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SYNTHESIS AND CHARACTERIZATION OF ALKYL-, HALO- AND HETERO-SUBSTITUTED DERIVATIVES OF THE POTENT PHOTOTOXIN α-TERTHIENYL

ANITA MAC EACHERN, CHANTAL SOUCY, LEONARD C. LEITCH, JOHN T. ARNASON, AND PETER MORAND*

Ottawa-Carleton Institute for Graduate Studies and Research
in Biology and Chemistry, University of Ottawa, Ottawa, Canada K1N 6N5

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Abstract - A number of derivatives of α-terthienyl were prepared including a series of naturally occurring compounds. A description of the syntheses of some new compounds, including 5-iodo, 5,5"-diiodo, 5,5"-diformyl, 5,5"-di-tert butyl, 5,-tert-butyl, 5-tert-butoxy, 5-trimethylsilyl, 5-thiomethyl, 5,5"-dithiomethyl and 5-carboxyl-5"-(trimethylsilyl) -2,2':5',2"-terthienyl is also given. An analysis of the ^{1}H NMR data of the derivatives is presented.

Recently, naturally occurring thiophene derivatives such as α-terthienyl(α-T, 1), have received a great deal of attention because of their phototoxic activity[1a-b]. Studies on the mechanism of toxicity[2,3] and fundamental photochemical[4] studies have shown that α-T is an efficient singlet oxygen generator, toxic to a number of target organisms[5]. In laboratory tests[6] and field trials[7] against mosquito larvae, α-T has demonstrated potent insecticidal activity, making it an excellent candidate for ongoing evaluation.

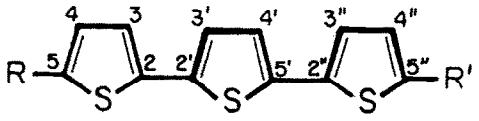
The α-T derivatives described in this paper were synthesized in order to examine their biological activities and physical properties, providing information that can be used to design the structure of a more efficient phototoxin. Several naturally occurring derivatives have been prepared and work is in progress to introduce radioactive labels in some of them for biosynthetic incorporation studies.

Isolation and extraction procedures from plant sources provide an inadequate supply of α-T for derivatization or extensive biological testing, necessitating development of a large scale synthesis. Several syntheses of α-T are reported in the literature,[8-13] including a small scale nickel-catalyzed cross-coupling reaction by Kumada et.al.[14]. We have scaled up this procedure (0.2 mol) and simplified the purification of α-T by using a soxhlet extraction method[7,15]. This has made it possible to prepare large amounts of α-T for the synthesis of derivatives and for field trials.

The structural assignments of derivatives were made by analyzing their ^{1}H NMR spectra from which the position and number of substituents on the α-T molecule were determined. Some spectra were complicated by overlapping peaks from the protons on the thiophene rings or the $CDCl_3$ solvent, as the signals are all located within one ppm for any derivative. Alternate solvents were used in these cases and when the derivative was insoluble in $CDCl_3$. The ^{1}H NMR data for the compounds synthesized (Scheme 1) are given in Tables 1 and 2.

Naturally Occurring Derivatives

The 5-methyl (2) and 5,5"-dimethyl (3, not a naturally occurring compound) derivatives of α-T have been synthesized[16] in low yields using the Ullmann procedure. The first method (A) for introducing the methyl group involved generation of the anion (n-BuLi) of α-T and quenching with CH_3I. Although one equiv. of base was used, this resulted in a mixture of 2 and 3 which was very difficult to purify. Kagan[17] also obtained a mixture of 5 and 5,5" carboxylated products using one equiv. of LDA to make the anion of α-T and quenching with $CO_{2(s)}$.



1	R=R'=H	9	R=I,R'=H
2	R=CH_3,R'=H	10	R=R'=I
3	R=R'=CH_3	11	R=$C(CH_3)_3$,R=H
4	R=CH_2OH,R'=H	12	R=R'=$C(CH_3)_3$
5	R=CHO,R'=H	13	R=$OC(CH_3)_3$,R'=H
6	R=R'=CHO	14	R=TMS,R'=H
7	R=Br,R'=H	15	R=R'=SCH_3
8	R=R'=Br	16	R=SCH_3R'=H
		17	R=CO_2H,R'=TMS

Scheme 1

Alternate routes to 2 by reduction of the 5-formyl derivative (5)(method B) or stepwise reduction via the 5-hydroxymethyl derivative (4)(method C) were both successful, eliminating purification difficulties. This represents the first efficient synthesis of 2.

5-Formyl-α-terthienyl (5) was prepared by the Vilsmeier reaction with N-methylformanilide and $POCl_3$ in 85% yield. The main product when using over 2 equiv. of reagent was 5 in 80% yield and only 19% of the desired 5,5"-diformyl derivative (6), which is not a naturally occurring compound. Recently, Nakayama[18] reported the synthesis of 5 in 75% yield using dimethylformamide and $POCl_3$. Using this latter method, α-T was treated with 3 equiv. of reagent and then an additional equiv. after 1 h to give 6 in 52.6% yield.

Halogenated Derivatives.

Halogenation of α-T was desirable not only to provide new compounds for biological testing but also to provide an entry for the introduction of other substituents. Bromination of α-T with 1 equiv. of NBS gave a mixture of 5- and 5,5" brominated derivatives. The position of the substituent is as expected, based on the results obtained for thiophene[19] and 2,2'-dithienyl[20].

