To my family and Rosalia


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THESIS
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The Synthesis of Some New Sulphur Containing Heterocycles

A thesis submitted to the

Board of the Faculty of Physical Sciences

in partial fulfilment of the requirements for

the Degree of Doctor of Philosophy

at the

University of Oxford

by

Cheuk Man Lee

The Queen's College
Oxford

Biochemistry
August 1983

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The Queen's College,
Oxford.
August 1983.

Cheuk Man Lee

Abstract

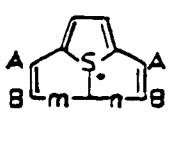
The Synthesis of Some New Sulphur Containing Heterocycles

Cheuk Man Lee — The Queen's College
Doctor of Philosophy — August 1983

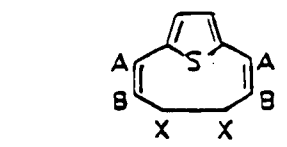
Earlier work on the synthesis of thiophenes and thiophenophanes is reviewed. The main objective of the research was to synthesize cyclic sulphonium salts, such as (1) or (1, but m=n=CH=CH), where aromaticity might be shown and the normal tetrahedral configuration of sulphur might be flattened.

Attempts to prepare (10) and (11), precursors for (1) and an analogue, by cyclization of 2-substituted 2,5-diphenylthiophenes failed. The main synthetic objective was (1, but m=n=CH=CH). The diyne (3) was prepared, but conversion to (5) by hydrogen sulphide was not achieved. The synthesis of (4) was accomplished by coupling (12) with ethynyltrimethylsilane under new conditions to (12, but X=C≡CSiMe$_3$), which with n-Bu$_3$SnH/Pd(PPh$_3$)$_4$, gave (13), a new type of selective reduction. Desilylation and intramolecular coupling afford (4), which is the first example of a dibenzo-fused{13}annulenone having partially saturated double bonds. Sodium sulphide treatment yielded (14), but prior reduction to (4, but Y=CHOH) then yielded (6), the first example of a dibenzo-fused thiophenophane. This scheme leading to (6) could have wide application. The iodo and triflate derivatives of (6) decomposed to (7) with no sign of (1, but m=n=(CH$_2$)$_2$), while (6, but Y= C=O)p-tosylhydrazone on LDA treatment gave (7), (7, but Y=ZCH=CH) and (8). Attempted dehydrogenation of (6, but Y= C=O) by DDQ or chloranil eliminated hydrogen sulphide yielding (4), while other reagents did not react or caused polymerization. A general synthesis of the ethynylaldehyde (15) was discovered in the synthesis of (16), a possible precursor of (2). Attempts to prepare (1, but m=CH=CH) were unsuccessful because of difficulties in synthesizing 2,5-disubstituted thiophenes of type (9). Some experiments towards the synthesis of (17) were made. Compound (18) was prepared by a 7-stage synthesis and demethylated to (19). Oxidative demethylation of (18) and oxidation of (19) using various reagents did not give (20).

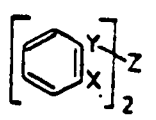
The thesis concludes with an experimental section (90 pages) and a bibliography (226 references).



	A	B	m	n
(1)		-(CH=CH)-	—	=CH
(2)	Ph	H	CH=CH	CH=CH



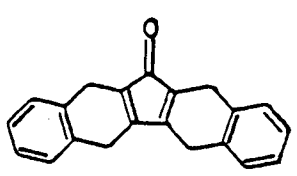
	A	B
(10)		-(CH=CH)-
(11)	Ph	H



	X	Y	Z
(12)	I	C≡CH	CH=CH	C=O
(13)	C≡CSiMe$_3$	(CH$_2$)$_2$	C=O



	X	Y	Z
(3)	C≡CH=CH	C=O	C≡CH=CH
(4)	(CH$_2$)$_2$	C=O	(CH$_2$)$_2$



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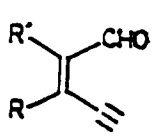

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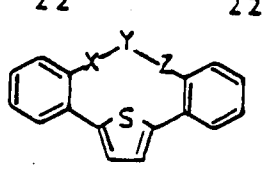
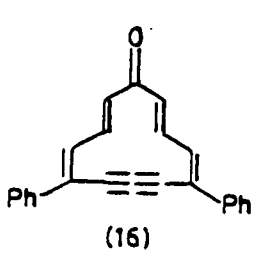


	X	Y	Z
(5)	C≡CH=CH	C=O	C≡CH=CH
(6)	(CH$_2$)$_2$	CHOH	(CH$_2$)$_2$
(7)	(CH$_2$)$_2$	C≡CH=CH	CH$_2$
(8)	(CH$_2$)$_2$	CH$_2$	C≡CH=CH
(9)	(CH$_2$)$_2$X		(CH$_2$)$_2$X



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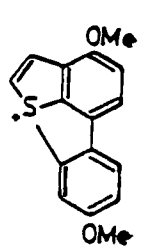

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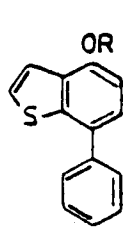
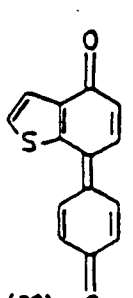


(18) R=Me
(19) R=H



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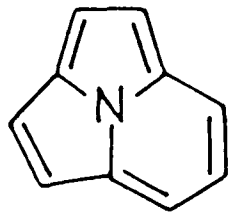
Chapter 1

Introduction

Despite {2,2,3}cyclazine (1) being known for more than twenty years,[1] it is only recently that its carbon analogue, the tricyclic {10}annulene (2), was prepared.[2] The sulphur analogue (3) is still unknown.



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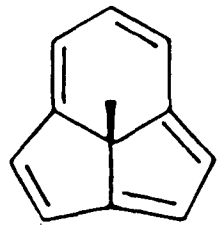

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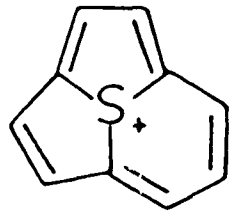

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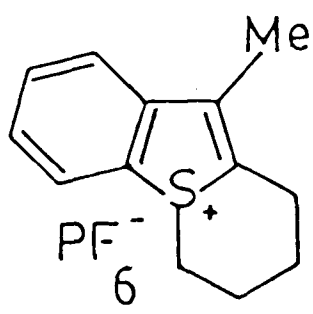
A literature search reveals that examples where a sulphur atom bridges two fully unsaturated rings are scarce or virtually unknown. Thus the work on 6,7,8,9-tetrahydro-10-methylthiopyrano{1,2-a}benzothiophenium ion (4) by Cotruro and Degani[3] probably represents the first example of a trigonally bonded bridged sulphonium heterocycle, while that of 2-methoxythienyl{3,2,1-de}-thianthrenium perchlorate (5) reported by Acheson et al[4] is the only example of a compound with a positive-charged sulphur atom resembling (3).



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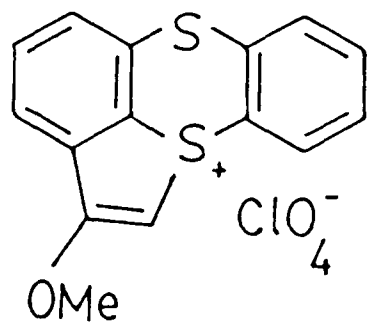

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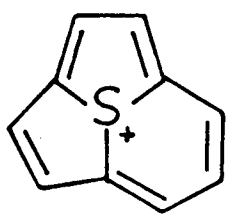
These sulphur bridge head heterocycles (3),(6)-(10) could have a central sulphur atom which is either formally tetravalent and uncharged {(6)} or trivalent and positively charged {(3),(7)-(10)}. An intermediate of type (12) has been postulated for the reaction of 2-imino-1,3-oxathiole (11) with dimethyl acetylenedicarboxylate

(scheme 1)[5] but it was not isolated. The concertedness of the reaction has yet to be proved.



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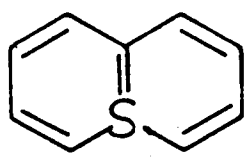

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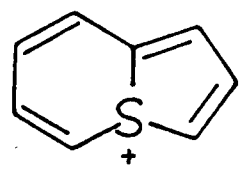

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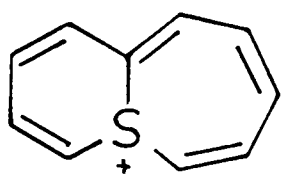

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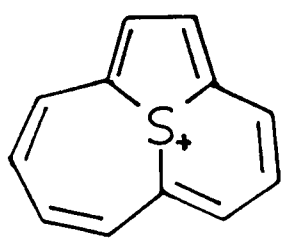

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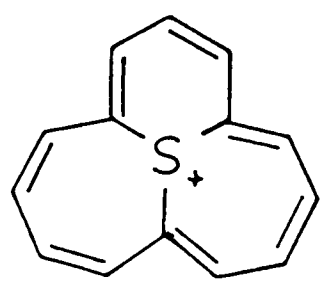

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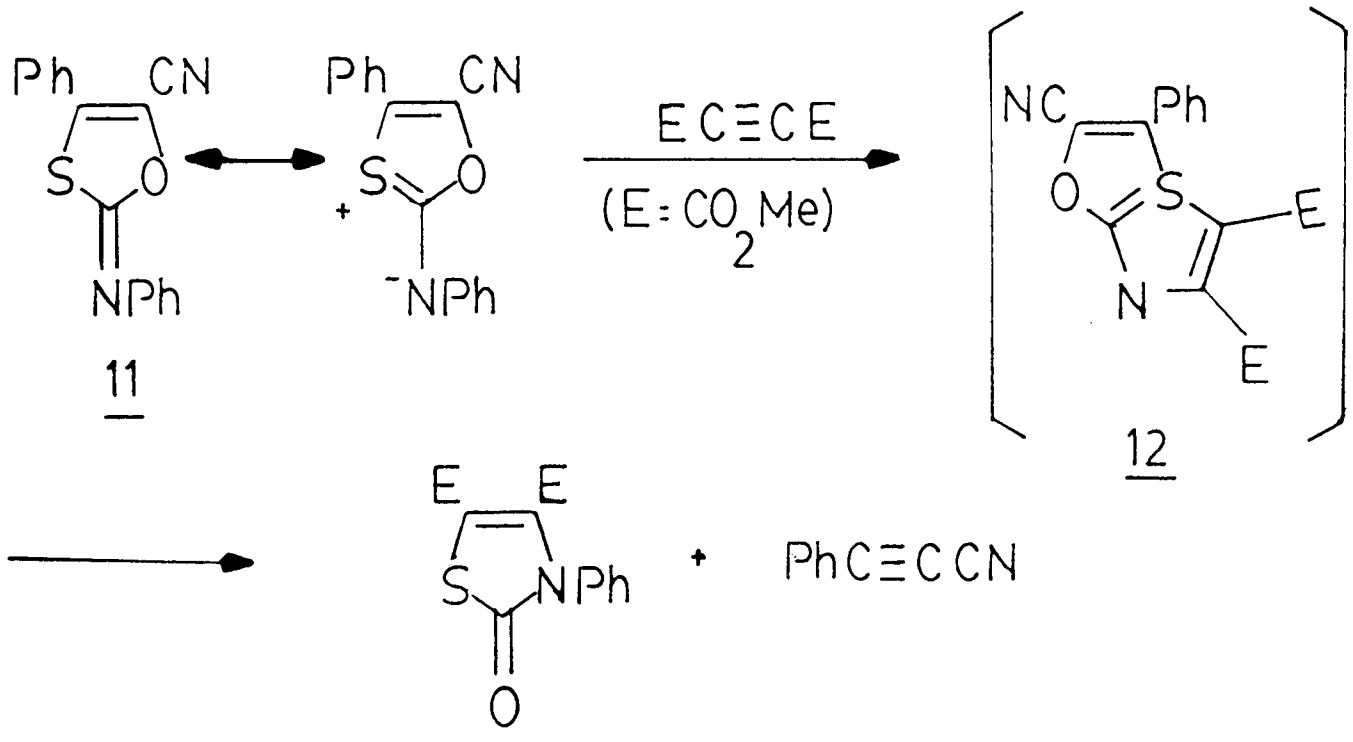
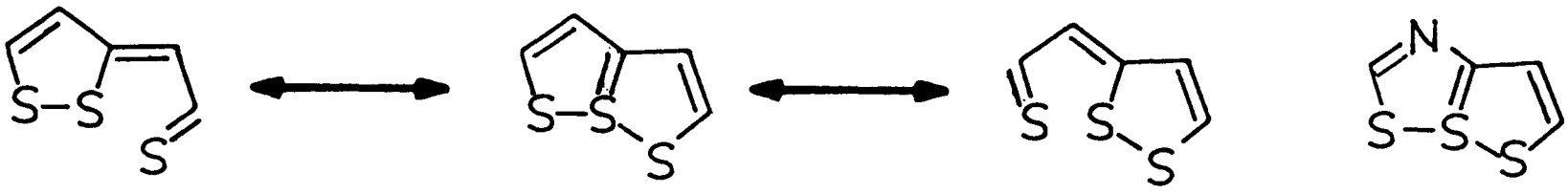


SCHEME 1

Thiathiophthenes (13)[6] and related systems, e.g. (15), contain a bridging sulphur atom. There is still controversy concerning whether or not the bicyclic structure (14) participates in resonance.[7]

Although X-ray photoelectron spectroscopy of (13) indicates the presence of only 2 types of sulphur atom, thereby supporting the symmetrical formula (14),[8] yet experimental evidence seems to be lending support to the conclusions from the calculationsby Gleiter et al, which suggest that (13) exists as a monocyclic system with a side chain. However, recent CNDO/2 calculations on (13) by Sletten[9] indicate partial bonding between the three sulphur atoms.



13 14 15

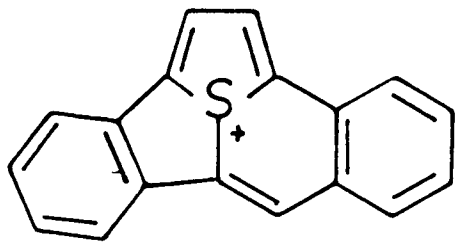
Theoretical calculations[10] including 3d orbitals indicate that the structure with equal S-S bond lengths represents a minimum on the potential energy curve for variation of the S-S distances but that the whole curve is rather flat. Clearly, these 'no-bond resonance' compounds are a very special type of the systems discussed here.

Fully unsaturated systems with a bridging sulphur atom could be energetically much more favourable than the corresponding open-chain compounds, i.e. be aromatic. In 1965, Zahradník[11] published a review on theoretical studies of sulphur containing heterocycles including (3) and (7)-(10). By using a simple HMO method (the Hückel approximation of the MO LCAO method), which ignored participation of the sulphur 3d orbitals, he showed that structure (3) and (7) should have high stability relative to similar structures where one or both of the five-membered rings had been expanded by vinyl units. However,

the prediction that structure (7) should be relatively stable is rather surprising, since it is an eight π system assuming that the sulphur lone pair is not involved in conjugation. Structure (3) has 10 π electrons and is expected to be stable and aromatic.

It seems clearly worth while trying to synthesize sulphur analogues of indolizine and cycl{3,2,2,}azine. The electron configuration round such a positively charged sulphur atom would be of significant interest. If the sulphur atom in the parent heterocycle is considered to have a formal sp^2 hybridisation, then the salt might be expected to have a planar geometry about sulphur, so that maximum overlap in an aromatic type (4n+2)π electron system could be retained. However, the slow inversion of a sulphur atom, as compared with nitrogen, when attached by single bonds to three carbon atoms, could imply that such a configuration, especially in (3), might not be so favourable energetically. In fact, in general the sulphonium salts exhibit pyramidal geometry with the sulphur atom lying approximately 0.8Å above the base of the pyramid defined by the three bonded carbon atoms and the C-$\overset{+}{S}$-C angles are all slightly less than tetrahedral.

It has been found that on analogy with tertiary amines,[12] the rates of racemization of sulphonium salts increase as the peripheral alkyl groups are successively replaced by aryl groups.[13] Darwish and Scott[13a] estimated that triarylsulphonium salts would racemize in methanol at 25°C with a rate constant of $8 \times 10^{-4} s^{-1}$, which corresponds to an activation energy of about 22 kcal mol^{-1} and a half-life of 15 min. With such a low estimated activation energy, it is not unreasonable to predict that the dibenzo-fused thiophenium salt (16) may exhibit a planar structure.



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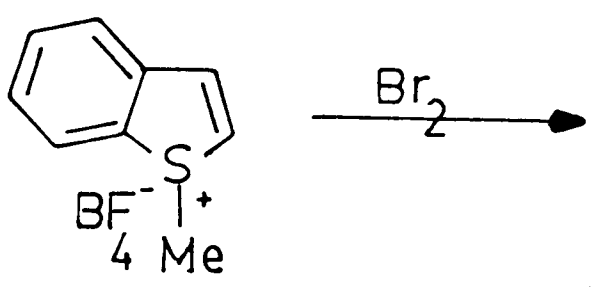
Recently, Acheson et al[14] suggested that 1,2,3,5-tetramethyl-benzo{b}-thiophenium tetrafluoroborate (17) should be considered as cyclic styrene derivative rather than as highly stabilised 10π aromatic system. The argument was based on the fact that not only the sulphur atom of (17) has pyrimidal bonding, as shown by X-ray data,[14] but also 1-methylbenzothiophenium tetrafluoroborate (18) forms the addition product (19) with bromine.[15] Further evidence was given by the ^{13}C NMR data[14] and an ab initio calculation, performed with a minimal basis set using 3TO-3G,[16] on the hypothetical thiophenium cation (20) for varying values of θ gave an energy maximum for the planar configuration (θ=180°).



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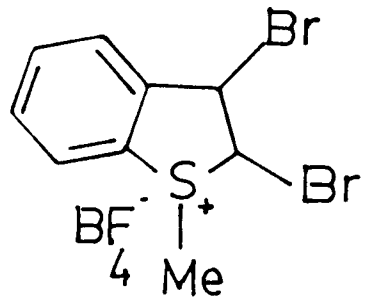

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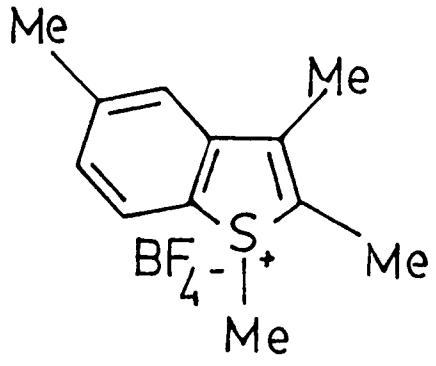

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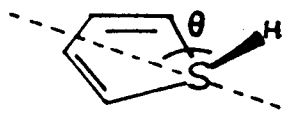

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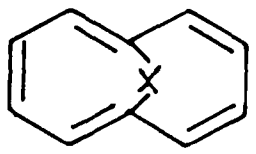
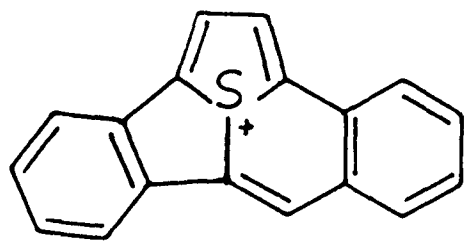
Based on the above observations, they cast doubt on the calculations by Zahradník,[11a] which suggest that structure (3) and (7) should be stable.

Thus, the aim of the present project is to synthesize these bridged-head sulphur heterocycles so as to test the validity of the calculations done by Zahradník, and to examine the configuration of the central sulphur atom. Investigation of the preparation and properties of {10}annulenes have been important in defining the scope and limitations of the concept of aromaticity. Although {10}annulenes are potentially aromatic according to the Hückel rule, planar or near planar geometry imposes either severe bond-angle strain or severe steric interaction on the system. However, planarity is not necessary for "aromatic" stability, as (21)[17] and (22)[18] are known, and as sulphonium salts can invert their configurations fairly easily the energy required to "flatten" a Sp^3 sulphonium salt might be obtained by the loss of some "aromaticity".



21 X = O
22 X = CH_2

Structure (3) was chosen as our target. It was thought that extra phenyl rings might help to stabilize the system and might also facilitate the handling of the intermediates involved, thus the system of the dibenzo derivative (16) was our first objective.



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Chapter 2

Literature survey on the syntheses of thiophenes and thiophenophanes

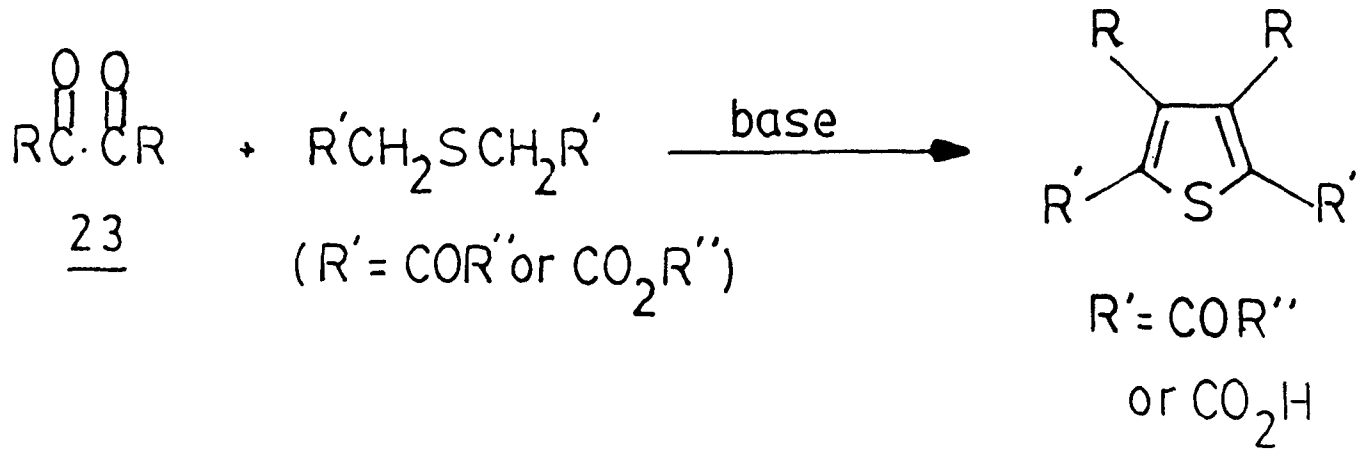
I) Synthesis of thiophenes

Since thiophene was discovered by V. Meyer in 1882, numerous synthetic methods have been developed for specific thiophenes. These methods can roughly be divided into 3 categories, namely 1) total ring synthesis, 2) synthesis from other thiophenes, and 3) from other ring systems.

