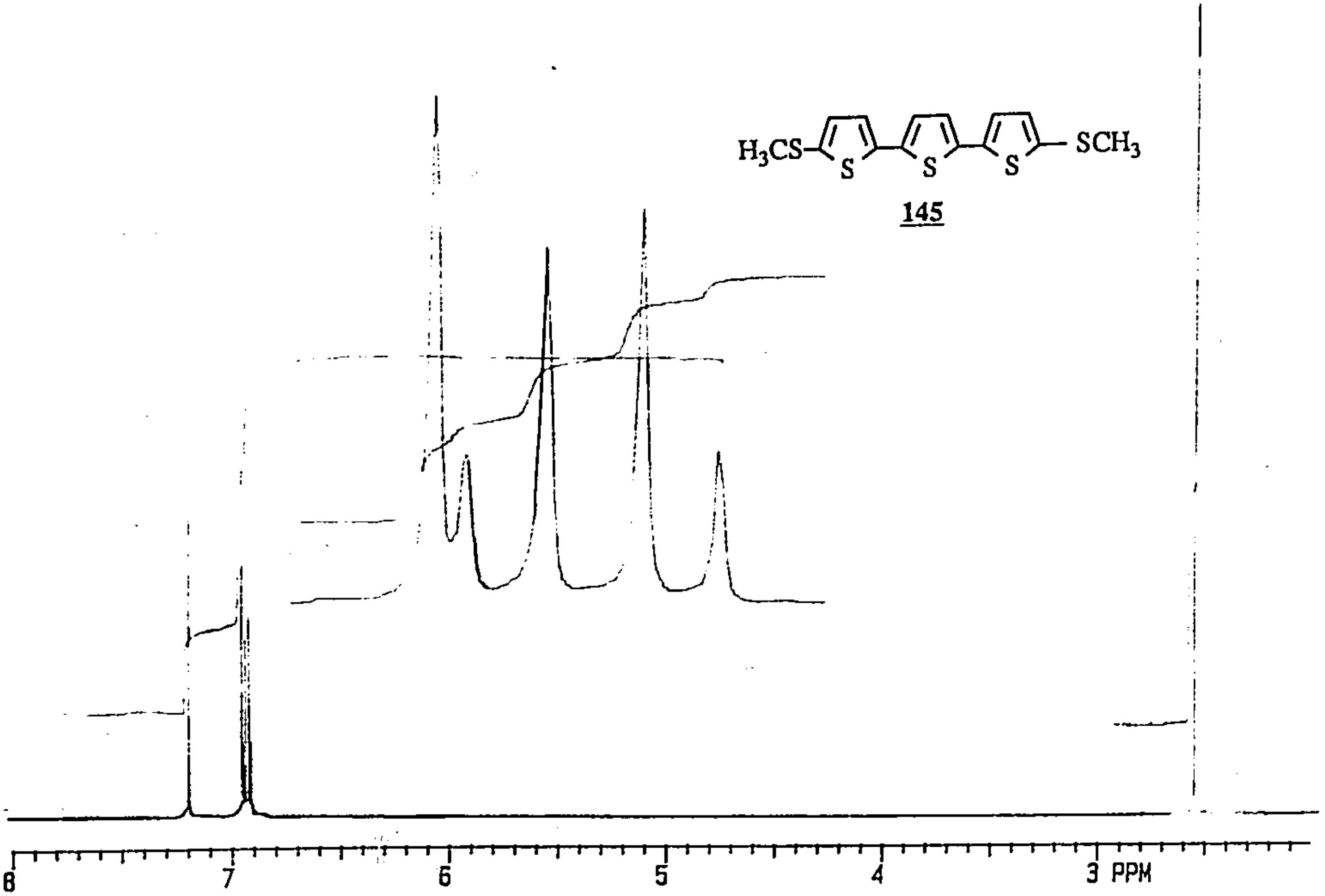


Figure 6. ^{1}H NMR Spectrum of 5,5″-Dithiomethyl-α-terthienyl 145.

TABLE IX. Toxicity of Derivatives and Analogues of α-Terthienyl to Mosquito Larvae (*Aedes Atropalpus*) and Brine Shrimp.

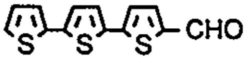
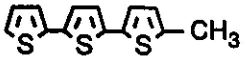
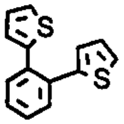
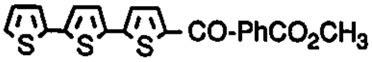
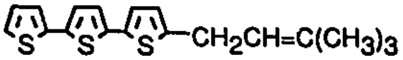
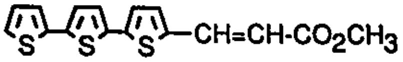
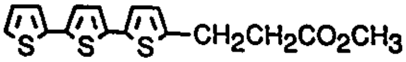
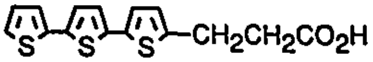
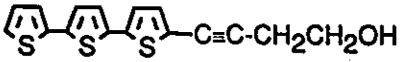
No.	Compounds	Yield %	Biological Activity	
			Mosquito Larvae LC_{50} nM	Brine Shrimp LC_{50} nM
3		75	163	0.75
130		75	132	1
131		75	78	2
132		56	192	6
133		71	1,684	10
134		⊕	*	1
135		⊕	*	8.64
136		⊕	1,337	0.54
137		⊕	3,404	0.99
138		65	259	0.57
140		3	*	*
141		30	*	0.74
142		56	*	27
143		44	3,543	94
144		67	*	0.54
145		14	*	1.73
146		35	*	2.09
147		44	*	20

TABLE IX (continued)

No.	Compounds	Yield %	Mosquito Larvae	Brine Shrimp
148		92	*	*
149		⊕	*	*
150		80	442	3
151		45	*	1
152		⊕	*	*
153		60	*	4
154		75	4,230	0.59
155		100	*	1.5
156		15	*	*
157		92	*	25
158		70	*	2
159		80	1,242	81
160		94	*	32
161		15	*	2
162		15	3,783	3
163		15	201	1
164		15	270	1
165		70	1,257	1

* To be determined. ⊕ Obatined as an inseparable mixture of 5- and 5,5″- isomers.

2.4 BIOLOGICAL ACTIVITY OF α-TERTHIENYL DERIVATIVES

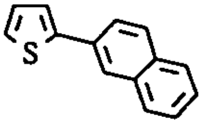
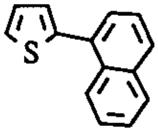
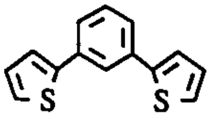
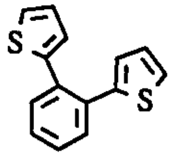
In order to have a better understanding of the effect of a substituent on the activity of α-T 3, screening for biological activity was performed on brine shrimp and mosquito larvae (see TABLE IX). The biological tests were performed by F. Duval and R. Marles in Profesor Arnason's laboratory. Concomitantly, the singlet oxygen production was measured by a laser flash[60-63] photolysis technique and the results are shown in TABLE XVIII.

Biological tests used α-T 3 as the reference compound. The compound to be tested was dissolved into ethanol (1 ml) and then diluted with water (250 ml). Sample populations of 20 insects were then treated with geometric dilution of the compound and the mortality recorded at 24 hours. LC_{50}'s were determined by probit analysis. The overall change in the observed biological activity profile of the substituted α-T 3 was analyzed considering the different factors outlined in Section 1.3.2. Each contribution of the different factors will be discussed in a qualitative manner.

Aside from the effect attributed to a specific substituent, the first factor studied was the nucleus of the pesticide molecule. To investigate the relation between the activity and the shape of the molecule, three geometrical isomers **117**, **118** and **141** were tested. The results of their biological activity on mosquito larvae are listed in TABLE X.

Looking at the structural features, it appears that having an angle less than 180° incorporated into the central framework of the molecule is (see below) an important consideration. From the results obtained[133] (see TABLE X), compound **117** which is more linear compared to **118**, was found to be less phototoxic than **118** . Therefore, an *ortho* substitution pattern **141** was synthesized but the results of biological tests are not yet available. It is predicted that compound **141** will be less phototoxic than **118**, by analogy with compounds **116** and **115**.

TABLE X. Biological Activity *versus* the Angle Incorporated into the Framework of the Molecule.

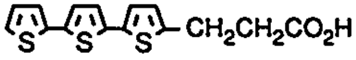
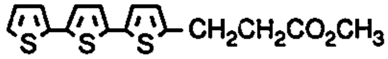
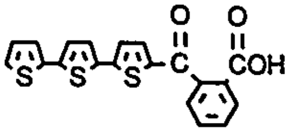
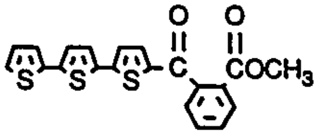
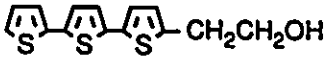
No.	Compounds	Angle	Biological Activity (nM)	
			Mosquito Larvae LC_{50} nM	Brine Shrimp LC_{50} nM
115		-135°	1,764	1,745
116		-135°	789	88.5
117		-180°	12,901	11.8
118		-120°	247	69
141		-60°	*	*

* To be determined.

2.4.1 Lipophilicity

As mentioned in Section 1.3.2, the site of action of α-T 3 is primarily at the cellular membrane. Consequently, highly lipophilic compounds would incorporate more readily into the cellular membrane. From previous studies it was shown that there is a linear correlation between the partition coefficient and the biological activity for analogues of α-T such as 115 to 118[133]. [Even though highly lipophilic, there was little variation in the partition coefficient for this series of derivatives of α-T 3.] For this reason the variation in the partition coefficients alone is not suitable to rationalize the large variation in the biological activity observed. Nonetheless, the lipophilicity factor must be responsible for some variation observed for a related series of substituent. TABLE XI summarizes the toxicity of α-T derivatives to brine shrimp. Compounds <u>143</u>, <u>159</u> and <u>158</u> demonstrate a small but significant increase in toxicity which parallel an increase in lipophilicity. A more significant increase in the activity is observed in going from the acid <u>148</u> to the more lipophilic ester <u>146</u>. However, the magnitude of the lipophilicity factor is not reliable. For instance, compounds <u>150</u> and <u>128</u> represent an increase in the lipophilicity and yet a decrease in the toxicity. While, compounds <u>128</u>, <u>3</u> and <u>138</u> behave accordingly. The results of mosquito larvae study are not yet all known and it is too

TABLE XI. Derivatives of α-T and Toxicity (Brine Shrimp).

No.	Derivatives of α-T	Toxicity in light $\frac{1}{LC_{50}}$ $(nM^{-1}x100)$
<u>143</u>		1.05
<u>159</u>		4.07
<u>158</u>		11.8
<u>148</u>		0.086
<u>146</u>		47.8
<u>150</u>		27.32
<u>128</u>*		9.43
<u>3</u>		133.3
<u>138</u>		175

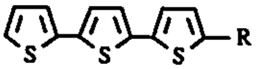
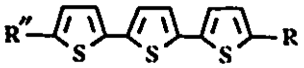
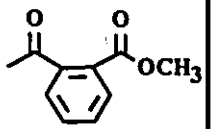
* Synthesized Previously.[133]

premature to speculate about the possible link between lipophilicity and activity. However, compounds 150 and 128 displays unexpected decrease in toxicity for an increase in lipophilicity (see TABLE XI).

2.4.2 Number of Substituents

Since the introduction of a single substituent most often reduces activity,the presence of two substituents was hypothesized to result in lowering the activity even further. TABLE XII summarizes the biological activity (mosquito larvae, brine shrimp) of the mono- and disubstituted derivatives of α-terthienyl 3. The comparison of the toxicity of the mono- and disubstituted derivatives of α-T 3 for the

TABLE XII. Biological Activity (Mosquito Larvae, Brine Shrimp) of Mono- and Disubstituted Derivatives of α-Terthieny.

No.	Substituent	Monosubstituted α-T 		Disubstituted α-T 	
	R=R″	Mosquito Larvae LC_{50} (nM)	Brine Shrimp LC_{50} (nM)	Mosquito Larvae LC_{50} (nM)	Brine Shrimp LC_{50} (nM)
144	$-SCH_3$	*	0.54	*	1.73
151	$-C(CH_3)_3$	*	0.86	*	3.91
131	-CN	78	2.45	192	6.17
130	-CHO	133	1.05	*	2.98
146		*	2.09	*	20.38
138	$-CH_3$	259	0.98	615	0.84
136	-Br	1,338	0.54	3,404	0.99
134	-I	*	1.20	*	8.64

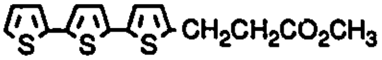
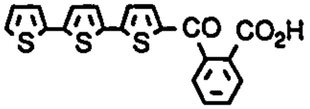
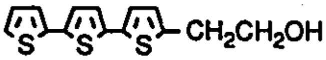
* To be determined.

same species (either brine shrimp or mosquito larvae) confirmed the hypothesis that the disubstituted derivatives of α-T 3 are less active than their corresponding monosubstituted α-T. One exception to this general trend is found in brine shrimp in the case of methyl substituted α-T **138**. The dimethyl was found to be more active than its corresponding monosubstituted derivative.

2.4.3 Singlet Oxygen Production

Many derivatives of α-T 3 possess larvicidal activity in the dark (TABLES XIII and XIV) but it is less pronounced than that observed in the light. This

TABLE XIII. Biological Activity Test (Brine Shrimp) and the Singlet Oxygen Production.

No.	Compounds	Activity in the light LC_{50} (nM)	Actvity in the dark LC_{50} (nM)	Corrected toxicity in the light (nM^{-1})	$^1O_2$ Production (moles/m^2/s)
3		0.75	125	1.32	9.2
144		0.54	42	1.82	10.8
154		0.59	52	1.67	11.7
158		8.46	563	0.11	5.4
130		1.05	279	0.95	6.2
148		1,167	9,976	7.5x10^{-4}	5.0
150		3.66	253	0.27	8.6
131		2.45	45	0.38	8.2
160		32	167	0.03	1.7
138		0.57	11	1.66	10.8
133		10	108	0.09	10
128		10	359	0.09	8.4

photoenhanced toxic activity is related to the production of $^1O_2$ by light sensitization (see Scheme 5, Section 1.3.3). Therefore, the dark toxicity must imply a different mechanism, which does not involve the presence of $^1O_2$. Consequently in order to have a more accurate correlation between the $^1O_2$ production and its effect on biological activity, the total activity observed in the presence of light must be corrected for observed activity in the dark. Substracting the toxicity observed in the dark from the total toxicity observed upon irradiation conditions gives the toxicity soley related to the photodynamic process.

e.g.

$$\begin{aligned} \text{Toxicity}_{(\text{Total})} &= \text{Toxicity}_{(\text{Light})} + \text{Toxicity}_{(\text{Dark})} \\ \text{Toxicity}_{(\text{Light})} &= \text{Toxicity}_{(\text{Total})} - \text{Toxicity}_{(\text{Dark})} \\ \text{Toxicity}_{(\text{Light})} &= \left(\frac{1}{LC_{50}}\right)_{(\text{UV})} - \left(\frac{1}{LC_{50}}\right)_{\text{Dark}} \end{aligned}$$

Figure 7 shows that the production of singlet oxygen does correlate very well with the observed toxicity on brine shrimp for α-T <u>3</u> substituted with a variety of non polar functionalities. Little toxicity is found when the rate of $^1O_2$ production is lower than 5 moles/m^2/s. In the case of higher rate of $^1O_2$ production the activity quickly increase. However, exception must be made for the presence of polar substituents such as -CH_2CH_2OH, -CH_2OH and -$CONH_2$. The toxicity of these derivatives is quite low in spite of the fact that a high rate of $^1O_2$ production has been measured. This lack of correlation suggests that other factors must override the effect of the singlet oxygen production. The high polarity of these substituents seems to be a dominant factor in lowering the activity (see Section 2.4.2).

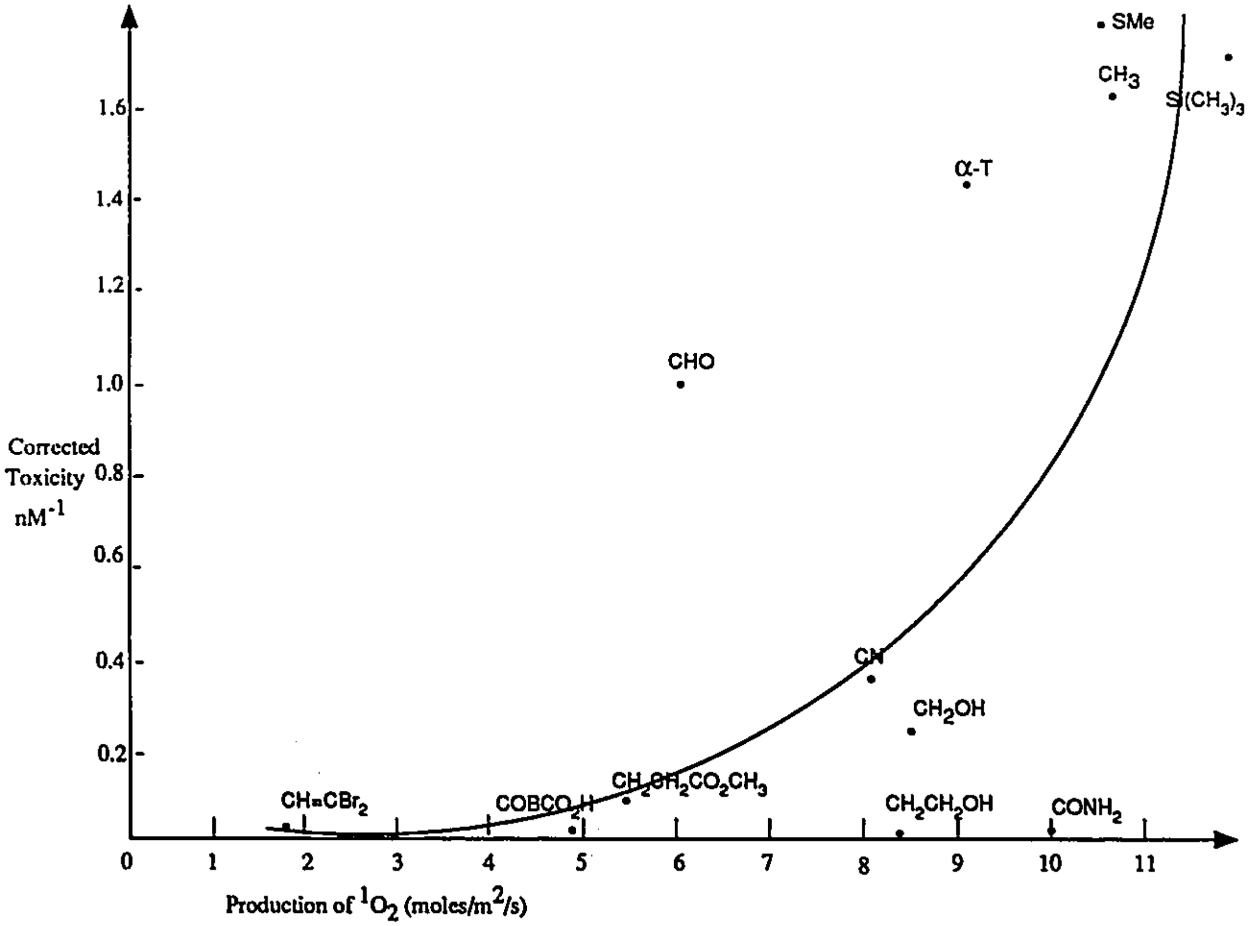
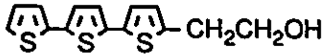


Figure 7. Plot of the Biological Activity (Brine Shrimp) *versus* Singlet Oxygen Production in moles/m^2/s Units for the Monosubstituted Derivatives of α-T 3.

The study of mosquito larvae (TABLE XIV) reveal a consistent by higher toxicity for derivative of α-T 3 on exposure to light. However, the relation between the production of $^1O_2$ and the toxicity is less obvious (*Figure 8*). Unfortunately, many toxicity results are not available yet. It seems rather that a plateau in the toxicity is reached quickly and does not increase with an increased in $^1O_2$ production. However, it is clear from Section 1.3.1 that $^1O_2$ must be responsible for higher activity in the light as compared in the dark. Therefore, one must come to the hypothesis that only a small amount of $^1O_2$ is required to disrupt vital function.

The correlation curve was drawn qualitatively. The data has not been analyzed mathematically.

TABLE XIV. Biological Activity Tests Performed on Mosquito Larvae and $^1O_2$ Production.

No	Compounds	Activity in the light LC_{50} nM	Activity in the Dark LC_{50} nM	Corrected Toxicity X 10^{-3} nM^{-1}	Rate of $^1O_2$ Production
3		163	295	2.7	9.2
150		442	798	1.0	8.6
128		386	332	0.42	8.4
131		78	137	5.4	8.2
138		259	620	2.2	10.8
133		1,685	6,164	0.43	10

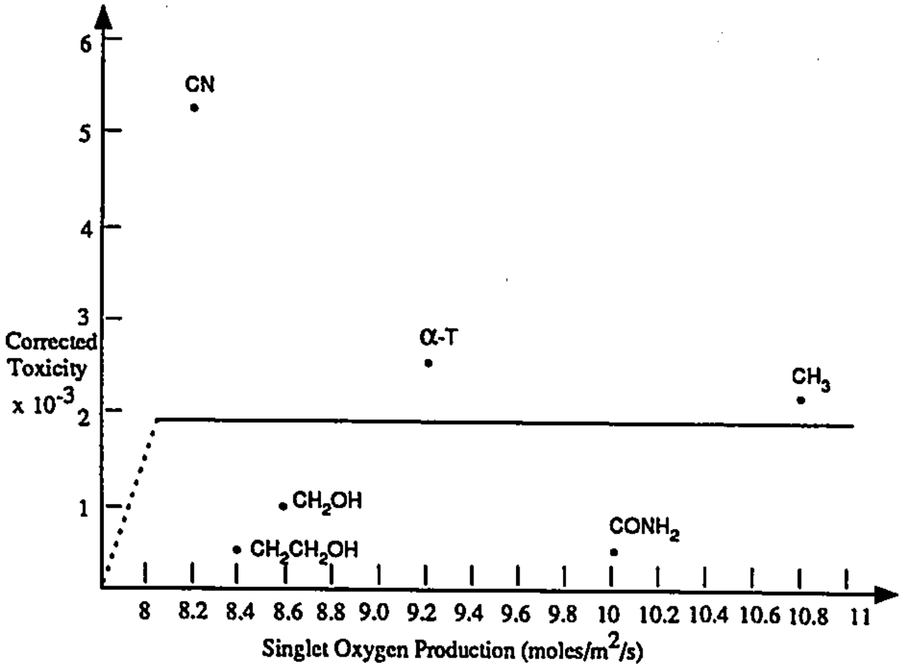


Figure 8. Plot of the Toxicity (Mosquito Larvae) *versus* Singlet Oxygen Production (moles/m^2/s) for the Monosubstituted Derivatives of α-T 3.

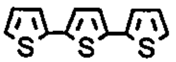
Unfortunately, the results of activity for derivatives having a lower rate of $^1O_2$ production are not available yet. Consequently, it is impossible to know at precisely which rate the activity levels off, but the threshold is less than 8 moles/m^2/s.

In analogy with the brine shrimp, it seems that a relatively more polar substituent such as $-CH_2OH$, $-CH_2CH_2OH$, $-CONH_2$ has a much reduced toxicity compared to more lipophilic derivatives such as -CN, -Me, and α-T 3.