TABLE 1. ^1H NMR Data[(a)] for 5,5"-Disubstituted Derivatives of α-Terthienyl

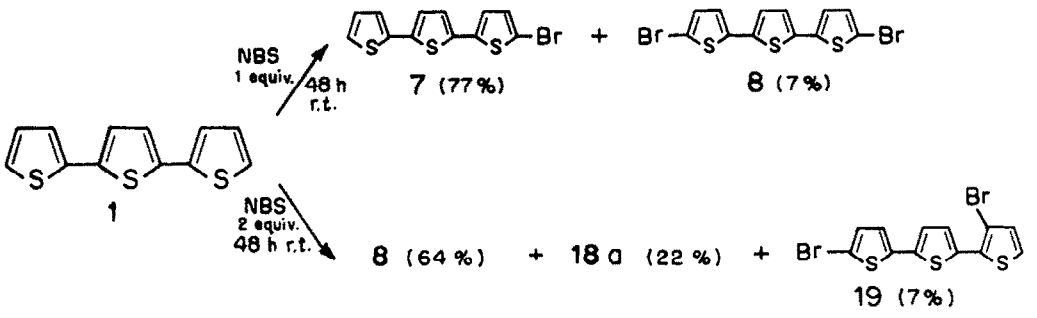
Compound	Chemical Shifts (ppm)			(Hz)	Substituent-H at C-5,5"
	H-4,4" (d,2H)	H-3,3" (d,2H)	H-3',4' (s,2H)	$J_{4,3}=J_{3",4"}$	
3	6.64[(b)]	6.92	6.94	3.51	δ2.46(s,6H,C<u>H</u>$_3$)
6	7.68	7.28	7.30	3.96	δ9.86(s,2<u>H</u>,CHO)
8	6.96	6.89	6.97	3.82	
10[(c)]	7.18	6.86	7.04	3.6*	
12	6.70	6.93	6.95	4.0	δ1.37(s,18H,C(C<u>H</u>$_3$)$_3$)
15	6.94[(d)]	6.98[(d)]	6.99	3.74	δ2.50(s,6H,SC<u>H</u>$_3$)

[(a)] $CDCl_3$ solvent, 300 MHz; [(b)] m due to the methyl group; [(c)] sparingly soluble. [(d)] q, J_{AB}=3.74, Δν= 7.35 Hz. Abbreviations used in the tables; s(singlet), d(doublet), dd(doublet of doublets), t(triplet), q(quartet), *determined directly from the spectrum. ^1H NMR data for 1 ($CDCl_3$): δ 7.20(dd,2H,H-5,5"), 7.01(dd,2H,H-4,4"), 7.69(dd,2H,H-3,3"), 7.06(s,2H,H-3',4'), $J_{4,5}=J_{4",5"}$= 5.13, $J_{3,4}=J_{3",4"}$=3.63, $J_{3,5}=J_{3",5"}$=1.10.

TABLE 2. ^{1}H NMR Data[a] for 5-substituted Derivatives of α-Terthienyl and 17

Compd.	Solvent	H-4 (d,1H)	H-3 (d,1H)	H-3' (d,1H)	H-4' (d,1H)	H-3" (dd,1H)	H-4" (dd,1H)	H-5" (dd,1H)	(Hz) $J_{3,4}$	$J_{3',4'}$	$J_{3",4"}$	$J_{4",5"}$	$J_{3",5"}$	Substituent-H at C-5
2	$CDCl_3$	6.65[b]	6.94	(6.97)	(7.02)	7.13	6.70	7.19	3.42	3.66	3.54	5.12	1.10	δ2.46(d,3H,J=1.0,$C\underline{H}_3$)
4	$CDCl_3$	6.90	7.01[c]	(7.05)[d]	(7.05)[d]	7.15	7.00	7.20	3.61	3.79	3.63	5.12	1.12	δ4.97(d,2H,J=6.0,$C\underline{H}_2OH$)
														δ1.79,(d,1H,J=6.0,$CH_2\underline{OH}$)
5	Acetone-d_6	7.93	7.47[e]	(7.30)	(7.49)	7.38	7.12	7.50	4.0	3.86	3.68	5.02	1.07	δ9.92(s,1H,$C\underline{H}O$)
7	$CDCl_3$	6.95	6.89	(6.99)	(7.05)	7.15	7.00	7.21	3.90	3.74	3.66	5.12	1.22	-
9	Acetone-d_6	7.30	7.02	(7.21)[f]	(7.20)[f]	7.31	7.09	7.45	3.79	3.5*	3.60	5.12	1.10	-
11	$CDCl_3$	6.72	6.96	(6.98)	(7.04)	7.14	6.99	7.18	3.67	3.78	3.65	5.10	1.16	δ1.38(s,9H,$C(C\underline{H}_3)_3$)
13	$CDCl_3$	6.29	6.82	(6.93)	(7.02)	7.13	6.99	7.18	3.89	3.76	3.69	5.12	1.14	δ1.39(s,9H,$OC(CH_3)_3$)
14	$CDCl_3$	7.12	7.20	(7.065)[g]	(7.059)[g]	7.15	7.00	7.20	3.42	3.5*	3.66	5.11	1.20	δ0.318(s,9H,$Si(C\underline{H}_3)_3$)
16	Acetone-d_6	7.05	7.17	(7.22)[h]	(7.17)[h]	7.30	7.08	7.44	3.76	3.85	3.63	5.16	1.10	δ2.53(s,3H,$SC\underline{H}_3$)
17[i]	Acetone-d_6	7.72	7.35	(7.41)	(7.29)	7.40	7.26	-	3.97	3.81	3.47	-	-	δ0.334(s,9H,5"-$Si(CH_3)_3$)
														δ2.82(broad s,5-$CO_2\underline{H}$)

[a] 300 MHz, [b] dd,J=3.42,1.0Hz, [c] doublet coincident with the dd at δ7.00, [d] q,J_{AB}=3.79,Δν=5.2 Hz, [e] identified by ^{1}H NMR decoupling experiments, [g] q,J_{AB}=3.5,Δν=2.7Hz, [g] q,J_{AB}=3.5,Δν=1.8 Hz, [h] q,J_{AB}=3.85,Δν=7.4 Hz, [i] where CO_2H is in position 5. Values in parentheses are tentative assignments and may be reversed. ^{1}H NMR data for 1 in acetone-d_6, δ7.43(dd,2H,H-5,5"), 7.08(dd,2H,H-4,4"), 7.29(dd,2H,H-3,3"), 7.219s,2H,H-3',4'), J values as in the caption for Table 1.