1) Total ring synthesis

This is by far the most developed method, including a) the Hinsberg synthesis from α-diketones (23) and activated methylene compounds,[19] b) the Paal reaction from γ-diketones (24) and P_2S_5[20] or the Lawesson's Reagent[21], c) bis-acetylenes (25) with sodium sulphide or equivalent,[22] d) nucleophilic addition to activated olefins (26)-(30),[23-27] e) insertion of sulphur or equivalent into an acyclic precursor (31)-(35),[28-32] f) from allenes (36)-(38),[33-35] g) from 3-amino substituted dithioacrylate esters or equivalent (39)-(40)[36,37], h) the Gewald synthesis,[38] i) from cyclic α-diketone (41)[39] and finally some industrial processes like the Socony vacuum process,[40] which uses butane and sulphur at elevated temperature to give thiophene itself and the Croda synthetic process,[41] which employs fuctionalized hydrocarbons and carbon disulphide.

a) Hinsberg synthesis



b) Paal reaction



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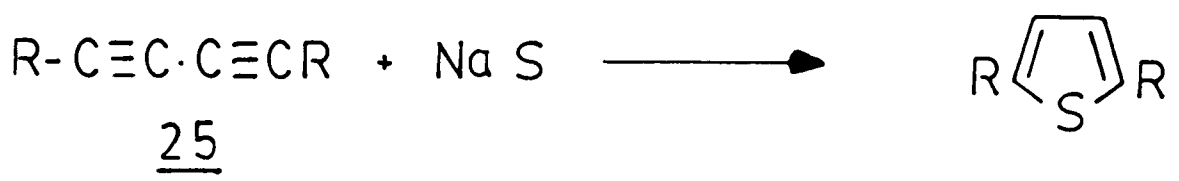
c) bis-acetylene with Na_2S or equivalent



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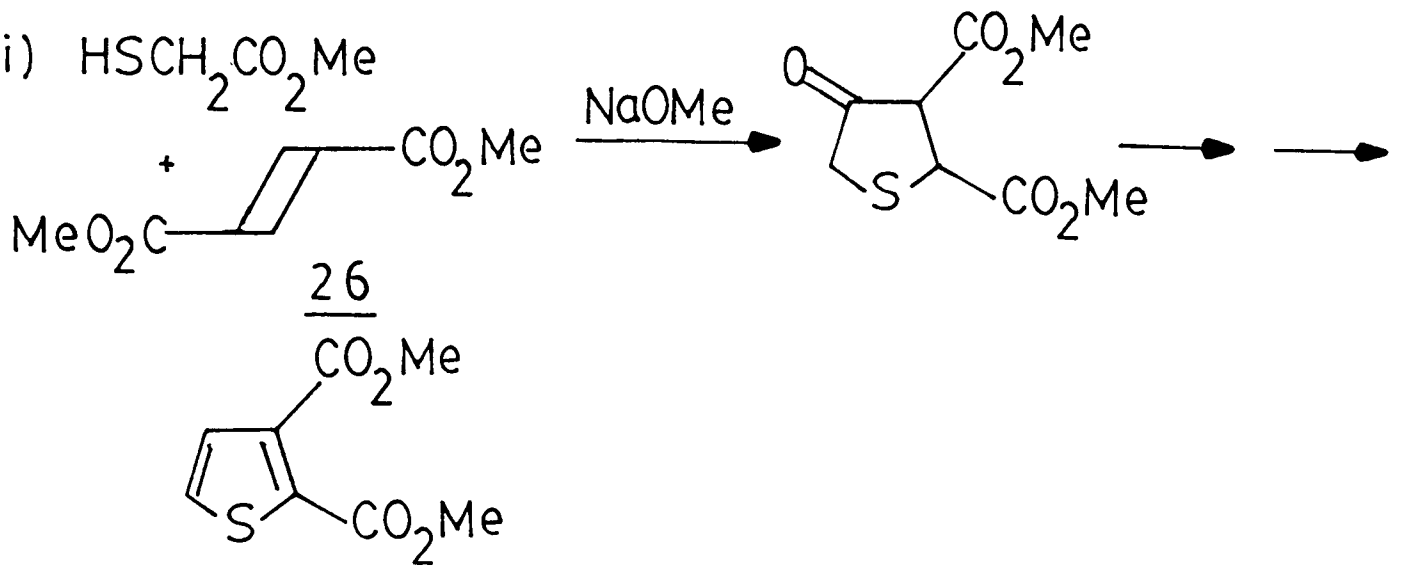
d) nucleophilic addition to activated olefin or acetylene

i)



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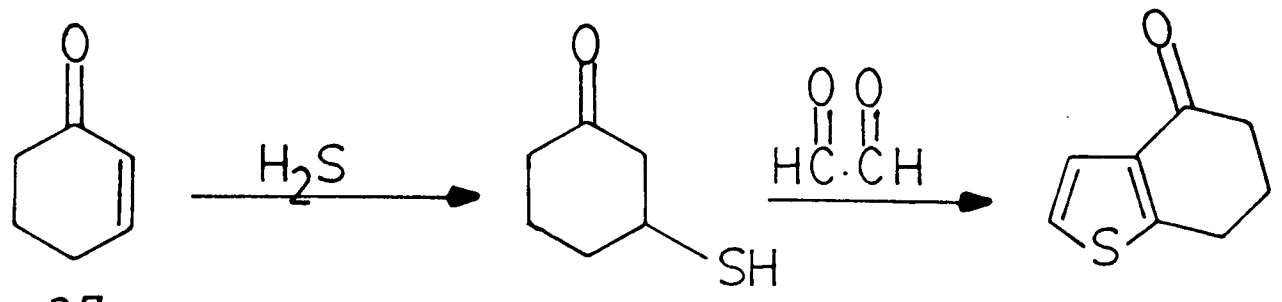

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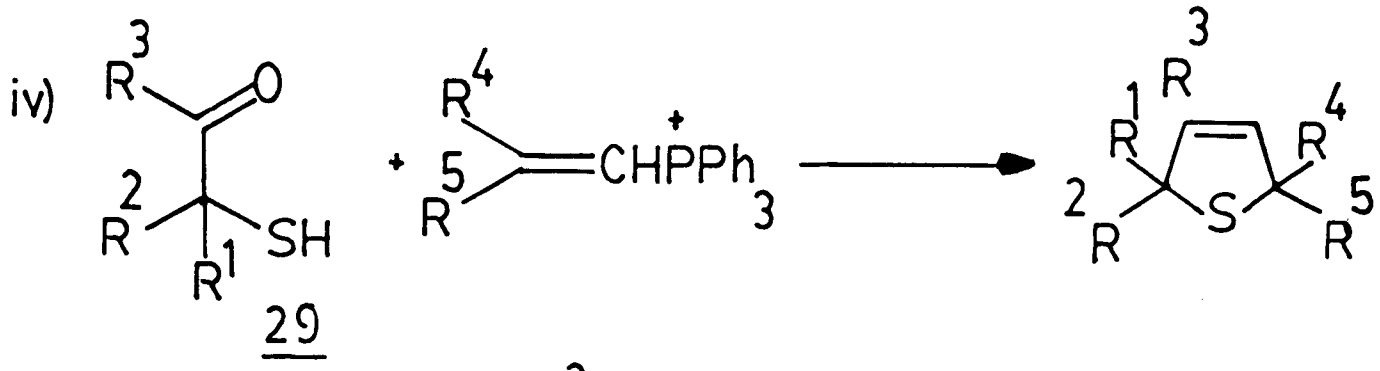
iii)



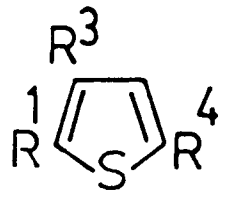
28

iv)

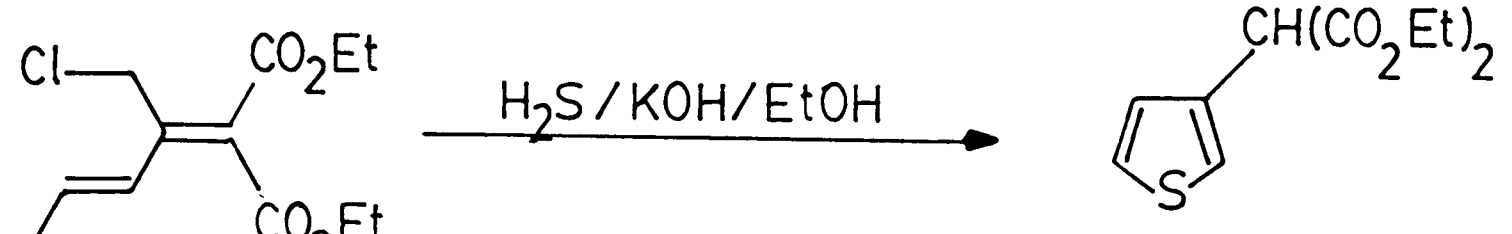


29

chloranil / t-butanol



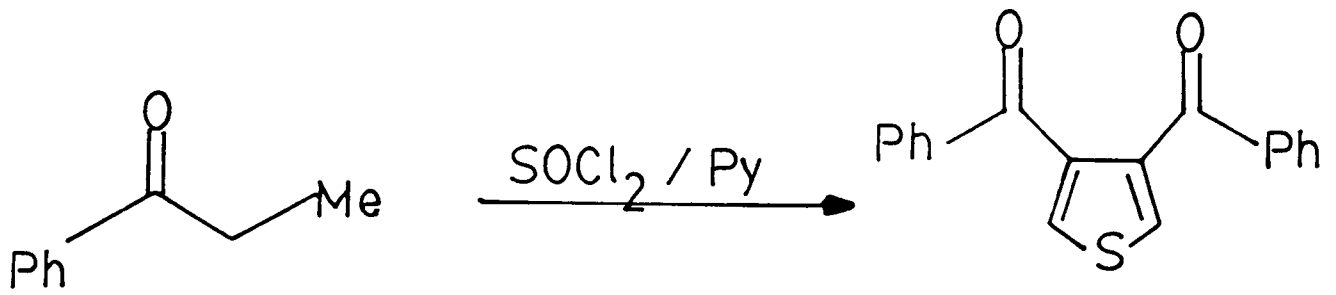
v)



30

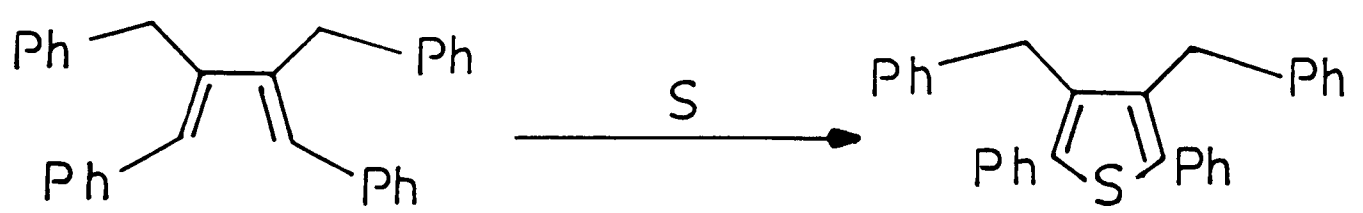
e) insertion of sulphur or equivalent into an acyclic precursor

i)



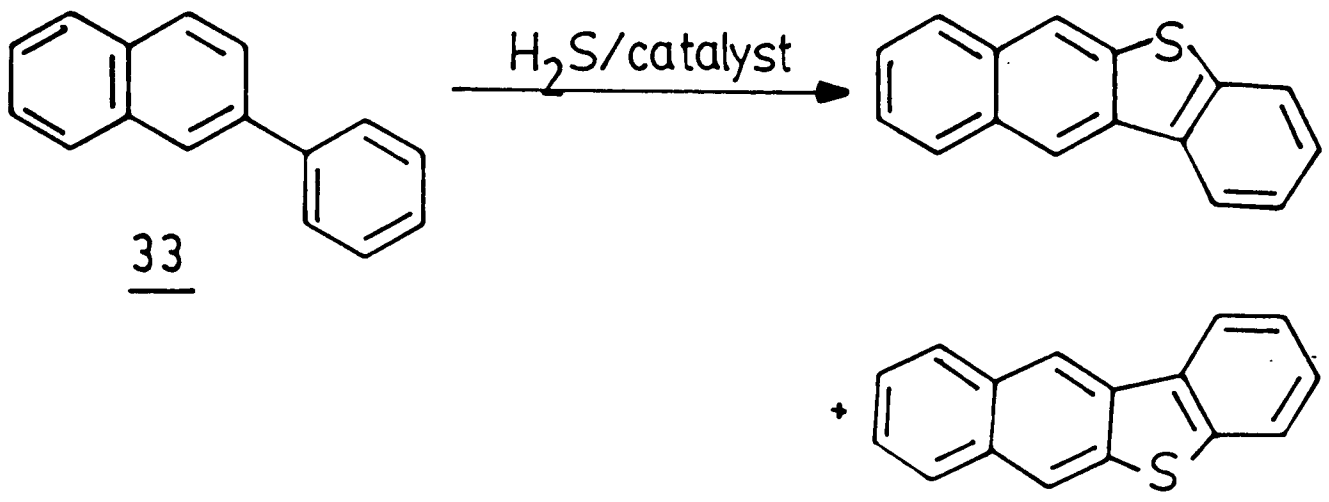
31

ii)



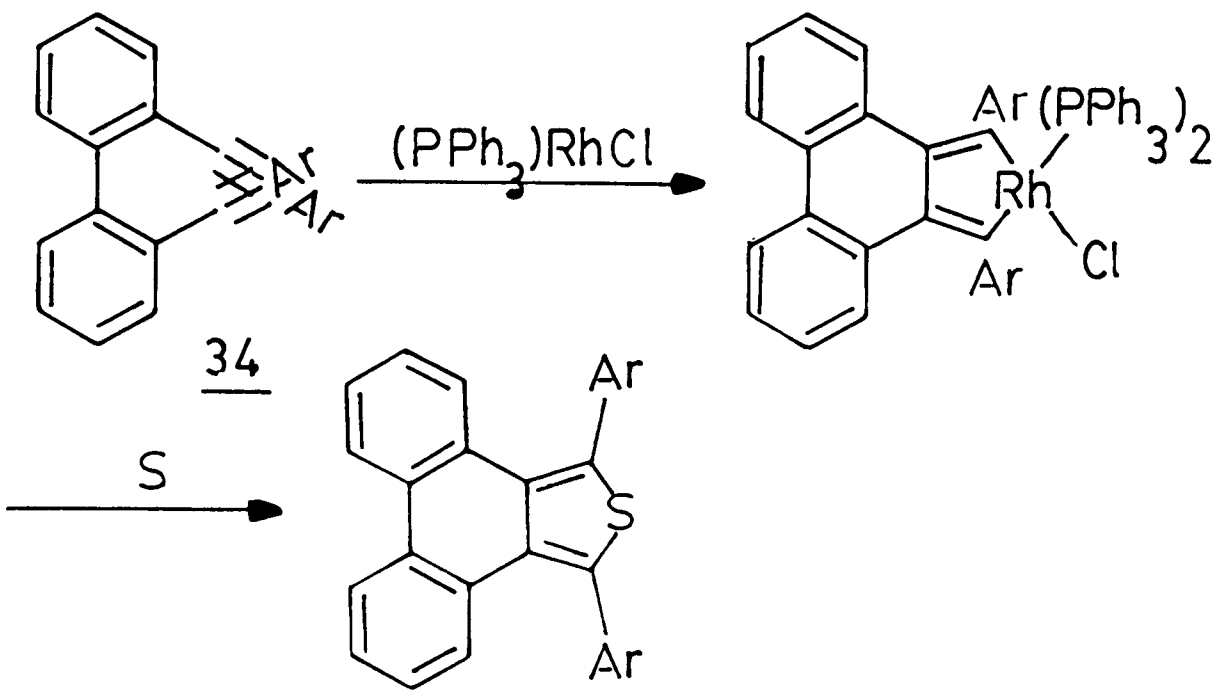
32

iii)



33

iv) via transition metal complexes



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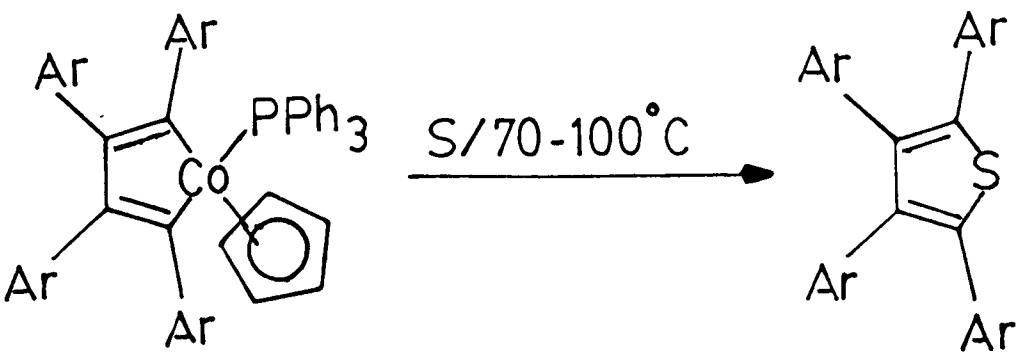
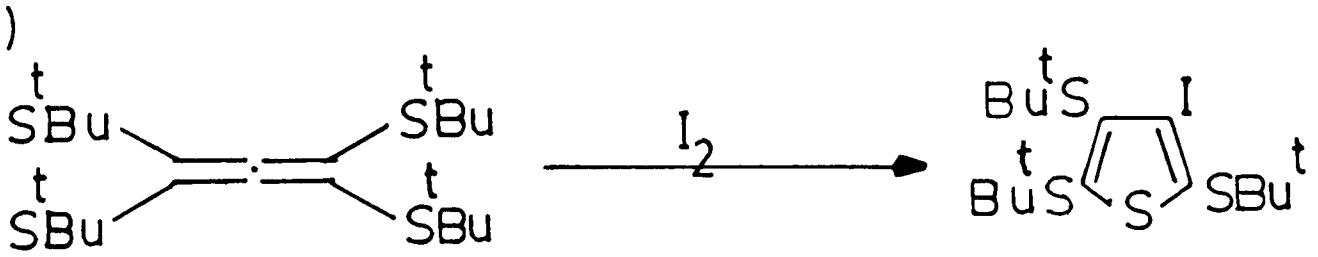


35

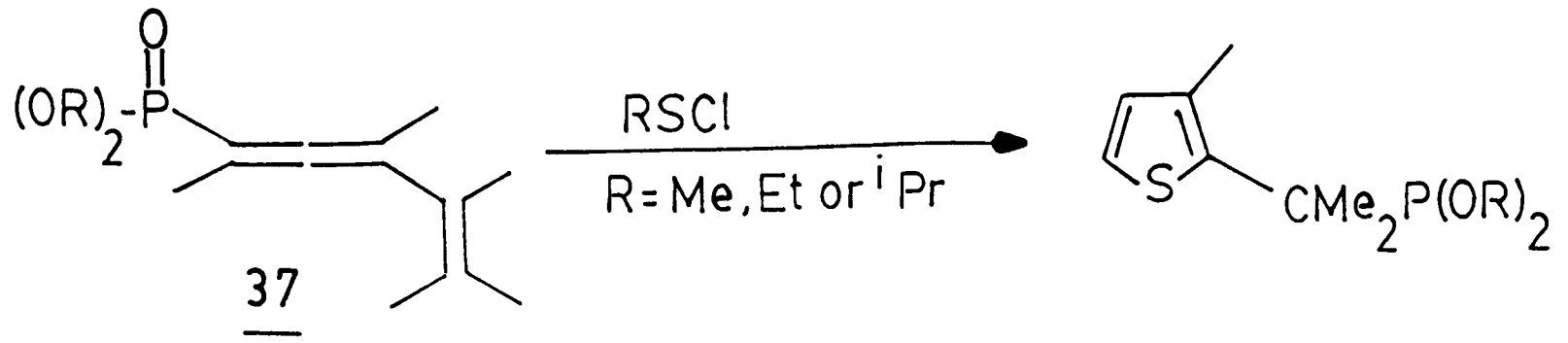
f) from allenes

i)



36

ii)



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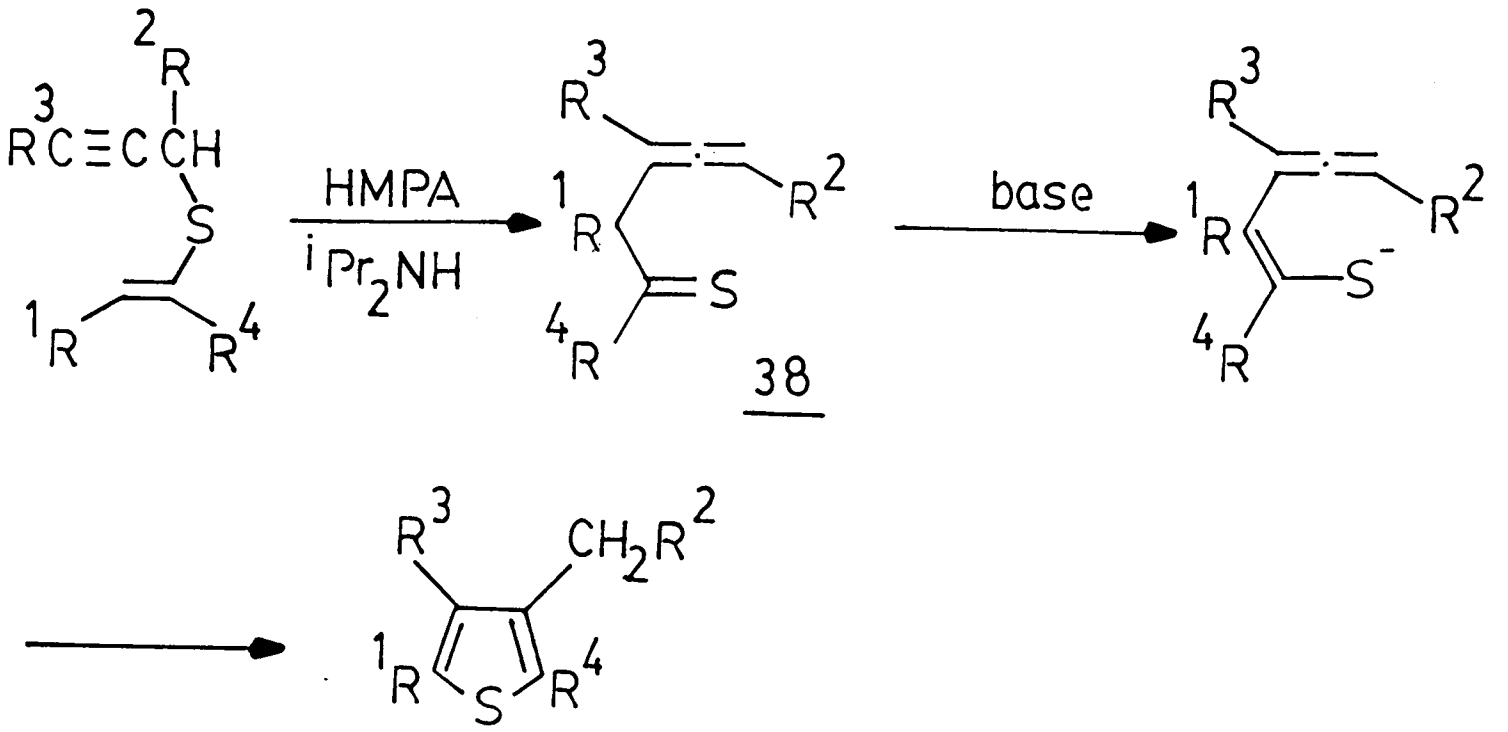
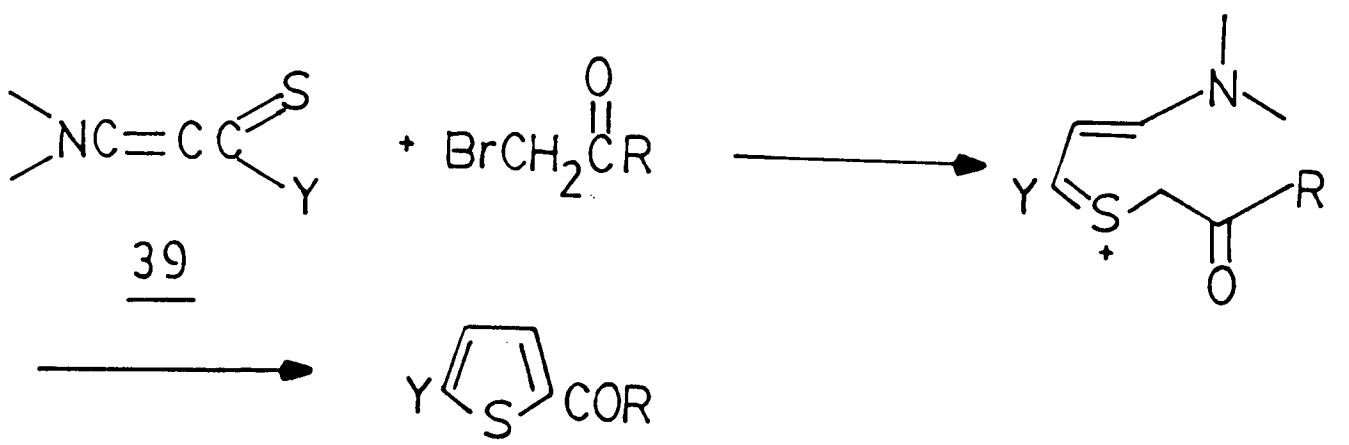
iii)