2.4.4 Electronic Effect

Another major task was to establish if the electronic nature of a substituent was responsible for the variation in the biological activity observed. At first view, from TABLE IX, a correlation is not obvious in the study performed on mosquito larvae, by comparing α-T 3 with conmpounds having different electron-withdrawing groups. 5-Carboxylic acid **143** was found to be 22 times less active and the carboxamide **133** 10 times less active. However, the 5-formyl **130** was almost as active, while the 5-cyano **131** was 2 times more active than α-T 3. Also, no correlation between the activity and electron-donating groups is observed. For example, 5-(1‴-hydroxymethyl)-α-T **150** was 2.7 times less toxic, the 5-(2‴-hydroxyethyl)-α-T **128** was 2.4 times less toxic while the 5-methyl-α-T **138** was 1.6 times less active than α-T 3. A similar conclusion can be drawn for the study carried out on brine shrimp. In order to obtain a more quantitative comparison between the biological activity and the electronic nature of a substituent, the following assumption was made. The electronic influence of a substituent "X" was compared by assigning the Hammet *sigma* constants (σ_{para}) found for *p*-substituted benzoic acid[156,157], to the α-terthienyl aromatic system. Support for this assumption comes from a more recent study which confirms that the correlation between the σ_{para} of *p*-substituted benzoic acid and the σ_α of 5-substituted-thiophene-2-carboxylic acid is valid. TABLE XV summarizes the biological activities with their corresponding

TABLE XV. Toxicity (Mosquito Larvae, Brine Shrimp) and *sigma* (σ_{para})[a] Constants.

No.	Compounds	Biological Activity		σ_{para}
		Brine Shrimp	Mosquito Larvae	
		$\frac{1}{LC_{50}}$ (nM^{-1})	$\frac{1}{LC_{50}}$ (nM^{-1}) X10^{-3}	
153[b]		0.26	*	-0.27
151		1.16	*	-0.19
138		1.02	3.8	-0.17
154		1.69	0.23	-0.07
3		1.33	6.1	0
144		1.85	*	0
134		0.83	*	0.18
136		1.85	0.74	0.23
143		0.01	0.28	0.45
131		0.41	12.7	0.66

[a]- *Sigma* Constant Values were taken from the Hydrolysis Study of *p*-Substituted Benzoic Acid[157].

[b]- σ-Value for *t*-Butoxy Group was Substituted for a Methoxy Group.

* To be determined.

sigma para (σ_{para}) constants. *Figures 9* and *10*, represent the toxicity as a function of *sigma* (σ_{para}) constants for the study on brine shrimp and mosquito larvae respectively. No correlation between the activity and the electronic nature of a substituent is observed for either species.

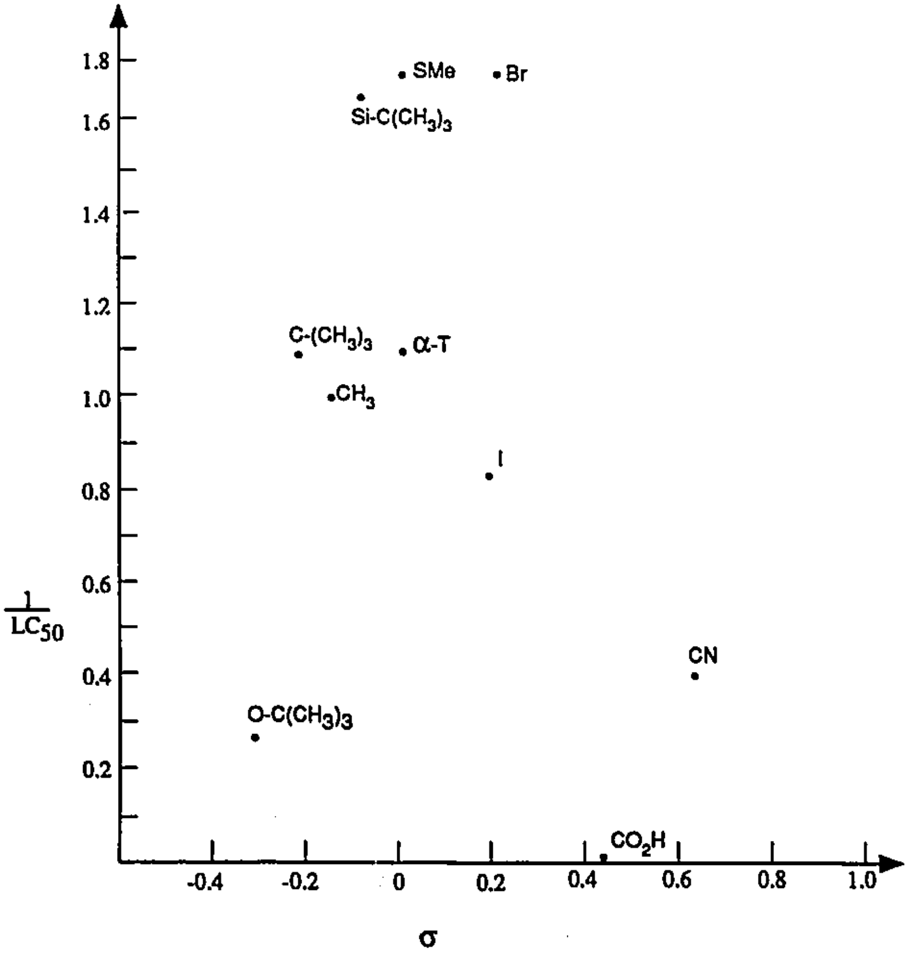


Figure 9. Toxicity to Brine Shrimp *versus sigma* (σ) Constant Values.

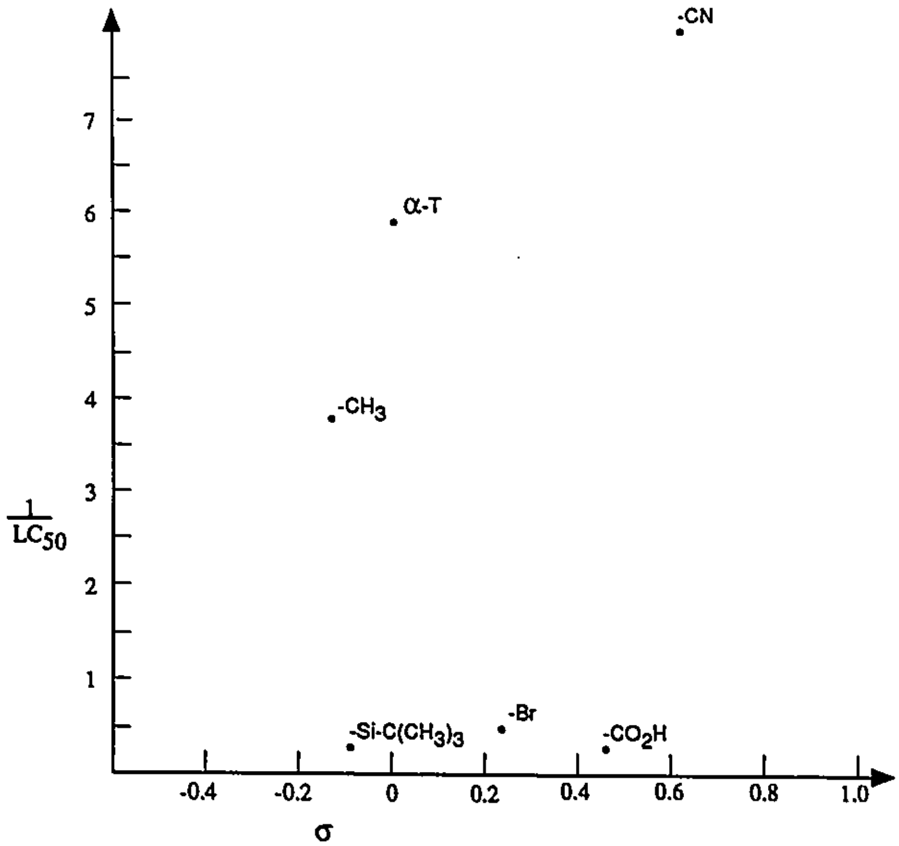


Figure 10. Toxicity to Mosquito Larvae *versus sigma* (σ) Constant Values.

2.4.6 Steric Effect

Up to this point, no major factor controlling the biological activity in both species (mosquito larvae and brine shrimp) has been uncovered. We then focused our efforts to investigate the implications of a steric parameter. Since only a few steric substituent constants $(E_s)^{158}$ for steric parameters are known, a quantitative treatment of the activity data will not be presented. Some qualitative information about steric effects could be obtained in this way. Unfortunately, a series of substituted α-T 3 derivatives with isomeric groups (such as *n*-butyl, *iso*-butyl, 2-methyl-*n*-propyl and *t*-butyl) has not yet been prepared. However some information can be obtained by comparing small groups with more bulky substituents.

Chain elongation resulted in a decrease in the activity in mosquito larvae studies.

Example-

	3		163		164	
	α-T	>	$-C\equiv CH$	>	$-C\equiv C-CH_3$	
LC_{50} nM (Mosquito Larvae)	163		201		270	
Very Active						Less Active

These correlations do not hold for the study carried out with brine shrimp where the observed activity seems to be unaffected by steric congestion. The following compounds regroup α-terthienyl derivatives substituted with weak electron-releasing groups. These results suggest that steric congestion is not a dominant factor controlling the biological activity in brine shrimps.

No. of Compound:	3		134		136		138		151	
Less Active	α-T	<	-I	<	-Br	<	-Me	<	-*t*-Bu	More Active
ΔG° (Kcal/mole):	0		0.47		0.48		1.70		5	
LC_{50} nM: (Brine Shrimp)	0.75		1.20		0.54		0.57		1.08	

To establish the relevance of the laboratory testing on insects, the three most active compounds (e.g. 5-methyl-α-T 138, 5-cyano-α-T 131 and α-T 3 were selected for field trial studies. With sufficient quantities of compound 3, 138 and 131 on hand, field trial assays revealed that the 5-cyano-α-terthienyl 131 was a better larvicide than α-terthienyl 3 which in turn was more active than 5-methyl-α-T 138, as predicted by the laboratory tests. The results for field trials are listed in TABLE XVI. It was encouraging to observe that on a molar basis, 5-cyano-α-terthienyl 131 was 4.5 times more toxic than α-terthienyl 3 with 90% mortality while the laboratory tests show a factor of the order of 2 only. While the cyano derivative exhibited high biological activity in field trials,

TABLE XVI. Trials in Simulated Pools effected in South Mountain Village (Eastern part of Ontario, Canada) on Exposure to Direct Sunlight.

-Product Dissolve in Octanol/Water (1988)
-4 Types of Insects

No.	Compounds	LC_{50} (ppb)	LC_{90} (ppb)
3	α-T	56 g/Ha	122
131	α-T-CN	16	30
138	α-T-Me	81	148

5-methyl-α-terthienyl **138** did extremely poorly. The latter instead of being of the order or 2.8 times more active than α-terthienyl **3** (as indicated by the preliminary screening tests), was in fact less active than α-terthienyl in field trials. This surprising result cast some doubt on the original data. Additional trials with 5-methyl-α-terthienyl **138** in the laboratory revealed that the original activity data was erroneous. Compound **138** was now found to display 1.5 times lower activity than for α-terthienyl **3** which is consistent with the field trial results.

In summary, the effects which influence the activity vary with the species treated. In the brine shrimp bioassay, the presence of a highly polar function (poorly lipophilic) plays a dominant role in lowering the activity. A high rate of singlet oxygen production usually means higher activity. An increase in lipophilicity enhances activity whereas the electronic nature demanded of a substituent has little effect on activity. Finally, a decrease in activity is observed for the disubstituted α-T derivatives compared to the corresponding mono derivatives.

In the study performed on mosquito larvae, the presence of a very polar group on α-T **3** predominates over all other effects and results in a decrease activity. Increased lipophilicity enhances the activity of these insecticides, especially in going from an acid to an ester. More importantly, an increase in steric hindrance created by the addition of a substituent α to a thiophene ring, results in a net decrease in activity. Variation in singlet oxygen production does not seem to significantly influence activity although light is believed to play a role (see Section 2.4.3) because of the resulting increase in activity. It is concluded that only a small rate of singlet oxygen is necessary.

Unfortunately, these rationalizations are not sufficient to explain the most active α-T derivative 131. Looking at the results with 5-cyano-α-T 131, one is forced to conclude that this substituent is bigger than a proton and yet is more active than α-terthienyl 3. Since electronic effects and singlet oxygen production have not been shown to play a significant role in mosquito larvae species an additional factor must override the steric demand of the cyano group.

With this concept, efforts were made by R. Marles to establish a quantitative structure-activity relationship (QSAR)[159] for a set of physicochemical properties responsible for the variation in the biological activity responses of α-T derivatives. The permeability of these compounds may occur by a process which may be influenced by physicochemical properties including electronic features, steric factors solvent-partioning and hydrophobic effects. The equation shown below was used for the series of compounds (bilinear model).

$$\text{Log } 1/C = a \log P - b \log (\beta P + 1) + C$$

Calculations from preliminary studies on α-T derivatives using calculated log P , showed a significant correlation between the activity and log P with an efficiency up to 99%. However, only few partition coefficients for α-T related compounds were determined for an octanol-water system[133]. More experimental data representing the partition coefficient are essential in order to correlate clearly the factors involved in the toxicity. Although, it is premature to give any definitive conclusion to this study, more work is required in the linear region of the log 1/C - log P relationship.

III- DERIVATIVES OF α–DITHIENYLS

3. RESULTS AND DISCUSSION

α-Dithienyl 175 and its derivatives have been isolated in several members of the *Compositae*[9,31,32,160]. This series of compounds was studied for their photoenhanced properties, since they possessed nematocidal[136b,161], antibiotic[42,47,53], ovicidal[162], algicidal[163], larvicidal[164] and antifeedant[165] activities. They were also found to inhibit germination[166] of some plants and to be phototoxic to some aquatic organisms[167]. Furthermore, they produce hemolysis[56,168] and photoinduced dermatitis[169]. To date there is no evidence that these compounds cause chromosomal damage[46].

In light of these observations, enzymological studies on the metabolism of α-dithienyl derivatives by Sutfeld[64] revealed the implication of enzymes such as (4″-acetoxybut-1″-ynyl)dithienyl-4-acetate esterase and acetyl-CoA-(4″-hydroxybut-1″-ynyl)dithienyl-4-O-acetyltransferase. Feeding experiments from the plant *Tagetes patula* indicated that substituted acetylenic α-dithienyl derivatives with an acetate moiety [e.g. 5-(4″-acetoxybut-1″-ynyl)-2,2′-dithienyl 177 and compound 178] were converted to the corresponding alcohol by these enzymes. Metabolism studies suggested that acetoxy or hydroxy derivatives of α-dithienyl undergo a process which may be controlled by

a) substrate avalability,

b) stage-dependency,

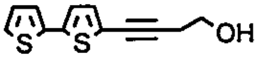
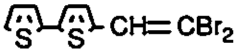
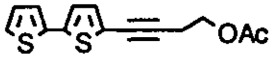
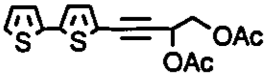
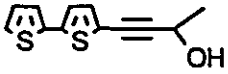
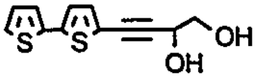
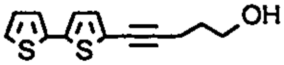
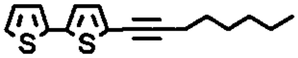
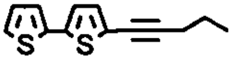
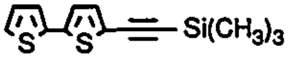
c) light regulation of isoenzyme synthesis or

d) coproduct inhibition.

This led us to synthesize a series of substituted acetylenic derivatives of α-dithienyl with carbon chain elongation containing functionalities such as hydroxy or acetoxy groups.

In the course of our study, it was found[63b] that α-dithienyl derivatives (TABLE XVII) were efficient photosensitizers producing singlet oxygen. Derivatives

TABLE XVII. Derivatives of α-Dithienyl Prepared in our Laboratory.

175		187	
176		188	
177		189	
178		190	
		194	
179		195	
180		196	
185		197	
186		198	

containing substituted 1″-alkynyl groups are listed in TABLES XVIII and XIX (end of this Section) which also summarizes the results of the activity tests performed on mosquito larvae and brine shrimp as well as the singlet oxygen production. These results indicate that α-dithienyl derivatives have the potential to be used for pest control.

Four compounds, including 5-(4″-hydroxybut-1″-ynyl)-α-dithienyl 176, 5-(4″-acetoxybut-1″-ynyl)-α-dithienyl 177, 5-(3″,4″-diacetoxybut-1″-ynyl)-α-dithienyl 178, 5-(3″,4″-dihydroxybut-1″-ynyl)-α-dithienyl 179 and 5-(3″-butene-1″-ynyl)-α-dithienyl 180 were synthesized by using the palladium-catalyzed coupling reaction in the presence of $\mathrm{Cu^I}$ halides (Scheme 52). The actual Grignard-Wurtz coupling procedure (described in Section 2.1.8) is not suitable for coupling an acetylene moiety with aryl halides. However, the palladium-catalyzed reaction was found to be a general method for the preparation of a wide range of monosubstituted α-dithienyls with

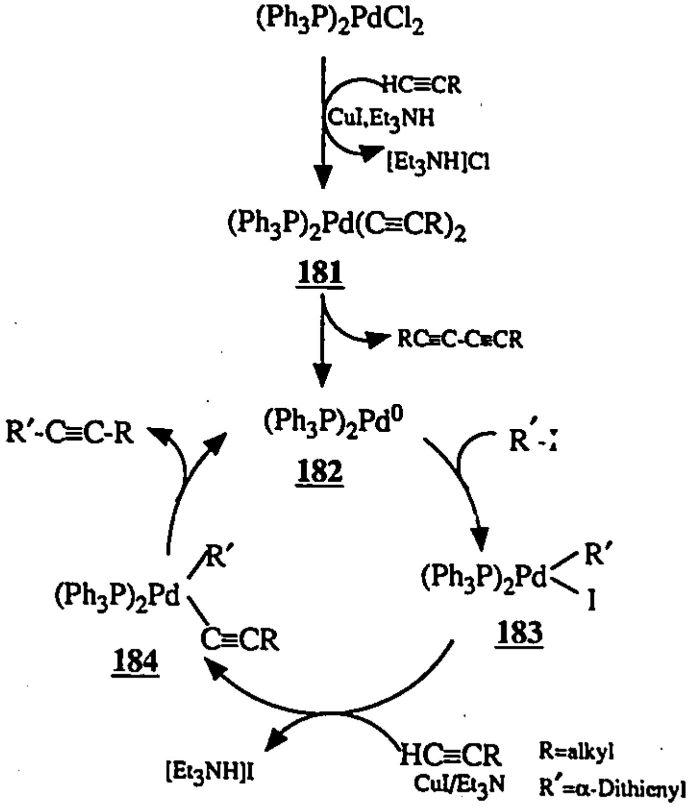
$$\text{Ar-I} \quad + \quad \text{HC}{\equiv}\text{CR} \xrightarrow[\text{CuI/Et}_3\text{N}]{(\text{Ph}_3\text{P})_2\text{PdCl}_2} \text{Ar-C}{\equiv}\text{CR}$$

Scheme 52.

various 1″-alkynyl groups.

3.1 PALLADIUM-CATALYZED COUPLING REACTION

The palladium-catalyzed reaction with Cu has been reported previously by Hagihara *et al.*[170a] and this was the method selected to prepare 5-substituted acetylene α-dithienyl derivatives. Although a detailed mechanistic study has not been carried out, it



Scheme 53.

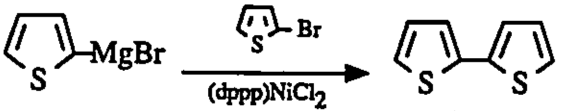
seems that the coupling reaction proceeds through a reactive Pd^0 intermediate *via* a series of oxidative addition and reductive elimination steps. Scheme 53 shows the proposed[170b] mechanism. Alkynylation of *bis*(triphenylphosphine)Pd^{II} dichloride [$(PPh_3)_2PdCl_2$] leads to initial formation of *bis*-[$(PPh_3)_2$dialkylnyl]Pd^{II} 181 which, through reductive elimination of 1,4-disubstituted butadiyne, gives the catalytic species *bis*-[$(PPh_3)_2$]Pd^0 182. Subsequent oxidative addition of aryl halides to 182, followed by alkynylation of the adduct 183, gives an aryl-alkynyl derivatives of Pd 184. The latter regenerates the original *bis*-[$(PPh_3)_2$]Pd^0 182 through reductive elimination of the substituents. The alkynylation of the starting catalyst $(Ph_3P)_2PdCl_2$ or an oxidative adduct 183 in the catalytic cycle shown in Scheme 53 is catalyzed by CuI in the presence of Et_3N.

3.2 DERIVATIVES OF α-DITHIENYL 175

For the preparation of these derivatives, α-dithienyl 175 was synthesized on a large scale and subsequent iodination produced enough the 5-iodo-α-dithienyl 185 required for the coupling reaction (see Scheme 52).

3.2.1 Preparation of α-Dithienyl 175

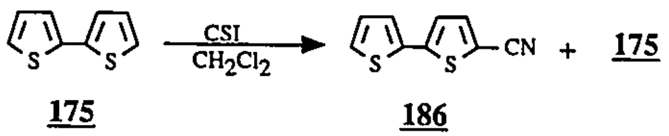
α-Dithienyl[171,172] 175 was prepared on a multigram scale (50 g) by treatment of 2-thienylmagnesium bromide in ether with a mixture of 2-bromothiophene (Scheme 54) and $(dppp)NiCl_2$ as catalyst to give the desired product in 92% isolated yield.



Scheme 54.

3.2.2 Preparation of 5-Cyano-α-dithienyl 186

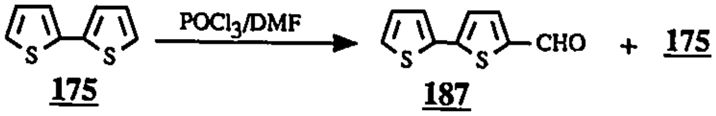
5-Cyano-α-dithienyl 186 was obtained by the cyanation reaction[140,141] of α-dithienyl 175 (Scheme 55) under the conditions described in Section 2.2.2.3. Column chromatography of the crude material gave a mixture of monocyano derivative 186 76% yield) along with a small amount of unreacted α-dithienyl 175.



Scheme 55.

3.2.3 5-Formyl-α-dithienyl 187

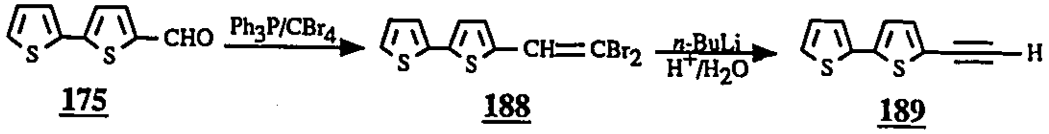
5-Formyl-α-dithienyl[139,173,174] 187 was prepared in 56% yield using the Vilsmeier formylation[138,139] reaction (Scheme 56) as described in Section 2.2.2.1 for α-T 3.



Scheme 56.

3.2.4 Preparation of 5-(2″-Dibromoethenyl)-α-dithienyl 188 and 5-Ethynyl-α-dithienyl 189

Upon treatment of PPh_3 with CBr_4 in the presence of 5-formyl-α-dithienyl 187, 5-(2″-dibromoethenyl)-α-dithienyl[172,175] 188 was obtained (Scheme 57) in almost quantitative yield. Dehydrobromination with *n*-BuLi gave



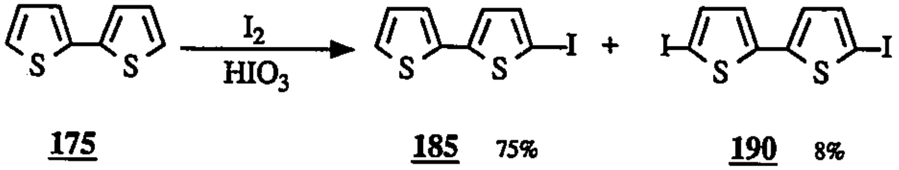
Scheme 57.

5-ethynyl-α-dithienyl <u>189</u> (*cf.* Section 2.2.5).

3.2.5 Preparation of 5-Iodo-α-dithienyl 185

A synthesis of <u>185</u> has been reported by Rossi *et al.*[172] in which α-dithienyl <u>175</u> was treated with mercuric chloride in the presence of sodium acetate, followed by iodination to afford 5-iodo-α-dithienyl <u>185</u> in 85% yield. This reaction was performed at r.t. for 20 hours, followed by Soxhlet extraction with CH_2Cl_2 (48 hours) and then fractional distillation.