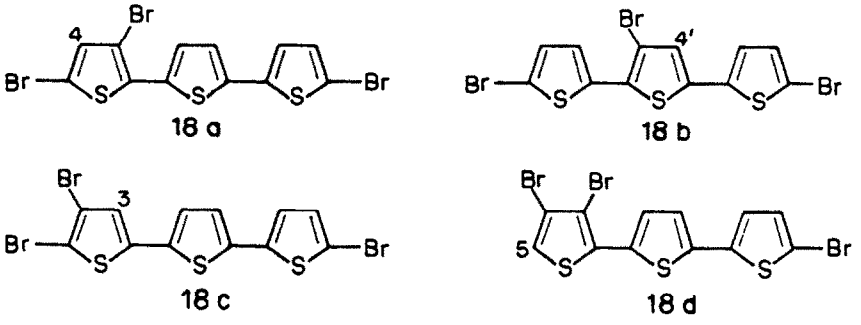
Scheme 2

Treatment of α-T with 2 equiv. of NBS resulted in a mixture of products, the major one being the 5,5"-dibromo derivative **8**. A minor product **19** was identified as an isomer of **8** from the MS data, and the structure determined from the ^{1}H NMR spectrum. The absence of doublet of doublets in the spectrum indicated that the two outer thiophene rings contained substituents. The assignment of one bromine to C-3" was made on the basis of two doublets (J=5.4 Hz) with chemical shifts close to those of 3-bromothiophene[21]. The four remaining doublets with J=3.8Hz indicated that the other bromine was located at C-5. The spectral data from **7** and **8** were used in assigning the doublets due to the protons on the 5-brominated ring, which should not be significantly affected by the 3"-bromo substituent. The proton at C-4, was identified by the noticeable upfield shift due to the bromine at C-3".

Another product isolated from the mixture in 22% yield was a tribrominated derivative. The ^{1}H NMR splitting pattern (see exptl. for **8**) restricted the number of possible structures to four (Scheme 3, **18a-d**). The absence of doublet or doublets with J~5.0 or 1.0Hz indicated that both "end" thiophene rings were substituted and that one of these rings contained a bromine in the C-5" position. This assignment is supported by the chemical shift values which are identical to those obtained for the analogous ring in **19**. In order to determine the position of the other two bromine atoms, the ^{13}NMR spectrum of this compound was recorded as well as for **7** and **8**.

A methine carbon (identified by its intensity) at 133.8 ppm showing the deshielding effect of bromine was assigned to each of the four possible isomers (Scheme 3 - the numbered positions). We were able to eliminate several of the isomers by comparing the shifts to those obtained for suitably brominated thiophenes. The chemical shift for C-5 of 3,4-dibromothiophene under the same exptl. conditions was 123.6, much lower than the shift observed, eliminating **18d** as a possible structure. When the ^{13}C shifts were assigned to **18b**, a shift of 127.5 ppm was attributed to C-4. This reflects the shift obtained for this carbon in an unsubstituted α-T molecule rather than a brominated one, eliminating **18b** as the structure.

For 2,3-dibromothiophene, C-4 has a chemical shift value of 131.7 ppm, slightly lower than the value of 133.8 attributed to C-3 in **18c**. While this shift discrepancy is not large, considering differing experimental conditions for obtaining the ^{13}C data and the influence of the adjacent thiophene rings in **18c**, a better case can be made for **18a** as the structure. One compelling piece of evidence for this structure is that the chemical shift of C-3 in 2,4-dibromothiophene[21] is identical to that attributed to C-4 in **18a** at 133.8 ppm. Also, rates of tritium exchange,[22] a process which occurs by electrophilic substitution and experimental results with other electrophiles (unpublished), show that the likelihood of substitution on α-T is greatest at C-5,5", followed by



Scheme 3

the C-3,3" position. Furthermore, a study of the bromination of 2,2'-dithienyl with NBS[20] showed that the activation energies for electrophilic substitution were lowest for the C-5,5' position of dithienyl followed by the C-3,3' position. While we have no evidence for any other tribrominated products other than **18a**, it is possible that others may occur in minute quantities.

Iodination of α-T was achieved in moderate yields using HgO and I_2 in $CHCl_3$. The 5-iodo derivative **9** was prepared in 45% yield, while the 5,5"-diiodo derivative **10** was synthesized in 24% yield by using 2 equiv. of reagents. The reaction also occurs in benzene or in CCl_4 and usually results in a mixture of **1**, **9** and **10**.