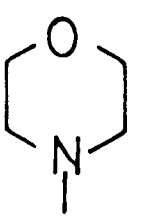
38

g) from 3-amino substituted dithioacrylate esters or equivalent

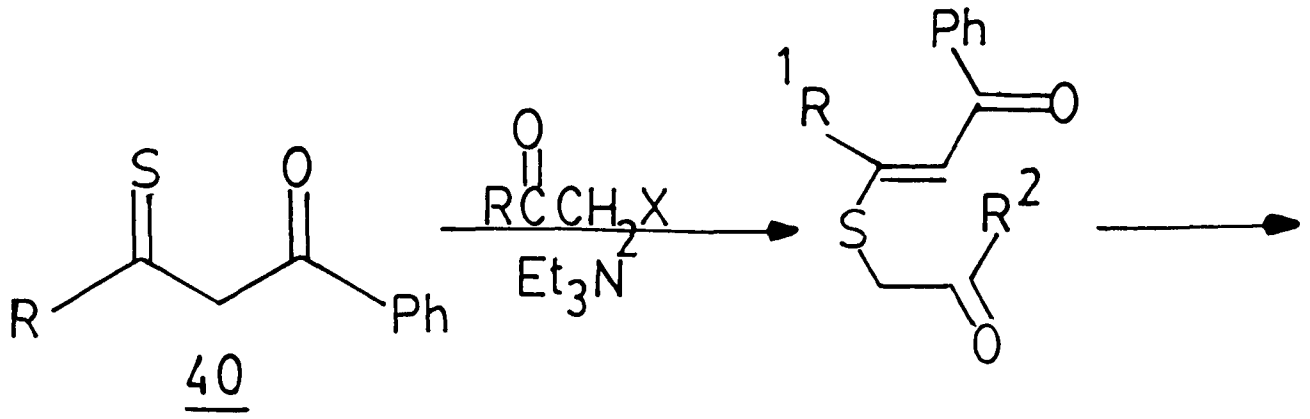
i)

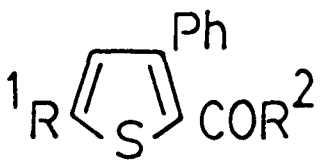


39

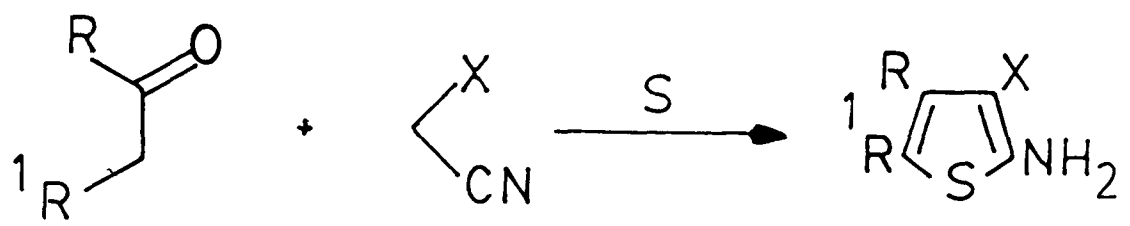
Y = SMe, PhNH, 

ii)



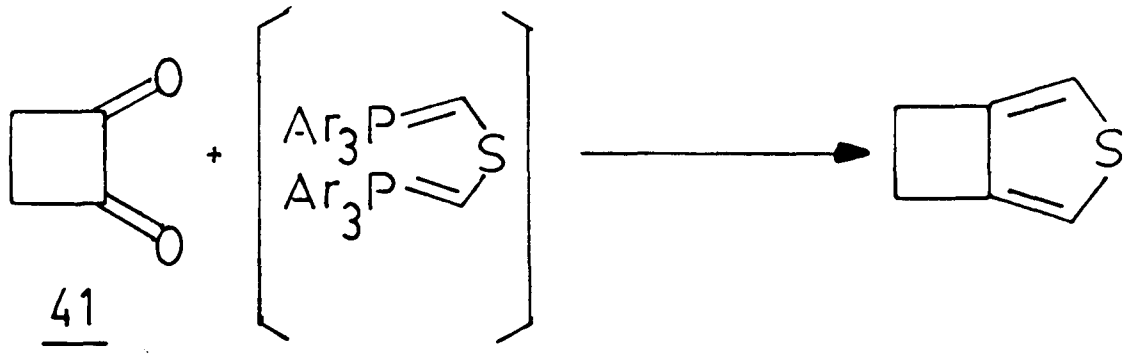


h) the Gewald synthesis



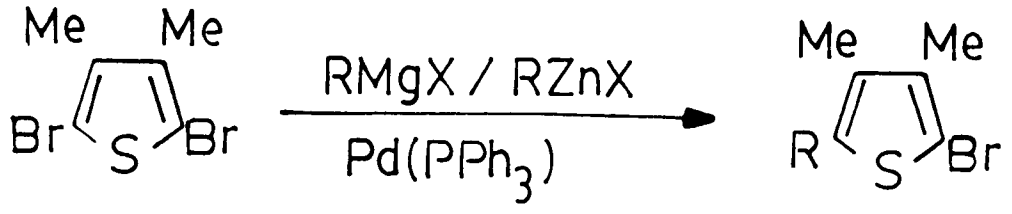
X = CO_2R, COR, CN or $CONH_2$

i) from cyclic ∝-diketone

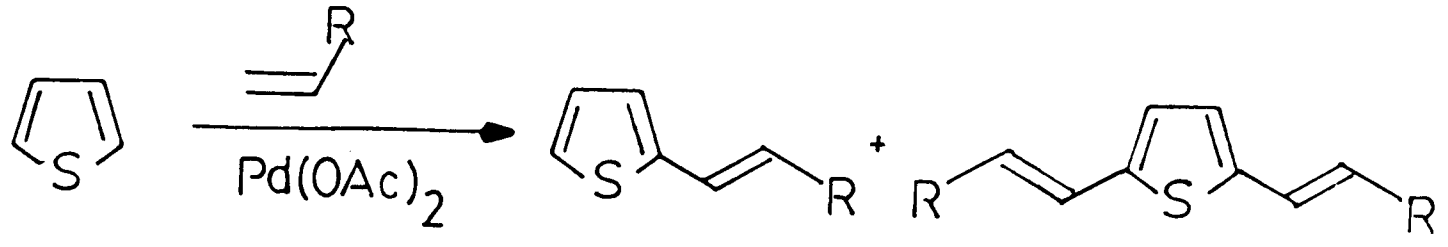


2) Synthesis from other thiophenes

There are many interconversions of substituted thiophenes, but some recently developed and potentially general methods are based on the transition metal complexes mediated coupling reactions between Grignard or organozinc reagents and halothiophenes. Carboxylation in one step is also feasible.

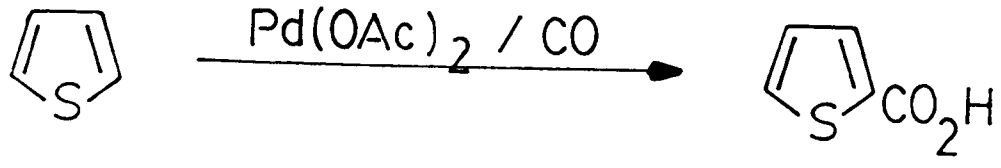


ref. 42

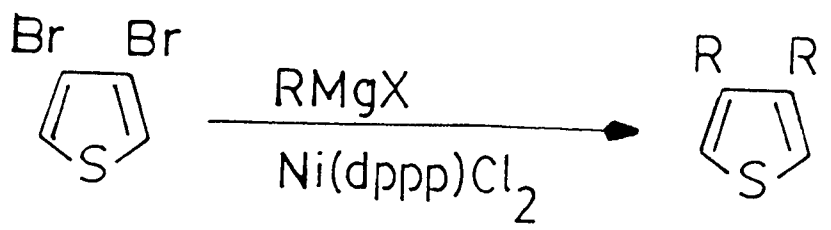


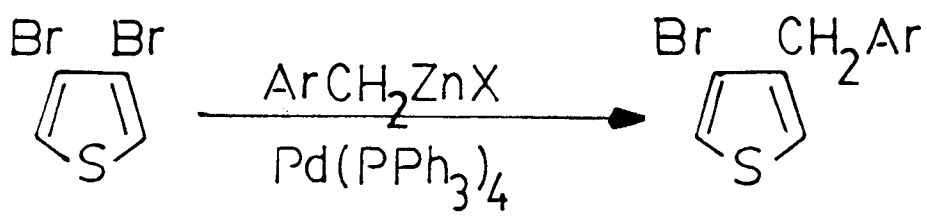
R = CN, Ph or CO_2Me

ref. 43



ref. 44





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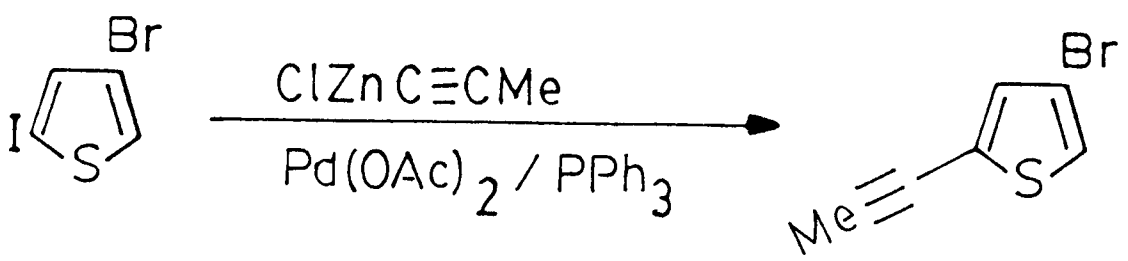
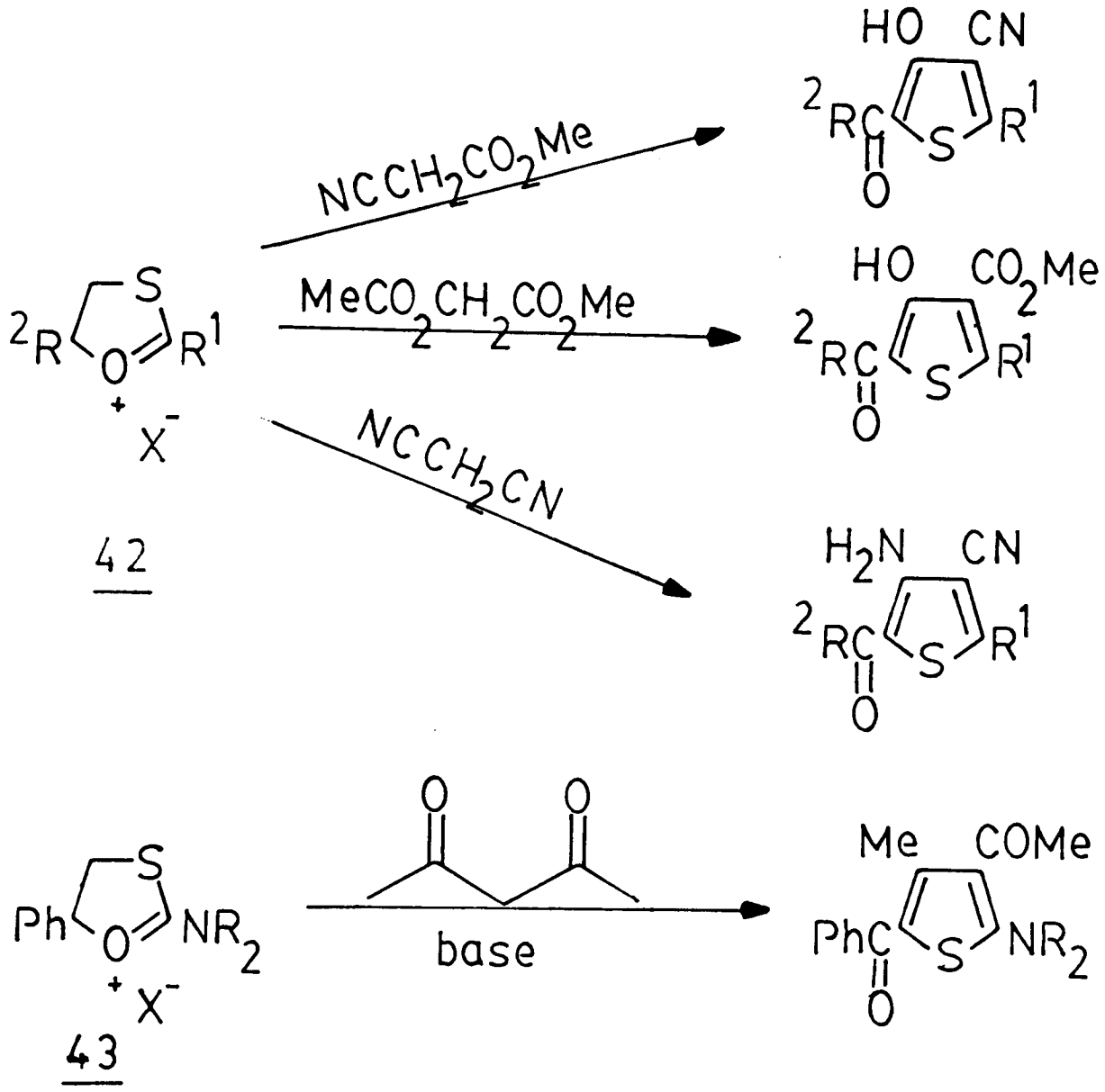


ref. 46

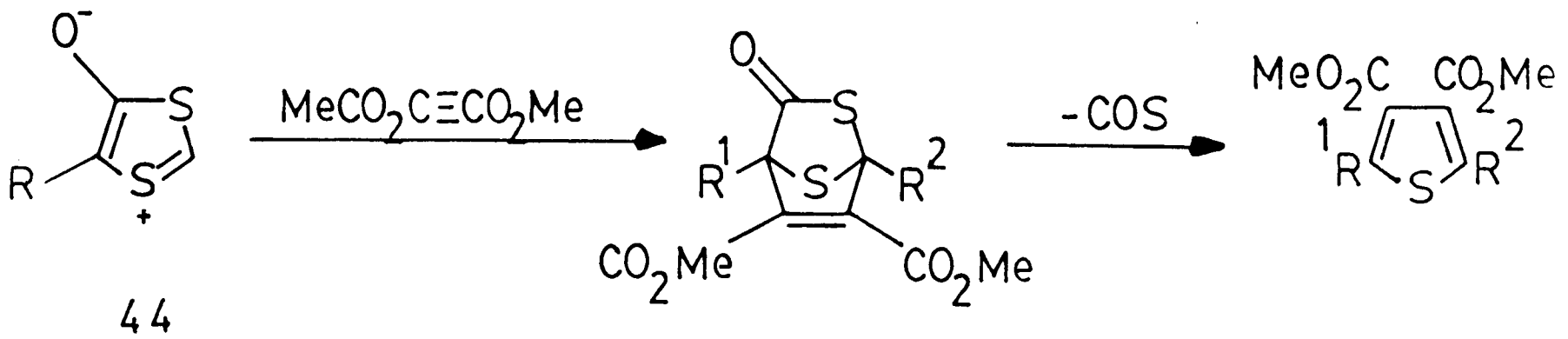
3) From other ring systems

These include the utilization of mesoionic compounds like 1,3-oxathiazolium salts (42),(43),[47] or 1,3-dithiolones (44)[48] or simply ring contraction of 3-bromo-thiocoumarin (45).[49] However, examples of these in the literature are scarce and are not finding general applicability.

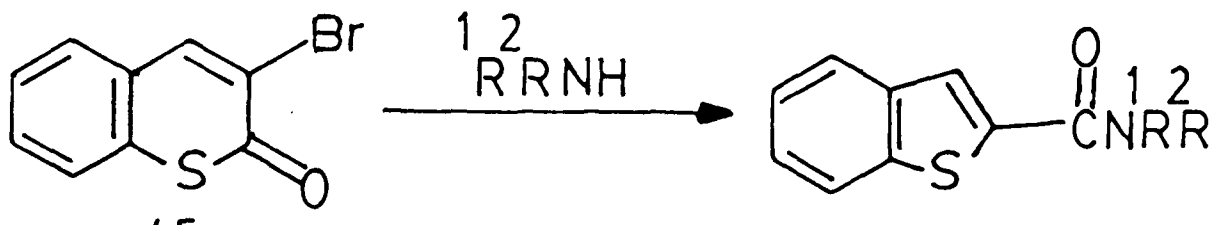
i) via 1,3-oxothiazolium salts



ii) via 1,3-dithiolones



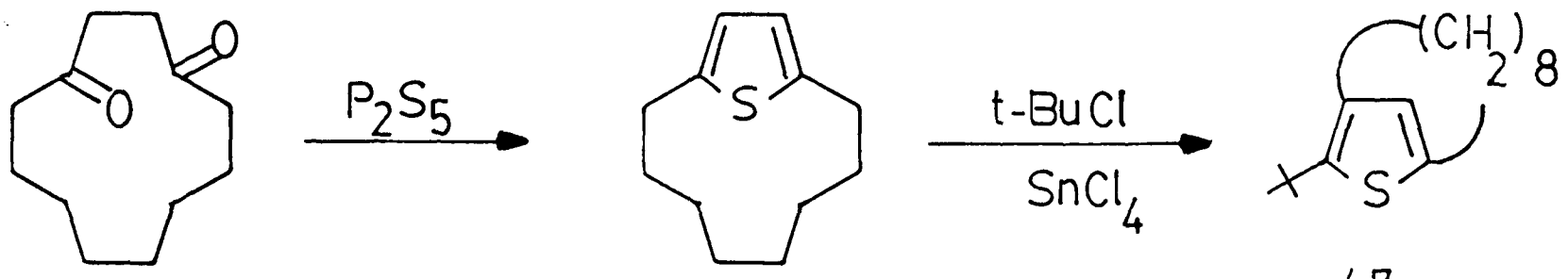
iii) ring contraction of 3-bromothiocoumarin



45

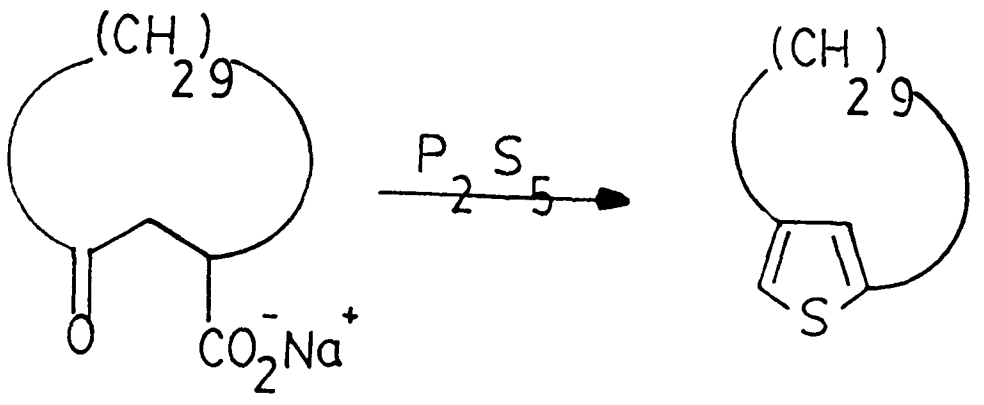
II) Synthesis of thiophenophanes

The chemistry of thiophenophanes is relatively unexplored, primarily because of the considerable difficulties attendant to their synthesis. Compounds (46)-(53)[50-57] have been synthesized for conformational studies; the layered ones (54)-(58)[58,59] for the investigation of transannular electronic interaction between benzene ring and thiophene ring; the thieno(or furano)(2,5)thiophenophane (59)-(61)[57,60,61] for the examination of the extent of through-space and through bond interaction between the heterocyclic rings; the acyloin derivatives (62) as useful intermediates for macrocyclic ketones (63)[62] and finally (64)[63] and (65)[64] as useful intermediates for other macrocycles.



46

47



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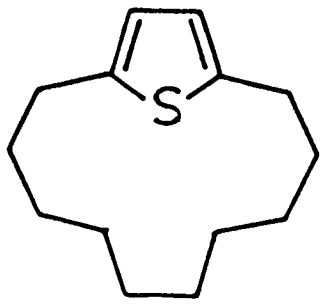

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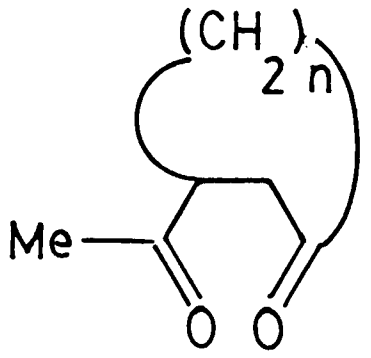
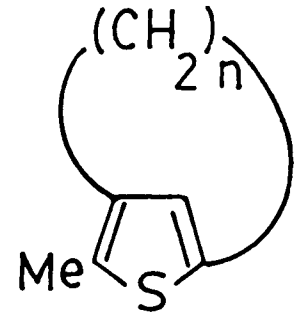


n= 6, 7 and 9



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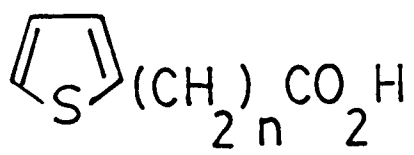
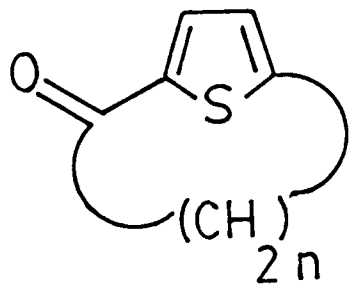


n=12,13,15,17 and 21



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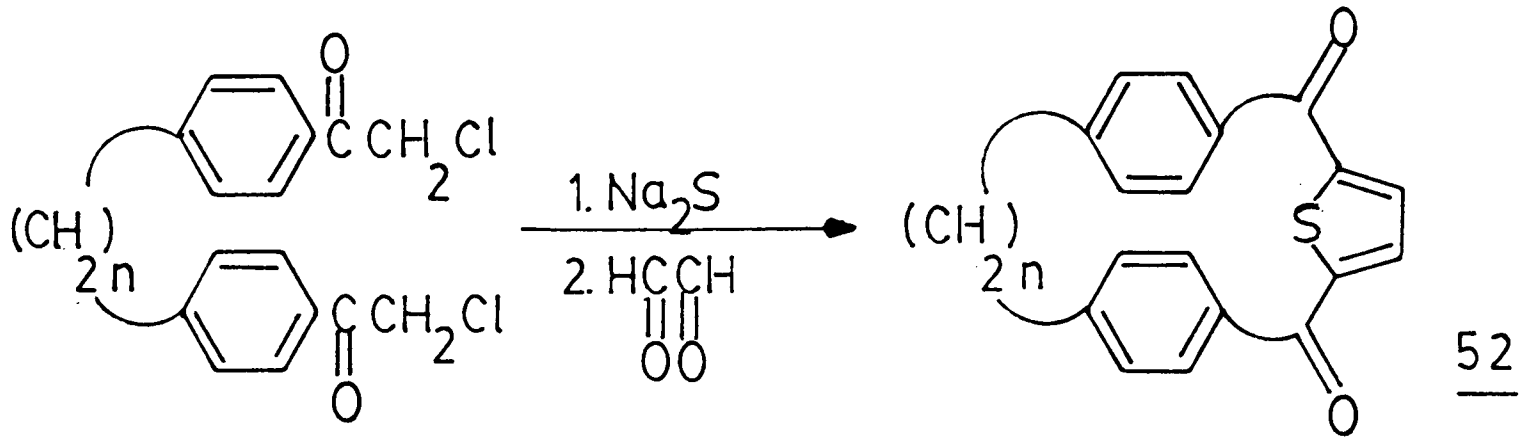

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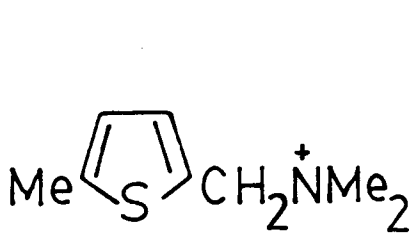

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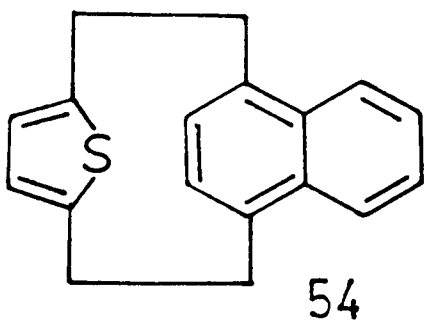

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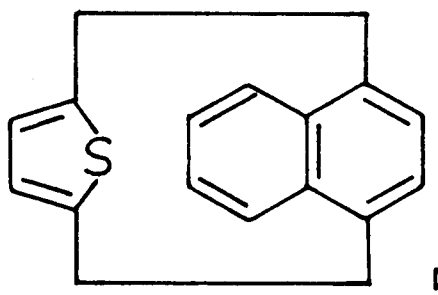

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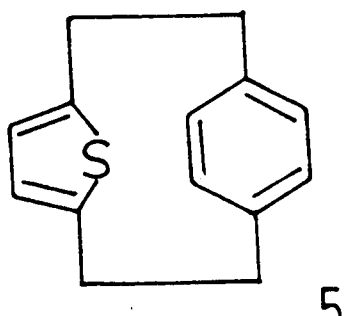