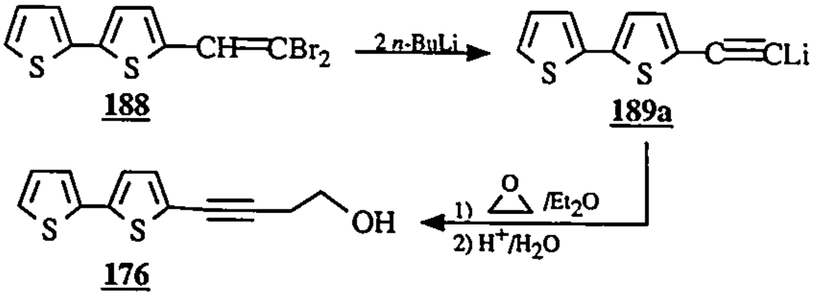
In order to reduce the reaction time, 5-iodo-α-dithienyl[176] <u>185</u> was prepared by adapting the procedure of Wirth *et al.*[177] on thiophene. α-Dithienyl <u>175</u> was treated with a solution of iodine and iodic acid (HIO_3) in glacial acetic acid and CCl_4, along with small a amount of H_2O and H_2SO_4 (Scheme 58). The two phase reaction was completed after heating at 40°C for 2 hours. Compound <u>185</u> and 5,5′-diiodo-α-dithienyl <u>190</u> were isolated in 75% and 8% yield. Distillation of the crude reaction mixture under reduced pressure gave the pure 5-iodo-α-dithienyl <u>185</u>. This efficient iodination reaction provided enough starting material <u>185</u> required for the subsequent coupling reactions.



Scheme 58.

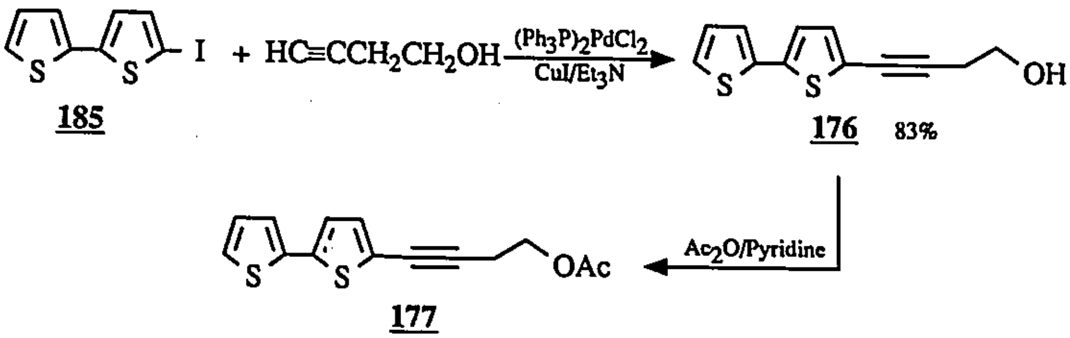
3.2.6 Preparation of 5-(4″-Hydroxybut-1″-ynyl)-α-dithienyl 176 and 5-(4″-Acetoxybut-1″-ynyl)-α-dithienyl 177

5-(4″-Hydroxybut-1″-ynyl)-α-dithienyl <u>176</u> was first prepared in this laboratory (Scheme 59) by treating the lithio derivative <u>189a</u> of 5-ethynyl-α-dithienyl, generated *in situ* from 5-(2″-dibromoethenyl)-α-dithienyl <u>188</u>, with an equivalent amount of ethylene oxide at 0°C in diethyl ether to give 176 in moderate yield (45%). Compound



Scheme 59.

176 was found to be identical (by TLC and ^{1}H NMR) with the one reported by Rossi *et al.*[172] and Phillips *et al.*[175]. This method however, was unsuitable for large scale preparation. Alternatively, 5-(4″-hydroxybut-1″-ynyl)-α-dithienyl 176 could be prepared more efficiently by using a palladium-catalyzed reaction[170b]. Thus 5-iodo-α-dithienyl 185 and 1-butyn-3-ol were coupled (Scheme 60) in triethylamine as solvent under a nitrogen

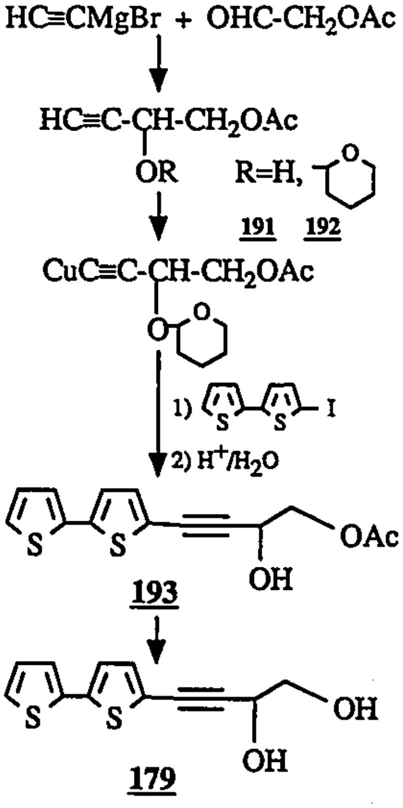


Scheme 60.

atmosphere and in the presence of $[(PPh_3)_2Pd^{II}Cl_2]$/CuI as catalyst, to give 176 in greater yield (83%). The reaction was almost complete (TLC analysis) within 30 minutes (r.t.). Longer reaction time (overnight or 18 hours) improved the yield slightly. The alcohol 176 was subsequently treated (Scheme 60) with acetic anhydride in pyridine to afford 5-(4″-acetoxybut-1″-ynyl)-α-dithienyl[178] 177 in almost quantitative yield.

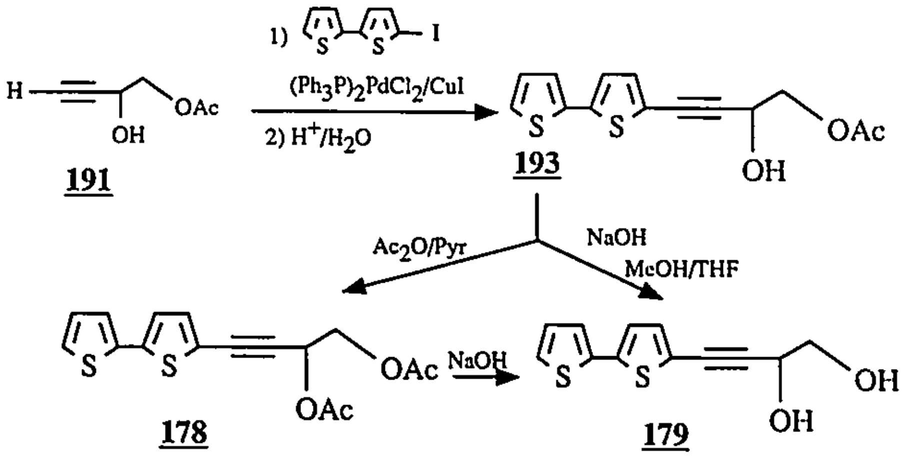
3.2.7 Preparation of 5-(3″,4″-Diacetoxybut-1″-ynyl)-α-dithienyl 178 and 5-(3″,4″-Dihydroxybut-1″-ynyl)-α-dithienyl 179

Compound 179 was previously prepared by Bohlmann *et al.*[179,180] (Scheme 61), by coupling 5-iodo-α-dithienyl 185 with the copper salt of protected glycoaldehydeacetate 192 to afford the acetate 193 (54% yield) which, after hydrolysis, gave 5-(3″,4″-dihydroxybut-1″-ynyl)-α-dithienyl 179 in 79% yield.[179]



Scheme 61.[179]

Compound 178 (Scheme 62) was prepared by using the same strategy but exploiting the chemistry of palladium. Excess acetylene was added to ethynylmagnesium bromide in THF cooled to -78°C.[179] The resulting ethynylmagnesium bromide was subsequently treated with the glycoaldehydeacetate to give, after fractional distillation under reduced pressure, 3-hydroxy-4-acetoxybut-1-yne 191[179] in 61% yield. Using the

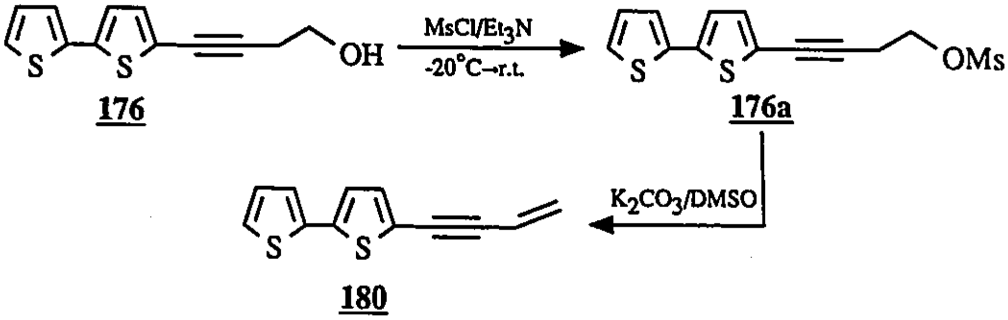


Scheme 62.

palladium-catalyzed procedure, 5-iodo-α-dithienyl 185 was coupled with 191 to give 5-(3″-hydroxy-4″-acetoxybut-1″-ynyl)-α-dithienyl 193[179] in excellent isolated yield (87%). Acetylation of the alcohol 193 gave the 5-(3″,4″-diacetoxybut-1″-ynyl)-α-dithienyl 178 in 90% yield. Hydrolysis of the acetate 193 or diacetate 178 with methanolic sodium hydroxide gave the corresponding diol[179] 179 in 51% yield.

3.2.8 Preparation of 5-(3″-Buten-1″-ynyl)-α-dithienyl 180

5-(3″-Buten-1″-ynyl)-α-dithienyl[172,173,181] 180 (Scheme 63) was obtained in low yield starting from the alcohol 176 which was first converted to the



Scheme 63.

mesylate 176a and subsequently treated with K_2CO_3 in DMSO. This compound 180 required storage at low temperature (-10°C), otherwise polymerization occurred readily at room temperature.[173] For this reason, 5-(3″-buten-1″-ynyl)-α-dithienyl 180 is an unlikely candidate as a pest control agent.

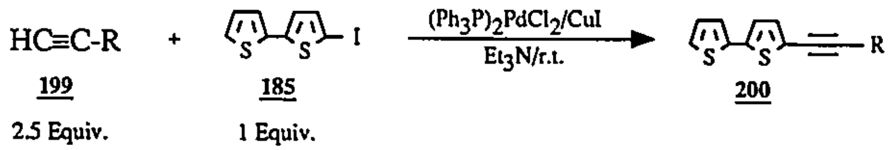
Biological activity tests revealed that both the alcohol 176 and the acetate 177 were more active than the corresponding diol 179 and diacetate 178. In light of these observations, a series of substituted α-dithienyls with triple bonds attached to a carbon chain with or without a hydroxy group were prepared using the palladium-catalyzed coupling method (see TABLES XVIII and XIX).

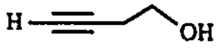
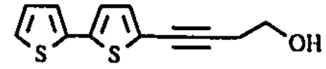
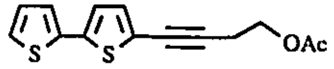
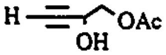
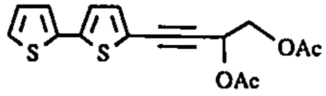
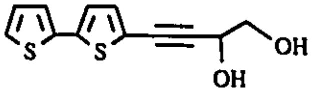
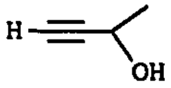
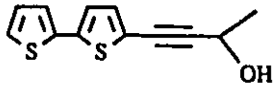
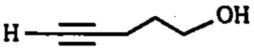
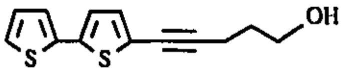
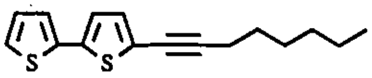
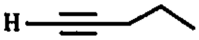
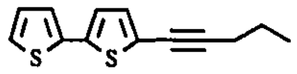
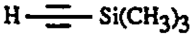
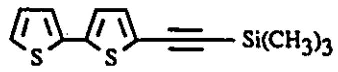
3.2.9 Preparation of 5-Substituted Acetylenic Derivatives of α-Dithienyl

Coupling reaction of 5-iodo-α-dithienyl 185 with 3-butyn-2-ol afforded 5-(3″-hydroxybut-1″-ynyl)-α-dithienyl[173,181] 194 in 86% isolated yield. Similarly, 5-iodo-α-dithienyl 185 was coupled with 4-pentyn-1-ol in triethylamine as solvent, to give the desired compound 5-(5″-hydroxypent-1″-ynyl)-α-dithienyl 195 in 70% isolated yield. 5-(2″-Oct-1″-ynyl)-α-dithienyl 196 was obtained from the usual coupling reaction of 185 with 1-octyne to afford a yellow transparent oil in 75% yield. 5-(2″-Pent-1″-ynyl)-α-dithienyl 197 was prepared in 86% yield from 1-pentyne and 5-iodo-α-dithienyl 185. 5-(2″-Trimethylsilyl-1″-ethynyl)-α-dithienyl 198 was obatined in 75% yield from the palladium-catalyzed reaction between 185 and trimethylsilylacetylene.

TABLE XVIII. Palladium-Catalyzed Reaction of α-Dithienyl Acetylenic Derivatives 200 by Coupling of 1″-Alkynes Derivatives 199 with 5-Iodo-2,2′-dithienyl 185.

No.



No.	1″-Alkynyl Derivatives	Reaction Time (hrs)	Isolated Yield (%)	Product
176		18	81	
177	*	3	92	
178		1	87	
179	*	2	55	
194		1	86	
195		18	70	
196		0.5	75	
197		2	86	
198		18	84	

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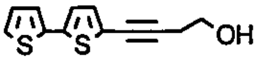
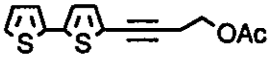
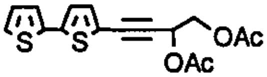
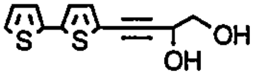
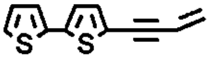
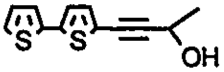
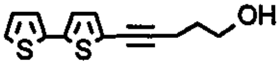
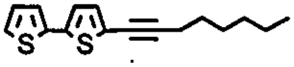
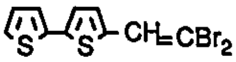
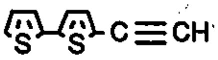
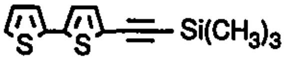
* Obtained by Hydrolysis or Acetylation of Compound 193.[179]

TABLE XIX. Biological Activity of α-Dithienyl Derivatives to Mosquito Larvae and Brine Shrimp and Production of Singlet Oxygen.

No.	Compounds	Biological Activity		Singlet Oxygen Production
		Mosquito Larvae LD_{50} nM	Brine Shrimp LD_{50} nM	moles/m^2/s
<u>176</u>		751	16.09	0.43
<u>177</u>		409	301	0.72
<u>178</u>		*	353	0.79
<u>179</u>		1262	380	0.63
<u>180</u>		*	37.8	0.62
<u>186</u>		*	215	0.60
<u>187</u>		*	3301	0.47
<u>194</u>		1556	82.6	0.83
<u>195</u>		*	527	*
<u>196</u>		*	9.4	*
<u>197</u>		*	7.14	0.55
<u>175</u>		*	*	*
<u>188</u>		*	*	*
<u>189</u>		*	*	*
<u>185</u>		*	*	*
<u>190</u>		*	*	*
<u>198</u>		*	*	*

* To be determined.

3.3 STRUCTURE DETERMINATION OF α-DITHIENYL DERIVATIVES

^{1}H NMR spectroscopy was used for structure elucidation of the monosubstituted derivatives of α-dithienyl **175**. Spectral assignments for most of the aromatic protons (TABLE XX) of compounds **176** to **198** were made on the basis of previous interpretation (see Section 2.3), showing the presence of three proton doublets on the C-3′, C-4′ and C-5′ positions of the dithienyl ring. Typical *J* values for these proton-proton couplings are in accordance with the previous finding on α-T **3**; $J_{5'-4'}$=5.0-5.1 Hz, $J_{5'-3'}$=1.0-1.2 Hz, $J_{3'-4'}$=3.0-3.8 Hz. The remaining two protons C-3 and C-4 exhibit signals with doublets in the *J*=3.7-3.9 Hz range. The latter C-3 and C-4 are readily recognized by the close proximity of their chemical shifts which occur downfield as a result of the influence of the substituent (deshielded in the presence of an electron-withdrawing group and shielded in the presence of an electron-donating group). The proton at C-4 is mostly affected by the neighbouring substituent. Futhermore, the NMR shows doublets of doublets, triplets or multiplets in the alkyl substituted acetylenic range (2.6-4.9δ) for the protons located on the butynyl side chain of the α-dithienyl ring.

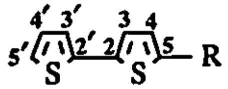


TABLE XX. ^{1}H NMR Data[a] for 5-Substituted Derivatives of α-Dithienyls.

No.	H-5′	H-4′	H-3′	H-3	H-4	Coupling Constants (Hz)				Substituent at C-5
	(dd,1H)	(dd,1H)	(dd,1H)	(d,1H)	(d,1H)	$J_{4',5'}$	$J_{3',5'}$	$J_{3',4'}$	$J_{3,4}$	
176	7.19	6.98	7.14	7.03	6.98	5.1	1.1	3.6	3.7	δ3.79(Q, 2H, J=6.0, J=12.3 Hz, $\mathrm{Ar\text{-}C{\equiv}CCH_2C\underline{H}_2OH}$) 2.70(t, 2H, J=6.2, J=12.4 Hz, $\mathrm{Ar\text{-}C{\equiv}CC\underline{H}_2CH_2OH}$) 1.78(t, 1H, J=6.0, J=6.3, J=12.4 Hz, $\mathrm{Ar\text{-}C{\equiv}CCH_2CH_2OH}$)
177	7.20	6.98	7.14	7.02	6.97	5.1	1.1	3.6	3.8	δ4.23(t, 2H, J=6.9, J=6.8 Hz, A_2B_2, $\mathrm{Ar\text{-}C{\equiv}CCH_2C\underline{H}_2OAc}$) 2.76(t, 2H, J=6.8, J=6.9 Hz, A_2B_2, $\mathrm{Ar\text{-}C{\equiv}CC\underline{H}_2CH_2OAc}$) 2.08(s, 3H, $\mathrm{Ar\text{-}C{\equiv}CCH_2CH_2O\text{-}CO\text{-}C\underline{H}_3}$)
178	7.22	6.99	7.16	7.12	7.00	4.9	1.1	3.6	3.7	δ5.84(dd, 1H, J_{vic}=3.7, J_{vic}=7.31 Hz, $\mathrm{Ar\text{-}C{\equiv}CC\underline{H}(OAc)CH_2OAc}$) 4.41(dd, 1H, J_{vic}=3.7, J_{gem}=11.7 Hz, $\mathrm{Ar\text{-}C{\equiv}CCH(OAc)C\underline{H}_2OAc}$) 4.29(dd, 1H, J_{vic}=7.31, J_{gem}=11.7Hz, $\mathrm{Ar\text{-}C{\equiv}CCH(OAc)C\underline{H}_2OAc}$) 2.10(s, 3H, $\mathrm{Ar\text{-}C{\equiv}CCH(O\underline{Ac})CH_2OAc}$) 2.09(s, 3H, $\mathrm{Ar\text{-}C{\equiv}CCH(OAc)CH_2O\underline{Ac}}$)
179	7.22	6.99	7.16	7.10	7.00	5.1	1.1	3.6	3.7	δ4.69(dd, 1H, J_{vic}=3.9, J_{vic}=6.4 Hz, $\mathrm{Ar\text{-}C{\equiv}CC\underline{H}(OH)CH_2OH}$) 3.83(dd, 1H, J_{vic}=4.0, J_{gem}=11.3 Hz, $\mathrm{Ar\text{-}C{\equiv}CCH(OH)C\underline{H}_2OH}$) 3.76(dd, 1H, J_{vic}=6.4, J_{gem}=11.3 Hz, $\mathrm{Ar\text{-}C{\equiv}CCH(OH)C\underline{H}_2OH}$)

[a] 300 or 200 MHz ^{1}H NMR.

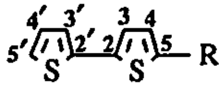


TABLE XX. (continued)

No.	H-5′ (dd,1H)	H-4′ (dd,1H)	H-3′ (dd,1H)	H-3 (d,1H)	H-4 (d,1H)	Coupling Constants (Hz) $J_{4',5'}$	$J_{3',5'}$	$J_{3',4'}$	$J_{3,4}$	Substituent at C-5
180	7.21	6.99	7.15	7.08	7.1	4.9	1.1	3.6	3.9	δ6.01(dd, 1H, J_{cis}=11.1, J_{trans}=17.5 Hz, Ar-C≡CC$\underline{H}$=CH$_2$) 5.70(dd, 1H, J_{trans}=17.5, J_{gem}=2.2 Hz, Ar-C≡CCH=C$\underline{H}_2$) 5.53(dd, 1H, J_{cis}=11.1, J_{gem}=2.1 Hz, Ar-C≡CCH=C$\underline{H}_2$)
185	6.99	7.18	7.10	6.82	7.13	5.1	1.1	3.8	3.8	I
186	7.33	7.04	7.25	7.11	7.49	5.1	1.1	3.6	3.9	CN
187	7.34	7.05	7.34	7.23	7.65	4.5	4.5	4.4	3.9	δ9.83(s, 1H, Ar-C$\underline{H}$O)
188	7.24	7.01	7.21	7.09	7.06	5.1	1.2	3.6	3.8	δ7.56(d, 1H, J=0.62 Hz, Ar-C$\underline{H}$=CBr$_2$)
194	7.22	6.99	7.15	7.07	6.99	5.1	1.1	3.6	3.9	δ4.77(dd, 1H, $J_{H\text{-}CH3}$=6.5, J=5.07 Hz, AR-C$\underline{H}$(OH)CH$_3$) 1.87(d, 1H, $J_{OH\text{-}CH3}$=4.9 Hz, Ar-C≡C-CH(O$\underline{H}$)CH$_3$) 1.54(d, 1H, $J_{CH3\text{-}OH}$=6.6 Hz, Ar-C≡C-CH(OH)C$\underline{H}_3$)

[a] 300 or 200 MHz ^{1}H NMR.

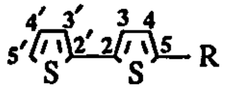


TABLE XX. (continued)

No.	H-5′ (dd,1H)	H-4′ (dd,1H)	H-3′ (dd,1H)	H-3 (d,1H)	H-4 (d,1H)	Coupling Constants (Hz) $J_{4',5'}$	$J_{3',5'}$	$J_{3',4'}$	$J_{3,4}$	Substituent at C-5
195[b]	7.18	6.96	7.12	6.96	6.96	5.1	1.0	3.6	3.9	δ3.78(t, 2H, J_{vic}=6.1, J_{gem}=12.1 Hz, Ar-C≡C-$(CH_2)_2$-C$\underline{H}_2$-OH) 2.55(Q, 4H, J=6.5, J=13.1, J=26.3 Hz, Ar-C≡CC$\underline{H}_2$C$\underline{H}_2$$CH_2$OH) 1.68(s, 1H, Ar-C≡C$CH_2CH_2CH_2O\underline{H}$)
196	7.18	6.98	7.13	6.99	6.97	5.0	1.1	3.6	3.8	δ2.42(t, 2H, J=6.8, J=7.1 Hz, Ar-C≡CC$\underline{H}_2$-$(CH_2)_4CH_3$) 1.45(m, 8H, Ar-C≡C-(C$\underline{H}_2$)$_5$-CH_3) 0.90(t, 3H, J=6.4, J=6.7 Hz, Ar-C≡C-$(CH_2)_5$-C$\underline{H}_3$)
197[c]	7.19	6.98	7.12	6.98	6.98	4.6	1.0	3.5	*	δ2.39(t, 2H, J=7.1, J=7.0 Hz, Ar-C≡CC$\underline{H}_2$$CH_2CH_3$) 1.61(m, 2H, Ar-C≡C$CH_2C\underline{H}_2$$CH_3$) 1.02(t, 3H, J=7.3, J=7.5 Hz, Ar-C≡CCH_2CH_2C$\underline{H}_3$)
198	7.20	6.99	7.15	7.11	6.98	5.0	0.8	3.1	3.8	δ0.24(s, 9H, Ar-C≡C-Si-(C$\underline{H}_3$)$_3$)

[a] 300 or 200 MHz ^{1}H NMR.