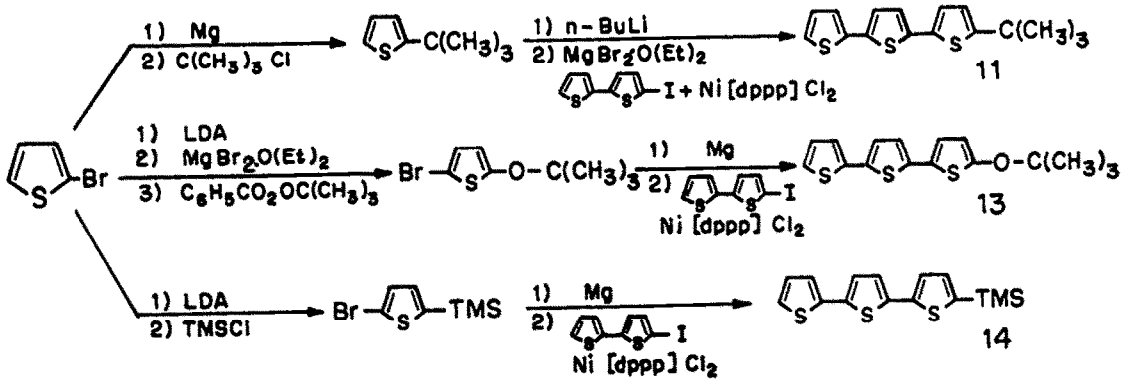
TABLE 3. ^{13}C NMR Data for α-Terthienyl and Brominated Derivatives[(a)]

Compound				Compound	
Position	1[(b)] δ(ppm)	8 δ(ppm)	Position	7	18a
C-5,C-5"	124.26	110.27	C-5	110.99	(111.60)
			C-4	130.64	133.83
C-4,C-4"	127.66	129.98	C-3	123.87	107.00
			C-2	138.54	(137.94)
C-3,C-3"	123.50	(123.15)	C-5'	(136.65)	132.38
			C-4'	(124.690)	124.14
C-2,C-2"	136.92	137.46	C-3'	(124.530)	127.46
			C-2'	(136.80)	(133.42)
C-2',C-5'	136.0	134.62	C-5"	124.26	(111.24)
			C-4"	127.89	130.68
C-3',C-4'	124.11	(123.76)	C-3"	123.67	123.86
			C-2"	135.00	(137.12)

[(a)] $CDCl_3$, 300 MHz, [(b)] from ref. 34, [(c)] Values in parentheses are tentative assignments.

Coupling Reactions.

A number of derivatives were prepared by the nickel-catalyzed cross-coupling reaction[23] previously used to synthesize α-T. 5-Iodo-2,2'-dithienyl **9** was coupled with the Grignard reagent of a number of substituted thiophenes which were prepared from 2-bromothiophene. This coupling reaction served to eliminate the problem of mixtures of mono-, di- or trisubstituted products obtained from direct substitution reaction on α-T. The cross-coupling reaction between 2-thienyl magnesium bromide and tert-butyl chloride (see Scheme 4), occurs in reasonable yield.



Scheme 4

The Grignard reagent was formed by a transmetallation reaction, treating 2-tert-butyl-5-lithiothiophene with $MgBr{\cdot}OEt_2$ and subsequent coupling of the latter with 5-iodo-dithienyl gave 5-tert-butyl α-T (**11**) in 45% yield.

Our initial attempt to prepare **11** was by a Friedel-Crafts reaction on α-T catalyzed by $AlCl_3$ and using tert-butyl chloride or bromide as the alkylating agent. When one or two equiv. of the halide were used, the reactions yielded mixtures of mono- and di-tert-butyl products and

possibly isomers of these compounds (C-2 and C-3 butylated products have been obtained for thiophene[24] using other catalysts). The same procedure, using excess tert-butyl chloride, proved to be an excellent method of synthesizing 5,5"-di-tert-butyl-α-T (12). This compound has previously been reported as a possible product in the tert-butylation of thiophene[25] catalyzed by stannic chloride with tert-butyl chloride as the alkylating agent.

Treatment of 2-bromothiophene with LDA produced 2-bromo-5-lithiothiophene which was treated with the appropriate reagent to give substituted thiophenes (see Scheme 4). In one case, the Grignard reagent was formed by transmetallation and then treated with tert-butyl-peroxybenzoate to give 2-bromo-5-(tert-butoxy)thiophene. In another case, the organolithium was treated with TMSCl to yield 2-bromo-5-(trimethylsilyl)thiophene. The Grignard reagents of both of these thiophenes were coupled with 5-iodo-dithienyl in good yield to give 5-tert-butoxy- (13) and 5-trimethylsilyl-α-T (14) respectively in good yield. The former was subject to degradation after 1 day at r.t. but maintained its integrity when stored at -10°C in the dark. 5-Carboxy-5"-trimethylsilyl-α-T was prepared in 93% yield by generating the anion of 14 with n-BuLi and subsequently adding excess CO_2.

Treatment of the anion of α-T with one equiv. of methyl disulfide gave mainly the 5-thiomethyl derivative 16 with a small percentage of 5,5"-dithiomethyl-α-T 15.

Biological Activity:

In previous publications, the biological activity[26] and the photochemistry[27] of some of these derivatives have been reported in some detail. Phototoxicity of 2, 9 and 10 toward mosquito larvae (aedes atropalpus) has shown 2 to be an efficient larvicide, slightly more toxic than 1. The latter two compounds were much less toxic than 1, with the monosubstituted derivative the more efficient of the two.

Experimental

General. M.p.'s were determined on a Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were recorded at r.t. on a Varian XL-300 or EM 360 NMR spectrometer using the deuterium signal of the solvent as the lock and TMS as the external standard. GC analysis was carried out on a Varian 6000 Vista GC model with an SEA 30, 10 m capillary column and using a Hewlett Packard integrator. TLC was performed on Baker-Flex pre-coated silica gel 1B2-F plates or Baker pre-coated glass plates. The silica gel for liquid chromatography was from Terrochem Laboratories and was either flash or classical type. A mode 7924 Chromatotron by Harrison research was also used in purifications with silica gel (Merck 7749 60 PF_{254}) plates. Elemental analyses were provided by H. Seguin at the National Research Council of Canada in Ottawa and M-H-W Laboratories. The ^1H NMR data for the compounds in Scheme 1 are in Table 1 and 2. The "usual workup" involves the addition of dilute HCl to the reaction mixture and extraction of the product with a suitable organic solvent such as diethyl ether or CH_2Cl_2. The organic solvent is then dried over $CaCl_2$ or $MgSO_4$, filtered, and the solvent removed under reduced pressure to obtain the crude product. α-T (1) was prepared as reported in a previous publication[8]. The catalyst dichloro[1,3-bis(diphenylphosphino)propane]-nickel(II) (Ni[dppp]Cl_2) was synthesized using a known preparation from the literature[28].