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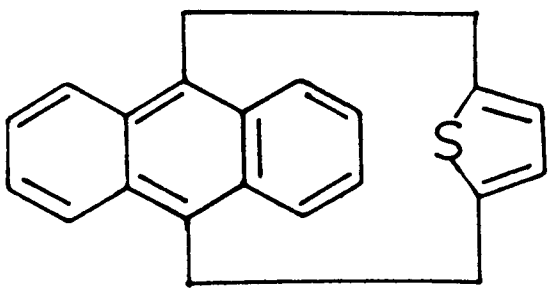

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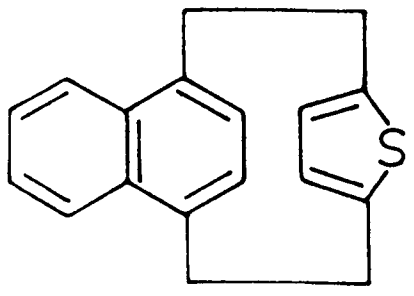

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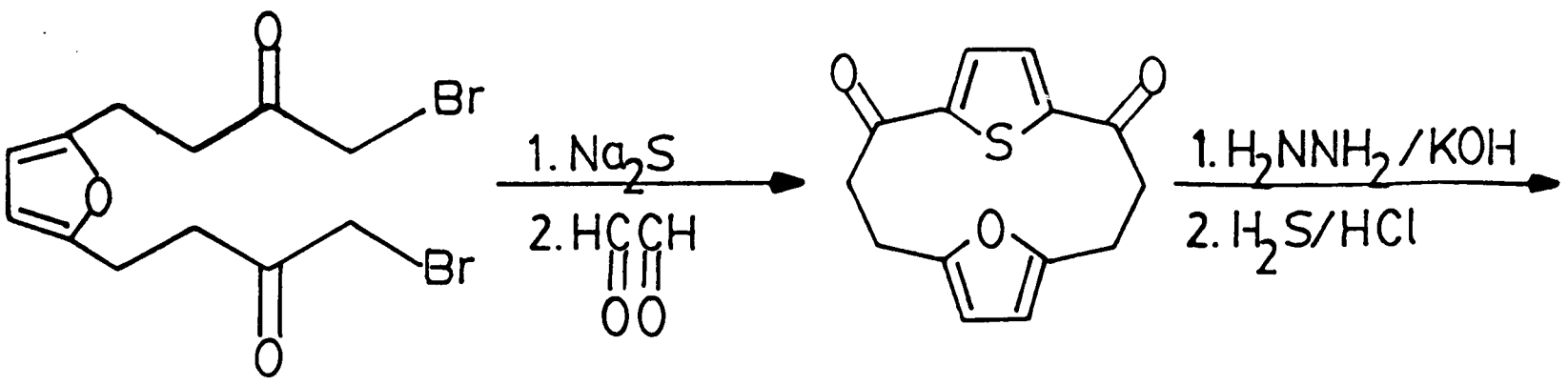

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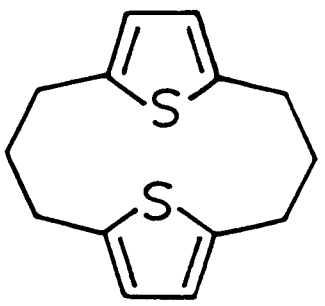

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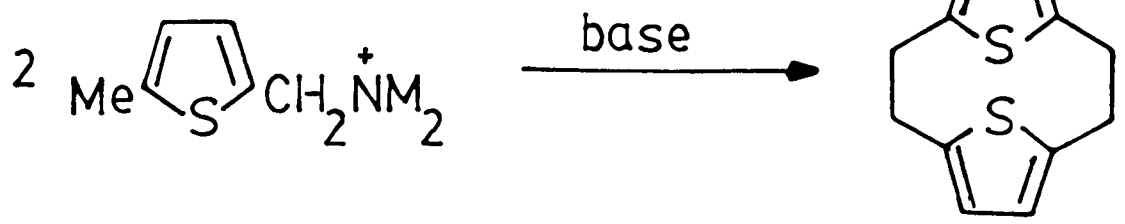

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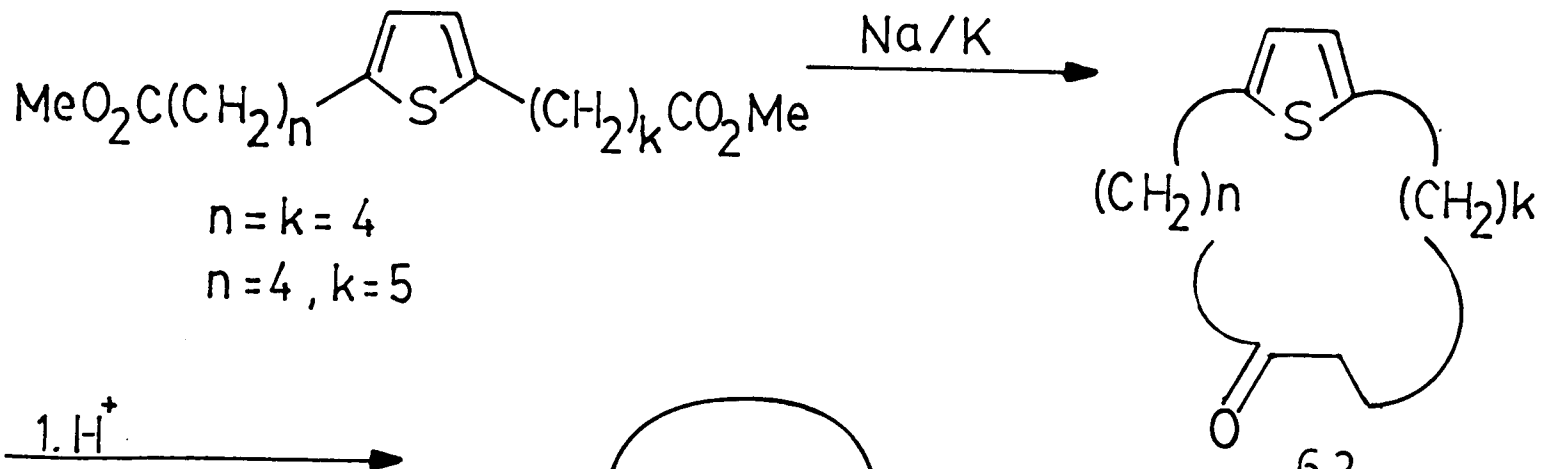
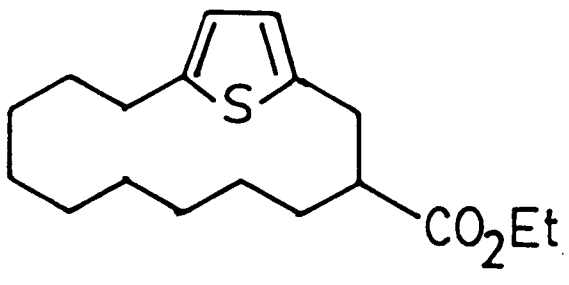


62

63



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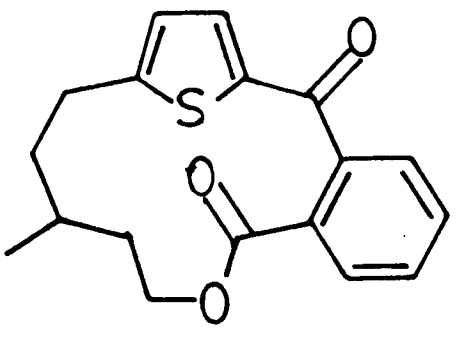
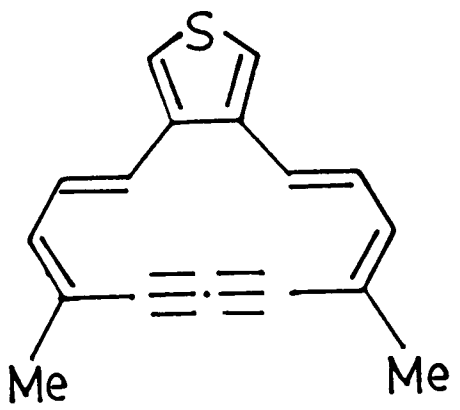
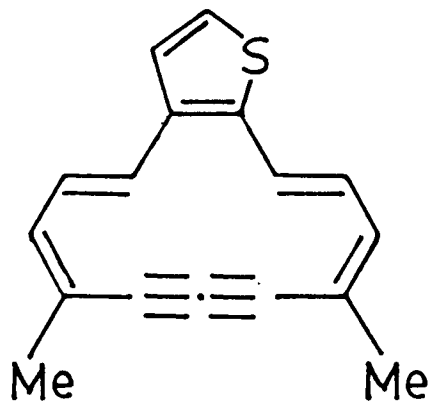


65

Although a few thiophenoid-fused annulenes (66),[65] (67),[65] (68)[66] and (69)[67] are known in the literature, however none of them are of {n}(2,5)thiophenophane type.



66



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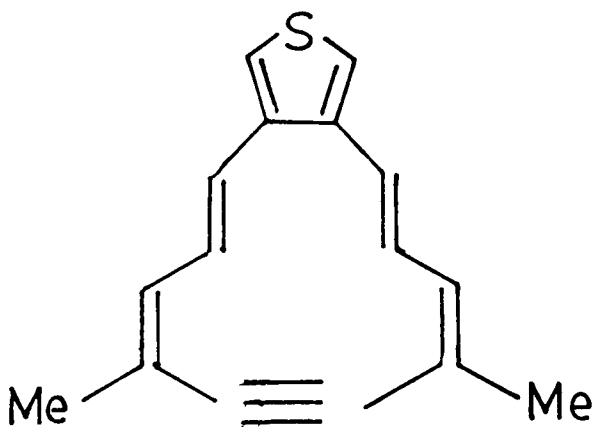
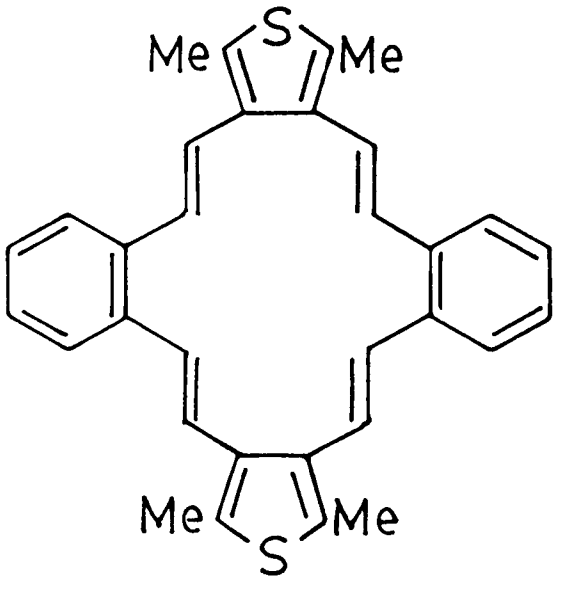


68

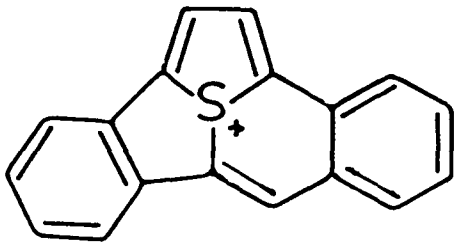


69

Of all the methods so far developed for the synthesis of thiophenophanes, some have been employed for particular thiophenophanes, some are clearly special cases, while the others involve starting materials that are difficult of access. Moreover, none of the thiophenophanes prepared are of the benzo-fused type. Thus, new synthetic approaches needed to be devised for our target (16).

Chapter 3

Attempted synthesis of 11c-thioniabenzo{b}cyclopenta{lm}fluorene (16) and 3,7-diphenyl-7b-thioniacyclopent{cd}indene (118)



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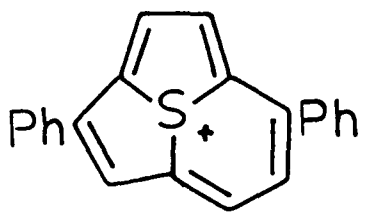
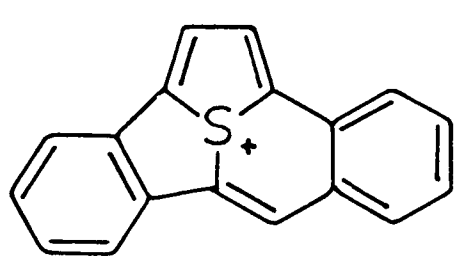
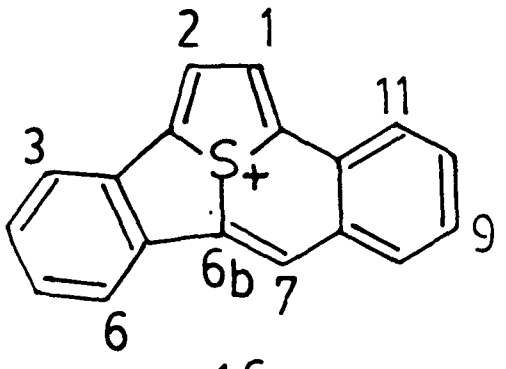


118

Part A

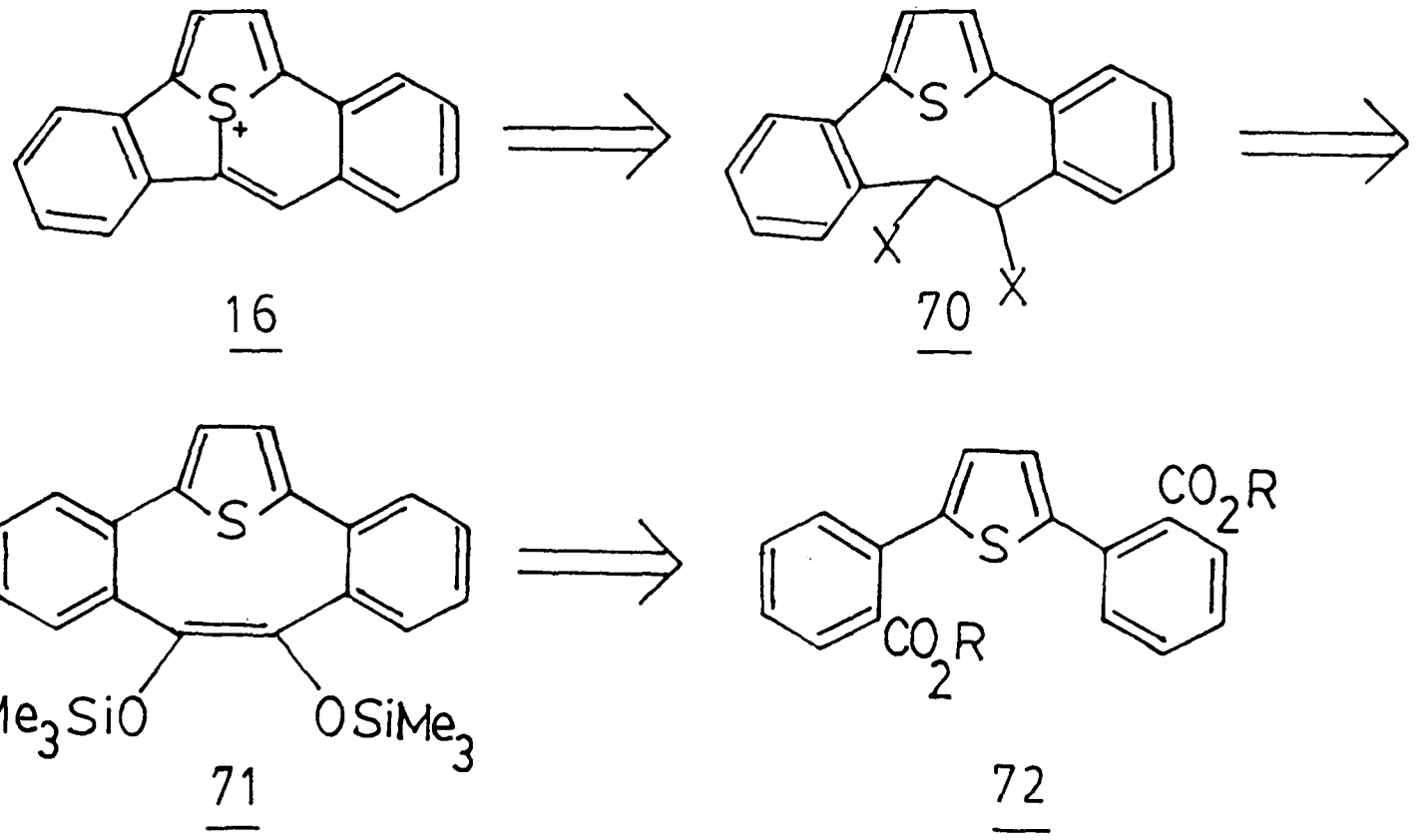


3.1 Synthetic approaches



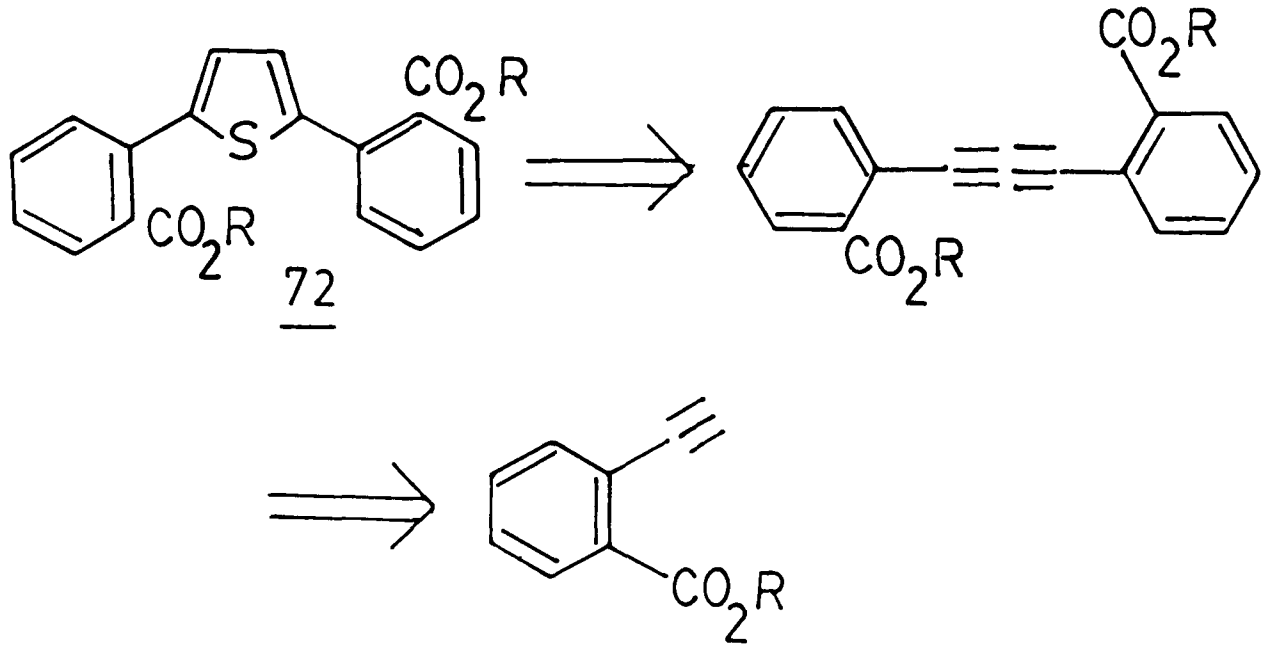
16

Supposing that the bond between the S atom and C-6b in (16) is to be formed, and by doing a simple retrosynthesis, it is not difficult to see that 1,2,5,6-dibenzo-3,4-disubstituted{6}(2,5)-thiophenophane (70, X=good leaving group) is the precursor of (16), which could perhaps be obtained from the acyloin derivative (71).



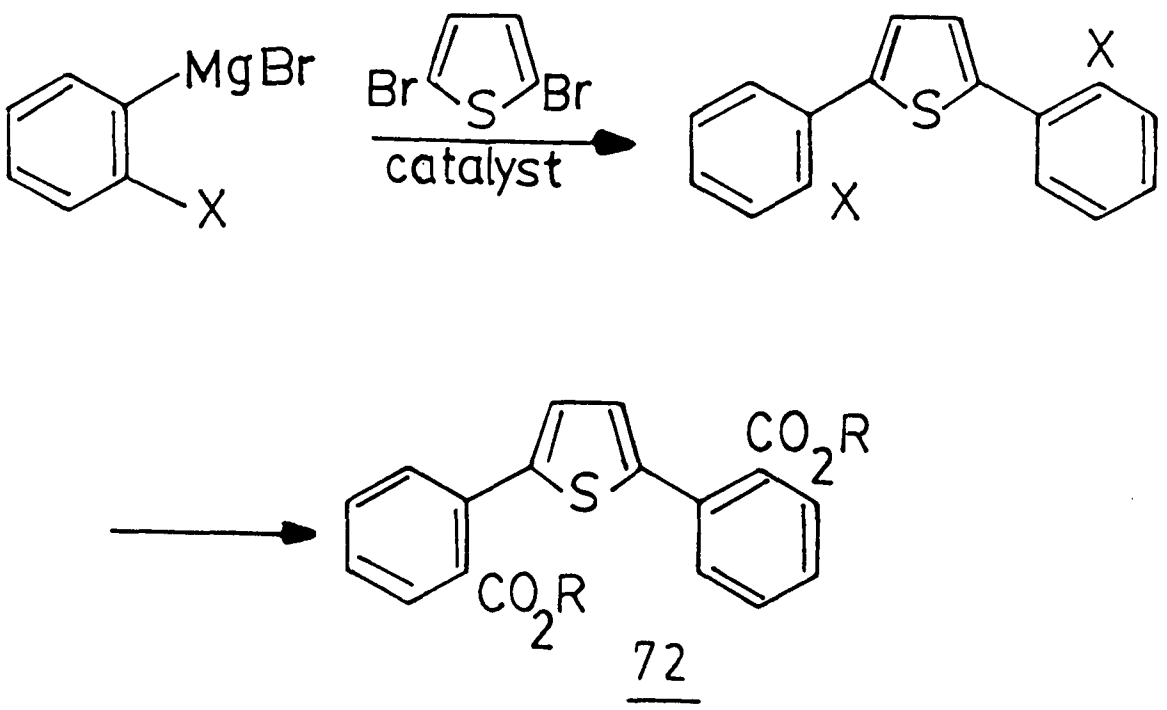
Few thiophenes of type (72) are known. Three synthetic methods have been employed: (i) addition of hydrogen sulphide or equivalent to 1,4-diphenylbutadiyne,[22,68] (ii) the classical Paal reaction,[20,21]

and (iii) the catalytic cross-coupling between 2,5-dibromothiophene and aryl magnesium[42,45] or zinc halide. The Paal reaction is the least attractive, in spite of an improved procedure (using Lawesson's Reagent)[21] because of the unavailability of 1,4-di(2-substituted phenyl)butan-1,4-diones. Since 1,4-diarylbutadiynes can be synthesized readily by intermolecular oxidative coupling of aryl acetylenes, the synthesis of (72) becomes



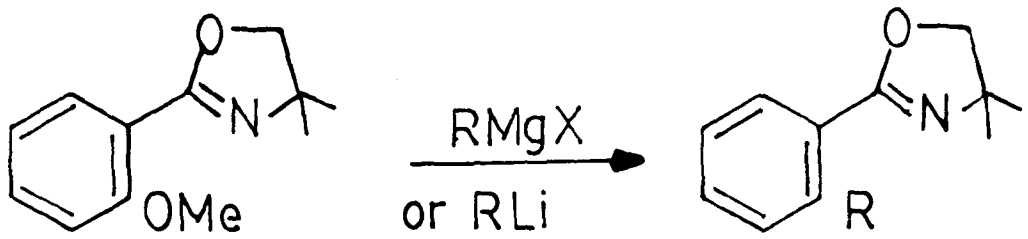
72

Equally, catalytic coupling between 2,5-dibromothiophene with the appropriate 2-substituted phenylmagnesium bromide should give (72).