[b]Multiplet for H-4, 4′.

[c] Multiplet for H-3, 4.

* To be determined.

3.4 BIOLOGICAL ACTIVITY OF α-DITHIENYL DERIVATIVES

As described in Section 2.4, biological tests with α-dithienyl derivatives were carried out on mosquito larvae and brine shrimp and performed by F. Duval and R. Marles. TABLE XIX lists the results for a series of compounds (LD_{50} values and the singlet oxygen production).

Since all the results of the biological studies are not available yet, it is difficult to ascertain if there is a trend to account for the variation in biological activity. However, the available results show (TABLE XIX) that a compound such as **177** (LD_{50}=409 nM) carrying an acetate moiety at the 4-position of the butynyl side chain was found to be more active than its corresponding alcohol **176** (LD_{50}=751 nM). It was also observed, among the structurally related alcohol derivatives tested, that compound **176** is more toxic than the derivatives **179** (LD_{50}=1262 nM) and **194** (LD_{50}=1556 nM). The presence of a hydroxy group located in a particular position seems to account for the diminished activity observed.

In brine shrimp species, compounds **196** (LD_{50}=9.4 nM) and **197** (LD_{50}=7.14 nM) were found to be the most active derivatives in the series. The larvicidal activity for the alcohols and acetates were found to be lower. Among the alcohol derivatives tested, compound **176** was found to be more toxic (LD_{50}=16.09 nM) than the derivatives **179**, **194** and **195**.

The influence of an electron-donating or withdrawing group is still not clear.

IV CONCLUSION

A variety of naturally occurring α-terthienyl derivatives bearing substituents at 5- and/or 5,5″-position have been succesfully synthesized by the nickel-catalyzed Grignard-Wurtz cross-coupling reaction. This methodology has been shown to be fairly general for the introduction of mono- and disubstituent, but is limited for the coupling to the molecules containing an aryl or alkyl halides with those of aryl Grignard reagent. In the case of aryl halides with aryl Grignard reagent, optimum yield is obtained (75%). When the ring contained alkenyl substituent such as 2-bromo-5-(3′-methyl-2′-butenyl)-thiophene, the desired derivatives was still readily obtained, though the yield was slightly lower (156, 15% yield).

The biological activity of most compounds synthesized have been evaluated as larvicide and phototoxic agent of mosquito larvae (*aedes atropalpus*) and brine shrimp in laboratory and in field trials. Among the derivatives synthesized, 5-cyano-α-terthienyl is the best and most effective compounds as pest control agent. It was also clear that the derivatives containing hindered substituents are less active but still remain toxic since all of them are good producers of singlet oxygen. Disubstituted α-terthienyl compounds were less active than their corresponding mono derivatives.

A variety of naturally occurring α-dithienyl derivatives bearing substituent at C-5 position have been succesfully synthesized by the palladium-catalyzed coupling reaction. This methodology is fairly general for the introduction of substituted 1″-alkynyl derivatives.

Preliminary result and conclusions are described on the previous page.

V EXPERIMENTAL

5. **GENERAL.**- Melting points were determined on a Hoover Uni-melt apparatus and are uncorrected. Ultraviolet spectra were obtained with 95% ethanol solutions on a HPLC spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 783 Ratio Recording Infrared spectrophotometer neat, with KBr or thin film. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian XL-300 or Gemini-200 spectrometers using $CDCL_3$ as solvent, unless otherwise specified. Chemical shifts are reported in ppm downfield from $(CH_3)_4Si$ as an internal standard. Multiplicities are reported as s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; b, broad. Low- and high-resolution mass spectra were recorded on a VG mass spectrometer with a DANI 7070 gas chromatograph. The mass spectral data (MS, HRMS) are reported as *m/z*, with the intensity indicated in parentheses as a percent of the base peak. Microanalyses were performed by M-H-W Laboratories, Phoenix AZ, U.S.A.

In addition to column chromatography, separations were carried out on a centrifugally accelerated, radial, thin-layer chromatograph (Chromatotron Model 7924 TM), using silica gel PF-254 with $CaS0_4 \cdot 1/2\ H_20$ type 60 (Merck 7749) as adsorbent. For column chromatography, silica gel (normal type) from Terochem Laboratories was used.

Tetrahydrofuran (THF) was dried as follows: THF (500 ml), sodium metal (5g) and benzophenone (10g) were refluxed under nitrogen until a deep blue color formed and persisted. After an additional 2 hours of gentle reflux, THF was distilled into an oven dried, nitrogen-flushed flask.

All solvents were distilled prior to utilization. Di*iso*propylamine and triethylamine were distilled over lithium aluminum hydride under a nitrogen atmosphere prior to use. The light petroleum ether used was of boiling range 30-60°C; ether refers to diethylether. All reactions were carried out under nitrogen unless otherwise noted;

hypodermic syringes were used to transfer solutions.

Starting Materials.

Substituted 1-alkyne derivatives such as 1-pentyne, 1-pentyn-5-ol, 1-octyne and 1-butyn-4-ol were purchased from Lancaster Synthesis Ltd. and used without further purification.

Work up.

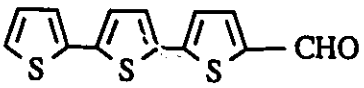
The work up of reactions was carried out by addition of saturated aqueous NH_4Cl solution or dilute hydrochloric acid (2M) to the reaction mixture and extraction of the product into an organic solvent such as diethyl ether or methylene chloride. The combined extracts were washed once with sat. aq. NH_4Cl soln., dried over anhydrous $MgSO_4$ and the solvent removed on a rotary evaporator.

5.1 **Nickel-Catalyzed Grignard-Wurtz Cross-Coupling Reaction-Procedure A.** To a solution of 5-substituted-2-thienyl magnesium bromide dissolved prepared *in situ* in ether was added dropwise 5-iodo-α-dithienyl **185** in ether along with a small amount of dichloro[1,3-*bis*(diphenylphosphinopropane)]Ni^{II} [(dppp)$NiCl_2$]as catalyst. The mixture was refluxed for approximatively 3 hours, then stirred at room temperature (r.t.) overnight or 18 hours. The mixture was hydrolyzed with 3N hydrochloric acid and then extracted with ether. The ether layer was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure without heating and the crude material was separated on silica gel (Chromatotron) eluting with an appropriate solvent.

5.2 Procedure for the Palladium-Catalyzed Coupling Reaction between 5-iodo-2,2′-dithienyl 185 and Substituted 1-Alkynes Derivatives-Procedure B. Cu^I iodide (80 mg, 0.42 mmol, 2 equivalents) and *bis*(triphenylphosphine)Pd^{II} dichloride [$(PPh_3)_2PdCl_2$, 180 mg, 0.21 mmol, 4 equivalents] were stirred at room temperature and under a nitrogen atmosphere in triethylamine (20 ml) for 15 min or until a dark green color appeared. 5-Iodo-α-dithienyl 185 (1 equivalent) and 1-alkyne derivatives (2.5 equivalents) were subsequently added resulting in the formation of a precipitate. After 18 hours of stirring at r.t., the solvent was removed under reduced pressure. Water (30 ml) was then added. The mixture was extracted with ether or CH_2Cl_2 (4 x 50 ml). The organic layers were combined, washed with water (10 ml) and dried over $MgSO_4$. Filtration and removal of the solvent under vacuo afforded a dark greenish solid. The crude product mixture was separated by Chromatotron (eluent: pet. ether/ether 1:1 ratio) unless otherwise indicated.

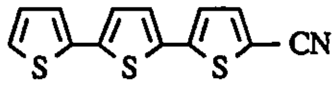
5.3 PREPARATION OF ANALOGUES AND DERIVATIVES OF α-TERTHIENYL.

5.3.1 Preparation of 5-Formyl-2,2′:5′,2″-terthienyl 130.



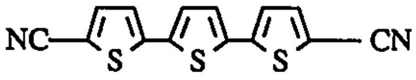
An ice-cooled solution of phosphorus oxychloride ($POCl_3$, 6.08 ml, 65 mmol) in N,N-dimethylformamide (DMF, 20 ml) was stirred for 15 minutes, and to this was added 2,2′:5′,2″-terthienyl 3 (5.5 g, 22 mmol) dissolved in DMF (10 ml). The reaction mixture was stirred at 0°C for an additional 15 minutes, then heated at 70°C for 1 hour to complete the reaction (TLC analysis). The reaction mixture was cooled to r.t. by adding ice followed by water (50 ml). The red-brown mixture was extracted with chloroform ($CHCl_3$, 6 x 50 ml), the organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. Work up and separation by column chromatography using hexane/chloroform (8:2 ratio) as eluent gave 130, (4.50 g, 73% yield) as a pure orange solid, m.p. 135-136°C, (lit.[20] m.p. 135-136°C); R_f(hexane/CH_2Cl_2 1:1)=0.18; UV λ_{max} (EtOH): 395 (ϵ 21,877), 268 (ϵ 6,760), 238 (ϵ 7,943); IR (KBr) ν_{max}: 3100, 2900, 1650 (CO), 1510, 1230, 1050, 840, 800, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 7.93(d, 1H, $J_{4\text{-}3}$= 3.61 Hz, H-4), 7.5(dd, 1H, $J_{5''\text{-}3''}$= 1.07 Hz, $J_{5''\text{-}4''}$= 5.02 Hz, H-5″), 7.49(d, 1H, $J_{4'\text{-}3'}$= 3.86 Hz, H-4′), 7.47(d, 1H, $J_{3\text{-}4}$= 4.0 Hz, H-3), 7.38(dd, 1H, $J_{3''\text{-}4''}$= 3.86 Hz, $J_{3''\text{-}5''}$= 1.07 Hz, H-3″), 7.30(d, 1H, $J_{3'\text{-}4'}$= 3.86 Hz, H-3′), 7.12(dd, 1H, $J_{4''\text{-}3''}$= 3.86 Hz, $J_{4''\text{-}5''}$= 5.02 Hz, H-4″); EIMS *m/z* (%): 276 (100), 248(12), 303(27); Anal. Calcd. for $C_{13}H_8OS_3$: C, 56.50; H, 2.89; S, 34.80. Found: C, 56.03; H, 2.87; S, 34.70.

5.3.2 Preparation of 5-Cyano-2,2′:5′,2″-terthienyl 131.



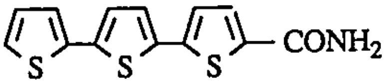
To a solution of α-terthienyl 3 (2.0 g, 8.05 mmol) in CH_2Cl_2 (40 ml) was added, over a 10 minute period, chlorosulfonyl isocyanate (CSI, 1.2 g, 0.73 ml, 8.5 mmol) dissolved in CH_2Cl_2 (10 ml) at -30°C. The N-chlorosulfonyl derivative of α-terthienyl-5-carboxamide separated as a crystalline solid and the mixture was stirred until the temperature reached 10°C. Dimethylformamide (1.2g, 1.3 ml, 16.8 mmol) was added to the cold solution (-30°C) during a 5 minute period and the mixture was stirred at -30°C for 1 hour. The temperature gradually rose to 25°C and ice was added. After the ice had melted, water (100 ml) was added and the organic layers separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 100 ml) and the organic layers combined and washed with water (3 x 15 ml). The solvent was removed under reduced pressure and the crude material separated by column chromatography using CH_2Cl_2 as eluent. Pure 131 was obtained as an orange solid, (1,65 g, 75% yield), m.p. 104-105°C; $R_f(CHCl_3)=0.46$; IR (KBr) ν_{max}: 3100, 2220, 1460, 1425, 1230, 1210, 1160, 1050, 845, 800, 715, 530 and 480 cm^{-1}; ^1H NMR (Acetone-d_6) δ: 7.81(d, 1H, $J_{4\text{-}3}=3.5$ Hz, H-4), 7.50(dd, 1H, $J_{5''\text{-}3''}=1.0$ Hz, $J_{5''\text{-}4''}=5.5$ Hz, H-5″), 7.46(d, 1H, $J_{3'\text{-}4'}=3.7$ Hz, H-3′), 7.42(d, 1H, $J_{4'\text{-}3'}=3.7$ Hz, H-4′), 7.38(dd, 1H, $J_{3''\text{-}5''}=1.0$ Hz, $J_{3''\text{-}4''}=3.5$ Hz, H-3″), 7.30(d, 1H, $J_{3\text{-}4}=3.5$ Hz, H-3), 7.12(dd, 1H, $J_{4''\text{-}3''}=3.5$ Hz, $J_{4''\text{-}5''}=5.5$ Hz, H-4″); EIMS: *m/z* (%): 273(100), 191(100), 146(20), 69(8.5); Anal. Calcd. for $C_{13}H_7S_3N$: C, 57.11; H, 2.58; S, 35.18; N, 5.12. Found: C, 57.10; H, 2.56; S, 35.10; N, 5.13.

5.3.3 Preparation of 5,5″-Dicyano-2,2′:5′,2″-terthienyl 132.



To a solution of α-terthienyl 3 (2.46 g, 9.9 mmol) in CH_2Cl_2 (20 ml) was added CSI (2.94 g, 1.8 ml, 20 mmol) in CH_2Cl_2 (3 ml) at r.t., followed by DMF (2.96 g, 3.1 ml, 40 mmol) The reaction mixture was stirred for 2 hours and left overnight. Work up as in the procedure describe for compound 131, gave 2.4 g (56% yield) of a mixture containing the monocyano derivative 131 and dicyano derivative 132 in a 30:70 ratio. Column chromatography (eluent: CH_2Cl_2) of the mixture afforded the dicyano derivative 132 as an orange solid, m.p. 165-170°C; R_f(hexane/CH_2Cl_2 1:1)=0.38; IR (KBr) ν_{max}: 2220, 1440, 1050, 870, 815, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.53(d, 2H, $J_{4\text{-}3=4''\text{-}3''}=3.9$ Hz, H-4, H-4″), 7.21(s, 2H, H-3′, H-4′), 7.15(d, 2H, $J_{3\text{-}4=3''\text{-}4''}=3.9$ Hz, H-3, H-3″); EIMS: *m/z* (%): 298(62), 167(33), 149(100), 71(34), 57(55), 43(40); Anal. Calcd. for $C_{14}H_6S_3N_2$: C, 56.34; H, 2.03; S, 32.23. Found: C, 56.29; H, 2.07; S, 32.41.

5.3.4 Preparation of 2,2′:5′,2″-Terthienyl-5-carboxamide 133.



To an aqueous NaOH solution (0.07 M, 100 ml) was added 5-cyano-α-terthienyl 131 (100 mg, 0.36 mmol) in ethanol (15 ml). The mixture was stirred for 1 hour at r.t. and then heated for 4 hours at 70°C when TLC analysis revealed that the reaction was complete. The reaction mixture was hydrolyzed with 6M HCl (10 ml) to give the precipitated carboxamide 133 (970 mg). The crude carboxamide derivative was chromatographed by Chromatotron (eluent: hexane) to give α-terthienyl-5--carboxamide 133, (75 mg, 72% yield) as a yellow solid, m.p. 140-141°C; IR (KBr) ν_{max}: 3165, 3390 (NH_2), 1680 (CO), 1390 (CN), 800 (α-T) cm^{-1}; ^1H NMR (acetone-d_6) δ: 7.67(d, 1H, $J_{4\text{-}3}$=3.5 Hz, H-4), 7.46(dd, 1H, $J_{5''\text{-}3''}$=1.0 Hz, $J_{5''\text{-}4''}$=5.0 Hz, H-5″), 7.33(d, 1H, $J_{3\text{-}4}$=3.50 Hz, H-3), 7.33(d,1H, $J_{3''\text{-}4''}$=3.50 Hz, $J_{3''\text{-}5''}$=1.0 Hz, H-3″), 7.29(d, 1H, $J_{3'\text{-}4'}$=3.5 Hz, H-3′), 7.25(d, 1H, $J_{4'\text{-}3'}$=3.50 Hz, H-4′), 7.10(dd, 1H, $J_{4''\text{-}3''}$=3.50 Hz, $J_{4''\text{-}5''}$=5.0 Hz, H-4″); EIMS *m/z* (%): 291(100), 275(29), 273(22), 203(25), 149(35), 129(26), 107(39), 91(96); HRMS: calcd. for $C_{13}H_9OS_3N$: 290.9847. Found: 290.9840; Anal. Calcd. for $C_{13}H_9OS_3N$: C, 53.58; H, 3.11; S, 33.01. Found: C, 53.80; H, 3.40; S, 33.26.

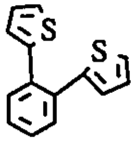
5.3.5 Preparation of 5-Methyl-2,2′:5′,2″-terthienyl 138.

Procedure C. Hydrazine monohydrate (20 mg, 0.39 mmol), 5-formyl-2,2′:5′,2″-terthienyl 130 (100 mg, 0.36 mmol), *n*-butanol (20 ml) and pulverized KOH (10 mg, 0.18 mmol) were placed in a 3-necked round-bottomed flask (50 ml) equipped with a drying tube. The mixture was stirred 5 minutes at r.t. and then refluxed for 3 hours. After stirring for 15 hours (r.t.), work up was performed using ammonium chloride (2 ml) solution. The crude product was separated by Chromatotron (eluent: hexane) to give 138, (88 mg, 93% yield).

Procedure D. Anhydrous ether (10 ml), $LiAlH_4$ (27 mg, 0.71 mmol), and $AlCl_3$ (95 mg, 0.71 mmol) were placed in an ice-cooled 3-necked round-bottom flask (50 ml) equipped with a condenser and under a nitrogen atmosphere. The mixture was stirred at 0°C for 0.5 hour, then 5-(1‴-hydroxymethyl)-2,2′:5′,2″-terthienyl 150 (70 mg, 0.25 mmol) was added to the flask in portions. Stirring was continued at 0°C for 1 hour and then at r.t. for 1 hour. Since TLC analysis indicated that the reaction was not complete, reflux was continued for another hour. Work up and chromatography (Chromatotron, eluent: *n*-pentane) afforded 138, (60 mg, 92% yield).

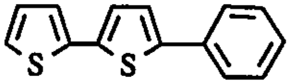
Procedure E. A solution of 2-methyl-thiophene (1.15 g, 11.7 mmol) dissolved in ether (15 ml) was treated with 2M *n*-BuLi (5.1 ml, 10.2 mmol) in hexane and stirred at 0°C for 20 minutes. $MgBr_2{\cdot}OEt_2$ (3.15 g, 12.2 mmol) was subsequently added to the cold solution and the reaction mixture was stirred at r.t. for 1 hour. The Grignard reagent generated *in situ* underwent coupling as described in Section 5.1 , with 5-iodp-α-dithienyl 185 (2.50 g, 8.55 mmol) in the presence of (dppp)$NiCl_2$ catalyst. The reaction mixture was put under reflux for 3 hours. Work up and column chromatography of the crude material (eluent: hexane) gave compound 138, (1.46 g, 65% yield). Procedures C, D and E gave a pale yellow solid, m.p. 94-94.5°C (lit.[4] m.p. 93-94.5°C); R_f(hexane)=0.16; UV λ_{max} (EtOH): 356 (ϵ 32,359), 251_{sh} (ϵ 13,182), 224 (ϵ 19,498); IR (KBr) ν_{max}: 3060, 1510, 1450, 1430, 1200, 1060, 830, 800, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.19(dd, 1H, $J_{5''-3''}$=1.10 Hz, $J_{5''-4''}$=5.12 Hz, H-5″), 7.13(dd, 1H, $J_{3''-5''}$=1.10 Hz, $J_{3''-4''}$=3.54 Hz, H-3″), 7.02(d, 1H, $J_{4'-3'}$=3.66 Hz, H-4′ or 3′), 6.97(d, 1H, $J_{3'-4'}$=3.66 Hz, H-3′ or 4′), 6.94(d, 1H, J_{3-4}=3.42 Hz, H-3), 6.70(dd, 1H, $J_{4''-3''}$=3.54 Hz, $J_{4''-5''}$=5.12 Hz, H-4″), 6.65(dd, 1H, J_{4-3}=3.42 Hz, J=1.0 Hz, H-4), 2.47(d, 3H, J=1.0 Hz, Ar-CH_3); EIMS *m/z* (%): 262(100), 261(26), 229(16), 217(2.7), 203(3.5), 184(3.7), 171(2.7), 69(2); Anal. Calcd. for $C_{13}H_{10}S_3$: C, 59.50; H, 3.84; S, 36.65. Found: C, 59.71; H, 4.00; S, 36.47.

5.3.6 Preparation of 1,2-(Di-2-thienyl)-benzene 140.



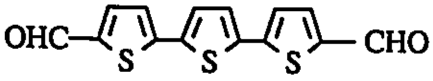
A solution of thiophene (2.0 g, 24 mmol) dissolved in ether (20 ml) was treated with 2.2 M *n*-BuLi (12 ml, 24 mmol) in hexane and stirred at 0°C. $MgBr_2{\cdot}OEt_2$ (6.14 g, 24 mmol) was subsequently added to the cold solution. The Grignard reagent generated *in situ* underwent coupling as described in Section 5.1, with *o*-1,2-dibromobenzene (2.80 g, 12 mmol) in the presence of (dppp)$NiCl_2$ catalyst. The reaction mixture was stirred at r.t. overnight, then put under reflux for 1 hour. Work up and column chromatography of the crude material (eluent: hexane) gave compound **140**, (170 mg, 3% yield) as a yellow pale oil. UV λ_{max} (EtOH): 288 (ϵ 7,585), 257 (ϵ 14,791); IR (film) ν_{max}: 3090, 1480, 1450, 1430, 1080, 850, 800, 770, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 6.87(dd, 2H, $J_{3'-5'}$=1.24 Hz, $J_{3'-4'}$=3.56 Hz, H-3′, 3″), 6.94(dd, 2H, $J_{4'-3'}$=3.58 Hz, $J_{4'-5'}$=5.05 Hz, H-4′, 4″), 7.25(d, 2H, $J_{5'-3'}$=1.26 Hz, $J_{5'-4'}$=5.06 Hz, H-5′, 5″), 7.49(m, 2H, benzene), 7.34(m, 2H, benzene); EIMS *m/z* (%): 242(100), 241(67), 240(20), 209(31), 197(38), 165(14); HRMS: calcd. for $C_{14}H_{10}S_2$: 242.0225. Found: 242.0237.

5.3.7 Preparation of 5-(2,2′-Dithienyl)-benzene 141.



Using the procedure as described in Section 5.1, phenylmagnesium bromide generated *in situ* from bromobenzene (700 mg, 4.4 mmol) and magnesium (110 mg, 4.5 mmol) in ether (20 ml), was treated with 5-iodo-2,2'-dithienyl **185** (1.3 g, 4.4 mmol) in the presence of (dppp)NiCl_2 catalyst and the reaction mixture was stirred overnight at r.t. Work up, followed by separation of the crude mixture (Chromatotron, eluent: hexane) afforded **141**, (325 mg, 30% yield) as a yellow solid, m.p. 121.5-124.5°C; R_f(hexane)=0.23; UV λ_{max} (EtOH): 339 (ϵ 25,703), 244 (ϵ 9,549); IR (KBr) ν_{max}: 3090, 3120, 1500, 1450, 1430, 1250, 1070, 850, 800, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.58(dd, 1H, $J_{5'-3'}$=1.50 Hz, $J_{5'-4'}$=6.80 Hz, H-5'), 7.58(d, 1H, J=9.34 Hz, benzene), 7.31(d, 1H, J=7.12 Hz, benzene), 7.20(dd, 1H, $J_{3'-5'}$=1.20 Hz, $J_{3'-4'}$=3.74 Hz, H-3'), 7.20(d, 1H, J_{3-4}=3.70 Hz, H-3), 7.18(d, 1H, J=2.30 Hz, benzene), 7.12(d, 1H, J_{4-3}=3.73 Hz, H-4), 7.00(dd, 1H, $J_{4'-3'}$=3.70 Hz, $J_{4'-5'}$=5.03 Hz, H-4'), 7.28(m, 1H, benzene); EIMS *m/z* (%): 242(100), 241(66), 240(20), 230(4.5), 209(27), 197(41), 121(18); HRMS: calcd. for $C_{14}H_{10}S_2$; 242.0225. Found: 242.0237; Anal. Calcd. for $C_{14}H_{10}S_2$: C, 69.38; H, 4.16; S, 26.45. Found: C, 68.98; H, 4.52; S, 25.96.