5-Methyl-2,2':5',2"-Terthienyl. (2)

Method A. α-Terthienyl (1.0 g, 4.0 mmol) was dissolved in dry THF in hexane (75 ml) and cooled to -78°C via an acetone/CO_2 bath. With N_2 flowing through the system, n-BuLi (2.08 M, 1.92 ml, 4.0 mmol) was added to the solution by syringe over 15 min. After 0.5 h methyl iodide (0.5 ml, 88.0 mmol) was slowly added by syringe. The mixture was stirred for 2h at -78°C and then allowed to warm up to r.t. After stirring at r.t. for 24 h, the reaction mixture was worked up in the usual way yielding a brown-green solid (1.12 g). The crude product was chromatographed on regular or flash silica (52 g) using petroleum ether as the eluant. A bright yellow solid (0.93 g) was isolated and the product ratio determined by reverse phase HPLC using a Varian MCH-5NCAP column eluted with H_2O/MeOH (1:19). Using integrated peak areas, the mixture was α-T (7%), 5-methyl-α-T (69%), and 5,5"-dimethyl-α-T (23%). Preparative HPLC using H_2O/MeOH (1:49) as eluant was performed using a Serva ODA 100 polyol column (22 mm x 500 mm, with 5 micro particle size) giving pure 2 as a yellow solid.

Method B. Hydrazine monohydrate (0.02 g, 0.39 mmol), 5-formyl-α-T (5)(0.1 g, 0.36 mmol) n-butanol (20 ml) and pulverized KOH (0.01 g, 0.18 mmol,20 ml) were placed in a 3-necked round-bottomed flask (50 ml) equipped with a drying tube. The mixture was stirred 5 min at r.t. and then refluxed for 3 h. After stirring 15 h at r.t., a saturated solution of NH_4Cl (2 ml) was added and the product extracted with $CHCl_3$. The mixture was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was separated using silica gel (Chromatotron) giving 2 in 93% yield.

Method C. Anhydrous ethyl ether (10 ml), LAH (0.027 g, 0.71 mmol) and $AlCl_3$ (0.095g, 0.71 mmol) were placed in an ice cooled 3-necked round-bottomed flask equipped with a condenser and under a N_2

atm. The mixture was stirred 0.5 h at 0°C before 5-methanol-α-T (4) (0.07 g, 0.25 mmol) was added to the flask in portions. The mixture was stirred for 1 h at 0°C and then raised to r.t. and stirred for 1 h. At this time TLC indicated the reaction was not complete so more ether (10 ml) was added to the mixture and it was refluxed for 1 h. The workup and separation were the same as for method B, yielding 0.60g (91.6%) of a pale yellow solid.

Each of the methods for preparing 2 gave a pale yellow solid m.p. 94°-94.5°C, Lit[16] m.p. 93-94.5°C. EIMS: m/z(%) 262(100), 261(23.8), 229(14.5).

5,5-Dimethyl-2,2':5',2" - Terthienyl. (3)

The procedure to make 3 was similar to that of method A for preparing 2 so only the modifications will be mentioned. n-BuLi in hexane (2.02 M, 3.96 ml, 8.0 mmol) was slowly added to a solution of α-terthienyl (1.0 g, 4.0 mmol) in tetrahydrofuran (75 ml) which was kept between -50 and -40°C in an acetone/CO_2 bath. The mixture was stirred at this temperature for 45 min at which time methyl iodide (0.75 ml, 12.0 mmol) was slowly added. It was stirred for a further 20 min and allowed to warm up to r.t. The reaction was then stirred for 24 h. After work-up, a green solid was isolated (1.23 g).

Liquid chromatography yielded a bright yellow solid (0.90 g) which was analysed by reverse phase HPLC indicating the mixture to be 5-methyl-α-T (16%) and 5,5"-dimethyl-α-T (82%). Preparative HPLC yielded a yellow-orange solid, m.p. 96-97°C, Lit.[16]; m.p. 98-99°C. EIMS: m/z(%) 276(100), 275(27.9). Analysis: Found: C, 60.34; H, 4.36; S, 35.04; $C_{14}H_{12}S_3$ requires C, 60.87; H, 4.34; S, 34.78.

5-Hydroxymethyl-(2,2':5',2"-Terthienyl). (4)

$NaBH_4$ (0.05 g, 0.09 m), was added to a solution of 5-formyl-α-T (5)(0.5 g, 1.8 mmol) in dry THF (20 ml) which was cooled to 0°C using an ice bath. The mixture was magnetically stirred for 2 h under an N_2 atmosphere, during which time the mixture warmed to r.t. The solvent was then removed under reduced pressure and H_2O (50 ml) cooled to 0°C was added. Acidification with 6M HCl to pH = 2 and filtration through a glass sintered funnel isolated the product as a yellow precipitate (0.4 g, 80% yield): m.p. 148-150°C, Lit[29]: m.p. 150-151°C. EIMS: m/z(%), 278(31.5), 361(100).