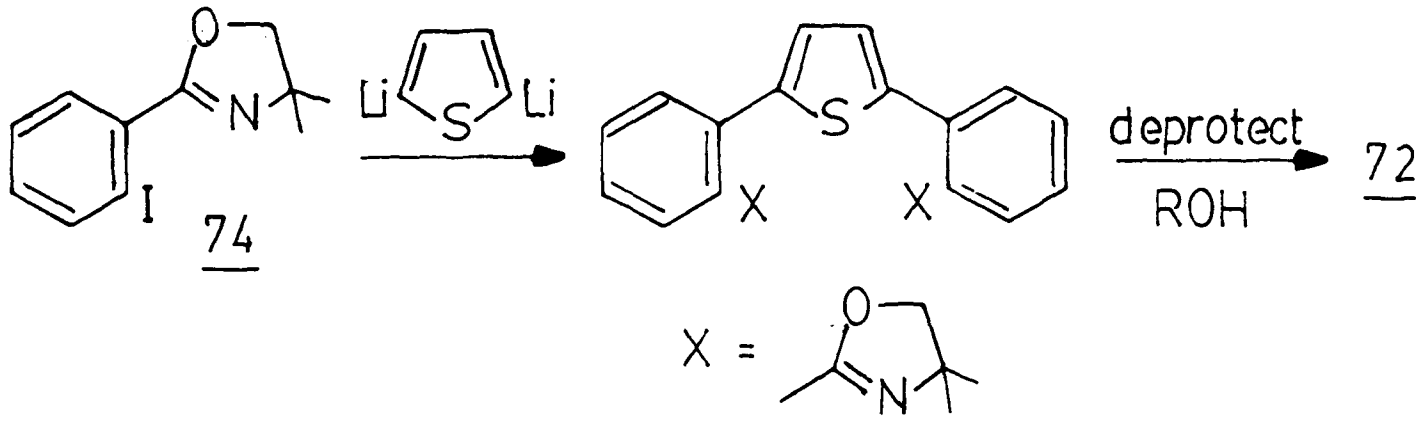
72

In 1978, Meyers et al[69] reported that the 2-oxazolinoanisole (73) undergoes an easy nucleophilic displacement of the methoxy group viz.,

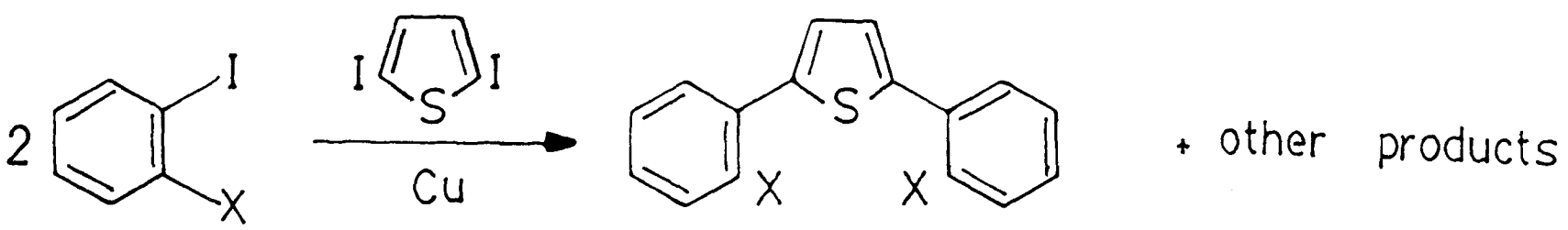


73

Unfortunately, 2-thienyl lithium did not react.[69] However, as iodide is a much better leaving group than methoxy, it seemed worth examining the reaction of (74) with 2,5-dilithiothiophene in the hope of obtaining (72).

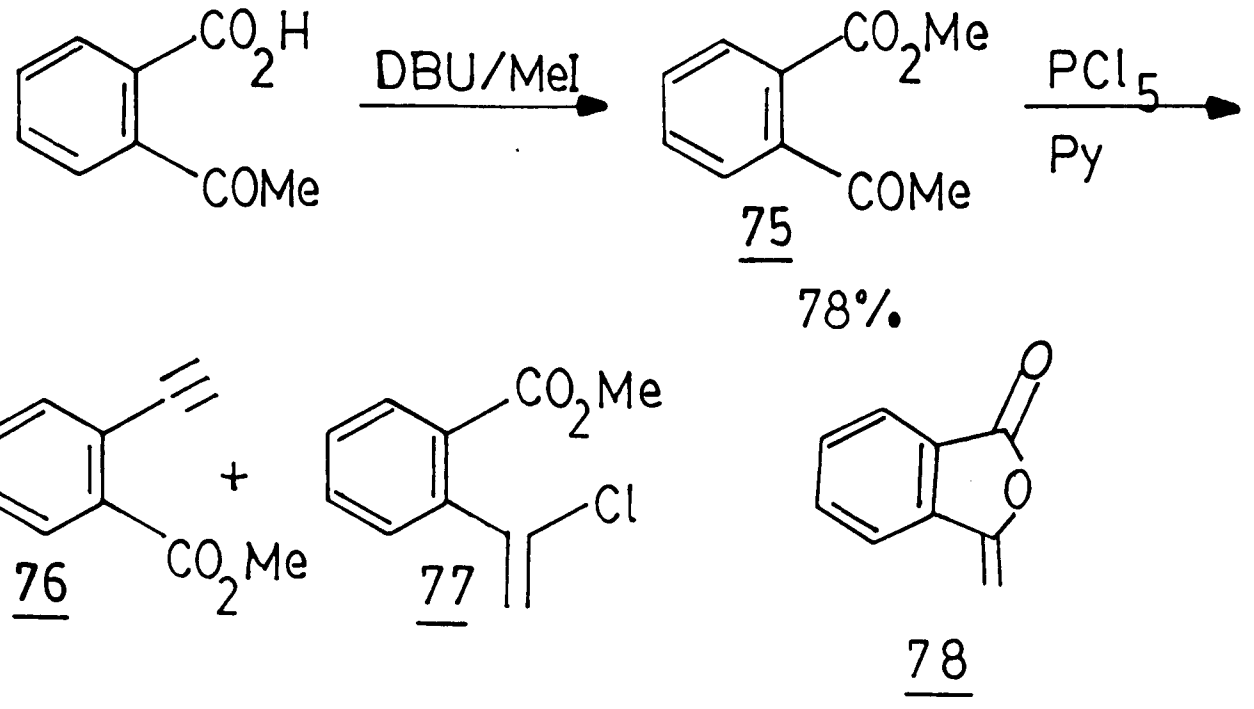


Finally, the classical Ullmann coupling reaction seemed worth examining viz.,

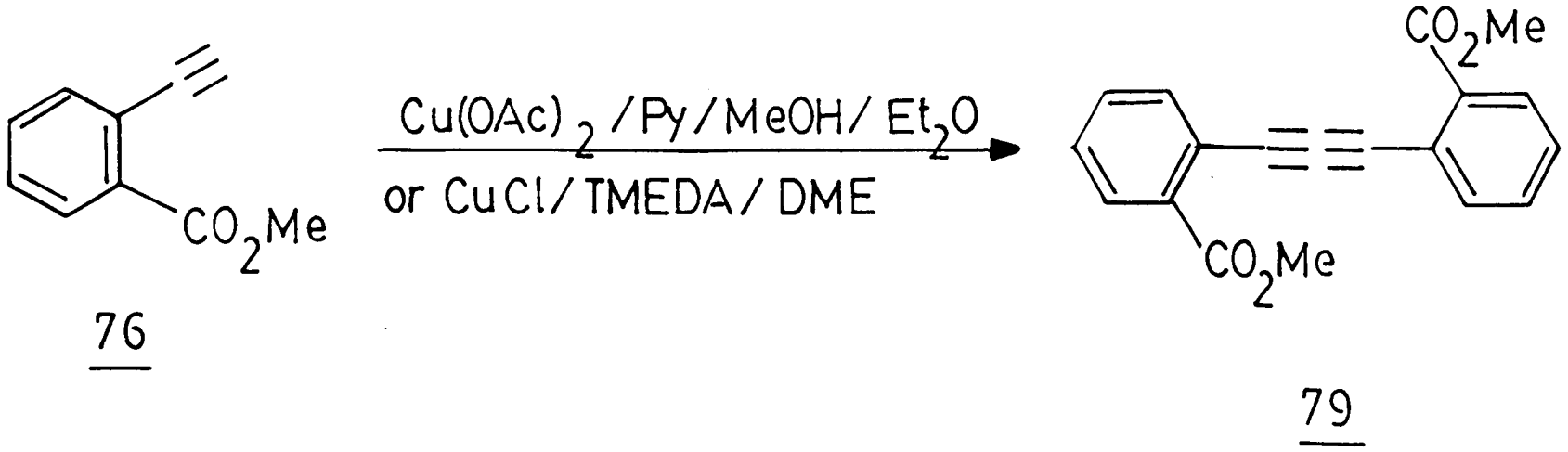


3.2 Results and discussions

In 1974, Ho et al[5] reported the first synthesis of methyl 2-ethynylbenzoate (76).

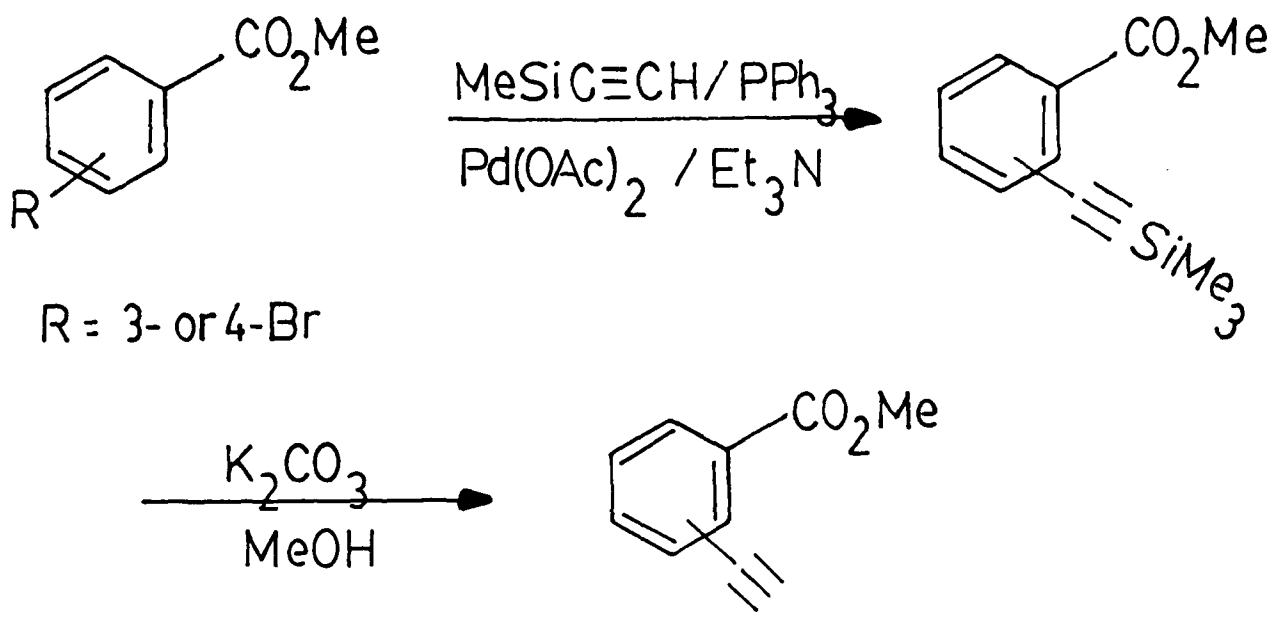


The original esterification was with diazomethane,[71] but this reagent was avoided by using DBU, iodomethane in benzene.[72] Repeating Ho's procedure gave (76), (77) and (78) in 47 : 12.5 : 3 ratio, estimated from the ^{1}H NMR of the chromatographed product. No serious attempt at separation was made, and the mixture was subjected to oxidative coupling. Eglinton's procedure[73] using anhydrous copper (II) acetate[74] in Py/MeOH/Et_2O (1 : 1 : 4) mixture and that of Hünig,[75] which was simpler in practice and employed copper (I) chloride, TMEDA in DME both gave 55% yield. Nevertheless, a better method was sought.

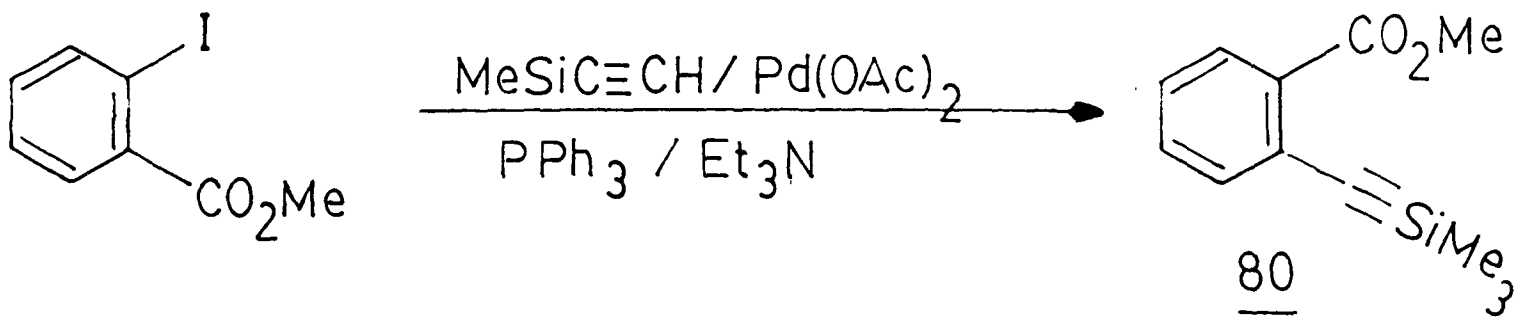


76 79

The recent report by Austin et al[76] on a new synthesis of methyl 3- and 4-ethynylbenzoate suggested we apply the method to the 2-isomer.



Coupling methyl 2-iodobenzoate and excess ethynyltrimethyl-silane, palladium acetate and triphenylphosphine as described, gave methyl 2-{(trimethylsilyl)ethynyl}benzoate (80) (45%) and unreacted methyl 2-iodobenzoate (55%).

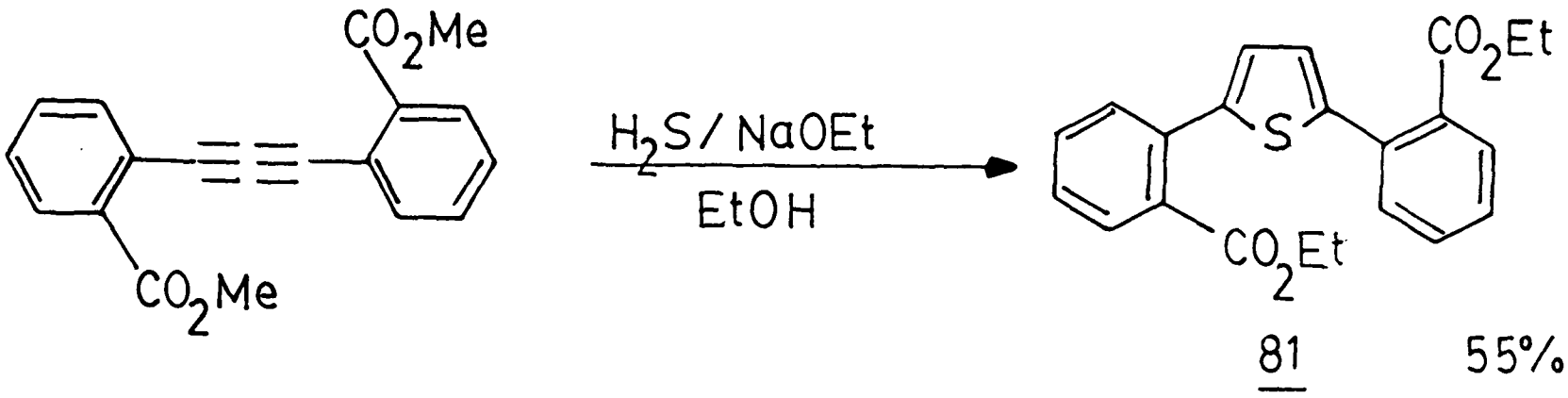


80

Methyl 2-iodobenzoate and (80) could not be separated by normal fractional distillation so the mixture was desilylated by potassium carbonate/MeOH, and coupled, using Hünig's condition,[73] to give (79) in 24% overall yield. 2-Bromobenzaldehyde combines with ethynyltrimethylsilane under similar conditions in 80-90% yield.

Employing Schulte's method[68] for constructing the thiophene

ring from 1,4-butadiyne, 1,4-bis(2-methoxycarbonylphenyl)butadiyne (79) was treated with sodium sulphide, generated in situ from hydrogen sulphide and sodium ethoxide in ethanol. The desired thiophene (81) was obtained as an orange oil, which decomposed on attempted vacuum distillation.

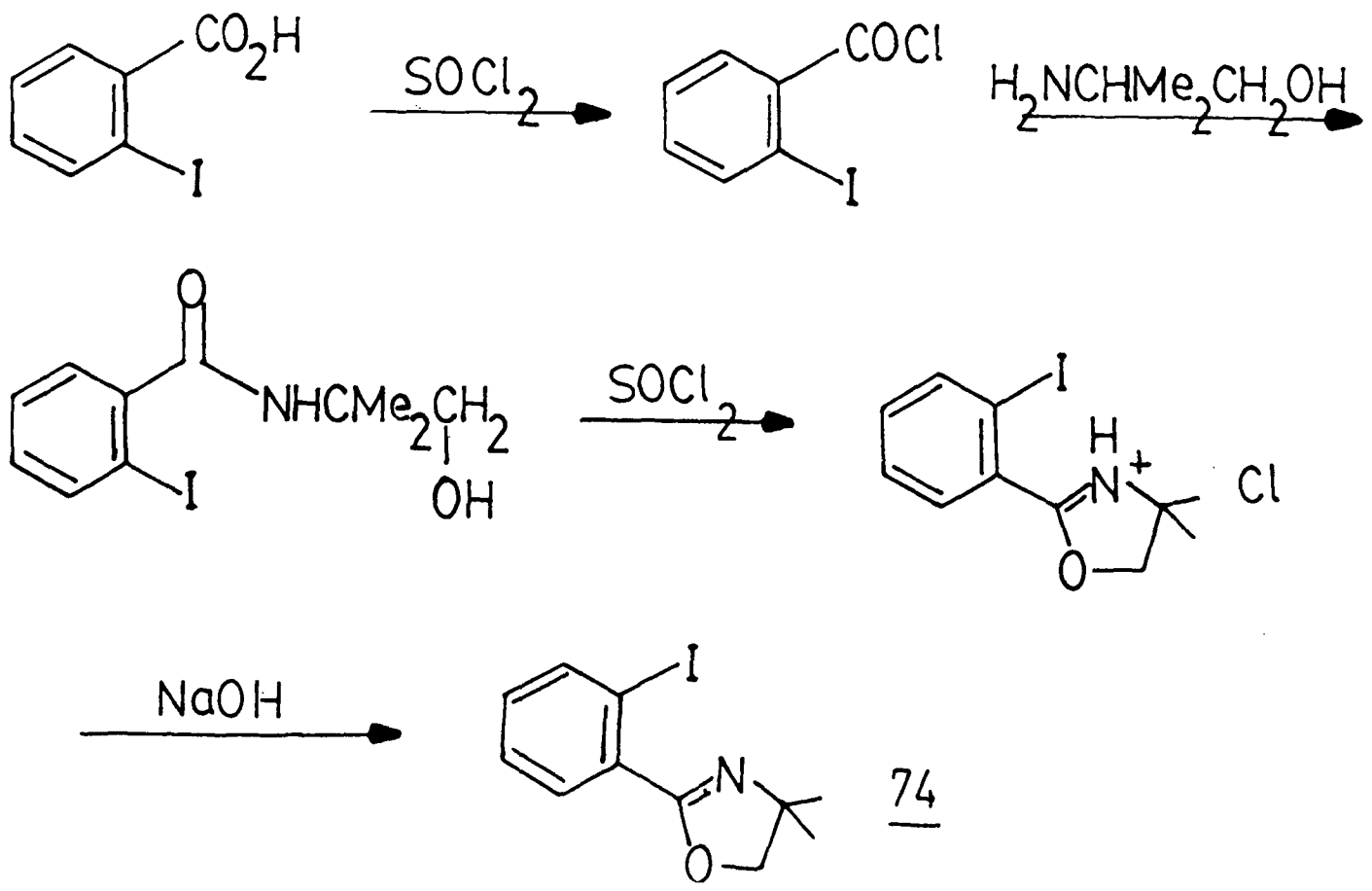


81 55%

The structure of (81) was fully supported by ^{1}H NMR and other spectra, and combustion analysis. Strangely enough, when methanolic sodium methoxide replaced the ethanolic ethoxide in the above reaction, the diyne was recovered unchanged.

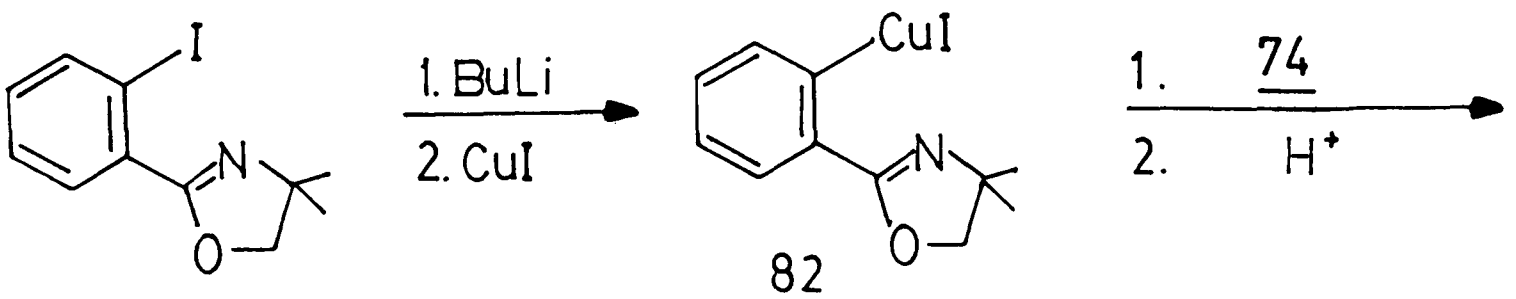
Unsuccessful attempts at synthesizing (81) by alternative method are now summarized.

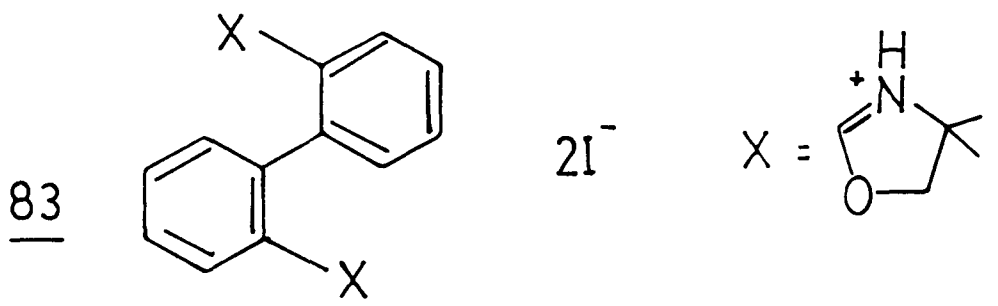
Using a similar report by Meyers et al,[77] 4,4-dimethyl-2-(2-iodophenyl)oxazoline (74) was synthesized (77% overall).



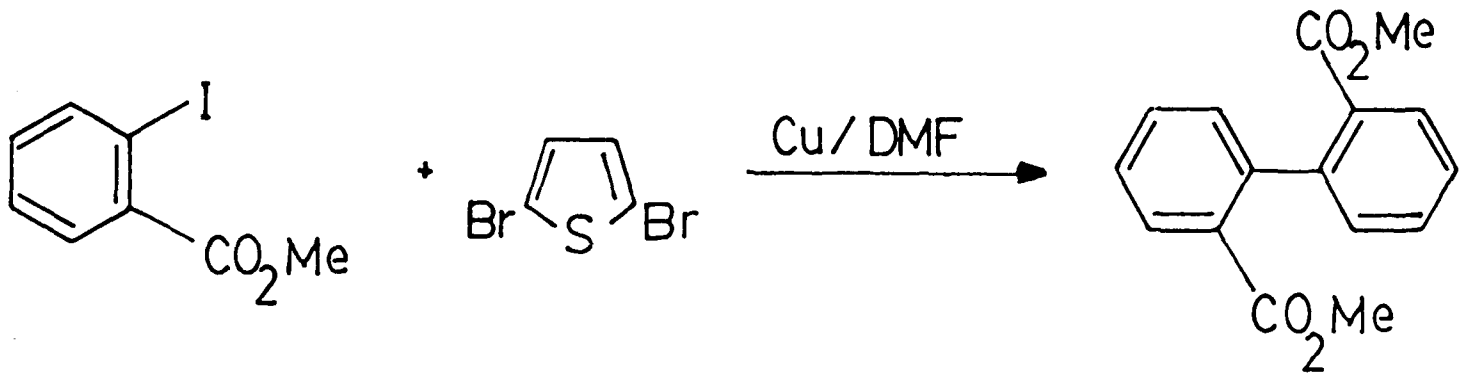
74

When (74) was allowed to react with 2,5-dilithiothiophene, from butyl lithium and 2,5-dibromothiophene, (74) was recovered unchanged. As suggested by Meyers,[69] the lithiothiophene is probably too stable to react. Addition of 1 equivalent of copper (I) iodide led to no improvement. However, when 2,5-dibromothiophene was treated with 5-fold excess of 4,4-dimethyl-2-(2-copperphenyl)oxazoline (82), generated from the corresponding oxazoline (74) and butyl lithium, in the presence of a 10-fold excess of copper (I) iodide in ether, apart from starting materials, a compound, probably (83), identified from its spectra was isolated by chromatography.