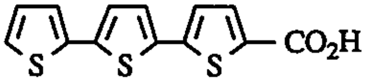
5.3.8 Preparation of 5,5''-Diformyl-2,2':5',2''-terthienyl 142.



Using the procedure described for **130** as in Section 5.3.1, 5-formyl-α-terthienyl **130** (2.4 g, 8.6 mmol) was formylated with $POCl_3$ (0.8 ml, 1 eq.) in DMF (10 ml). The reaction mixture was heated at 70°C for 1 hour, followed by the usual work up. Column chromatography of the crude mixture (eluent: CH_2Cl_2) gave the diformyl derivative **142**, (648 mg, 53% yield) as an orange solid, m.p. 220-221°C; UV λ_{max} (EtOH): 408 (ϵ 28,840), 277 (ϵ 5,888); IR (KBr) ν_{max}: 3100, 1650, 1450, 1220, 1050, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.68(d, 2H, $J_{4,3=3'',4''}$=3.96 Hz, J=Hz, H-4,4''), 7.28(d, 2H, H-3,3''), 7.30(s, 2H, H-3',4'), 9.86(s, 2H, CHO); EIMS *m/z* (%): 304(100), 275(6.4), 231(18), 203(6), 149(11), 91(53), 73(15), 43(55); HRMS: calculated for $C_{14}H_8S_3O_2$:

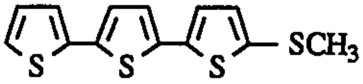
303.9680. Found: 303.9670.

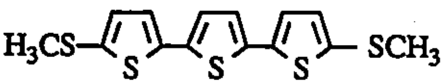
5.3.9 Preparation of 2,2′:5′,2″-Terthienyl-5-carboxylic Acid 143.



Following a literature procedure[142], compound 143 was obtained in 68% yield based on the LDA used. α-Terthienyl 3 (2.5 g, 10.0 mmol) was treated with a solution of LDA (5 mmol) generated *in situ* and the resulting mixture was stirred at -78°C for 1 hour. Carbon dioxide was added and the mixture was stirred at -78°C for 2 hours, then r.t. overnight. Acidification of the mixture with 3% aq. HCl followed by filtration yielded a mixture which contained the mono- and dicarboxylic acid derivatives of α-terthienyl. Column chromatography of the mixture (eluent: acetone/hexane 1:9 ratio) afforded the carboxylic acid derivative 143 (1.2 g) as a yellow solid, α-T 3 (1.4 g) and a small amount of the dicarboxylic acid derivative 143a (0.01 g). α-Terthienyl-5-carboxylic acid had, m.p. 239-240°C, (lit.[142] m.p. 239-240°C); UV λ_{max} (EtOH): 367 (ϵ 28,183), 257 (ϵ 8,511); IR (KBr) ν_{max}: 3200-2500, 1670, 1300, 1450, 850, 800 cm^{-1}; EIMS *m/z (%)*: 292(100).

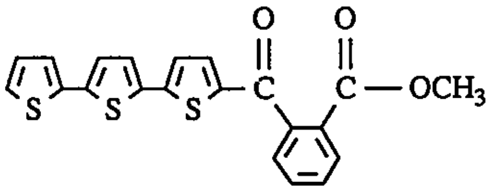
5.3.10 Preparation of 5-Thiomethyl and 5,5″-Dithiomethyl-2,2′:5′,2″-terthienyl 144, 145.





2,2′:5′,2″-Terthienyl 3 (200 mg, 0.8 mmol) dissolved in anhydrous THF (10 ml) was placed in a round-bottomed flask (100 ml). The mixture was cooled to -30°C by using an acetone/CO_2 bath. *n*-BuLi in hexane (1.6 M, 0.50 ml) was added by syringe to the mixture and stirred at -40°C for 45 minutes. The flask was subsequently cooled to -70°C and methyl disulfide (75 mg, 0.8 mmol) was added. The reaction mixture was stirred at -70°C for 0.5 hour. The temperature of the bath was permitted to rise to -30°C and the mixture stirred for an additional 1.5 hours. Usual work up left a yellow-orange precipitate which was separated by Chromatotron eluted with hexane/MeOH (progressively increasing the polarity gradient). **5-Thiomethyl-2,2′:5′,2″-terthienyl 144** was isolated as a yellow solid (160 mg, 67% yield), m.p. 91-92°C; R_f(hexane)=0.20; UV λ_{max}: (EtOH): 367 (ϵ 29,512), 251 (ϵ 9,549); IR (KBr) ν_{max}: 3060, 2910, 1490, 1420, 1200, 1060, 860, 835, 790 and 695 cm^{-1}; ^1H NMR (acetone-d_6) δ: 7.44(dd, 1H, $J_{5''\text{-}3''}$=1.10 Hz, $J_{5''\text{-}4''}$=5.16 Hz, $\underline{H}$-5″), 7.30(dd, 1H, $J_{3''\text{-}4''}$=3.63 Hz, $J_{3''\text{-}5''}$=1.10 Hz, $\underline{H}$-3″), 7.22(d, 1H, $J_{4'\text{-}3'}$=3.85 Hz, $\underline{H}$-4′ or 3′), 7.17(d, 1H, $J_{3'\text{-}4'}$=3.85 Hz, $\underline{H}$-3′ or 4′), 7.08(dd, 1H, $J_{4''\text{-}3''}$=3.63 Hz, $J_{4''\text{-}5''}$=5.16 Hz, $\underline{H}$-4″), 7.05(d, 1H, $J_{4\text{-}3}$=3.76 Hz, $\underline{H}$-4), 7.17(d, 1H, $J_{3\text{-}4}$=3.76 Hz, $\underline{H}$-3), 2.50(s, 3H, Ar-SC$\underline{H}_3$); EIMS *m/z* (%): 294(99.6), 279(100), 246(32.6), 235(10), 190(5), 147(15), 117(12), 69(12); Anal. Calcd. for $C_{13}H_{10}S_4$: C, 53.02; H, 3.42; S, 43.55. Found: C, 52.95; H, 3.54; S, 43.77. A second compound **5,5″-dithiomethyl-2,2′:5′,2″-terthienyl 145** was eluted (35 mg, 14%) as a yellow solid, m.p. 134.5-135°C; UV λ_{max} (EtOH): 379 (ϵ 29, 512), 247 nm (ϵ 9,120; IR (KBr) υ_{max}: 3060, 2910, 1425, 1200, 965, 850 and 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.99(s, 2H, $\underline{H}$-3′,4′), 6.98(d, 2H, $J_{4\text{-}3,4''\text{-}3''}$=3.74 Hz, $\underline{H}$-4,4″), 6.95(d, 2H, $J_{3\text{-}4,3''\text{-}4''}$=3.74 Hz, $\underline{H}$-3,3″); EIMS *m/z* (%): 340(99.2), 325(100), 310(38.5); Anal. Calcd. for $C_{14}H_{12}S_5$: C, 49.37; H, 3.55; S, 47.07. Found: C, 49.39; H, 3.72; S, 47.21.

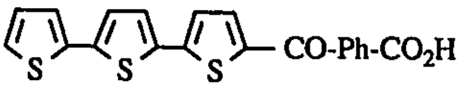
5.3.11 Methyl 5-(2‴-Carboxybenzoyl)-2,2′:5′,2″-terthienyl 146.



To a solution of α-terthienyl 3 (347 mg, 1.40 mmol) in ether (25 ml) was added 1.6 M *n*-BuLi in hexane (0.86 ml) at -40°C and the reaction mixture was stirred for 30 minutes. $MgBr_2 \cdot OEt_2$ (370 mg, 1.40 mmol) was subsequently added (-40°C) and stirring was continued for 30 minutes while the solution was allowed to warm to 0°C. The mixture was cooled to -70°C and phthalic anhydride (207 mg, 1.39 mmol) was added. The temperature was increased to 25°C and the mixture stirred for 1 hour. Work up left a mixture containing the mono and diacid derivatives (610 mg). Methylation with an etheral diazomethane solution at 0°C followed by Chromatotron using $CHCl_3$ as eluent, gave the methyl monoester 146, (200 mg, 35%) as a pale yellow solid, m.p. 105-106°C; $R_f(CH_2Cl_2)=0.32$; UV λ_{max} (EtOH): 400 (ε 36,307), 262 (ε 11,220), 219 (ε 20,892); IR (KBr) ν_{max}: 3080 (CH), 2960 (CH_2), 1690 (ketone CO), 1645 (ester CO), 1300 (C-O-C), 800 (α-T) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.03(ddd, 1H, $J_{3'''\text{-}4'''}=7.4$ Hz, $J_{3'''\text{-}5'''}=1.6$ Hz, $J_{3'''\text{-}6'''}=0.7$ Hz, $\underline{H}$-3‴), 7.63(ddd, 1H, $J_{4'''\text{-}3'''}=7.4$ Hz, $J_{4'''\text{-}5'''}=7.5$ Hz, $J_{4'''\text{-}6'''}=1.5$ Hz, $\underline{H}$-4‴), 7.56(ddd, 1H, $J_{5'''\text{-}4'''}=7.5$ Hz, $J_{5'''\text{-}6'''}=7.4$ Hz, $J_{5'''\text{-}3'''}=1.6$ Hz, $\underline{H}$-5‴), 7.48(ddd, 1H, $J_{6'''\text{-}5'''}=7.4$ Hz, $J_{6'''\text{-}4'''}=1.5$ Hz, $J_{6'''\text{-}3'''}=0.7$ Hz, $\underline{H}$-6‴), 7.25(dd, 1H, $J_{5''\text{-}4''}=5.2$ Hz, $J_{5''\text{-}3''}=1.2$ Hz, $\underline{H}$-5″), 7.23(d, 1H, $J_{4\text{-}3}=3.9$ Hz, $\underline{H}$-4), 7.19(dd, 1H, $J_{3''\text{-}4''}=3.6$ Hz, $J_{3''\text{-}5''}=1.2$ Hz, $\underline{H}$-3″), 7.14(d, 1H, $J_{4'\text{-}3'}=4.0$ Hz, $\underline{H}$-4′), 7.10(d, 1H, $J_{3\text{-}4}=3.9$ Hz, $\underline{H}$-3), 7.08(d, 1H, $J_{3'\text{-}4'}=4.0$ Hz, $\underline{H}$-3′), 7.02(dd, 1H, $J_{4''\text{-}5''}=5.2$ Hz, $J_{4''\text{-}3''}=3.6$ Hz, $\underline{H}$-4″), 3.73(s, 3H, $CO_2C\underline{H}_3$); EIMS *m/z* (%): 410(100), 149(41), 129(100), 57(87); Anal. Calcd. for $C_{21}H_{14}O_3S_3$: C, 61.44; H, 3.43; S, 23.43. Found: C, 61.52; H, 3.31; S, 23.18; and;

Dimethyl 5,5″-*bis*(2‴-Carboxybenzoyl)-2,2′:5′,2″-terthienyl 148; (347 mg, 44%), m.p. 215-216°C; $R_f(CH_2Cl_2)$=0.08; UV λ_{max} (EtOH): 415 (ϵ 9,120), 272 (ϵ 3,019), 251 (ϵ 3,801); IR (KBr) ν_{max}: 3080 (CH), 2950 (CH_2), 1730 (ketone CO), 1640 (ester CO), 1300 (C-O-C), 800 (α-T) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 8.03(ddd, 1H, $J_{6'''-5'''}$=7.3 Hz, $J_{6'''-4'''}$=1.4 Hz, $J_{6'''-3'''}$=0.6 Hz, H-6‴), 7.62(ddd, 1H, $J_{5'''-4'''}$=7.3 Hz, $J_{5'''-6'''}$=7.3 Hz, $J_{5'''-3'''}$=1.5 Hz, H-5‴), 7.56(ddd, 1H, $J_{4'''-5'''}$=7.3 Hz, $J_{4'''-3'''}$=7.2 Hz, $J_{4'''-6'''}$=1.4 Hz, H-4‴), 7.47(ddd, 1H, $J_{3'''-4'''}$=7.2 Hz, $J_{3'''-5'''}$=1.5 Hz, $J_{3'''-6'''}$=0.6 Hz, H-3‴), 7.26(s, 2H, H-3′, H-4′), 7.15(d, 2H, $J_{3-4,3''-4''}$=3.9 Hz, H-3, H3″), 7.12(d, 2H, $J_{4-3=4''-3''}$=3.9 Hz, H-4, H-4″), 3.73(s, 6H, 2 x CO_2CH_3); FABMS *m/z* (%): 572(0.2), 461(31), 369(93), 277(100), 186(100), 185(100), 149(94), 94(100), 93(100); Anal. Calcd. for $C_{30}H_{20}O_6S_3$: C, 62.92; H, 3.51; S, 16.79. Found: C, 63.13; H, 3.76; S, 16.66.

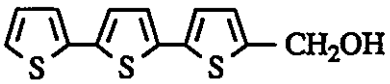
5.3.12 5-(2‴-Carboxybenzoyl)-2,2′:5′,2″-terthienyl 147.



The methyl monoester 146 was hydrolyzed with 2M NaOH solution (2 ml) in methanol (10 ml) with stirring overnight. The methanol was removed under vacuum at room temperature and water (10 ml) was added. The solution was then acidified with 2M HCl followed by extraction with CH_2Cl_2 (3 x 25 ml). After removal of the solvent under reduced pressure, the pure monoacid 148 was obtained (179 mg, 93% yield) as a yellow solid, m.p. 238-239°C; UV λ_{max} (EtOH): 394 (ϵ 33,884), 261 (ϵ 10,232), 238 (ϵ 13,803); IR (KBr) ν_{max}: 3090-2500 (COOH), 1690 (ketone CO), 1650 (acid CO), 1280 (C-O-C), 800 (α-T) cm^{-1}; ^{1}H NMR (dimethylsulfoxide-d_6) δ: 7.98(ddd, 1H, $J_{3'''-4'''}$=7.5 Hz, $J_{3'''-5'''}$=1.8 Hz, $J_{3'''-6'''}$=0.7 Hz, H-3‴), 7.72(ddd, 1H, $J_{4'''-3'''}$=7.5 Hz, $J_{4'''-5'''}$=7.4 Hz, $J_{4'''-6'''}$=1.5 Hz, H-4‴), 7.68(ddd, 1H, $J_{5'''-4'''}$=7.4 Hz, $J_{5'''-6'''}$=7.3 Hz, $J_{5'''-3'''}$=1.8 Hz, H-5‴), 7.59(dd, 1H, $J_{5''-4''}$=5.1 Hz, $J_{5''-3''}$=1.2 Hz, H-5″), 7.54(d, 1H,

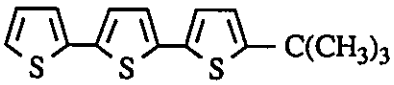
J_{4-3}=3.8 Hz, $\underline{H}$-4), 7.52(ddd, 1H, $J_{6'''-5'''}$=7.3 Hz, $J_{6'''-4'''}$=1.5 Hz, $J_{6'''-3'''}$=0.7 Hz, $\underline{H}$-6'''), 7.42(dd, 1H, $J_{3''-4''}$=3.6 Hz, $J_{3''-5''}$=1.2 Hz, $\underline{H}$-3''), 7.38(d, 1H, $J_{4'-3'}$=4.0 Hz, $\underline{H}$-4'), 7.36(d, 1H, J_{3-4}=3.8 Hz, $\underline{H}$-3), 7.19(d, 1H, $J_{3'-4'}$=4.0 Hz, $\underline{H}$-3'), 7.13(dd, 1H, $J_{4''-5''}$=5.1 Hz, $J_{4''-3''}$=3.6 Hz, $\underline{H}$-4''); EIMS *m/z* (%): 396(100), 203(43), 275(32), 69(60), 43(71); Anal. Calcd. for $C_{20}H_{12}O_3S_3$: C, 60.59; H, 3.04; S, 24.26. Found: C, 60.76; H, 3.05; S, 24.19.

5.3.13 Preparation of 5-(1'''-Hydroxymethyl)-2,2':5',2''-terthienyl 150.



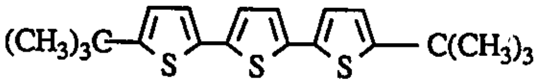
Sodium borohydride (50 mg, 0.18 mmol) was added to an cold solution (0°C, ice bath) of 5-formyl-2,2':5',2''-terthienyl 130 (500 mg, 1.8 mmol) dissolved in anhydrous THF (20 ml). The reaction mixture was stirred for 2 hours, during which time the bath temperature rose to 25°C. After completion of the reaction (TLC analysis), the solvent was removed under reduced pressure and cold water (0°C, 50 ml) was added. Acidification with 6M HCl to pH 2 and filtration through a sintered glass funnel gave the product 150, (400 mg, 80% yield) as a yellow precipitate, m.p. 148-150°C (lit.[148] 150-151°C); $R_f(CH_2Cl_2)$=0.12; UV λ_{max} (EtOH): 356 (ϵ 27,542), 253 (ϵ 11,220); IR (KBr) ν_{max}: 3400, 3080, 2920, 1450, 1200, 1160, 1060, 1000, 840, 800, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.20(dd, 1H, $J_{5''-3''}$=1.12 Hz, $J_{5''-4''}$=5.12 Hz, $\underline{H}$-5''), 7.15(dd, 1H, $J_{3''-5''}$=1.12 Hz, $J_{3''-4''}$=3.63 Hz, $\underline{H}$-3''), 7.05(2d, 2H, $J_{3'-4'}$=3.79 Hz, $\underline{H}$-3',4'), 7.01(d, 1H, J_{3-4}=3.61 Hz, $\underline{H}$-3), 7.00(dd, 1H, $J_{4''-3''}$=3.63 Hz, $J_{4''-5''}$=5.12 Hz, $\underline{H}$-4''), 6.90(d, 1H, J_{4-3}=3.61 Hz, $\underline{H}$-4), 4.97(d, 2H, *J*=6.00 Hz, Ar-$C\underline{H}_2OH$), 1.79(d, 1H, *J*=6.00 Hz, Ar-$CH_2O\underline{H}$); EIMS *m/z* (%): 278(31.5), 361(100), 249(3), 136(6.7); HRMS: calculated for $C_{13}H_{10}S_3O$: 277.9895. Found: 277.9901.

5.3.14 Preparation of 5-*t*-Butyl-2,2′:5′,2″-terthienyl 151.



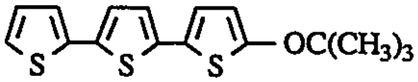
n-BuLi in hexane (1.6 M, 2.04 ml) was added by syringe at r.t. to a solution of 2-*t*-butyl-thiophene 171 (460 mg, 3.28 mmol) in ether (10 ml). The mixture was stirred for 5 minutes and then heated under reflux for 1 hour. After cooling to 0°C, $MgBr_2{\cdot}OEt_2$ (0.95 g, 3.67 mmol) was added and the reaction mixture was stirred at r.t. for 0.5 hour. 5-Iodo-2,2′-dithienyl 185 (0.96 g, 3.30 mmol), prepared by a literature procedure[177], was dissolved in ether (2 ml) and added to the mixture along with (dppp)$NiCl_2$ (10 mg) catalyst. The reaction mixture was stirred at r.t. for 15 hours. Work up and column chromatography (eluent: *n*-pentane) yielded compound 152, (452 mg, 45% yield) as a pale yellow solid, m.p. 66.5-67.6°C; R_f(hexane)=0.21; UV λ_{max} (EtOH): 356 (ϵ 27,542), 251 (ϵ 9,772); IR (KBr) ν_{max}: 3080, 2980, 1510, 1450, 1370, 1250, 1210, 1080, 1050, 840, 800, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.18(dd, 1H, $J_{5''-3''}$=1.16 Hz, $J_{5''-4''}$=5.10 Hz, H-5″), 7.14(dd, 1H, $J_{3''-5''}$=1.16 Hz, $J_{3''-4''}$=3.65 Hz, H-3″), 7.04(d, 1H, $J_{4'-3'}$=3.78 Hz, H-4′ or 3′), 6.99(dd, 1H, $J_{4''-3''}$=3.65 Hz, $J_{4''-5''}$=5.10 Hz, H-4″), 6.98(d, 1H, $J_{3'-4'}$=3.78 Hz, H-3′ or 4′), 6.96(d, 1H, J_{3-4}=3.76 Hz, H-3), 6.72(d, 1H, J_{4-3}=3.67 Hz, H-4), 1.38(s, 9H, Ar-$C(CH_3)_3$); EIMS *m/z* (%): 304(57), 289(92), 274(16), 248(15), 221(100), 219(91), 137(41), 109(4), 73(13.5); HRMS: calculated for $C_{16}H_{16}S_3$: 304.0415. Found: 304.0418; Anal. Calcd. for $C_{16}H_{16}S_3$: C, 63.11; H, 5.29; S, 31.59. Found: C, 62.96; H, 5.19; S, 31.68.

5.3.15 Preparation of 5,5″-Di-*t*-butyl-2,2′:5′,2″-terthienyl 152.



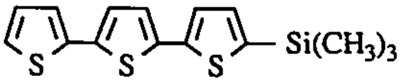
α-Terthienyl 3 (2.4 g, 9.6 mmol) was treated with $AlCl_3$ (2.0 g, 15 mmol) and *t*-butyl chloride[151,152] (8 ml, 120 mmol) in CH_2Cl_2 (150 ml) as solvent and the reaction mixture was stirred at r.t. for 24 hours. Work up and column chromatography (eluent: hexane) afforded **152**, (2.6 g, 72% yield) as a yellow solid, m.p. 134-135°C; UV λ_{max} (EtOH): 379 (ϵ 29,512), 247 (ϵ 9,120); ^{1}H NMR (CDCl$_3$) δ: 6.95(s, 2H, $\underline{H}$-3′,4′), 6.93(d, 2H, $\underline{H}$-3,3″), 6.70(d, 2H, $J_{4,3=3'',4''}$=4.0 Hz, $\underline{H}$-4,4″), 1.37(s, 18H, C(C$\underline{H}_3$)$_3$); CIMS *m/z* (%): 361(96), 360(64), 345(31); Anal. Calcd. for $C_{20}H_{24}S_3$: C, 66.61; H, 6.70; S, 26.67. Found: C, 66.98; H, 6.69; S, 25.56.

5.3.16 Preparation of 5-*t*-Butoxy-2,2′:5′,2″-terthienyl 153.



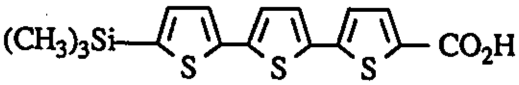
Mg turnings (350 mg, 14.4 mmol) and ether (2 ml) were placed in a flask (100 ml) equipped with an additional funnel. A crystal of I_2 was added followed by 2-bromo-5-*t*-butoxy-thiophene **172** (2.98 g, 12.7 mmol) dissolved in ether (10 ml) and the reaction mixture was heated under reflux for 1 hour. After cooling to r.t., a solution of 5-iodo-2,2′-dithienyl **185** (3.8 g, 13 mmol) in ether (5 ml) along with (dppp)NiCl$_2$ catalyst were added. The reaction mixture was heated under reflux and monitored by TLC analysis. After 4 hours, the reaction mixture was allowed to come to r.t. and stirring was continued for an additional 3 hours. Work up left a brown solid residue (7.78 g) which was separated by column chromatography (eluent: hexane) to afford **153**, (2.25 g, 55% yield) as a yellow solid, m.p. 124-125-°C; R$_f$(hexane)=0.21; UV λ_{max} (EtOH): 364 (ϵ 23,988), 250 (ϵ 8,709); IR (KBr) ν_{max}: 3060, 2980, 2920, 1505, 1480, 1450, 1420, 1360, 1140, 840, 800 and 680 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.18(dd, 1H, $J_{5''\text{-}3''}$=1.14 Hz, $J_{5''\text{-}4''}$=5.12 Hz, $\underline{H}$-5″), 7.13(dd, 1H, $J_{3''\text{-}5''}$=1.14 Hz, $J_{3''\text{-}4''}$=3.69 Hz, $\underline{H}$-3″), 7.02(d, 1H, $J_{3'\text{-}4'}$=3.76 Hz, $\underline{H}$-3′ or 4′), 6.99(dd, 1H, $J_{4''\text{-}3''}$=3.69 Hz, $J_{4''\text{-}5''}$=5.12 Hz, $\underline{H}$-4″), 6.93(d, 1H, $J_{4'\text{-}3'}$=3.76 Hz, $\underline{H}$-4′ or 3′), 6.82(d, 1H, $J_{3\text{-}4}$=3.89 Hz, $\underline{H}$-3), 6.29(d, 1H, $J_{4\text{-}3}$=6.29 Hz, $\underline{H}$-4), 1.39(s, 9H, Ar-O-C(C$\underline{H}_3$)$_3$); EIMS *m/z* (%): 320(28), 264(100), 263(6.7), 235(7), 203(7); Anal. Calcd. for $C_{16}H_{16}OS_3$: C, 59.96; H, 5.03; S, 30.01. Found: C, 60.00; H, 5.70; S, 30.00.