5-Formyl-2,2':5',2"-Terthienyl. (5)

N-methylformanilide (0.52 ml, 4.4 mmol) and $POCl_3$ (0.37 ml, 4.0 mmol) were mixed and left to stand for 15 min to allow the reagent to form. A solution of α-T (1.0 g, 4.0 mM) in CH_2Cl_2 (10 ml) was added with stirring. The reaction mixture was stirred for 24 h at r.t. before pouring it into dilute HCl (50 ml) and stirring for 1 h. The CH_2Cl_2 extract was freed of solvent in vacuo leaving an orange solid (1.33 g) as residue. Flash column chromatography with $CHCl_3$ as eluant yielded an orange product (0.93 g, 85% yield); m.p. 135-136°C, Lit.[30]: m.p. 135-136°C. EIMS: m/z(%), 276(100). Analysis: found: C, 56.03; H, 2.87; S, 34.7; $C_{13}H_8S_3O$ requires C, 56.50; H, 2.89; S, 34.8.

5,5"-Diformyl-2,2':5',2"-Terthienyl. (6)

$POCl_3$ (0.46 ml, 5.0 mmol) was added to N-methylformanilide (0.86 ml, 7.0 mmol) and the mixture left to stir under a N_2 atmosphere for 0.5 h to allow the reagent to form. α-T (0.517 g, 2.08 mmol) in CH_2Cl_2 (10 ml) was added slowly to the mixture which turned a deep red color. The mixture was stirred for 48 h under N_2 at r.t. and then poured into dilute HCl. After the usual workup, 1.3 g of an orange solid was isolated. Column chromatography using silica gel (classical) and CH_2Cl_2/hexane (progressing from 50% CH_2Cl_2 to 100%) isolated a bright orange solid (0.467 g, 80% yield) identified as the 5-monoformylated product and a dark orange solid (0.11 g, 18% yield) which was the 5,5"-diformylated product, m.p. 220-221°C. HRMS: calculated for $C_{14}H_8O_2S$, 303.968. Found: 303.967.

5-Bromo-2,2':5',2"-Terthienyl. (7)

α-T (0.5 g, 2.0 mmol) was dissolved in CCl_4 (20 ml) and NBS (0.358 g, 2.0 mmol) was added to the solution. The mixture was mechanically stirred for 42 h at r.t. The solution was then filtered through cotton wool to remove the imide. The filtrate was removed under reduced pressure yielding 0.589 g of a green solid. GC analysis showed that the mixture contained α-T (16%), 5-bromo-α-T (77%) and 5,5"-dibromo-α-T (7%). Liquid Chromatography using silica gel (flash) with 1% benzene/pet. ether eluant afforded partial separation of the mixture with fractions containing pure material. For 7, a yellow solid was isolated, m.p. 136-137.5°C, EIMS: m/z(%), 326(88), 328(100). ^{13}C NMR data is in Table 3. Analysis: found: C, 44.17; H, 2.10; S, 29.45, Br, 24.59; $C_{12}H_7S_3Br$ requires C, 44.04; H, 2.14; S, 29.36; Br, 24.5.

5,5"-Dibromo-2,2':5',2"-Terthienyl. (8)

NBS (0.797 g, 4.4 mmol) was added to α-T (0.5 g, 2.0 mmol) in CCl_4 (20 ml) and the mixture stirred for 48 h at r.t. Filtration and evaporation of the solvent yielded a yellow green residue (0.795 g). TLC (pet. ether eluant) showed three reaction products, two of which were obtained pure in a partial separation of the mixture using silica gel with pet. ether eluant. The main product was **8**, m.p. 156-157°C. Lit.[16]: m.p. 160-161°C. EIMS: m/z(%), 404(48), 406(100), 408(55.4). The second less polar product was 3,5,5",-tribromo-α-T (**18a**), m.p. 105.5-106.5°C, EIMS: m/z(%), 482(39.6), 484(57.5), 485(74.3), 486(62.7), 487(22) 488(50). ^{1}H NMR ($CDCl_3$) - δ7.20 (d,1H,J=3.88,H-3'), 7.03(d,1H,J=3.88,H-4'), 6.97(s,1H,H-4), 6.94(d,1H'J=3.87,H-4"), 6.97(d,1H, J=3.87,H-3"). ^{13}C NMR data for **8** and **18a** are in Table 3. HPLC using a C-18 Ultrasphere ODA column (20 cm x 10 mm with 5 micron particle size) and MeOH eluant was used to determine the yield and to isolate the third product. The mixture was determined to be **8** (64%), **18** (22%), and 5,3"dibromo-α-T (**19**, 7% yield). ^{1}H NMR ($CDCl_3$) of **19**: δ 6.94(d,1H,J=3.88, H-3), 6.97(d,1H,J=3.88,H-4), 7.05(d,1H'J=3.84,H-3'), 7.29(d,1H,J=3.84,H-4'), 7.00(d,1H'J=5.39,H-4") 7.18(d,1H',J=5.39,H-5"); EIMS: m/z(%), 404(48), 406(100), 408(60).

5-Iodo-2,2':5'2"-Terthienyl. (9)

α-T (1.00 g, 4.0 mmol) was dissolved in $CHCl_3$ (50 ml), and I_2 (1.19 g, 4.5 mmol) was added. HgO (0.72 g, 3.3 mmol) was added in small portions over 3 h. The mixture was left to stir at r.t. for 24 h. At this time TLC (pet. ether eluant) showed the presence of starting material, and the 5-iodo derivative of α-T. The HgI_2 was filtered off and the solution washed with sodium thiosulfate (300 ml, 10%). The $CHCl_3$ was then dried over $MgSO_4$ and removed under reduced pressure yielding a brown solid (2.8 g).