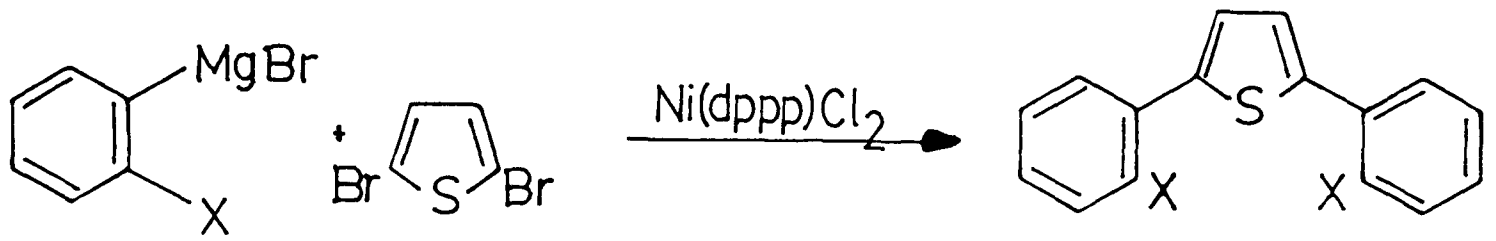


Disappointed by these results, the Ullmann coupling reaction was examined for the synthesis of 2,5-diarylthiophenes. Unfortunately, heating 2,5-dibromo or diiodothiophene (1 equivalent), copper (6 equivalents) and methyl 2-iodobenzoate for varying periods of time resulted in preferential self-coupling of the last to give 2,2'-methoxycarbonylbiphenyl (84) as the only isolable product, identified from its spectra and combustion analysis.



84

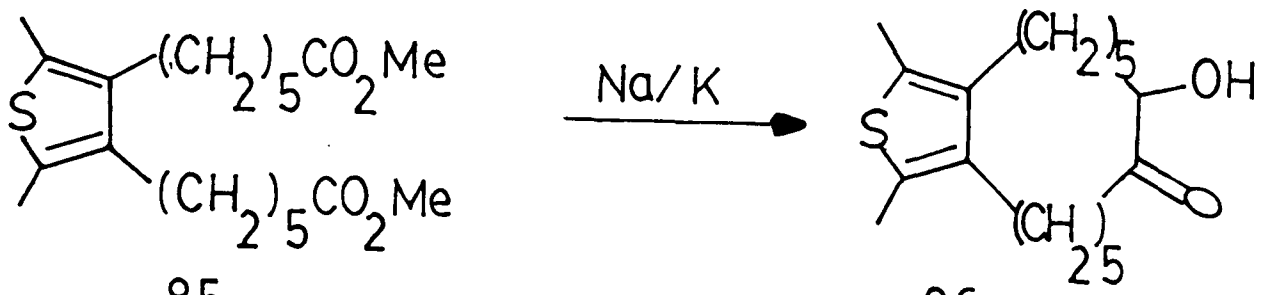
Kumada's report[78] on the facile coupling between 2,5-dibromothiophene and phenylmagnesium bromide, in the presence of dichloro{1,3-bis(diphenylphosphino)propane}nickel(II) ($Ni(dppp)Cl_2$), to give 2,5-diphenylthiophene in high yield prompted us to investigate the reaction below.



Disappointingly a very complex, yet consistent, mixture of products (TLC showed at least 7-10 components) was obtained using either Et_2O or THF and times ranging from 5 to 16 h. No attempts were made to identify the individual components. This rather surprising result, in contrast to the clean and high yield reported[78] when 2-substituents are absent was confirmed for other 2-substituents as described later. A tentative explanation for this anomalous behaviour is offered (p.48).

Concluding that addition of hydrogen sulphide or equivalent to 1,4-diarylbutadiynes represents the best method for making 2,5-diarylthiophenes, efforts were then directed towards the synthesis of {6}(2,5)thiophenophane (70) from (71) via the acyloin

condensation. Refluxing a mixture of 2,5-bis(2-ethoxycarbonylphenyl)-thiophene (81) with 4 equivalents of finely divided sodium and chlorotrimethylsilane (4 equivalents) in xylene for varying periods of time (6-20 h), under the optimum conditions described[79] caused no reaction. The corresponding methyl ester (72, R=Me) behaved similarly. Gol'dfarb et al[62] reported that the ordinary acyloin condensation conditions were unsuitable for thiophene esters, in agreement with Schuetz et al.[80] They attributed that to the degradative action of sodium on the thiophene ring under the reaction conditions and the deactivation of the sodium by the sulphur-containing degradation product. In fact, when (81) was subjected to the acyloin condensation, the sodium was covered with a dark colour coating, presumably the sulphur-containing degradation product mentioned above, after 10-20 min. However, Gol'dfarb discovered that (85) with K-Na alloy gave the acyloin (86) in 70% yield,[62] and that completely substituted thiophenes gave the best result.[81]

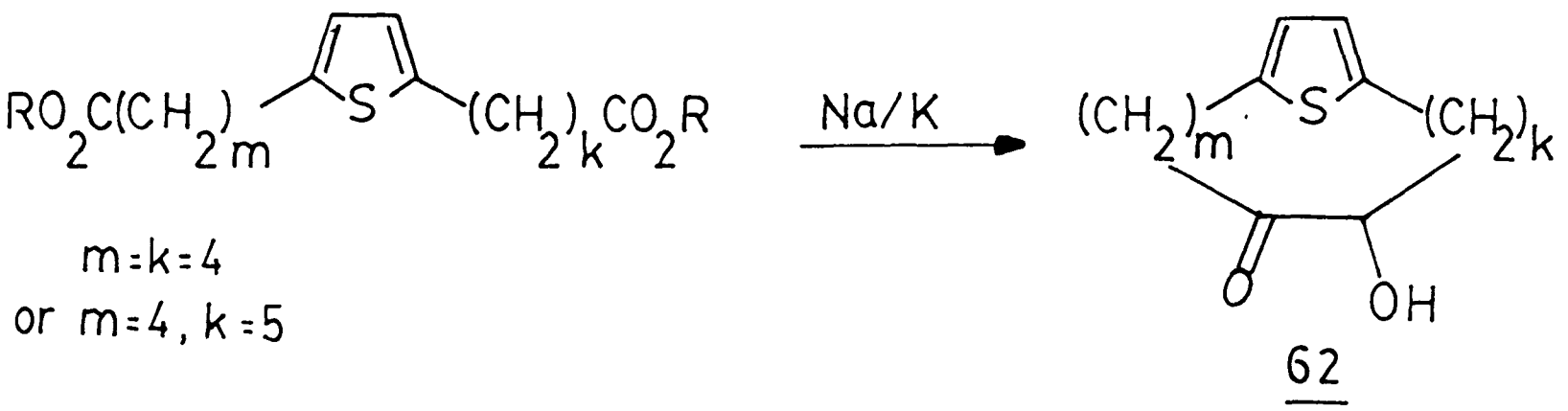


85 86

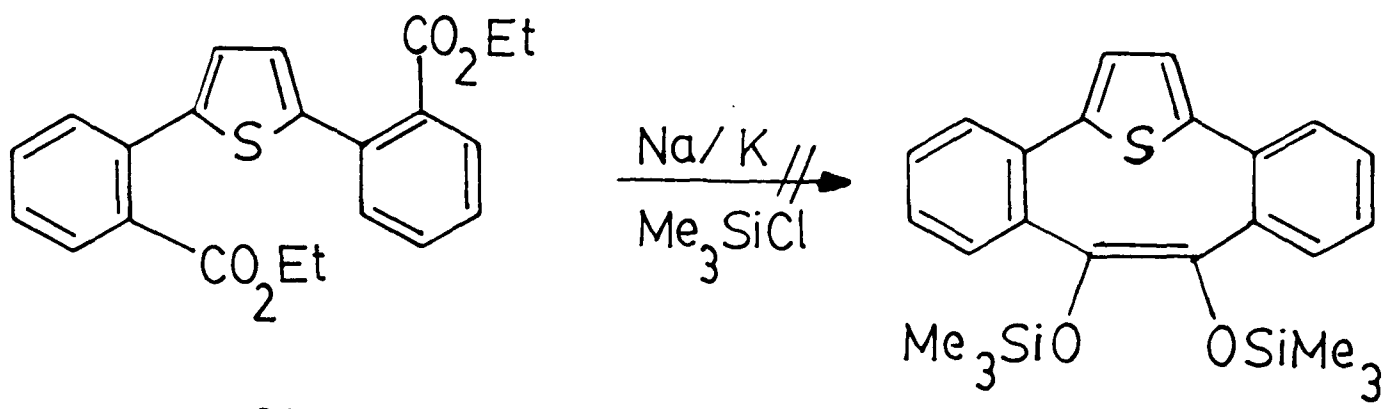
With the above report in mind, the 2,5-bis(2-ethoxycarbonyl-thiophene (81) was subjected to Na-K alloyed induced acyloin condensation under the condition reported. Again the initial ester was recovered.

First proposed by Hansley[82] and elaborated by Prelog[83] and Stoll[84] the acyloin condensation of dicarboxylic acid esters

is one of the most reliable methods for forming large and medium size ring.[79] According to the literature,[85] cyclization should be facilitated by the presence of a 'rigid group', thus 2,5-disubstituted thiophene carboxylic esters, having the thiophene ring acting as the rigid group, should be expected to undergo the acyloin condensation easily. Since Gol'dfarb et al[62,81] successfully prepared the cyclic acyloins (62, k=4,5, m, 4,5) in high yield, the failure of (81) to undergo a similar condensation under a similar condition suggests that there is too much strain in the ring of structure (71) for it to be easily formed.



62

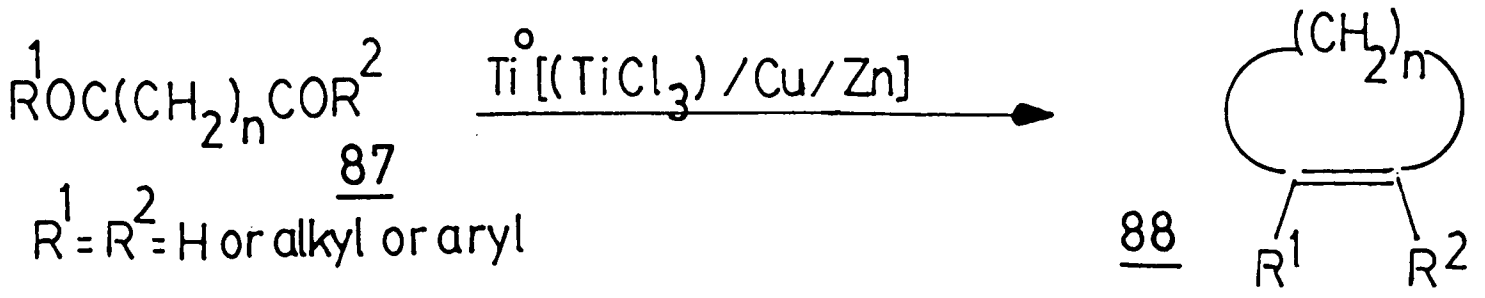


81 71

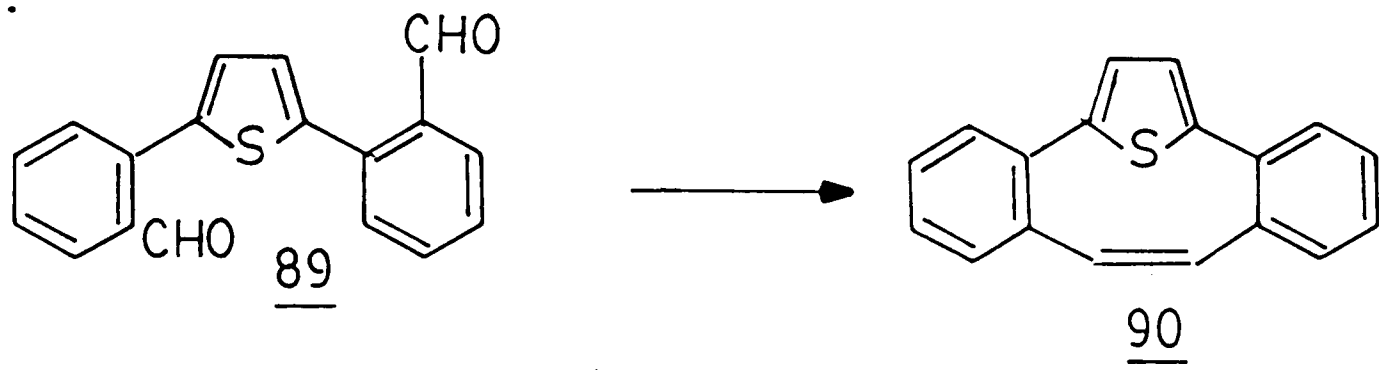
The smallest (2,5)thiophenophane known is {8}(2,5)thiophenophane[50,57] and none of them are of benzo-fused.

A similar well-established reaction for forming medium to large size rings is McMurray's titanium-induced reductive coupling of carbonyl compounds (87, n=2-14 or 20), under high dilution condition,

to olefin (88)[86] in 50-95% yield.

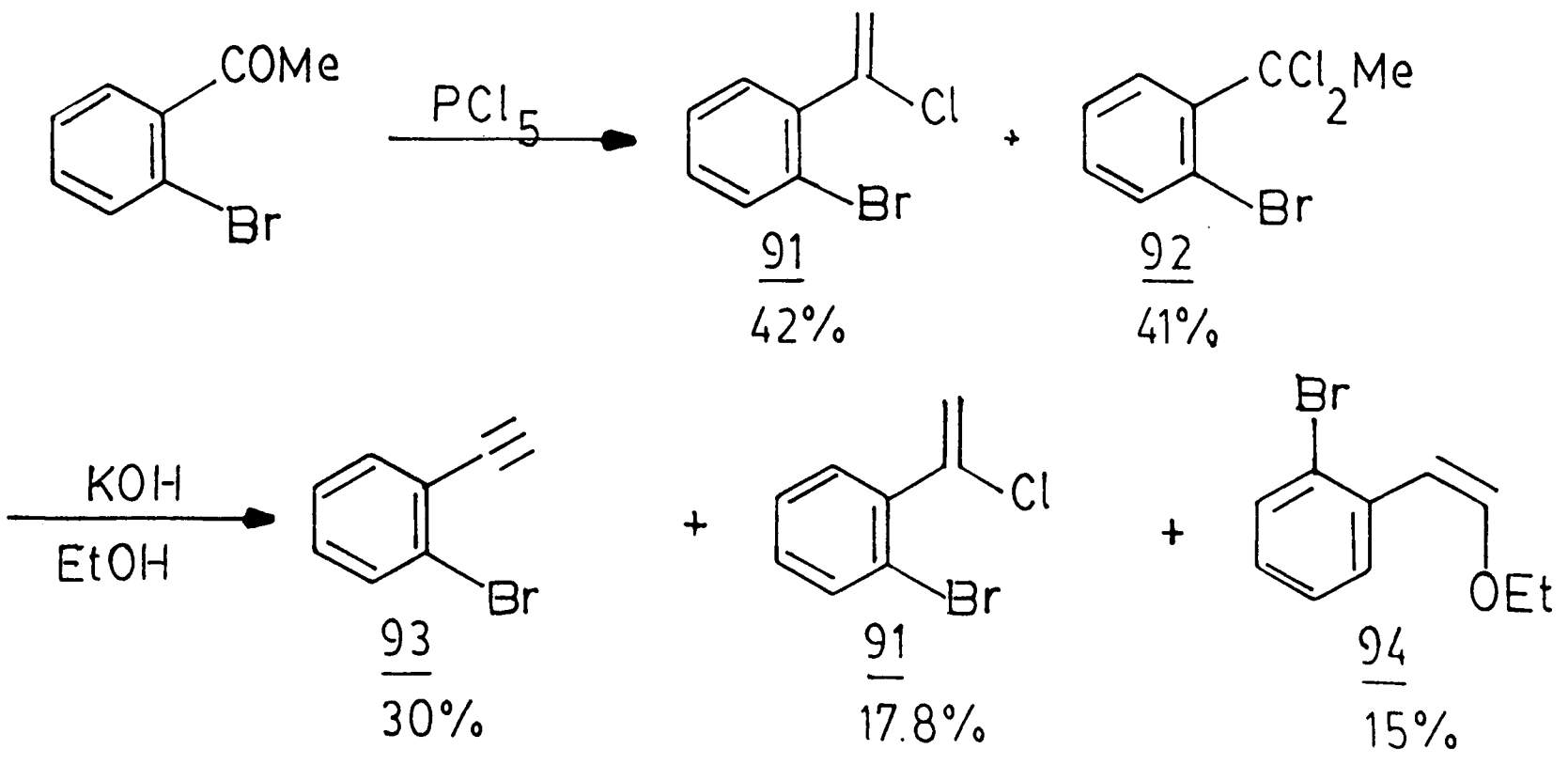


Such a methodology suggests that (89) might be thus converted to (90).

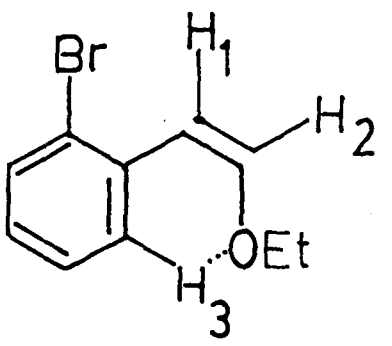


Although (89) might be obtained from the hard won diester (81) by reduction to the diol and chromic acid oxidation, other syntheses were examined. The first examined was from 2-bromo-1-ethynylbenzene, noted twice in the literature,[87] although no preparative details are given.

Treatment of 2-bromoacetophenone[88] with phosphorous pentachloride gave (91) and (92) in roughly 1:1 ratio. Subsequent dehalogenation with alcoholic potash yielded 2-bromo-1-ethynylbenzene (93), (91) and Z-(2-bromophenyl)ethoxyethene (94). The last apparently arose from the addition of ethanol to (93), a well-known side reaction.[89]

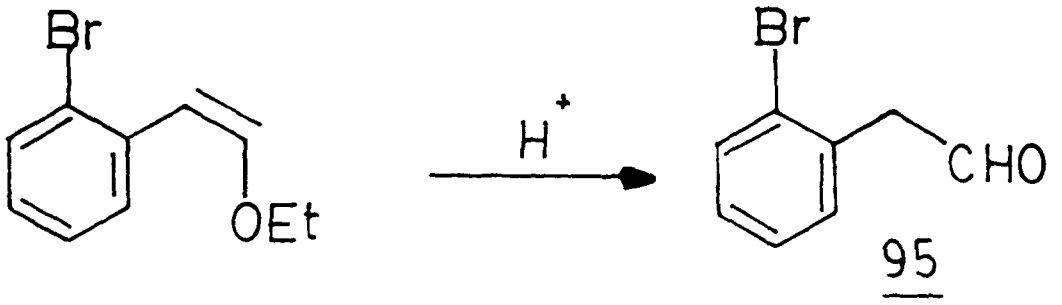


Longer reaction time led to both (91) and (93) being consumed, and after 15 h refluxing, only (94) could be isolated (55%). The cis-stereochemistry of (94) was established from its ^{1}H NMR spectrum, δ 5.55(1H, d, J 7.3Hz) and δ 6.20(1H, d, J 7.3Hz) for H_1 and H_2, while H_3, being intramolecular hydrogen bonded to the ethoxy group, resonates as a low field doublet at δ 8.05 (dd, J 6.8Hz + 1.5Hz).



94

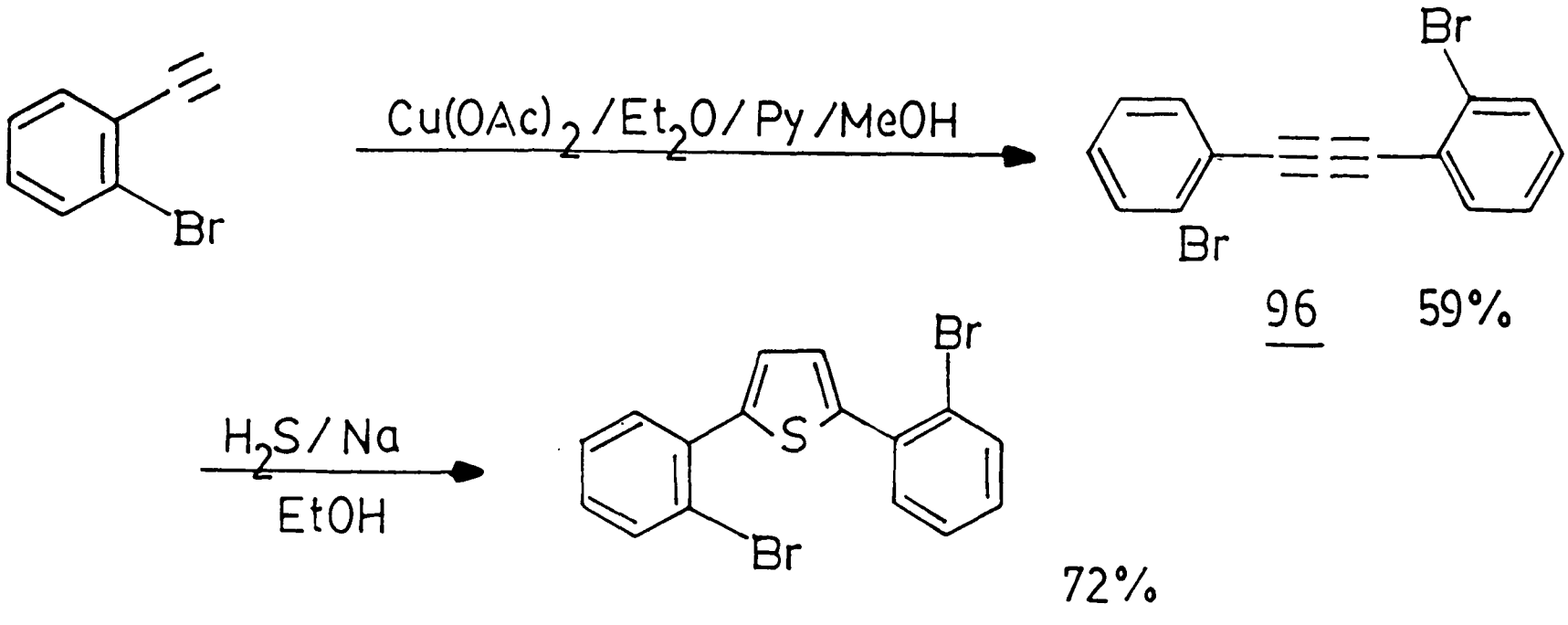
On acid hydrolysis it gave 2-bromophenylacetaldehyde (95).



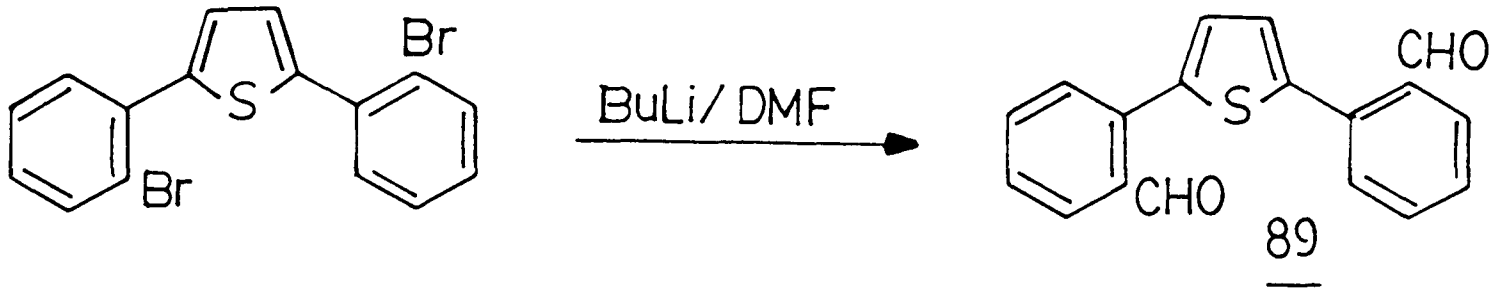
95

It is interesting that while in 2-nitrophenylacetaldehyde the benzylic protons show no coupling to the aldehyde proton,[90] suggesting that they are about 90° to each other, a small coupling (J 1.3) is observed in 2-bromophenylacetaldehyde (95).