5.3.17 Preparation of 5-Trimethylsilyl-2,2′:5′,2″-terthienyl 154.



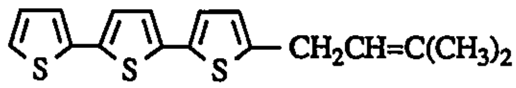
2-Bromo-5-trimethylsilyl-thiophene 173 (11.2 g, 47 mmol) dissolved in ether (50 ml) was added to a flask (250 ml) containing Mg turnings (2.0 g, 83 mmol) in ether (50 ml) and a crystal of I_2. After complete addition, the reaction mixture was heated under reflux for 1 hour. 5-Iodo-2,2′-dithienyl 185 (13.9 g, 47 mmol) dissolved in ether (10 ml) was added dropwise to the mixture along with (dppp)$NiCl_2$ catalyst, and stirred for 2 hours. The reaction mixture was then heated under reflux for 4 hours and stirring was continued overnight (16 hours) at r.t. Work up gave a dark brown residue which was separated by column chromatography (eluent: hexane) to afford 154, (13.0 g, 75% yield) as a bright yellow solid, m.p. 85-86°C; R_f(pet. ether)=0.19; UV λ_{max} (EtOH): 356 (ϵ 38,018), 254 (ϵ 13,182); IR (KBr) ν_{max}: 3060, 2960, 1430, 1250, 1080, 1000, 835, 800, 750 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.20(dd, 1H, $J_{5''\text{-}3''}$=1.20 Hz, $J_{5''\text{-}4''}$=5.11 Hz, H-5″), 7.20(d, 1H, $J_{3\text{-}4}$=3.42 Hz, H-3), 7.15(dd, 1H, $J_{3''\text{-}4''}$=3.66 Hz, $J_{3''\text{-}5''}$=1.20 Hz, H-3″), 7.12(d, 1H, $J_{4\text{-}3}$=3.42 Hz, H-4), 7.07(d, 1H, $J_{4'\text{-}3'}$=3.50 Hz, H-4′ or 3′), 7.06(d, 1H, $J_{3'\text{-}4'}$=3.50 Hz, H-3′ or 4′), 7.00(dd, 1H, $J_{4''\text{-}3''}$=3.66 Hz, $J_{4''\text{-}5''}$=5.11 Hz, H-4″), 0.32(s, 9H, Ar-Si(CH_3)$_3$); EIMS *m/z* (%): 320(100), 305(93).

5.3.18 Preparation of 5-Carboxyl-5″-trimethylsilyl-2,2′:5′,2″-terthienyl 155.



A solution of LDA generated *in situ* from 2.5M *n*-BuLi in hexane (0.33 ml, 0.82 mmol) and di*iso*propylamine (83 mg, 0.82 mmol) was stirred at -30°C for 0.5 hour in a 3-neck round-bottom flask (50 ml) in THF (20 ml) as solvent. The mixture was subsequently cooled to -70°C, at which time compound 154 (300 mg, 0.82 mmol) was added. Stirring was continued for 0.5 hour and when $CO_{2(s)}$ (excess) was added, a yellow precipitate formed. Work up left a yellow solid which was washed with *n*-pentane and pet. ether in order to remove unreacted 154. Compound 155 was obtained (318 mg) in 93% yield as a yellow solid, m.p. 230-230.5°C; R_f(acetone)=0.08; UV λ_{max} (EtOH): 376 (ϵ 41,686), 261 (ϵ 11,481). $230_{(sh)}$ (ϵ 15,848); IR (KBr) ν_{max}: 3420, 3060, 2940, 1650 (CO), 1500 (C=C), 1460, 1440, 1300 (C-O), 1250, 1100, 1070, 985, 830 (C-Si), 800, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.72(d, 1H, $J_{4\text{-}3}$=3.97 Hz, H-4), 7.41(d, 1H, $J_{4'\text{-}3'}$=3.81 Hz, H-4′ or 3′), 7.29(d, 1H, $J_{3'\text{-}4'}$=3.81 Hz, H-3′ or 4′), 7.40(dd, 1H, $J_{3''\text{-}4''}$=3.47 Hz, H-3″), 7.35(d, 1H, $J_{3\text{-}4}$=3.97 Hz, H-3), 7.26(d, 1H, $J_{4''\text{-}3''}$=3.47 Hz, H-4″), 2.82(br. s, 1H, 5-CO_2H), 0.33(s, 9H, 5″-$Si(CH_3)_3$); EIMS *m/z* (%): 364(100), 349(86); Anal. Calcd. for $C_{16}H_{16}O_2S_3Si$: C, 52.71; H, 4.42; S, 26.38. Found: C, 45.76; H, 4.02; S, 21.51.

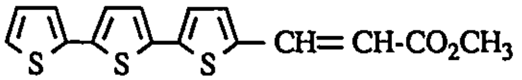
5.3.19 Preparation of 5-(3‴-Methyl-2‴-butenyl)-2,2′:5′,2″-terthienyl 156.



To a solution of Grignard reagent prepared by heating under reflux for 2 hours 5-iodo-2,2′-dithienyl 185 (397 mg, 1.35 mmol) with Mg turnings (33 mg, 1.35 mmol) in ether (10 ml), was added dropwise a solution of 2-bromo-5-(3‴-methyl--2‴-butenyl)-thiophene 174 (314 mg, 1.35 mmol) in ether (2 ml) along with (dppp)$NiCl_2$ (10 mg) catalyst. The reaction mixture was stirred overnight at r.t. Work up and separation of the crude material by Chromatotron (eluent: *n*-pentane) afforded 156, (48 mg, 11% yield) as a pale yellow solid, m.p. 71-72°C; R_f(hexane)=0.27; UV λ_{max} (EtOH):

356 (ϵ 23,988), 250 (ϵ 9,120); IR (KBr) ν_{max}: 2920 (CH_2:), 1735 (CH:) and 800 (α-T) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.18(dd, 1H, $J_{5''-4''}$=5.1 Hz, $J_{5''-3''}$=1.2 Hz, H-5″), 7.13(dd, 1H, $J_{3''-4''}$=3.6 Hz, $J_{3''-5''}$=1.2 Hz, H-3″), 7.03(d, 1H, $J_{3'-4'}$=3.8 Hz, H-3′), 6.99(dd, 1H, $J_{4''-5''}$=5.1 Hz, $J_{4''-3''}$=3.6 Hz, H-4″), 6.97(d, 1H, $J_{4'-3'}$=3.8 Hz, H-4′), 6.96(d, 1H, J_{3-4}=3.6 Hz, H-3), 6.67(dt, 1H, J_{4-3}=3.6 Hz, $J_{4\text{-}CH2}$=1.1 Hz, H-4), 5.35(tq, 1H, $J_{:CH\text{-}CH2}$=7.3 Hz, $J_{:CH\text{-}CMe2}$=1.4 Hz, CH=CMe_2), 3.48(d, 2H, $J_{CH2\text{-}:CH}$=7.1 Hz, Ar-CH_2), 1.75(d, 3H, $J_{CH3\text{-}:CH}$=1.0 Hz, CH_3), 1.70(d, 3H, $J_{CH3\text{-}:CH}$=1.0 Hz, CH_3); EIMS *m/z* (%): 316(27), 301(12), 287(5), 248(100), 231(7), 230(60), 136(100), 135(27) 69(16) and 39(27); Anal. Calcd. for $C_{17}H_{16}S_3$: C, 64.51; H, 5.09; S, 30.39. Found: C, 64.26; H, 5.09; S, 30.47.

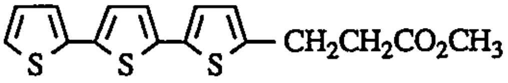
5.3.20 Preparation of Methyl 2,2′:5′,2″-Terthienyl-5-[(E)-3‴-acrylate] 157.



To a solution of 5-formyl-2,2′:5′,2″-terthienyl **130**[135] (715 mg, 2.58 mmol) in THF (200 ml) was added methyl(triphenylphosphoranylidene)acetate[153] (1.28 g, 3.87 mmol). The resulting solution was heated under reflux for 13 hours, then cooled to r.t. and evaporated to dryness. Part of the residue dissolved in $CHCl_3$ (20 ml) and the insoluble product was filtered and washed with $CHCl_3$ (2 ml) to afford **157**, (794 mg, 92% yield) as a yellow solid, m.p. 199-200°C; R_f(CH_2Cl_2/EtOAc 1%)=0.38; UV λ_{max} (EtOH): 404 (ϵ 19,498), 250 (ϵ 5,623); IR (KBr) ν_{max}: 3090 (CH), 3080, 2940 (CH), 1700 (CO), 1615 (C=C), 1310 (COC), 1170, 800 (α-T) cm^{-1} ^1H NMR ($CDCl_3$) δ: 7.79(d, 1H, $J_{:CH\text{-}:CH}$=15 Hz, α-T-CH:), 7.56(dd, 1H, $J_{5''-4''}$=5.1 Hz, $J_{5''-3''}$=1.1 Hz, H-5″), 7.54(d, 1H, J_{4-3}=3.9 Hz, H-4), 7.39(d, 1H, $J_{4'-3'}$=3.8 Hz, H-4′), 7.38(d, 1H, J_{3-4}=3.9 Hz, H-3), 7.38(dd,1H, $J_{3''-4''}$=3.7 Hz, $J_{3''-5''}$=1.1 Hz, H-3″), 7.32(d, 1H, $J_{3'-4'}$=3.8 Hz, H-3′), 7.11(dd, 1H, $J_{4''-5''}$=5.1 Hz, $J_{4''-3''}$=3.7 Hz, H-4″), 6.24(d, 1H, $J_{:CH\text{-}:CH}$=15 Hz, :$CHCO_2Me$), 3.71(s, 3H, CO_2CH_3); EIMS *m/z* (%): 332(100), 301(21), 274(19), 227(5); Anal. Calcd. for

$C_{16}H_{12}O_2S_3$: C, 57.84; H, 3.64; S, 28.93. Found: C, 57.80; H, 3.73; S, 28.89.

5.3.21 Preparation of Methyl 2,2′:5′,2″-Terthienyl-5-(3‴-propionate) 158.

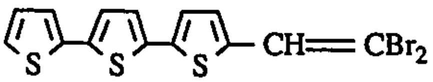


A solution of 157 (794 mg, 2.38 mmol) in ethyl acetate (350 ml) containing 10% Pd/C catalyst (1.0 g) was stirred under H_2 at 30 *psi* for 48 hours at r.t. The mixture was filtered and the filtrate evaporated under pressure to give the crude product (575 mg). Separation of the residue by Chromatotron and elution with hexane/CH_2Cl_2 (1:1 ratio), gave 158, (560 mg, 70% yield) as a pale yellow solid, m.p. 113-114°C; R_f(Pet. ether/CH_2Cl_2 1:1)=0.17; UV λ_{max} (EtOH): 355 (ϵ 23,988), 251 (ϵ 10,000), 226 (ϵ 9,772); IR (KBr) ν_{max}: 2930 (CH_2), 1730 (CO), 1200 (COC), 800 (α-T) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.19(dd, 1H, $J_{5''\text{-}4''}$=5.1 Hz, $J_{5''\text{-}3''}$=1.1 Hz, $\underline{H}$-5″), 7.14(dd, 1H, $J_{3''\text{-}4''}$=3.7 Hz, $J_{3''\text{-}5''}$=1.1 Hz, $\underline{H}$-3″), 7.04(d, 1H, $J_{3'\text{-}4'}$=3.8 Hz, $\underline{H}$-3′), 6.99(dd, 1H, $J_{4''\text{-}5''}$=5.1 Hz, $J_{4''\text{-}3''}$=3.7 Hz, $\underline{H}$-4″), 6.98(d, 1H, $J_{4'\text{-}3'}$=3.8 Hz, $\underline{H}$-4′), 6.96(d, 1H, $J_{3\text{-}4}$=3.6 Hz, $\underline{H}$-3), 6.71(dt, 1H, $J_{4\text{-}3}$=3.6 Hz, $J_{4\text{-}:CH2}$=0.8 Hz, $\underline{H}$-4), 3.12(td, 1H, $J_{CH2\text{-}CH2}$=7.5 Hz, $J_{:CH2\text{-}4}$=0.8 Hz, $C\underline{H}_2CH_2CO_2Me$), 3.69(s, 3H, $CO_2C\underline{H}_3$), 2.67(t, 2H, $J_{CH2\text{-}CH2}$=7.5 Hz, $C\underline{H}_2CO_2Me$); EIMS *m/z* (%): 334(67), 261(100), 235(81), 209(51), 192(44), 153(72); Anal. Calcd. for $C_{16}H_{14}O_2S_3$: C, 57.46; H, 4.22; S, 28.76. Found: C, 57.39; H, 4.34; S, 28.63.

5.3.22 Preparation of 2,2′:5′,2″-Terthienyl-5-(3‴-propionic acid) 159.

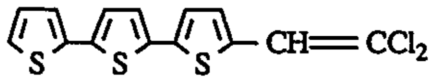
To a solution of 158 (558 mg, 1.67 mmol) dissolved in MeOH/THF (1:1 ratio, 50 mL) was added 4M NaOH solution in H_2O (4.0 ml, 13 mmol) and the reaction mixture was stirred at r.t. for 48 hours. After evaporating (25°C) to dryness, the residue was suspended in water (400 ml) and acidified with 2M HCl solution until pH 2 was reached. The yellow solid that formed was filtered, washed with water (10 ml) and dried under vacuum to afford <u>159</u>, (445 mg, 85% yield) as a yellow solid, m.p. 186-187°C; $R_f(CH_2Cl_2)=0.03$; UV λ_{max} (EtOH): 350 (ϵ 31,670); IR (KBr) ν_{max}: 3200-2500 (COOH), 2920 (CH_2), 1700 (CO), 1220 (COC), 800 (α-T) cm^{-1}; ^1H NMR (Acetone-d_6) δ: 7.52(dd, 1H, $J_{5''-4''}=5.1$ Hz, $J_{5''-3''}=1.2$ Hz, <u>H</u>-5″), 7.32(dd, 1H, $J_{3''-4''}=3.6$ Hz, $J_{3''-5''}=1.2$ Hz, <u>H</u>-3″), 7.25(d, 1H, $J_{3'-4'}=3.8$ Hz, <u>H</u>-3′), 7.17(d, 1H, $J_{4'-3'}=3.8$ Hz, <u>H</u>-4′), 7.14(d, 1H, $J_{3-4}=3.6$ Hz, <u>H</u>-3), 7.09(dd, 1H, $J_{4''-5''}=5.1$ Hz, $J_{4''-3''}=3.6$ Hz, <u>H</u>-4″), 6.85(d, 1H, $J_{4-3}=3.6$ Hz, <u>H</u>-4), 3.34(br.s, 1H, $CO_2\underline{H}$), 3.01(t, 2H, $J_{CH2-CH2}=7.2$ Hz, $C\underline{H}_2CH_2CO_2H$), 2.59(t, 2H, $J_{CH2-CH2}=7.3$ Hz, $C\underline{H}_2CO_2H$); EIMS *m/z* (%): 320(57), 261(100), 251(11); Anal. Calcd. for $C_{15}H_{12}O_2S_3$: C, 57.81; H, 3.64; S, 28.93. Found: C, 58.08; H, 3.72; S, 28.79.

5.3.23 <u>Preparation of 5-(2‴-Dibromoethenyl)-2,2′:5′,2″-terthienyl 160.</u>



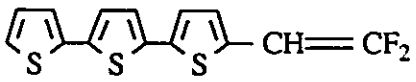
Triphenylphosphine PPh_3(2.13 g, 8.10 mmol) and CBr_4 (1.34 g, 4.05 mmol) were stirred in anhydrous CH_2Cl_2 (20 ml) at 0°C. To the cold solution was added 5-formyl-2,2′:5′,2″-terthienyl <u>130</u> (560 mg, 2.02 mmol) within a 5 minute period (otherwise decreased in the yield was observed). The reaction was completed within 5-10 minutes (TLC analysis), water (20 ml) was added and the organic phase extracted with CH_2Cl_2 (4 x 50 ml). The combined extracts were washed with a saturated NaCl solution (2 x 20 ml), then dried over $MgSO_4$ at r.t. for 1 hour. Filtration and evaporation to dryness, followed by separation of the crude product by Chromatotron (eluent: n-pentane/CH_2Cl_2 3:1 ratio) gave <u>160</u>, (826 mg, 94% yield) as a pale yellow solid, m.p. 145-146°C; $R_f(CH_2Cl_2)=0.81$; UV λ_{max} (EtOH): 391 (ϵ 28,840), 244 (ϵ 11,220); IR (KBr) ν_{max}: 3050, 1440, 1425, 1280, 1060, 865, 835, 800, cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.57(d, 1H, Ar-CH=CBr_2), 7.22(dd, 1H, $J_{5''-3''}$=1.18 Hz, $J_{5''-4''}$=5.09 Hz, H-5″), 7.17(dd, 1H, $J_{3''-4''}$=1.13 Hz, $J_{3''-5''}$=3.64 Hz, H-3″), 7.13(d, 1H, $J_{3'-4'}$=3.79 Hz, H-3′), 7.11(dd, 1H, J_{4-3}=3.89 Hz, $J_{4\text{-}CH:}$=0.60 Hz, H-4), 7.07(d, 1H, $J_{4'-3'}$=3.79 Hz, H-4′), 7.06(d, 1H, J_{3-4}=3.81 Hz, H-3), 7.00(dd, 1H, $J_{4''-3''}$=3.62 Hz, $J_{4''-5''}$=5.12 Hz, H-4″); EIMS *m/z* (%): 432(95), 272(100), 227(13), 136(38), 69(17); Anal. Calcd. for $C_{14}H_8S_3Br_2$: C, 38.90; H, 1.86; S, 22.25. Found: C, 39.13; H, 1.69; S, 22.11.

5.3.24 Preparation of 5-(2‴-Dichloroethenyl)-2,2′:5′,2″-terthienyl 161.



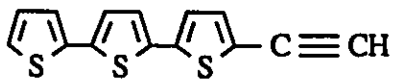
To a stirred solution of PPh_3 (414 mg, 1.58 mmol) and excess anhydrous CCl_4 (20 mL) cooled at 0°C, was added 5-formyl-2,2′:5′,2″-terthienyl **130** (110 mg, 0.39 mmol). Since no reaction appeared to occur at 0°C (TLC analysis), the reaction mixture was warmed to r.t. and then refluxed for 16 hours. Removal of the solvent under reduced pressure and column chromatography of the crude product (eluent: hexane) afforded **161**, (30 mg, 15% yield) as a pale yellow solid, m.p. 141-142°C; R_f(hexane/CH_2Cl_2)=0.44; UV λ_{max} (EtOH): 388 (ϵ 34,673), 242 (ϵ 14,454); IR (KBr) ν_{max}: 3020, 1590, 1440, 1420, 1060, 925, 835, 800, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.23(dd, 1H, $J_{5''-3''}$=1.10 Hz, $J_{5''-4''}$=5.12 Hz, H-5″), 7.17(dd, 1H, $J_{3''-5''}$=1.10 Hz, $J_{3''-4''}$=3.66 Hz, H-3″), 7.12(d, 1H, $J_{3'-4'}$=3.78 Hz, H-3′), 7.08(d, 1H, $J_{4'-3'}$=3.78 Hz, H-4′), 7.08(d, 1H, J_{3-4}=3.78 Hz, H-3), 7.06(d, 1H, J_{4-3}=3.90 Hz, H-4), 7.02(dd, 1H, $J_{4''-3''}$=3.62 Hz, $J_{4''-5''}$=5.08 Hz, H-4″), 6.98(s, 1H, Ar-CH=CCl_2); CIMS *m/z* (%): 343(15.5), 342(100), 308(19), 272(21), 135(18), 69(63), 57(98), 43(97); Anal. Calcd. for $C_{14}H_8S_3Cl_2$: C, 48.98; H, 2.35; S, 28.01. Found: C, 49.14; H, 2.52; S, 27.88.

5.3.25 Preparation of 5-(2‴-Difluoroethenyl)-2,2′:5′,2″-terthienyl 162.



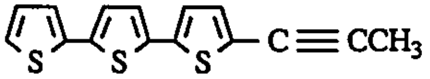
Similar to the above procedure, 5-formyl-2,2′:5′,2″-terthienyl 130 (200 mg, 0.72 mmol) was added to a solution containing PPh_3 (760 mg, 2.9 mmol) and CBr_2F_2 (300 mg, 1.42 mmol) in CH_2Cl_2 (20 ml) stirred at 0°C. The reaction mixture was stirred for 15 minutes, then heated under reflux for 18 hours to complete the reaction (TLC analysis). Work up and separation by Chromatotron (eluant: hexane) afforded 162, (61 mg, 27% yield) as a pale yellow solid, m.p. 125-126°C; R_f(hexane)=0.22; UV λ_{max} (EtOH): 368 (ϵ 24,547), 252 (ϵ 7,413), 231 (ϵ 9,772); IR (KBr) ν_{max}: 3100, 1700, 1430, 1300, 800, 700 cm^{-1};^{1}H NMR ($CDCl_3$) δ: 7.21(dd, 1H, $J_{5''\text{-}3''}$=1.14 Hz, $J_{5''\text{-}4''}$=5.10 Hz, H-5″), 7.15(dd, 1H, $J_{3''\text{-}5''}$=1.16 Hz, $J_{3''\text{-}4''}$=3.61 Hz, H-3″), 5.06(d, 1H, $J_{4'\text{-}3'}$=H3.80 z, H-4′), 6.86(d, 1H, $J_{3'\text{-}4'}$=3.85 Hz, H-3′), 5.49(dd, 1H, $J_{CH=CF2}$=1.95 Hz, $J_{:CH=CF2}$=26.06 Hz, Ar-CH=CF_2), 7.01(dd, 1H, $J_{4''\text{-}3''}$=3.62 Hz, $J_{4''\text{-}5''}$=5.12 Hz, H-4″), 7.04(d, 1H, J=1.84 Hz, J=3.69 Hz, H-4, H-3); EIMS *m/z* (%): 310(100), 265(4.5), 203(3), 189(3), 155(12), 69(6); Anal. Calcd. for $C_{14}H_8S_3F_2$: C, 54.17; H, 2.59; S, 30.98. Found: C, 53.98; H, 2.76; S, 30.77.

5.3.26 Preparation of 5-Ethynyl-2,2′:5′,2″-terthienyl 163.



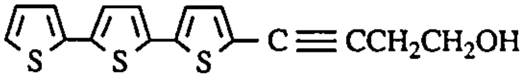
5-(2‴-Dibromoethenyl)-2,2′:5′,2″-terthienyl 160 (200 mg, 0.46 mmol) was treated with 1.6 M *n*-BuLi (0.30 ml) at -78°C and stirred for 1 hour then at 25°C for an additionnal hour. Work up and separation of the crude material by Chromatotron (eluent: *n*-pentane) produced the acetylenic derivative[172,173] 163, (82 mg, 65% yield) as a pale yellow solid, m.p. 95-96°C; R_f(hexane)=0.21; UV λ_{max} (EtOH): 372 (ϵ 33,113), 258 (ϵ 10,964), 236 (ϵ 12,302); IR (KBr) ν_{max}: 3270, 3070, 2100, 1430, 1260, 1070, 840, 800, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.22(dd, 1H, $J_{5''-3''}$=1.16 Hz, $J_{5''-4''}$=5.11 Hz, H-5″), 7.17(dd, 1H, $J_{3''-5''}$=1.16 Hz, $J_{3''-4''}$=3.63 Hz, H-3″), 7.16(d, 1H, $J_{4\text{-C≡CH}}$=0.4 Hz, $J_{4\text{-}3}$=3.80 Hz, H-4), 7.06(d, 1H, $J_{3'-4'}$=3.86 Hz, H-3′), 7.06(d, 1H, $J_{3\text{-}4}$=3.58 Hz, H-3), 7.01(dd, 1H, $J_{4''-3''}$=3.63 Hz, $J_{4''-5''}$=5.11 Hz, H-4″), 6.99(d, 1H, $J_{4'-3'}$=3.84 Hz, H-4′), 3.39(d,1H, $J_{\text{Ar-C≡CH-4}}$=0.38 Hz, Ar-C≡CH); EIMS *m/z* (%): 272(100), 227(8.8), 195(5), 136(11), 32(48); Anal. Calcd. for $C_{14}H_8S_3$: C, 61.72; H, 2.96; S, 35.31. Found: C, 61.54; H, 3.14; S, 35.12.