The product was dissolved in hexane, and the insoluble material filtered off (220 mg). It was mostly ıe 5-iodinated product. On cooling, 5-iodo-α-terthienyl (342 mg) crystallized from the hexane as a tan-yellow powder. A second crop of product (116 mg) with a small amount of α-T present was also recovered. **9** was crystallized in 45% crude yield. Some of the crystallized product was purified by column chromatography using flash silica gel with pet. ether as eluant, giving yellow crystals, m.p. 138-139°C. HRMS calculated for $C_{12}H_7IS_3$, 373.875. Found: 373.879.

5,5"-Diiodo-2,2':5',2"-Terthienyl. (10)

α-T (2.48 g, 10.0 mmol), HgO (3.0 g, 13.8 mmol) and I_2 (4.36 g, 17.0 mmol), were added to $CHCl_3$ (75 ml) and the reaction stirred for 18 h at r.t. TLC (pet. ether eluant) showed the presence of α-terthienyl, so further HgO (1.0 g, 4.6 mM) and I_2 (2.0 g, 7.9 mM) were added and the reaction stirred for 24 h. Filtration of HgI_2 and removal of benzene on a rotary evaporator afforded a pale brown solid. Hot benzene was added to the solid and the undissolved material, the diiodinated product, was filtered off (1.2 g, 24% yield). Recrystallization from benzene using carbon black to remove impurities gave **10** as bright yellow plates, m.p. 202-203°C. HRMS: calculated for $C_{14}H_6I_2S_3$, 499.772. Found: 499.771.

2-tert-Butyl-Thiophene.

Mg turnings (1.0 g, 41.6 mmol) were placed in a 3-necked round-bottomed flash with an inlet and outlet allowing N_2 to pass through. Dry diethyl ether and a crystal of I_2 were added to the Mg and the mixture stirred at r.t.. 2-Bromothiophene (6 g, 38.6 mmol) dissolved in diethyl ether (10 ml) was then added dropwise. The mixture was refluxed for 15 min on an asbestos mantel, and then cooled to 0°C on an ice bath. 2-Chloro-2-methyl propane (3.407 g, 38 mmol) was slowly added and the mixture allowed to warm to r.t. at which time it was stirred for 15 min. Addition of $Ni[dppp]Cl_2$ caused the mixture to slowly reflux. It was then heated to reflux for 4 h, stirred at r.t. for 15 h and refluxed again for 4 h. A pale yellow precipitate began to form. After the usual workup, 9.96 g of a crude oil was isolated. The crude oil was distilled under vacuum (60-63°C/0.05 torr) giving a pale yellow oil[31] (2.04 g, 40% yield) that was kept under N_2 at -5 to 0°C in order to avoid decomposition. ^{1}H NMR (CCl_4, 60 MHz) δ 1.1 (s,9H,2-C(CH_3)$_3$), 6.4-6.9 (m,3H).

5-tert-Butyl-2,2':5',2"-Terthienyl. (11)

n-BuLi in hexane (1.6M, 2.04 ml) was added by syringe at r.t. to 2-tert butyl-thiophene (0.458 g, 3.26 mmol) in diethyl ether (10 ml) under a N_2 atmosphere. The mixture was stirred for 5 min and then refluxed for 1 h at which time $MgBr{\cdot}OEt_2$ (0.95 g, 3.67 mmol) was added at 0°C. The mixture was then stirred at r.t. for 0.5 h. 5-Iodo-2,2'-dithienyl (0.96 g, 3.3 mmol), prepared by a literature method[32] was dissolved in diethyl ether (2 ml) and added to the mixture along with $Ni[dppp]Cl_2$ (10 mg). The mixture was then stirred for 15 h at r.t. before the usual workup which yielded 45% of pure compound. Analysis: found: C, 62.96; H, 5.19; S, 31.68; $C_{16}H_{16}S_3$ requires C, 63.11; H, 5.29; S, 31.68.

5',5"-Di-tert-Butyl-2,2':5',2"-Terthienyl. (12). $AlCl_3$ (2.0 g, 15 mmol) was added to a vigorously stirred solution of α-T (2.4 g, 10 mmol) and tert-butyl chloride 8.0 ml, 120 mmol) in CH_2Cl_2 (150 ml). The mixture was stirred for 24 h at r.t. and poured into cold H_2O (150 ml). The usual workup left a brown solid residue (4.7 g). 12 was crystallized from EtOH as tan crystals (2.6 g, 72% yield), m.p. = 134-135°C, CIMS: m/z (%) 361 (95.5), 360 (64), 345 (31). Analysis: Found: C, 66.98; H, 6.69; S, 25.56; $C_{20}H_{24}S_3$ required C, 66.66; H, 6.66, S; 25.0.

2-Bromo-5-(tert-butoxy)-thiophene.

LDA was prepared in an acetone/CO_2 cooled flask (-40°C) under a N_2 atmosphere (3.46 ml, 24.68 mmol). The mixture was stirred for 0.5 h, and the flask cooled to -70°C. 2-Bromothiophene (4.0 g, 24.5 mmol) in diethyl ether (20 ml) was added to the mixture and stirred for 0.5 h. After warming the mixture to -30°C, $MgBr_2 \cdot OEt_2$ (5.7 g, 24.8 mmol) was added and the mixture stirred for a further 0.5 h. The temperature of the bath was lowered to -70°C and tert-butyl peroxybenzoate (4.75 g, 25 mmol) was slowly added dropwise. The bath was allowed to warm to r.t. and the mixture stirred for 15 h. After the usual workup, a red-gold oil (4.44 g) was isolated. The oil was purified by Chromatotron using a silica gel plate and eluant yielding 2-bromo-5-tert-butoxythiophene[33] as a yellow transparent oil (3.41 g, 60% yield). EIMS: m/z (%) 234 (10), 57 (100).

2-Bromo-5-(trimethylsilyl)-thiophene.