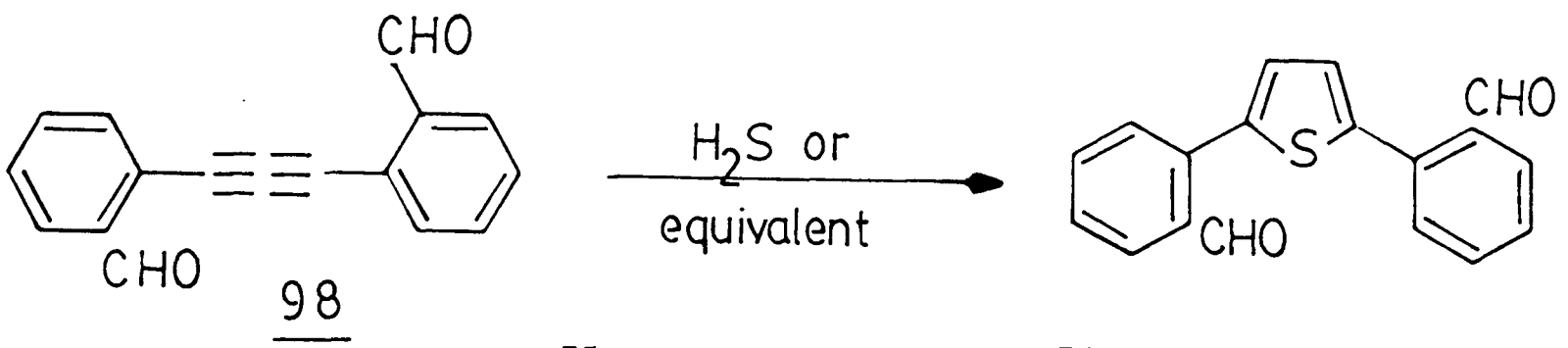
Oxidative coupling of 2-bromo-1-ethynylbenzene using Eglington[73] or Hünig's[75] procedure gave 1,4-bis(2-bromophenyl)butadiyne (96) which on treatment with hydrogen sulphide and ethanolic sodium ethoxide gave the desired 2,5-bis(2-bromophenyl)thiophene (97).



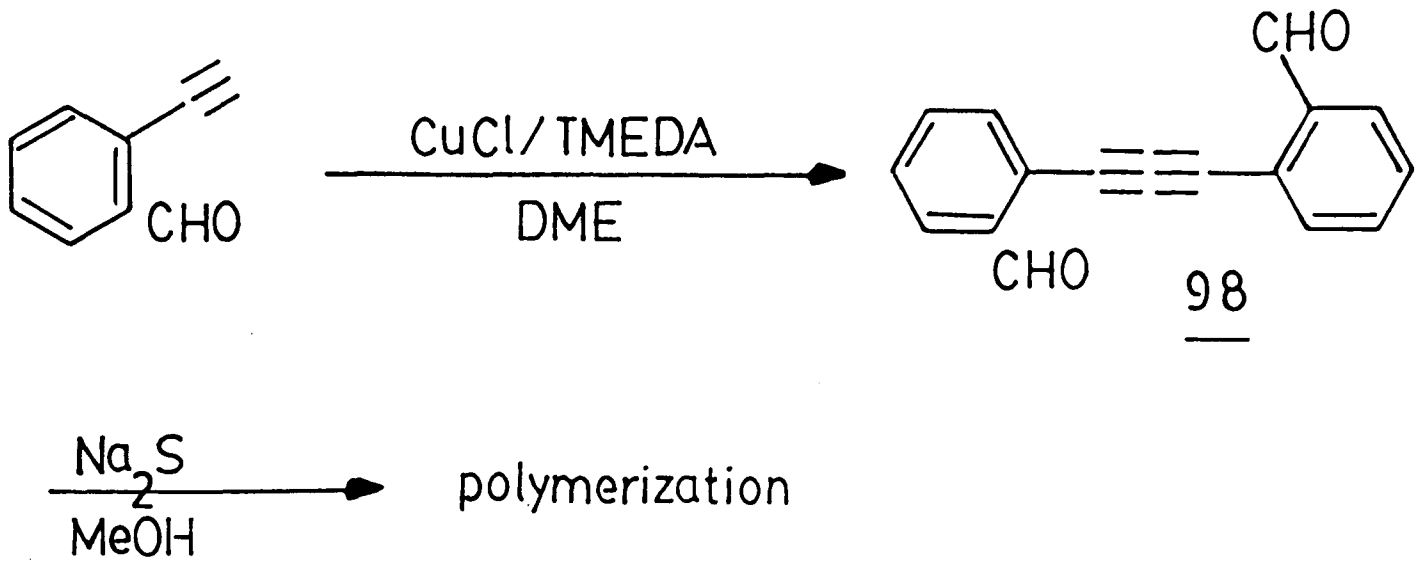
Although (97) failed to give 2,5-bis(2-formylphenyl)thiophene (89) on successive reaction with magnesium and methyl orthoformate,[91] butyl lithium and DMF successfully converted (97) smoothly to (89) in 44%.



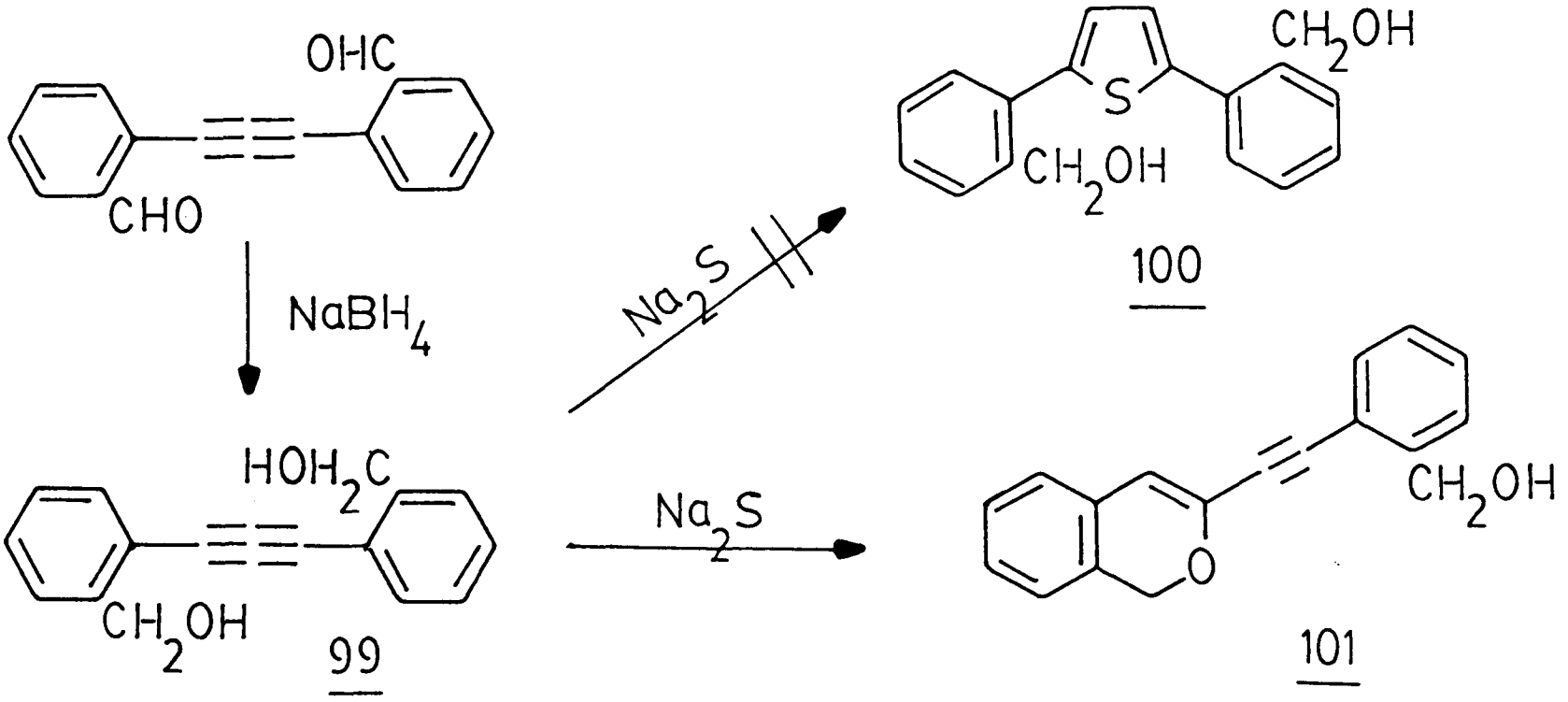
Attempts were also made to synthesize 1,4-bis(2-formylphenyl) butadiyne (98), hoping that hydrogen sulphide would give (89).



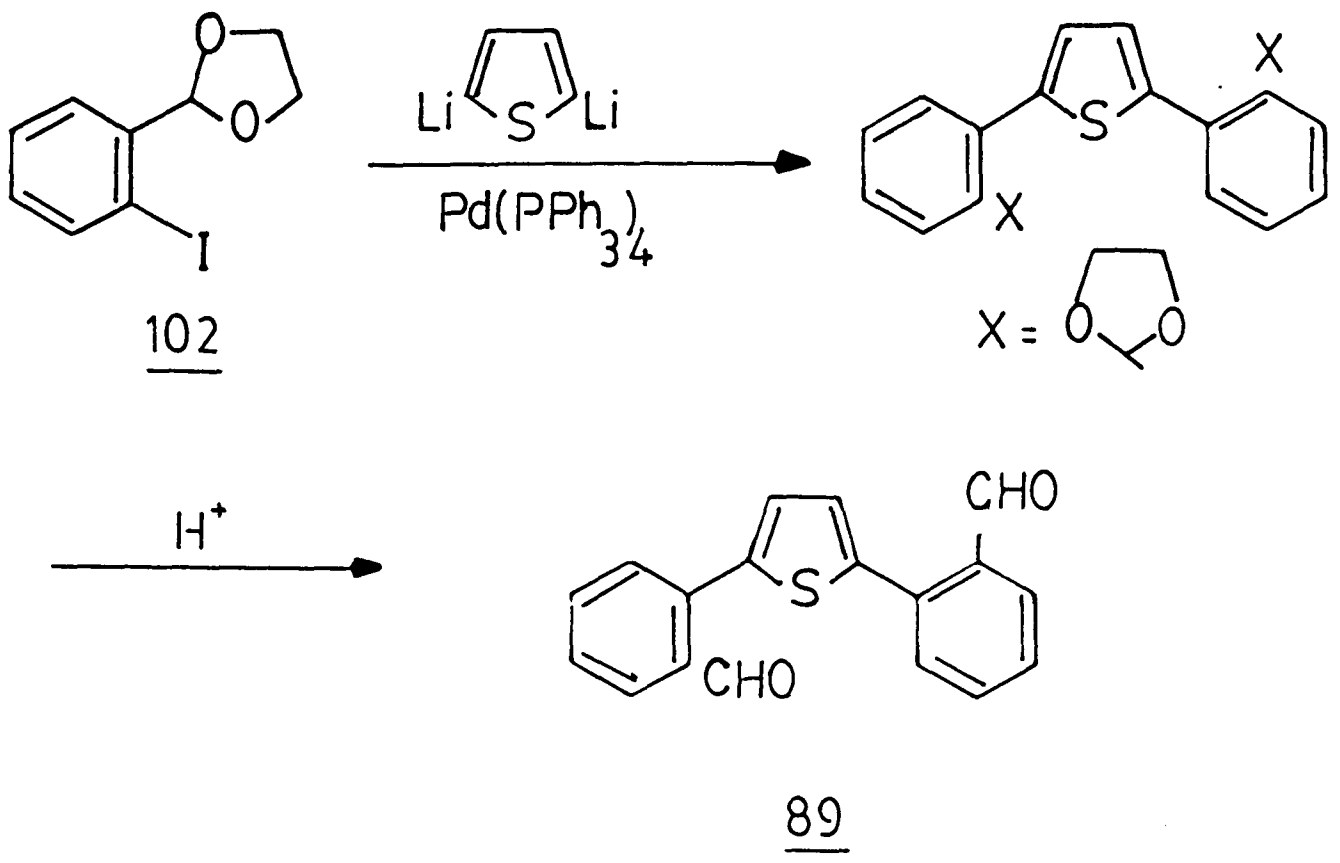
Using Hünig's procedure,[75] 2-ethynylbenzaldehyde[76] was converted to 1,4-bis(2-formylphenyl)butadiyne (98) in 13% yield. Unfortunately, sodium sulphide in refluxing methanol[22] led to extensive polymerization.



Reduction using sodium borohydride smoothly converted (98) to the expected diol (99) in 50% yield. However, sodium sulphide in refluxing methanol did not convert (99) into the desired thiophene (100), but into (101), identified from its spectra and analytical data.



Finally a palladium mediated coupling reaction between 2,5-dilithiothiophene and 2-(2-iodophenyl)-1,3-dioxolan (102) was investigated,[92] hoping that (89) could be formed directly.

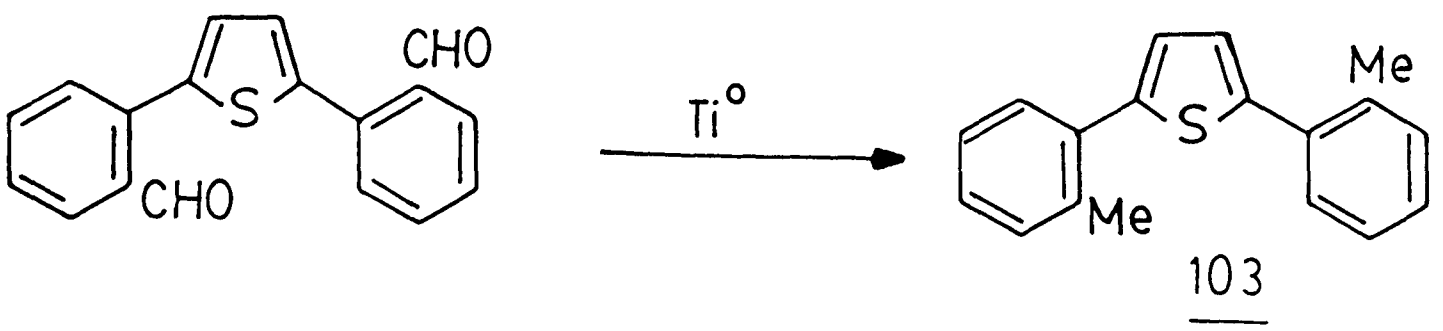


102

89

Unfortunately, reacting (102) with 2,5-dilithiothiophene, generated from 2,5-dibromothiophene with 4 equivalents of tert-butyl lithium, in the presence of $Pd(PPh_3)_4$ at RT for 2 days led to quantitative recovery of (102). Possibly hydrogen exchange between 2,5-dilithiophene and (102) took place.

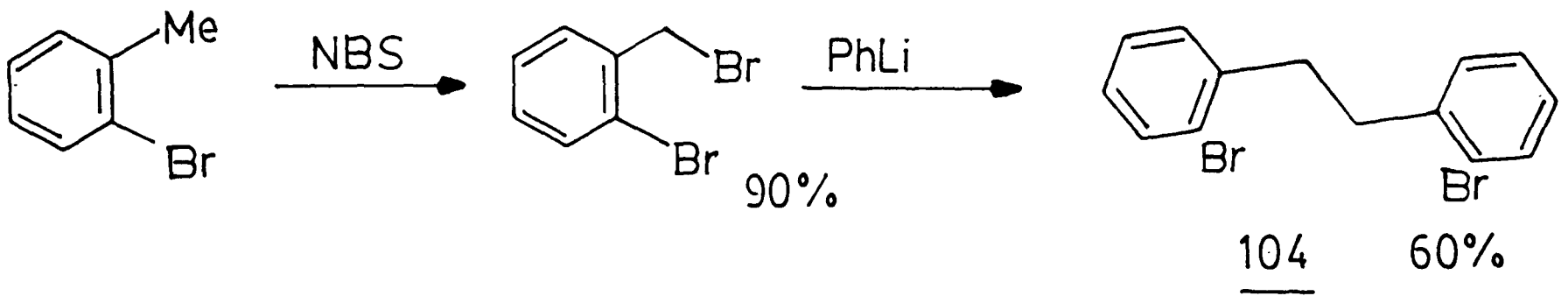
Titanium induced intramolecular coupling of the dialdehyde (89) was carried out under the conditions reported by McMurry et al[86] and yielded pale yellow prisms of (103). ^1H NMR spectrum showed no sign of the expected olefinic protons and instead, apart from a thiophene singlet and aromatic protons, a singlet at δ 2.50 was observed and integration showed a ratio of 5:3. M.S. gave m/e 264 as M^+. Apparently reduction of the aldehyde functions took precedence over intramolecular coupling to (90).

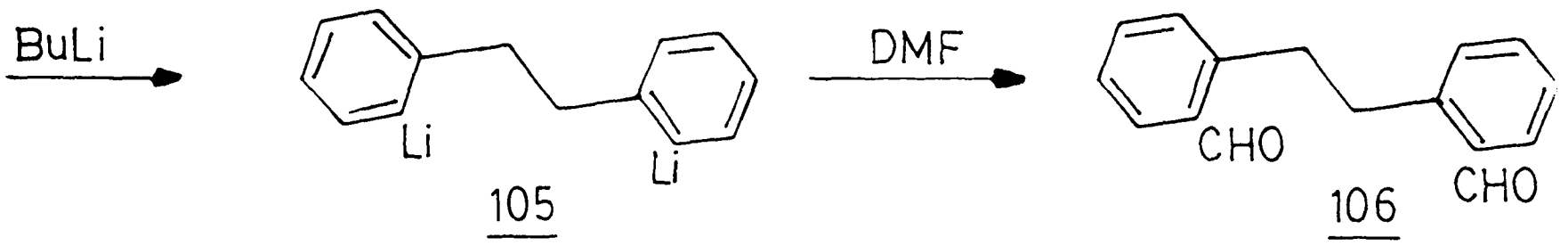


103

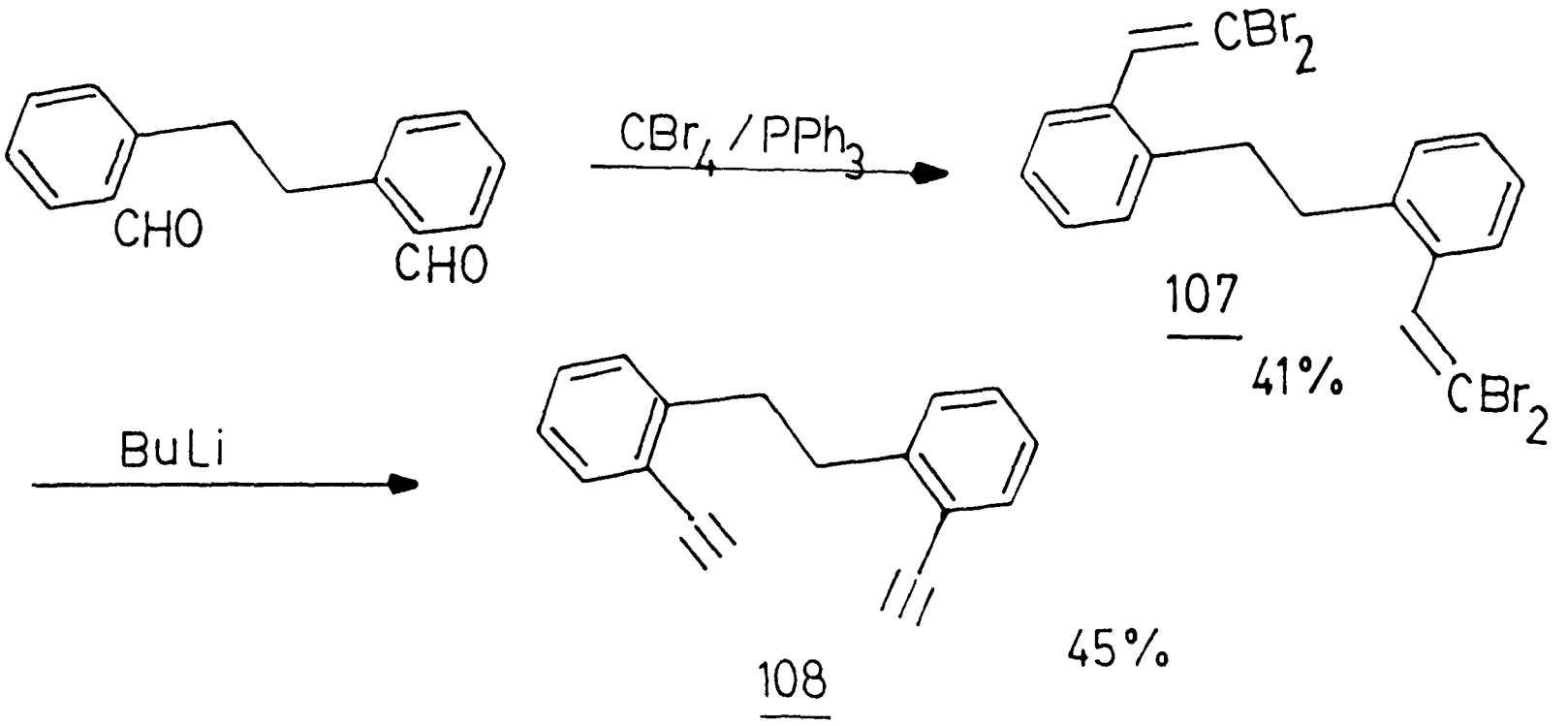
In view of the difficulties encountered in cyclising the thiophene derivatives, it was now decided to aim for (108), effect the cyclization of the big ring through oxidative coupling, and put the thiophene ring in last.

Starting from 2-bromotoluene and using two known transformations[93] we prepared 2,2'-dibromobibenzyl (104). Subsequent formylation of 2,2'-dilithiobibenzyl (105), prepared by a metal halogen interchange, with DMF gave the expected dialdehyde (106).

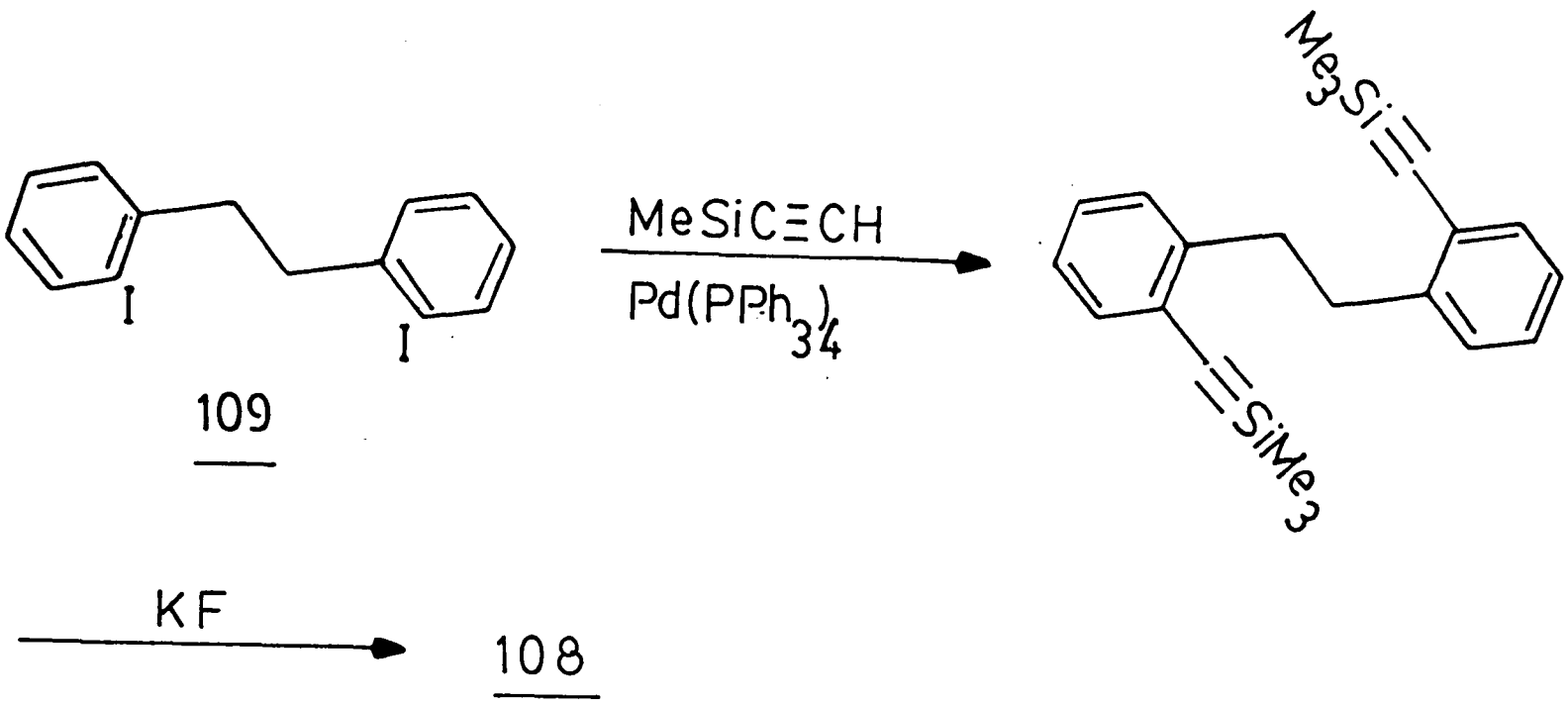




Conversion of (106) to the dibromoolefin (107) was readily achieved by treatment with carbon tetrabromide and triphenylphosphine[120] and subsequent dehalogenation with butyl lithium gave the desired diacetylene (108).