5.3.27 Preparation of 5-(2‴-Prop-1‴-ynyl)-2,2′:5′,2″-terthienyl 164.



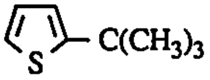
5-(2‴-Dibromoethenyl)-2,2′:5′,2″-terthienyl **160** (329 mg, 0.76 mmol) was treated with 1.6 M *n*-BuLi (0.95 ml, 1.52 mmol) in THF (20 ml) stirred at -78°C for 1 hour, then at 25°C for 1 hour, before adding CH_3I (0.05 ml, 0.54 mmol). Addition of water (10 ml) and extraction with CH_2Cl_2 (4 x 20 ml) followed by separation of the crude product by Chromatotron (eluent: *n*-pentane) gave **164**, (33 mg, 15% yield) as a pale yellow solid, m.p. 95-96°C; R_f(hexane)=0.13; UV λ_{max} (EtOH): 374 (ϵ 33,113), 257 (ϵ 10,232), 234 (ϵ 12,022); IR (KBr) ν_{max}: 3060, 2900, 2100, 1550, 1500, 1430, 1060, 830, 800, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.21(dd, 1H, $J_{5''-3''}$=1.19 Hz, $J_{5''-4''}$=5.10 Hz, H-5″), 7.16(dd, 1H, $J_{3''-5''}$=1.17 Hz, $J_{3''-4''}$=3.64 Hz, H-3″), 7.06(d, 1H, $J_{3'-4'}$=3.83 Hz, H-3′), 7.04(d, 1H, $J_{4'-3'}$=3.80 Hz, H-4′), 7.01(dd, 1H, $J_{4''-3''}$=3.62 Hz, $J_{4''-5''}$=5.11 Hz, H-4″), 6.99(dd, 1H, $J_{4\text{-}3}$=3.82 Hz, H-4 or H-3), 6.97(d, 1H, $J_{3\text{-}4}$=3.80 Hz, H-3 or H-4), 2.08(s, 3H, Ar-C≡CH$_3$); EIMS *m/z* (%): 286(100), 285(20), 274(5.8), 253(13), 240(5), 227(3), 209(3), 195(3), 177(3), 158(3), 143(1.4), 121(9.6), 69(9.7); Anal. Calcd. for $C_{15}H_{10}S_3$: C, 62.89; H, 3.52; S, 33.58. Found: C, 62.81; H, 3.59; S, 33.49.

5.3.28 Preparation of 5-(4‴-Hydroxybut-1‴-ynyl)-2,2′:5′,2″-terthienyl 165.



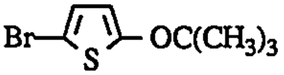
5-Iodo-2,2′:5′,2″-terthienyl 134 (70 mg, 0.18 mmol) was coupled with 3-butyn-1-ol (39 mg, 0.56 mmol) by using the palladium-catalyzed reaction described in Section 5.2. The reaction was almost complete after 30 minutes (TLC analysis); stirring was continued overnight at r.t. Work up and separation of the crude mixture (Chromatotron, eluent: hexane) afforded **165**, (33 mg, 56% yield) as a yellow solid, m.p. 146-147°C; UV λ_{max} (EtOH): 374 (ϵ 31,622); IR (KBr) ν_{max}: 3300, 1750, 1600, 1450, 1050, 850, 800, 700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.21(dd, 1H, $J_{5''-3''}$=1.10 Hz, $J_{5''-4''}$=5.08 Hz, H-5″), 7.15(dd, 1H, $J_{3''-5''}$=1.09 Hz, $J_{3''-4''}$=3.61 Hz, H-3″), 7.05(d, 1H, $J_{4'-3'}$=4.39 Hz, H-4′ or H-3′), 7.04(d, 1H, J_{3-4}=3.82 Hz, H-3), 7.03(d, 1H, $J_{3'-4'}$=4.51 Hz, H-3′ or H-4′), 7.00(dd, 1H, $J_{4''-3''}$=3.63 Hz, $J_{4''-5''}$=5.10 Hz, H-4″), 6.97(d, 1H, J_{4-3}=3.82 Hz, H-4), 3.80(t, 2H, J=6.25 Hz, Ar-C≡C-CH$_2$CH$_2$OH), 2.71(t, 2H, J=6.23 Hz, Ar-C≡C-CH$_2$CH$_2$OH), 1.69(s, 1H, Ar-C≡C-CH$_2$CH$_2$OH); EIMS *m/z* (%): 316(100), 285(92), 253(10), 129(16).

5.3.29 Preparation of 2-*t*-Butyl-thiophene 171.



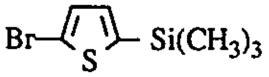
Mg turnings (1.0 g, 41.6 mmol), ether (15 ml) and a crystal of I$_2$ were placed in a 3-necked round-bottomed flask (100 ml) and the solution was stirred at r.t. 2-Bromothiophene (6 g, 38.6 mmol) dissolved in ether (10 ml) was added dropwise. After complete addition, the Grignard reagent was heated under reflux for 15 minutes and then cooled to 0°C by using an ice bath. 2-Chloro-2-methyl propane (3.40 g, 38 mmol) was added slowly, then the mixture was allowed to warm to r.t. and stirring was continued for 15 minutes. Addition of (dppp)NiCl$_2$ catalyst caused the reaction mixture to reflux and refluxing was continued for 4 hours, following by stirring at r.t. for 15 hours and refluxing for an additionnal 4 hours. A pale yellow precipitate formed. Work up produced a brown oil (9.96 g) which was separated by fractionnal distillation to give <u>171</u>, (2.04 g, 40% yield) as a pale yellow oil[152] which was kept under a N_2 atmosphere berween -5°C and 0°C, to preserve its integrity, (b.p. 60-63°C/0.05 torr); IR (film) ν_{max}: 3060, 2940, 1450, 1320 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ: 1.1(s, 9H, 2-C(C<u>H</u>$_3$)$_3$), 6.4-6.9(m, 3H, Ar<u>H</u>); EIMS *m/z* (%): 140(23.5), 125(100), 97(21), 85(13).

5.3.30 <u>Preparation of 2-Bromo-5-*t*-butoxy-thiophene 172.</u>



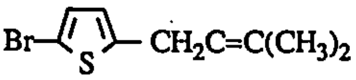
Lithium di*iso*propylamine solution in ether (20 ml) prepared *in situ* from di*iso*propylamine (3.46 ml, 24.6 mmol) and *n*-BuLi in hexane (2.5 M, 9.8 ml) at -30°C in an acetone/CO_2 bath was stirred for 0.5 hour, then cooled to -70°C. 2-Bromothiophene (4.0 g, 24.5 mmol) dissolved in ether (20 ml) was added to the solution and stirring was continued for 0.5 hour. After warming the mixture to -30°C, $MgBr_2{\cdot}OEt_2$ (5.7 g, 24.8 mmol) was added and stirring was continued for 0.5 hour. The temperature of the bath was lowered to -70°C and *t*-butylperoxybenzoate (4.75 g, 25 mmol) was added dropwise. After complete addition, the bath was allowed to warm to r.t. and the mixture stirred overnight. Work up gave a reddish oil (4.44 g) which was separated by Chromatotron (eluent: hexane) to give <u>172</u>[151], (3.42 g, 60% yield) as a yellow transparent oil, R_f(hexane/CH_2Cl_2 95:5)=0.32; ^1H NMR 60 MHz ($CDCl_3$) δ: 6.8(d, 1H, <u>H</u>-3), 6.2(d, 1H, <u>H</u>-4), 1.4(s, 9H, Ar-O-C(C<u>H</u>$_3$)$_3$); EIMS *m/z* (%): 235(1.2), 234(10), 179(95), 178(91), 112(12.8), 98(10), 57(100).

5.3.31 <u>Preparation of 2-Bromo-5-trimethylsilyl-thiophene 173.</u>



Lithium di*iso*propylamine in THF (20 ml) prepared *in situ* from di*iso*propylamine (6.20 g, 61.3 mmol) and 2.5 M *n*-BuLi (24.5 ml) was placed in a flask (100 ml) cooled to -70°C *via* an acetone/CO_2 bath. The mixture was stirred for 0.5 hour during which time the temperature of the bath rose to -25°C. The bath was then cooled to -70°C and 2-bromothiophene (10 g, 61.3 mmol) was added and the reaction mixture stirred for 0.5 hour. Trimethylsilyl chloride (7.8 ml, 61.3 mmol) was then added and the bath temperature was permitted to warm to room temperature. After stirring for 0.5 hour, usual work up was performed and a brown oil was obtained. The crude oil was distilled under vacuum by using a fractionating column packed with glass bead isolating 2-bromo-5-trimethlsilyl-thiophene **173** as a colorless oil, (11 g, 77% yield); b.p. 31°C/0.05 torr, (lit.[151] b.p. 58°C/0.5 torr); ^{1}H NMR ($CDCl_3$) δ: 0.03(s, 9H, Ar-Si($C\underline{H}_3)_3$), 6.95(dd, 2H, *J*=3 Hz, $\underline{H}$-3,4); HRMS: calculated for $C_7H_{11}SBrSi$: 233.9530. Found: 234.9519.

5.3.32 Preparation of 2-Bromo-5-[4-(2-methyl-2-butenyl)]-thiophene 174.



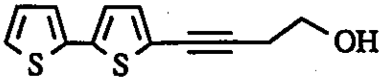
1.6 M *n*-BuLi (2.0 ml) and diisopropylamine (310 mg, 3.06 mmol) were stirred at -40°C for 30 min., then cooled to -70°C at which time 2-bromothiophene (500 mg, 3.06 mmol) was added dropwise and the mixture stirred at -70°C for 30 minutes. 4-Bromo-2-methyl-2-butene (457 mg, 3.06 mmol) was subsequently added and stirring was continued overnight while the solution was allowed to warm slowly to r.t. Work up left a residual oil which was fractionnally distilled under vacuum to give compound **174**, (357 mg, 45% yield) as a colorless oil, (b.p. 90°C/1.3 torr); R_f(hexane)=0.42; IR (KBr) ν_{max}: 3080, 2980, 2920, 1510, 1450, 840, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 6.82(d, 1H,

$J_{3\text{-}4}$=3.7 Hz, H-3), 6.51(d, 1H, $J_{4\text{-}3}$=3.7 Hz, $J_{4\text{-CH2}}$=1.2 Hz, H-4), 5.30(tq, 1H, $J_{\text{:CH-CH2}}$=7.3 Hz, $J_{\text{:CH-CH3}}$=1.5 Hz, :CH), 3.41(d, 2H, $J_{\text{CH2-:CH}}$=6.8 Hz, CH_2), 1.73(d, 3H, $J_{\text{CH3-:CH}}$=1.1 Hz, CH_3), 1.67(s, 3H, CH_3); EIMS *m/z* (%): 230(59), 217(33), 215(33), 151(31), 136(100), 135(27).

5.3.33 Preparation of 2,2′-Dithienyl 175.

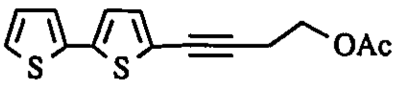
According to the procedure described in Section 5.1, a solution of 2-thienylmagnesium bromide prepared *in situ* from 2-bromothiophene (50.0 g, 0.30 mole) and Mg turnings (7.45 g, 0.30 mole), was added dropwise along with (dppp)$NiCl_2$ catalyst to 2-bromothiophene (50.0 g, 0.31 mole) dissolved in anhydrous ether. The mixture was refluxed for 8 hours, then stirred at r.t. overnight. Work up followed by column chromatography (eluent: hexane) afforded **175**, (48 g, 96% yield) as a pale yellow solid, m.p. 32-33°C (lit.[172] m.p. 33°C, lit.[183] m.p. 33°C); IR (KBr) ν_{max}: 3100, 1420, 1210, 1050, 820, 700 cm^{-1}; ^1H NMR 60 MHz ($CDCl_3$) δ: 7.10-7.40(m, 6H, aromatic-H); EIMS *m/z* (%): 166(100), 165(21), 134(40), 121(87), 108(20), 95(7), 82(11) and 69(34).

5.3.34 Preparation of 5-(4″-Hydroxybut-1″-ynyl)-2,2′-dithienyl 176.



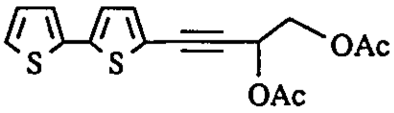
Following the procedure described in Section 5.2, 5-iodo-2,2′-dithienyl **185** (3.2 g, 10.9 mmol) was coupled with 3-butyn-1-ol (1.93 g, 27.5 mmol). Work up and column chromatography (eluent: pet. ether/ether 1:1 ratio) gave **176**, (2.06 g, 81% yield) as a pale yellow solid, m.p. 65-66°C (lit.[172] m.p. 71-72°C, lit.[175] 66-67°C); R_f=0.29; UV λ_{max} (EtOH): 333 (ϵ 28,840), 241 (ϵ 8,317); IR (KBr) ν_{max}: 3200, 2900, 1760, 1600, 1425, 1190, 1040, 890, 840, 800 and 700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.19(dd, 1H, $J_{5'-3'}$=1.18 Hz, $J_{5'-4'}$=5.11 Hz, H-5′), 7.14(dd, 1H, $J_{3'-5'}$=1.17 Hz, $J_{3'-4'}$=3.63 Hz, H-3′), 7.03(d, 1H, J_{3-4}=3.76 Hz, H-3), 6.98(dd, 1H, $J_{4'-3'}$=3.64 Hz, $J_{4'-5'}$=5.07 Hz, H-4′), 6.98(d, 1H, J_{4-3}=3.83 Hz, H-4), 3.79(q, 2H, J=6.04 Hz, J=12.34 Hz, Ar-C≡C-CH$_2$-CH$_2$-OH), 2.70(t, 2H, J=6.23 Hz, J=12.45 Hz, Ar-C≡C-CH$_2$-CH$_2$-OH), 1.78(t, 1H, J=6.04 Hz, J=6.37 Hz, J=12.41 Hz, Ar-C≡C-CH$_2$-CH$_2$-OH); EIMS *m/z* (%): 234(40), 203(100), 171(5.6), 158(3), 127(1.5), 115(7.7) and 69(11); Anal. Calcd. for $C_{12}H_{10}OS_2$: C, 61.50; H, 4.30; S, 27.36. Found: C, 61.74; H, 4.49; S, 27.57.

5.3.35 Preparation of 5-(4″-Acetoxybut-1″-ynyl)-2,2′-dithienyl 177.



5-(4″-Hydroxybut-1″-ynyl)-2,2′-dithienyl 176 (732 mg, 3.12 mmol) was treated with acetic anhydride (1 ml) in pyridine (2 ml) and stirred at 0°C for 15 minutes, the temperature was allowed to rise at r.t. and the reaction was complete within 3 hours (TLC analysis). Work up followed by separation of the crude oil by Chromatotron (eluent: pet. ether/ether 1:1 ratio) afforded 177, (790 mg, 92% yield) as a pale yellow solid, m.p. 46-47°C; R_f=0.66; UV λ_{max} (EtOH): 333 (ϵ 30,902), 238 (ϵ 10,232); IR (KBr) ν_{max}: 3100, 2980, 2920, 2300, 1750, 1470, 1430, 1400, 1250, 1050, 890, 850, 800, 700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.20(dd, 1H, $J_{5'-3'}$=1.14 Hz, $J_{5'-4'}$=5.10 Hz, H-5′), 7.14(dd, 1H, $J_{3'-5'}$=1.14 Hz, $J_{3'-4'}$=3.61 Hz, H-3′), 7.02(d, 1H, J_{3-4}=3.80 Hz, H-3), 6.98(dd, 1H, $J_{4'-3'}$= 3.6 Hz, $J_{4'-5'}$=5.2 Hz, H-4′), 6.97(d, 1H, J_{4-3}=3.6 Hz, H-4), 4.23(t, 2H, J=6.9 Hz A_2B_2, J=6.8 Hz A_2B_2, Ar-C≡C-CH$_2$CH$_2$-OAc), 2.76(t, 2H, J=6.89 Hz A_2B_2, J=6.97 Hz A_2B_2, Ar-C≡CCH$_2$CH$_2$-OAc), 2.08(s, 3H, Ar-C≡CCH$_2$CH$_2$-OCO-CH$_3$); EIMS *m/z* (%): 276(16), 216(100), 203(18), 117(43), 43(40); Anal. Calcd. for $C_{14}H_{12}O_2S_2$: C, 60.84; H, 4.37; S, 23.20. Found: C, 59.89; H, 4.12; S, 25.58.

5.3.36 Preparation of 5-(3″,4″-Diacetoxybut-1″-ynyl)-2,2′-dithienyl 178.

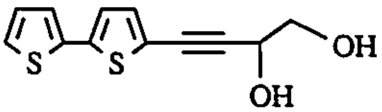


3-Hydroxy-4-acetoxybut-1-ynyl 191 (1.0 g, 7.8 mmol) was synthesized according to reference 179. Using the procedure described Section 5.2, 3-hydroxy-4-acetoxybut-1-ynyl[179] 191 was coupled with 5-iodo-α-dithienyl 185 (910 mg, 3.1 mmol) in Et_3N (20 ml) as solvent. Work up and column chromatography (eluent: pet. ether/ether 1:1 ratio) afforded impure 5-(3″-hydroxy-4″-acetoxybut-1″-ynyl)-α-dithienyl 193 (1.66 g) as a yellow oil (racemic mixture). This oil was chromatographed once more (chromatotron, eluent: pet. ether/ether 3:1 ratio and increasing to 1:1) to afford pure 193, (888 mg, 87% yield) as a pale yellow solid, m.p. 58-59°C; IR (KBr) ν_{max}: 3500-3200, 2960, 2120, 1740, 1390, 1290, 1100, 1050, 700 cm^{-1}; ^1H NMR 60 MHz ($CDCl_3$) δ: 6.90-7.35(m, 5H, Aromatic), 4.70-5.10(m, 1H, Ar-C≡C-CH(OH)-CH_2OAc), 4.30-4.50(d, 2H, Ar-C≡C-CH(OH)-CH_2OAc), 3.80-4.10(br.s, 1H, Ar-C≡C-CH(OH)-CH_2OAc), 2.20-2.30(s, 3H, Ar-C≡C-CH(OH)-CH_2OCOCH_3).

Compound 193 (888 mg, 3.03 mmol) was acetylated with acetic anhydride (0.85 ml, 9.1 mmol) in pyridine (15 ml) at r.t. Work up and separation of the crude material (Chromatotron, eluent: pet. ether/ether) afforded 5-(3″,4″-diacetoxybut-1″-ynyl)-α-dithienyl 178, (926 mg, 90% yield) as a pale yellow oil, UV λ_{max} (EtOH): 335 (ϵ 21,877), 243 (ϵ 4,897); IR (film) ν_{max}: 2960, 2220, 1750, 1370, 1230, 1050, 800, 765, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.22(dd, 1H, $J_{5'-3'}$=1.17 Hz, $J_{5'-4'}$=4.94 Hz, H-5′), 7.16(dd, 1H, $J_{3'-4'}$=3.63 Hz, $J_{3'-5'}$=1.17 Hz, H-3′), 7.12(d, 1H, J_{3-4}=3.77 Hz, H-3), 7.00(d, 1H, J_{4-3}=3.63 Hz, H-4), 6.99(dd, 1H, $J_{4'-3'}$=3.55 Hz, $J_{4'-5'}$=5.30 Hz, H-4′), 5.84(dd, 1H,

J_{vic}=7.31 Hz, Ar-C≡CCH(OAc)CH$_2$OAc), 4.41(dd, 1H, J_{vic}=3.7, J_{gem}=11.7 Hz, Ar-C≡CCH(OAc)CH$_2$OAc), 4.29(dd, 1H, J_{vic}=7.31, J_{gem}=11.7 Hz, Ar-C≡CCH(OAc)CH$_2$OAc), 2.10(s, 3H, Ar-C≡CCH(OAc)CH$_2$OAc), 2.09(s, 3H, Ar-C≡CCH(OAc)CH$_2$OAc); EIMS *m/z* (%):334(10), 274(27), 232(49), 219(19), 43(100); Anal. Calcd. for $C_{16}H_{14}O_4S_2$: C, 57.46; H, 4.22; S, 19.14. Found: C, 57.40; H, 4.33; S, 19.27.

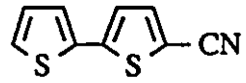
5.3.37 Preparation of 5-(3″,4″-Dihydroxybut-1″-ynyl)-2,2′-dithienyl 179.



To a stirred solution of NaOH (5M, 1 ml) in ethanol (95%, 20 ml) at 0°C (1 minute) was added 5-(3″-hydroxy-4″-acetoxybut-1″-ynyl)-α-dithienyl 193 (218 mg, mmol) dissolved in EtOH (95%, 2 ml). The reaction mixture was stirred at 0°C for 2 hours, then at r.t. for 1 hour when the reaction appeared to be complete (TLC analysis). The solvent was partially removed under reduced pressure and the remaining solution acidified with dilute H_2SO_4 (3%) to pH 1. The solution was extracted with ether (6 X 25 ml), then with CH_2Cl_2 (4 X 25 ml). The combined extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure. Separation of the crude product by Chromatotron (eluent: CH_2Cl_2, EtOAc, MeOH with increasing polarity gradient) afforded 5-(3″,4″-dihydroxybut-1″-ynyl)-α-dithienyl 179, (80 mg, 55% yield) a pale yellow solid, m.p. 108-110°C, (lit.[179] m.p. 92°C); UV λ_{max} (EtOH): 334 (ϵ 28,840), 238 (ϵ 9,772); IR (KBr) ν_{max}: 3400-3200 (OH), 2960, 2220 (C≡CH), 1420, 1200, 1090, 1030, 870, 840, 800, 700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.22(dd, 1H, $J_{5'\text{-}3'}$=1.16 Hz, $J_{5'\text{-}4'}$=5.13 Hz, H-5′), 7.16(dd, 1H, $J_{3'\text{-}4'}$=3.62 Hz, $J_{3'\text{-}5'}$=1.10 Hz, H-3′), 7.10(d, 1H, $J_{3\text{-}4}$=3.91 Hz, H-3), 6.99(dd, 1H, $J_{4'\text{-}3'}$=3.62 Hz, H-4′), 7.00(d, 1H, $J_{4\text{-}3}$=3.72 Hz, H-4), 4.69(dd, 1H, $J_{CHX\text{-}HA}$=3.95 Hz, $J_{Hx\text{-}Hb}$=6.39 Hz, H_x), 3.83(dd, 1H, $J_{Ha\text{-}Hx}$=4.01 Hz, J_{gem}=11.3 Hz, H_A), 3.76(dd, 1H,

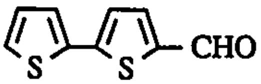
J_{vic}=6.40 Hz, J_{gem}=11.3 Hz, $\underline{H}_B$); EIMS *m/z* (%): 250(41), 232(12), 219(100), 190(89), 158(13), 69(21).