Diisopropylamine (6.2064 g, 61.33 mmol) in freshly distilled THF (20 ml) was placed in a flask cooled to -70°C via an acetone/CO_2 bath. The reaction was done under a nitrogen atm. At a bath temperature of -40°C, n-BuLi in hexane (24.5 ml, 2.5 M) was added by syringe to the flask. The mixture was stirred for 0.5 h 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, 61.33 mmol) was added and the mixture stirred for 0.5 h. Trimethylsilyl chloride (7.8 ml, 61.33 mmol) was then added and the bath temperature was permitted to warm to r.t. After stirring for 0.5 h the usual workup was performed and a brown oil was obtained. The oil was distilled under vacuum (31°C, 0.05 Torr, Lit.[33]: b.p. 58°C, 0.5 mm), using a fractionating column packed with glass beads isolating 2-bromo-5-(trimethylsilyl)-thiophene as a colorless oil in 77% yield (11.16 g). ^1H NMR($CDCl_3$), δ =0.30(s,9H), 6.95(dd,2H,J_{AB} = 3Hz).

5-tert-butoxy-2,2':5',2"-Terthienyl. (13)

Mg (0.35 g, 14.4 mmol) turnings and diethyl ether (2 ml) were placed in a flask containing a N_2 inlet/outlet and an additional funnel. A crystal of I_2 was added to the mixture and then 2-bromo-5-(tert-butoxy)-thiophene (2.9876 g, 12.7 mmol) in diethyl ether (10 ml) was slowly added to the flask. The mixture was refluxed for 1 hr and the cooled to r.t. at which time 5-iodo-2,2'-dithienyl (3.8 g, 13 mmol) in diethyl ether (5 ml) and a pinch of $Ni(dppp)Cl_2$ were added. The mixture was refluxed for 1 h and the reaction followed by TLC. The mixture was stirred for an additional 3 h and then worked up the usual way, leaving a brown solid residue (7.782 g). Chromatography using silica gel on a chromatograph plate and hexane as eluant yielded 13 as a bright yellow solid (2.25 g, 55% yield), m.p. 124-125°C. EIMS: m/z (%), 320 (28), 264 (100). Analysis: found: C, 60.0; H, 5.7; S, 30.0; $C_{16}H_{16}S_3O$ requires C, 60.05; H, 4.99; S, 29.95.

5-Trimethylsilyl-2-2,:5',2"-Terthienyl. (14)

2-Bromo-5-(trimethylsilyl)-thiophene (11.16 g, 47 mmol) in diethyl ether (50 ml) was added to a flask containing Mg turnings (2.0 g, 83 mmol) in diethyl ether (50 ml) and a crystal of I_2. The reaction was performed under a N_2 atmosphere. After complete addition, the mixture was refluxed for 1 h. 5-Iodo-2,2'-dithienyl (13.9 g, 47 mmol) dissolved in diethyl ether (10 ml) was added to the mixture slowly with $Ni[dppp]Cl_2$ (pinch) added gradually. The mixture was stirred for 2 h, refluxed for 4 h and stirred for a further 16 h at r.t. After the usual workup, a dark brown residue was obtained. The residue was purified using a silica gel plate (Chromatotron) yielding 13.01 g (75%) of 14 as a bright yellow solid, m.p. 85-86°C. EIMS: m/z (%), 320 (100), 305 (93).

5,5"-Dithiomethyland 5-Thiomethyl-2,2':5,2"-Terthienyl. (15,16)

α-T (0.2 g, 0.2 mmol) dissolved in dry THF (10 ml) was placed in a round-bottomed flask equipped with N_2 inlet/outlet taps. The mixture was cooled to -30°C using an acetone/CO_2 bath and n-BuLi in hexane (1.6 M, 0.37 ml) added by syringe to the mixture. It was stirred for 45 min at -40°C. The flask was then cooled to -70°C and methyl disulfide (0.075 g, 0.8 mmol) was added and the mixture stirred for 0.5 h at -70°C. The temperature of the bath was permitted to rise to -30°C and the mixture stirred for 1.5 h. The usual workup left a yellow-orange precipitate which was purified using silica gel (Chromatotron) with hexane/MeOH (progressively increasing the polarity of solvents. 5-thiomethyl-α-T was isolated as a yellow solid (0.160 g, 67% yield) m.p. 91-92°C. EIMS: m/z(%) 294 (99.6), 279 (100), 246 (32.6). Analysis: found: C, 52.95, H, 3.54; S, 43.77;

$C_{13}H_{10}S_4$ requires C, 53.02, H, 3.42; S, 43.55. 14% was the 5"-dithiomethyl derivative, a yellow solid, m.p. 134.5-135°C. EIMS: m/z (%), 340 (99.2), 325 (100), 310 (38.5). Analysis: found: C, 49.39; GH, 3.72; S, 47.21; $C_{14}H_{12}S_5$ requires C, 49.40; H, 3.67; S, 47.07.

5-Carboxyl-5"-trimethylsilyl-α-Terthienyl (17)

A 3-necked round-bottomed flask with N_2 inlet/outlet taps was cooled to -30°C via an acetone/CO_2 bath. THF (20 ml), diisopropylamine (0.0831 g, 0.82 mmol) and n-BuLi in hexane (2.5 M, 0.33 ml, 0.82 mmol) were added respectively and the mixture stirred for 0.5 h. The bath was cooled to -70°C and 14 (0.3 g, 0.82 mmol) was added and stirred for 0.5 h. $CO_{2(s)}$ (excess) was added to the mixture and a yellow precipitate formed. After the usual workup a yellow solid was washed with n-pentane and pet. ether to remove unreacted 14. 93.2% yield (0.318 g) of 15 was isolated as a yellow powder, m.p. 230-30.5°C, EIMS: m/z (%), 364 (100), 349 (86).

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