5.3.38 Preparation of 5-Cyano-2,2′-dithienyl 186.



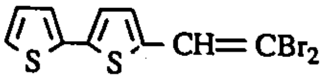
According to the procedure described in Section 5.3.2 for compound **151**, 5-cyano-2,2′-dithienyl **186** was obtained in 76% yield (1.9 g) by treating 2,2′-dithienyl **175** (2.0 g, 0.01 mole) with CSI (1.6 ml, 0.02 mole). Work up, followed by column chromatography (eluent: *n*-pentane/CH_2Cl_2 1:1 ratio) afforded **186** as a pale yellow solid, m.p. 75-76°C; R_f(hexane/CH_2Cl_2 1:1)= 0.43; UV λ_{max} (EtOH): 329 (ϵ 22,387), 258 (ϵ 7,079), 230 (ϵ 10,964); IR (KBr) ν_{max}: 3100, 2220, 1550, 1450, 1050, 850, 800, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.49(d, 1H, $J_{4\text{-}3}$=3.95 Hz, $\underline{H}$-4), 7.33(dd, 1H, $J_{5'\text{-}3'}$=1.14 Hz, $J_{5'\text{-}4'}$=5.11 Hz, $\underline{H}$-5′), 7.25(dd, 1H, $J_{3'\text{-}5'}$=1.14 Hz, $J_{3'\text{-}4'}$=3.68 Hz, $\underline{H}$-3′), 7.11(d, 1H, $J_{3\text{-}4}$=3.93 Hz, $\underline{H}$-3), 7.04(dd, 1H, $J_{4'\text{-}3'}$=3.69 Hz, $J_{4'\text{-}5'}$=5.10 Hz, $\underline{H}$-4′); EIMS *m/z* (%): 191(100), 146()9.7, 121(8.9), 45(51); HRMS: calculated for $C_9H_5NS_2$: 190.9864. Found: 190.9847; Anal. Calcd. for $C_9H_5NS_2$: C, 56.52; H, 2.63; S, 33.53. Found: C, 56.37; H, 3.01; S, 33.27.

5.3.39 Preparation of 5-Formyl-2,2′-dithienyl 187.



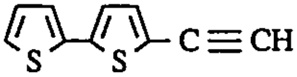
Following the procedure described in Section 5.3.1, $POCl_3$ (6.48 ml, 69.5 mmol) in DMF (20 ml) was stirred at 0°C for 15 minutes. α-Dithienyl **175** (3.85 g, 23.2 mmol) dissolved in DMF (10 ml) was added under the conditions already described. Work up and column chromatography (eluent: hexane/chloroform 8:2 ratio), afforded **187**, (2.5 g, 56% yield) as a yellow solid, m.p. 56-57°C, (lit.[173] m.p. 54.5-55.5°C°C, lit.[174a] m.p. 57-57.5°C); R_f(hexane/CH_2Cl_2)=0.23; UV λ_{max} (EtOH): 353 (ϵ 23,988), 268 (ϵ 5,248); IR (KBr) ν_{max}: 3100, 2980, 1730, 1660, 1450, 1230, 1050, 850, 810, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.65(d, 1H, $J_{4\text{-}3}$=3.95 Hz, $\underline{H}$-4), 7.34(d, 2H, J=4.48 Hz, $\underline{H}$-3′, $\underline{H}$-5′), 7.23(d, 1H, $J_{3\text{-}4}$=3.92 Hz, $\underline{H}$-3), 7.05(t, 1H, $J_{4'\text{-}3'}$=4.39 Hz, $J_{4'\text{-}5'}$=4.40 Hz, $\underline{H}$-4′), 9.83(s, 1H, Ar-C$\underline{H}$O); EIMS *m/z* (%): 194(100), 193(87), 166()10, 165(7), 121(47); HRMS: calculated for $C_9H_6OS_2$: 193.9860. Found: 193.9858; Anal. Calcd. for $C_9H_6OS_2$: C, 55.65; H, 3.11; S, 33.01. Found: C, 55.46; H, 3.36; S, 33.19.

5.3.40 Preparation of 5-(2″-Dibromoethenyl)-2,2′-dithienyl 188.



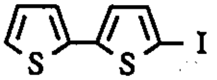
Using the procedure described in Section 5.3.23, 5-(2″-dibromoethenyl)-2,2′-dithienyl 138 was obtained in 99% yield (4.5 g) by treating 5-formyl-α-dithienyl 187 (2.5 g, 12.8 mmol) with PPh_3 (13.5 g, 51.5 mmol) and CBr_4 (8.5 g, 25.5 mmol). Column chromatography (eluent: hexane/CH_2Cl_2 1:1 ratio) gave 188 as a pale yellow solid, m.p. 111-112°C, (lit.[173] m.p. 112-112.5°C); R_f(CH_2Cl_2)=0.85; IR (KBr) ν_{max}: 3080, 3020, 1445, 1430, 1310, 1290, 1080, 1065, 1050, 870, 850, 840, 800, 720, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.56(d, 1H, J=0.62 Hz, Ar-C$\underline{H}$=CBr_2), 7.24(dd, 1H, $J_{5'\text{-}3'}$=1.2 Hz, $J_{5'\text{-}4'}$=5.1 Hz, $\underline{H}$-5′), 7.21(dd, 1H, $J_{3'\text{-}5'}$=1.1 Hz, $J_{3'\text{-}4'}$=3.6 Hz, $\underline{H}$-3′), 7.09(d, 1H, $J_{3\text{-}4}$=4.4 Hz, $\underline{H}$-3 or $\underline{H}$-4), 7.06(d, 1H, $J_{4\text{-}3}$=3.8 Hz, $\underline{H}$-4 or $\underline{H}$-3), 7.01(dd, 1H, $J_{4'\text{-}3'}$=3.6 Hz, $J_{4'\text{-}5'}$=5.1 Hz, $\underline{H}$-4′); EIMS *m/z* (%): 350(91), 348(45), 190(100), 145(14), 95(25), 69(19).

5.3.41 Preparation of 5-Ethynyl-2,2′-dithienyl 189.



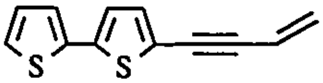
5-Ethynyl-2,2′-dithienyl **189** was obtained in low yield (15% yield) by following the procedure described in Section 5.3.26. The dibromoolefin **188** (1 g, 2.8 mmol) was treated with *n*-BuLi (4.4 ml, 2M, 8.5 mmol) at -30°C. Work up and separation of the crude product (Chromatotron, eluent: *n*-pentane) gave the desired compound **189** as an oil[172,173]; IR (film) ν_{max}: 3290, 2100, 800 cm^{-1}; ^{1}H NMR 60 MHz (CDCl$_3$) δ: 6.8-7.2(m, 5H, aromatic), 3.34(s, 1H, Ar-C≡CH); EIMS *m/z* (%): 190(100), 156(6), 145(15), 121(19),95(9); HRMS: calculated for $C_{10}H_6S_2$: 189.9911. Found: 189.9909. Compound **189** was too unstable to attempt elemental analysis.

5.3.42 Preparation of 5-Iodo-α-dithienyl 185 and 5,5′diiodo-2,2′-dithienyl 190.



By adapting a literature procedure[177], 5-iodo-2,2′-dithienyl **185** was obtained in 75% yield. In a round-bottom flask (100 ml) was placed in the following order: α-dithienyl **175** (9.5 g, 57 mmol), acetic acid (18 ml), water (6.8 ml), CCl$_4$ (18 ml), H$_2$SO$_4$ (0.32 ml), iodine (4.6 g, 36 mmol) and iodic acid HIO$_3$ (1.8 g, 10 mmol). The two phase reaction mixture was stirred vigourously at 40°C for 2 hours to complete the reaction (TLC analysis). The reaction mixture was cooled to r.t., water (20 ml) was added and the crude material was extracted with CH$_2$Cl$_2$ (3 X 100 ml). The combined organic layers were washed with H$_2$O (50 ml), sat. solution of sodium thiosulfate (3 X 100 ml) and once more with water (20 ml). The organic phase was dried over MgSO$_4$ and the solvent removed under reduced pressure. Column chromatography of the mixture (eluent: hexane) followed by fractionnal distillation of the green solid using a glass bead column showed that the mixture contained 2,2′-dithienyl **175** , 5-iodo-α-dithienyl[177] **185** (12.5 g, 75% yield) and 5,5′-diiodo-α-dithienyl **190** (1.9 g, 8% yield). The monoiodo derivative **185** could be obtained by fractionnal distillation, b.p. 85-88°C/0.005 torr, (lit.[172] b.p. 108-109°C/0.03 torr); m.p. 31-32-°C, (lit[184] m.p. 32°C); IR (neat) ν_{max}; 1410, 1200, 1050, 840, 800 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.18(dd, 1H, $J_{4'-3'}$=3.8 Hz, $J_{4'-5'}$=5.1 Hz, H-4′), 7.13(d, 1H, J=3.8 Hz, H-4 or H-3), 7.10(dd, 1H, $J_{3'-4'}$=3.6 Hz, $J_{3'-5'}$=1.1 Hz, H-3′), 6.99(dd, 1H, $J_{5'-3'}$=1.0 Hz, $J_{5'-4'}$=5.0 Hz, H-5′), 6.82(d, 1H, J=3.8 Hz, H-3 or H-4); EIMS *m/z* (%): 292(100), 165(20), 121(59), 146(5), 108(5).

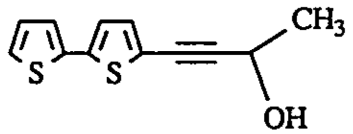
5.3.43 Preparation of 5-(3″-Buten-1″-ynyl)-2,2′-dithienyl 180.



5-(4″-Hydroxybut-1″-ynyl)-2,2′-dithienyl **176** (242 mg, 1.03 mmol) was mesylated with methanesulfonyl chloride (0.106 ml) in CH$_2$Cl$_2$ (20 ml) and Et$_3$N (0.18 ml) at -20°C rising to r.t. for 20 minutes when the reaction was found to be complete (TLC analysis). The solvent was removed under reduced pressure. The residue was subsequently treated with K$_2$CO$_3$ (170 mg) in dimethyl sulfoxide and heated at 90-100°C for 2 hours. Chromatography (Chromatotron, eluent: hexane) afforded **180**, (13 mg, 5% yield) as a yellow oil which tended to polymerize on long exposure to air and light[173,181,185]. R$_f$(hexane/CH$_2$Cl$_2$ 1:1)=0.28.; UV λ_{max} (EtOH): 343 (ϵ 35,481), 252 (ϵ 10,964), 219 (ϵ 13,182); IR (CDCl$_3$) ν_{max}: 3100, 2200, 1610, 1410, 1200 and 800 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.21(dd, 1H, $J_{5'-3'}$=1.10 Hz, $J_{5'-4'}$=4.90 Hz, H-5′), 7.15(dd, 1H, $J_{3'-5'}$=1.20 Hz, $J_{3'-4'}$=3.66 Hz, H-3′), 7.08(d, 1H, J_{3-4}=3.99 Hz, H-3), 7.01(d, 1H, J_{4-3}=3.97 Hz, H-4), 6.99(dd, 1H, $J_{4'-3'}$=3.68 Hz, $J_{4'-5'}$=5.08 Hz, H-4′), 6.01(dd, 1H, J_{cis} =11.1 Hz, J_{trans}=17.5 Hz, Ar-C≡C-CH=CH$_2$), 5.70(dd, 1H, J_{trans}=17.5 Hz, J_{gem}=2.23 Hz, Ar-C≡C-CH=CH$_2$), 5.53(dd, 1H, J_{cis}=11.1 Hz, J_{gem}=2.17 Hz, Ar-C≡C-CH=CH$_2$); EIMS *m/z* (%): 216(100), 171(20), 164(6), 122(46), 117(87), 118(84), 44(42), 28(100); HRMS:

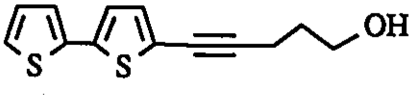
calculated for $C_{12}H_8S_2$: 216.0066. Found: 216.0028.

5.3.44 Preparation of 5-(3″-Hydroxybut-1″-ynyl)-2,2′-dithienyl 194.



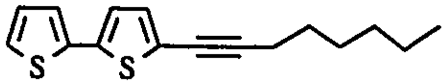
Using the procedure described in Section 5.2, 5-iodo-2,2′-dithienyl 185 (1.12 g, 3.8 mmol) was coupled with 3-methyl-1-butyne-3-ol (690 mg, 9.8 mmol) in triethylamine (20 ml) as solvent. After completion of the reaction (TLC, 1 h), usual work up, followed by separation of the crude material (Chromatotron, eluent : hexane, CH_2Cl_2, methanol in increasing polarity gradient) gave 194, (773 mg, 86% yield) as a yellow solid, m.p. 57-58°C, (lit.[173] m.p. 58-58.5°C, lit.[181] m.p. 59°C); $R_f(CHCl_3)=0.30$; UV λ_{max} (EtOH): 333 (ϵ 25,118), 235 (ϵ 10,000); IR (KBr) ν_{max}: 3350, 2220, 1520, 1430, 1135, 1190, 1100, 1030, 920, 850, 800 and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.22(dd, 1H, $J_{5'-3'}=1.17$ Hz, $J_{5'-4'}=5.10$ Hz, H-5′), 7.15(dd, 1H, $J_{3'-5'}=1.14$ Hz, $J_{3'-4'}=3.61$ Hz, H-3′), 7.07(d, 1H, $J_{3-4}=3.93$ Hz, H-3 or H-4), 6.99(dd, 1H, $J_{4'-3'}=3.42$ Hz, $J_{4'-5'}=5.24$ Hz, H-4′), 6.99(d, 1H, $J_{4-3}=3.69$ Hz, H-4 or H-3), 4.77(dd, 1H, $J_{H-CH}=6.51$ Hz, $J=5.07$ Hz, Ar-C≡CCH(OH)-CH3), 1.87(d, 1H, $J_{OH-CH3}=4.93$ Hz, Ar-CCCH(OH)CH3), 1.54(d, 1H, $J_{CH3-OH}=6.62$ HZ, Ar-C≡CCH(OH)-CH3); EIMS *m/z* (%): 234(23), 219(24), 190(100), 158(7.7), 145(14), 121(11), 95(10.6), 69(16); Anal. Calcd. for $C_{12}H_{10}OS_2$: C, 61.51; H, 4.30; S, 27.36. Found: C, 60.55; H, 4.46; S, 26.93.

5.3.45 Preparation of 5-(5″-Hydroxypent-1″-ynyl)-2,2′-dithienyl 195.



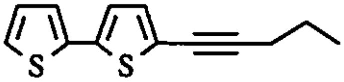
As described in Section 5.3, 5-iodo-α-dithienyl 185 (1.0 g, 3.5 mmol) was coupled with 4-pentyn-1-ol (1 ml, 8.8 mmol) and the reaction was almost complete after 2 hours (TLC analysis). The reaction mixture was stirred overnight at r.t., work up and chromatography (Chromatotron, eluent: CH_2Cl_2) afforded 195, (608 mg, 70% yield) as a pale yellow oil, $R_f(CH_2Cl_2)=0.15$; UV λ_{max} (EtOH): 334 (ϵ 28,840), 240 (ϵ 8,511); IR (film) ν_{max}: 3350, 3100, 2960, 2220, 1510, 1430, 1200, 1050, 950, 850, 800 and 700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.18(dd, 1H, $J_{5'-3'}=1.0$ Hz, $J_{5'-4'}=5.13$ Hz, H-5′), 7.12(dd, 1H, $J_{3'-5'}=1.08$ Hz, $J_{3'-4'}=3.65$ Hz, H-3′), 6.96(d, 1H, $J_{3-4}=3.91$ Hz, H-3 or H-4), 6.96(m, 2H, H-4, H-4′), 3.78(t, 2H, $J_{vic}=6.09$ Hz, $J_{gem}=12.17$ Hz, Ar-C≡C-$(CH_2)_2$-CH_2OH), 2.55(q, 2H, $J_1=6.57$ Hz, $J_2=13.15$ Hz, $J_3=26.29$ Hz, Ar-C≡C-$CH_2CH_2CH_2$OH), 1.68(s, 1H, Ar-C≡CCH_2CH_2CHOH); EIMS *m/z* (%): 248(100), 203(42), 192(20), 179(17), 166(14), 127(12), 115(10); Anal. Calcd. for $C_{13}H_{12}OS_2$: C, 62.87; H, 4.86; S, 25.82. Found: C, 63.04; H, 5.00; S, 25.69.

5.3.46 Preparation of 5-(2″-Oct-1″-ynyl)-2,2′-dithienyl 196.



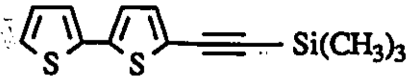
As described in Section 5.2, 5-iodo-2,2′-dithienyl 185 (568 mg, 1.95 mmol) was coupled with 1-octyne (536 mg, 4.86 mmol) in triethylamine (20 ml) in the presence of $(PPh_3)_2PdCl_2$ and CuI as catalysts. The reaction was complete within 15 minutes (TLC analysis), work up, followed by separation of the crude material (Chromatotron, eluent: *n*-pentane) afforded 196, (400 mg, 75% yield) as a yellow oil, UV λ_{max} (EtOH): 334 (ϵ 21,877), 243 (ϵ 5,754); IR (film) ν_{max}: 2940, 2240, 1510, 1460, 1430, 1240, 1190, 1050, 850, 800 and 700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.18(dd, 1H, $J_{5'-3'}=1.17$ Hz, $J_{5'-4'}=5.08$ Hz, H-5′), 7.13(dd, 1H, $J_{3'-5'}=1.17$ Hz, $J_{3'-4'}=3.63$ Hz, H-3′), 6.98(dd, 1H, $J_{4'-3'}=3.66$ Hz, $J_{4'-5'}=5.48$ Hz, H-4′), 6.99(d, 1H, $J_{3-4}=3.88$ Hz, H-3 or H-4), 6.97(d, 1H, $J_{4-3}=3.87$ Hz, H-4 or H-3), 2.42(t, 2H, $J=6.82$ Hz, $J=7.1$ Hz, Ar-C≡C-CH_2-$(CH_2)_4$-CH_3), 1.45(m, 8H, Ar-C≡C-($\mathrm{C\underline{H}_2}$)$_4$-$\mathrm{CH_3}$), 0.90(t, 3H, *J*=6.41 Hz, *J*=6.73 Hz, Ar-C≡C-($\mathrm{CH_2}$)$_5$-$\mathrm{C\underline{H}_3}$); EIMS *m/z* (%): 274(31), 203(22), 166(100), 134(11), 121(31), 108(8), 69(15) and 45(19); Anal. Calcd. for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61; S, 23.36. Found: C, 69.97; H, 6.63; S, 23.48.

5.3.47 Preparation of 5-(2″-Pent-1″-ynyl)-2,2′-dithienyl 197.



As described in the above procedure, 5-iodo-2,2′-dithienyl 185 (700 mg, 2.39 mmol) was coupled with 1-pentyne (408 mg, 5.98 mmol) in triethylamine (25 ml), in the presence of $(Ph_3P)_2PdCl_2$ and CuI as catalysts. The reaction was complete within 2 hours at r.t. (TLC analysis) and work up followed by chromatography (Chromatotron, eluent: *n*-pentane) afforded 197, (477 mg, 86% yield) as a yellow oil, R_f(hexane)=0.18; UV λ_{max} (EtOH): 334 (ε 23,988), 243 (ε 6,165); IR (film) ν_{max}: 3120, 3080, 2970, 2940, 2880, 2840, 2215, 1510, 1460, 1380, 1340, 1310, 1280, 1210, 1190, 1080, 1050, 840, 800 and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 7.19(dd, 1H, $J_{5'\text{-}3'}$=1.0 Hz, $J_{5'\text{-}4'}$=4.58 Hz, $\underline{H}$-5′), 7.12(dd, 1H, $J_{3'\text{-}5'}$=1.0 Hz, $J_{3'\text{-}4'}$=3.58 Hz, $\underline{H}$-3′), 6.98(m, 3H, $\underline{H}$-4′, $\underline{H}$-3, $\underline{H}$-4), 2.39(t, 2H, *J*=7.16 Hz, *J*=7.04 Hz, Ar-C≡C-$\mathrm{C\underline{H}_2CH_2CH_3}$), 1.61(m, 2H, Ar-C≡$\mathrm{CCH_2C\underline{H}_2CH_3}$), 1.02(t, 3H, *J*=7.3 Hz, *J*=7.5 Hz, Ar-C≡$\mathrm{CCH_2CH_2C\underline{H}_3}$); EIMS *m/z* (%): 232(96), 231(12), 216(2), 203(100), 184(4), 166(16), 158(6), 145(3), 127(7), 115(7) and 69(12); HRMS: calculated for $C_{13}H_{12}S_2$: 232.0381. Found: 232.0359.

5.3.48 Preparation of 5-(2″-Trimethylsilyl-1″-ethynyl)-2,2′-dithienyl 198.



As described in to the procedure in Section 5.2, 5-iodo-α-dithienyl 185 (2.0 g, 6.8 mmol) was coupled with trimethylsilylacetylene (700 mg, 7.1 mmol). Work up and chromatography (Chromatotron, eluent: hexane) afforded **198**[172], (1.5 g, 84% yield) as a yellow solid, m.p. 43.8-44.8°C; IR (KBr) ν_{max}: 2960, 2160, 1500, 1430, 1250, 1170, 1050, 850, 750, 700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ: 7.20(dd, 1H, $J_{5'\text{-}3'}$=0.62 Hz, $J_{5'\text{-}4'}$=5.06 Hz, H-5′), 7.15(dd, 1H, $J_{3'\text{-}4'}$=3.11 Hz, $J_{3'\text{-}5'}$=1.0 Hz, H-3′), 7.11(d, 1H, $J_{3\text{-}4}$=3.82 Hz, H-3 or H-4), 6.98(d, 1H, $J_{4\text{-}3}$=4.64 Hz, H-4 or H-3), 6.99(d, 1H, $J_{4'\text{-}3'}$=3.09 Hz, $J_{4'\text{-}5'}$=5.09 Hz, H-4′), 0.24(s, 9H, Ar-C≡C-Si(CH$_3$)$_3$); EIMS *m/z* (%): 262(61), 247(100), 171(7.6), 124(10); HRMS: calculated for $C_{13}H_{14}S_2Si$: 262.0307; Found: 262.0301. Anal. Calcd. for $C_{13}H_{14}S_2Si$: C, 59.49; H, 5.37; S, 24.43. Found: C, 59.63; H, 5.44; S, 24.16.

CLAIMS TO ORIGINAL RESEARCH

A. The Nickel-Catalyzed Grignard-Wurtz cross-coupling reaction for preparing monosubstituted derivatives of α-terthienyl <u>3</u> by coupling the Grignard reagent of 2-bromo-5-substituted-thiophene with 5-iodo-2,2′-dithienyl **<u>185</u>** has shown to be a useful procedure for the monoderivatives of α-T <u>3</u> with identification of reaction products.

B. The palladium-catalyzed coupling reaction between 5-iodo-2,2′-dithienyl **<u>185</u>** with various substituted 1-alkynes derivatives is a useful procedure for preparing 5-(2″-substituted-1″-ethynyl)-2,2′-dithienyl derivatives.

C. The following new α-terthienyl derivatives were prepared, characterized and used in the biological activity studies:

1. Methyl 5-(2‴-Carboxybenzoyl)-α-terthienyl
2. Dimethyl 5,5″-(Carboxybenzoyl)-α-terthienyl
3. 5-(1‴-Carboxybenzoyl)-α-terthienyl
4. 5-(3‴-Methyl-2‴-butenyl)-α-terthienyl
5. 5-(2‴-Dichloroethenyl)-α-terthienyl
6. 5-(2‴-Difluoroethenyl)-α-terthienyl

D. The iodination reaction of α-dithienyl **<u>185</u>** was examined.

E. The following new α-dithienyl derivatives were prepared and characterized and used in the biological activity studies:

1. 5-(5″-Hydroxybut-1″-ynyl)-α-dithienyl
2. 5-(2″-Pent-1″-ynyl)-α-dithienyl
3. 5-(2″-Oct-1″-ynyl)-α-dithienyl

PUBLICATIONS FROM THIS WORK

1. Mac Eachern A., Soucy C., Leitch L.C., Arnason J.T. and Morand P.*, SYNTHESIS AND CHARACTERIZATION OF ALKYL-, HALO- AND HETERO-SUBSTITUTED DERIVATIVES OF THE POTENT PHOTOTOXIN α-TERTHIENYL., *Tetrahedron,* (1988), 44, 2403-2412.

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