An alternative simple approach to (108) could be based on the coupling reaction between 2,2'-diiodobibenzyl (109) and ethynyl-trimethylsilane and subsequent desilylation.



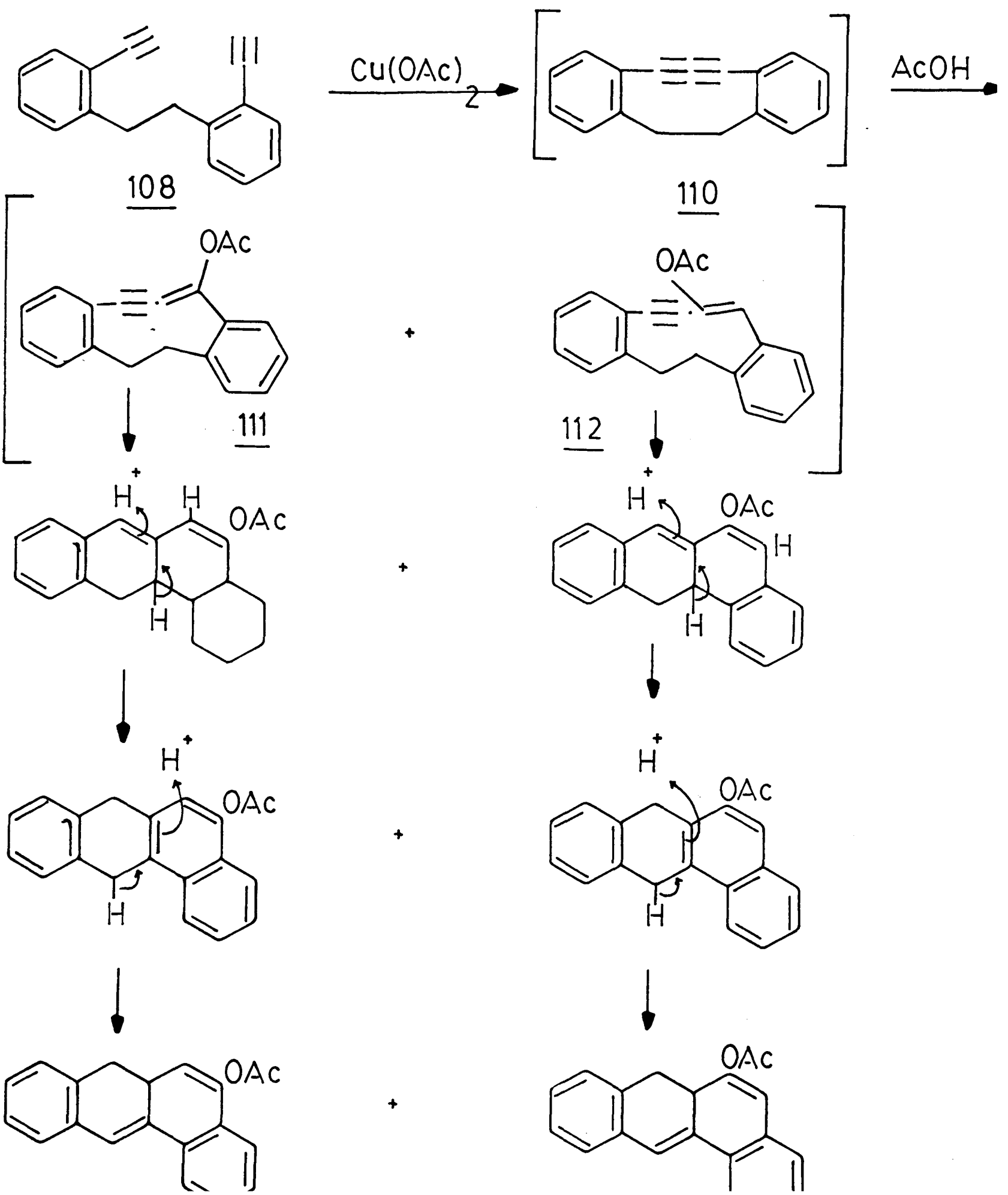
109

108

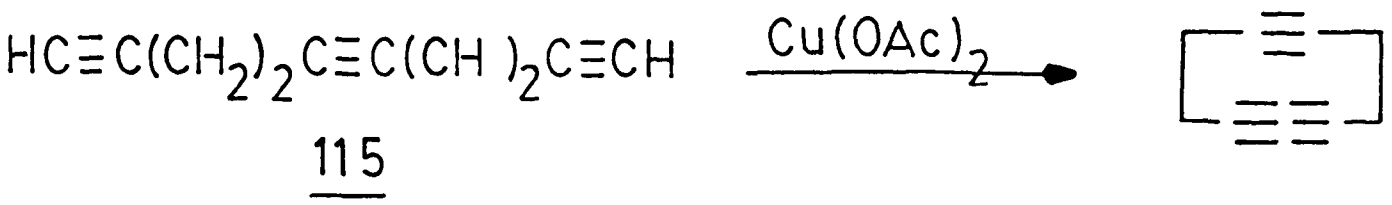
Unfortunately the reported synthesis of (109)[94] could not be reproduced. Attempts to induce coupling between 2-iodobenzyl lithium bromide under conditions reported for 2-bromobenzyl lithium bromide[93] failed and addition of iron(III)chloride as catalyst[95] gave no improvement. In all cases 2-iodobenzyl bromide and 2-iodotoluene were obtained.

Intramolecular oxidative coupling of (108) under high dilution condition, as described by Sondheimer et al[96] gave a pale yellow oil. ^{1}H NMR spectrum showed δ 2.10 (3H,s), 2.20 (1H,b), 3.25 (2H,m), 5.70 (1H,m) and 7.15 (9H,m); IR 1760 cm^{-1} and MS m/e 288 for M^+. The singlet at δ 2.10, the ester carbonyl absorption at 1760 cm^{-1} and molecular weight suggested that an acetoxy group had been added. Presumably the cyclic dimer (110) was an unstable intermediate,

which immediately undergoes addition of the elements of acetic acid, from the coupling reagent. The resulting mixture of enol acetates (111) and (112) undergo further ring closure and prototropic shift to give the tetracyclic product (113) and (114).



Such an addition of acetic acid across a highly-strained diacetylene was observed by Sondheimer et al,[97] whereby they isolated a mixture of enol acetates (116) and (117) from the intramolecular oxidative coupling of 1,5,9-decatriyne (115) using copper acetate under high dilution condition.



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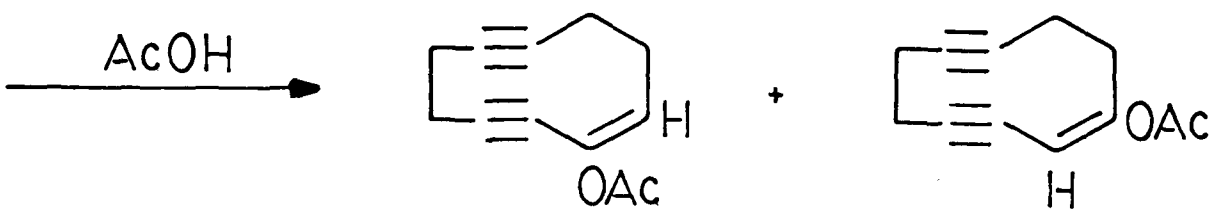
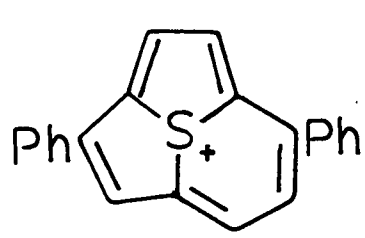
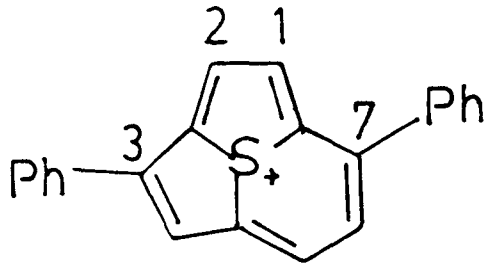


116 117

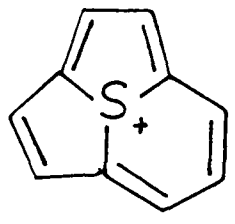
Part B



In the initial stage of the attempted synthesis of (16), the preparation of (118) was also investigated. It was expected to resemble (3) more closely in properties than (16), but the two phenyl groups were retained to stabilize the positive charge developed on the central sulphur atom.

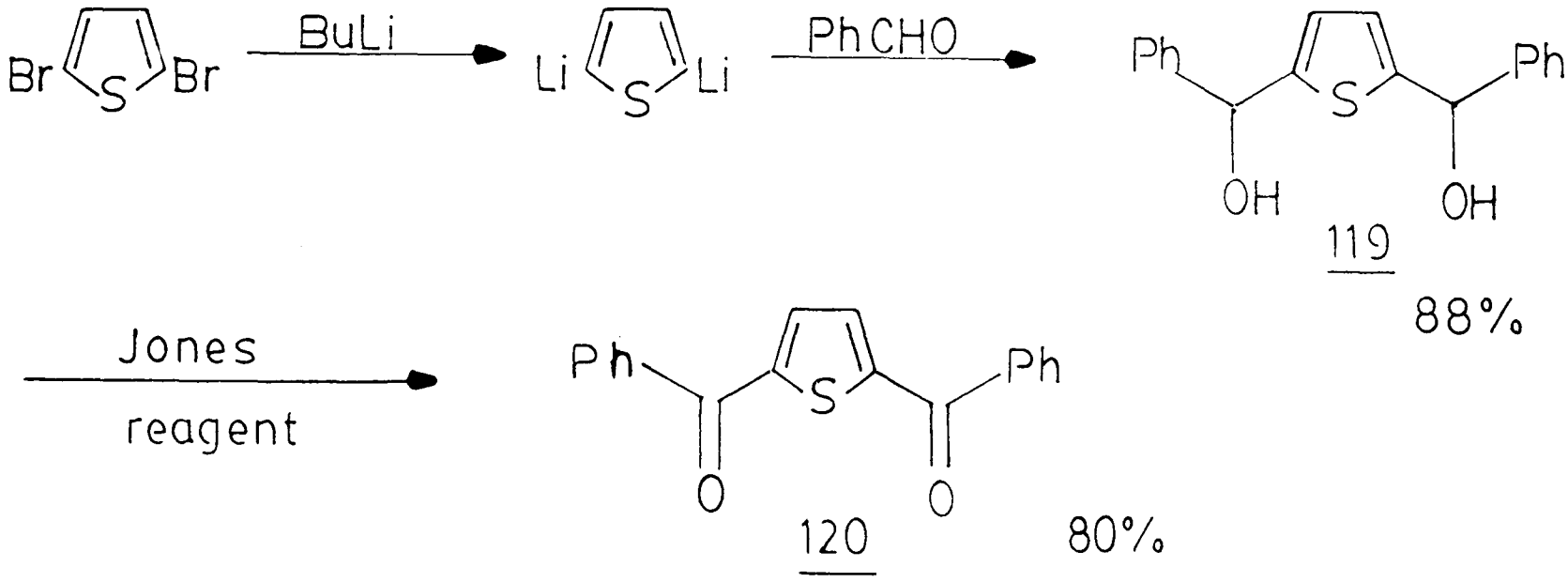


118



3

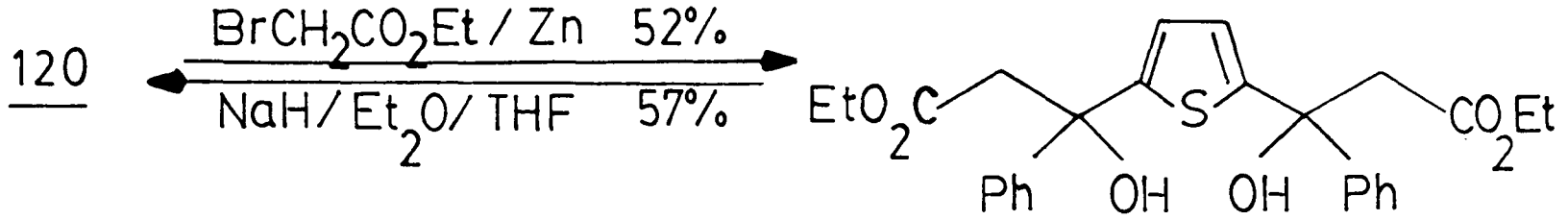
Metallation of 2,5-dibromothiophene with n-butyl lithium at -78°C and reaction with benzaldehyde gave 2,5-bis(α-hydroxybenzyl)thiophene (119), which was oxidized to the ketone (120).



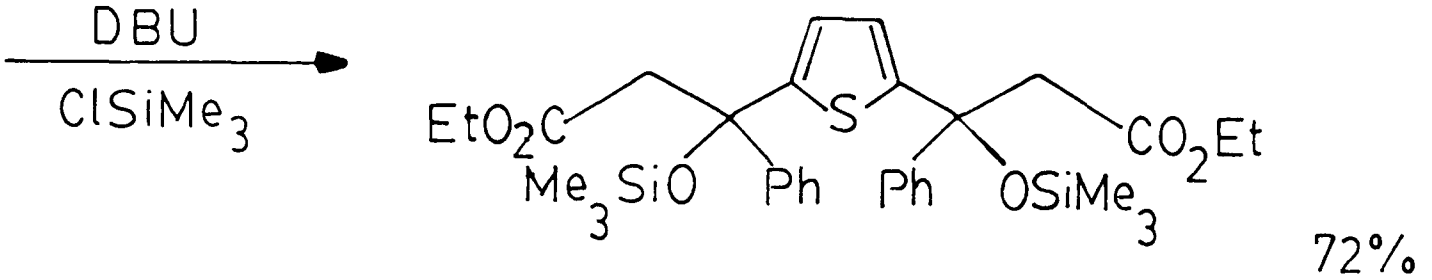
On the other hand, Friedel-Crafts acylation of benzene using 2,5-thiophenecarboxylic acid and phosphorous pentoxide gave only 10% yield of (120).

The Reformatsky reaction with ethyl bromoacetate converted (120) smoothly to diethyl 2,5-thiophene-bis-3-(3-hydroxy-3-phenylpropionate)

(121). Reproducible results were obtained only when freshly purified ethyl bromoacetate and activated zinc were used. Before the proposed acyloin condensation, the two hydroxy groups needed to be protected. Sodium hydride and iodomethane in ether at room temperature for 2 days did not react probably due to the poor solubility of (121), and addition of THF as a co-solvent caused an unexpected decomposition of (121) to 2,5-dibenzoylthiophene (120).



121

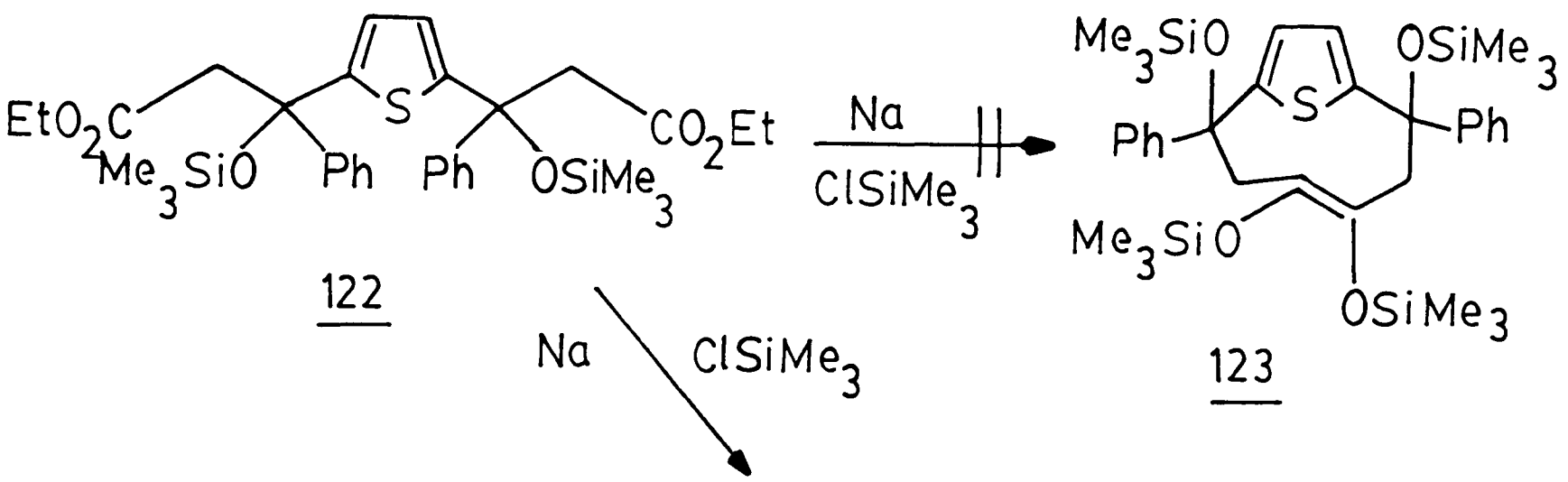


122

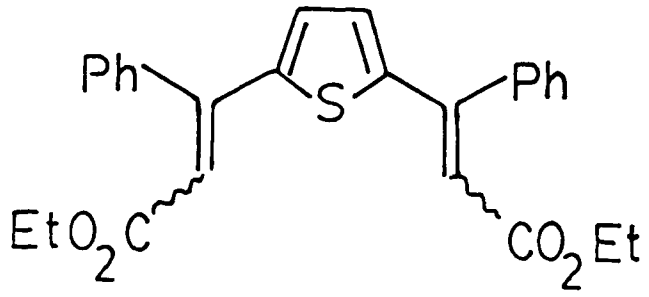
Although dimethyl sulphate/potassium carbonate in refluxing acetone and chlorotrimethylsilane and pyridine in CH_2Cl_2 at RT for 24 h gave no reaction, replacing the pyridine by DBU in the last reaction gave (122). Although high vacuum distillation of (122) caused decomposition (combustion analysis data suggested the loss of Me_3SiOH after distillation) its purity and structure were firmly established from its spectra.

The acyloin reaction on (122) was carried out under the usual conditions[79] with chlorotrimethylsilane. After 5 h refluxing, TLC

showed no (122) remaining. The ^{1}H NMR of the crude reaction product showed no silyl proton resonances, four new singlets at δ 6.10, 6.20, 6.30 and 6.60, tentatively assigned as olefinic proton resonances. As for (81), ring closure of (122) to form (123) did not occur and elimination of trimethylsilanol to (124) occurred instead.

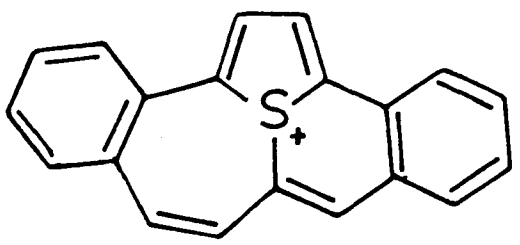


122 123

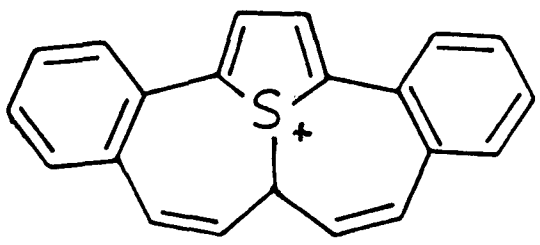


124

As it had now become clear that the closure of the larger ring in the thiophenophane system (70) could not easily be achieved, attention was now turned to the synthesis of larger rings (125) and (126) where the strain would be less.



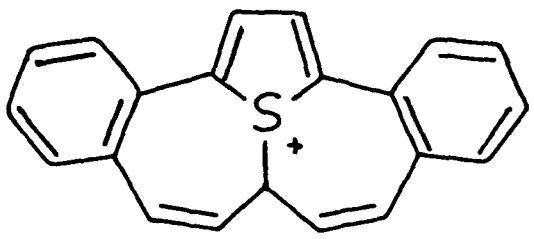
126



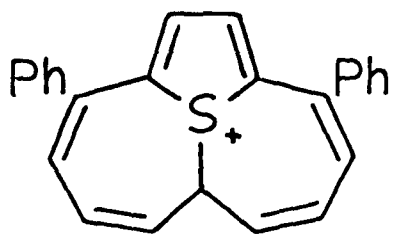
125

Chapter 4

Attempted synthesis of 8a<u>H</u>-14c-thioniadibenzo{<u>b</u>,<u>i</u>}cyclopenta{<u>k</u>l}-heptalene (125) and 3,10-diphenyl-6a<u>H</u>-10b-thioniacyclopenta{<u>ef</u>}heptalene (201)

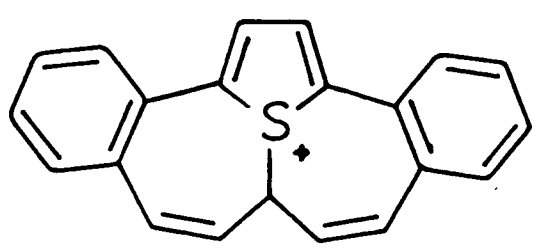


125



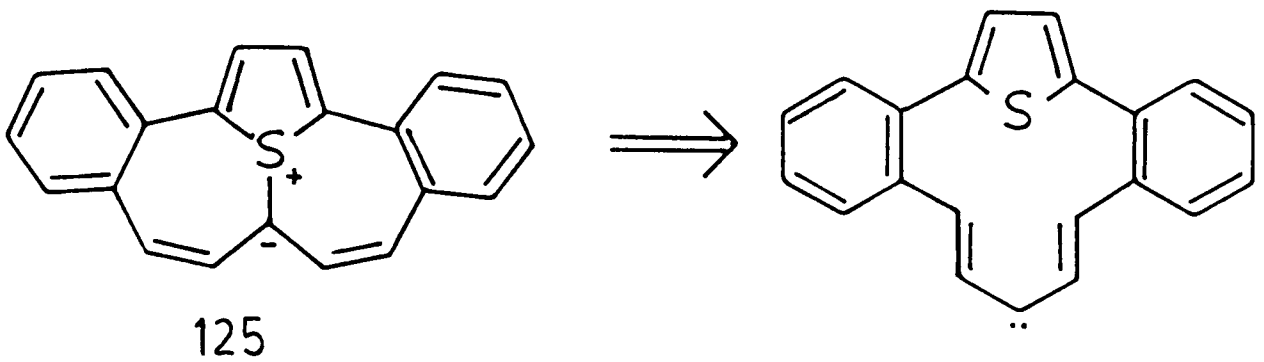
201

Part A



4.1 Synthetic considerations

Using a similar retrosynthesis as before, 1,2,8,9-dibenzo-3,6-dien-5-keto-{9}(2,5)thiophenophane (195) can be a precursor of (125).



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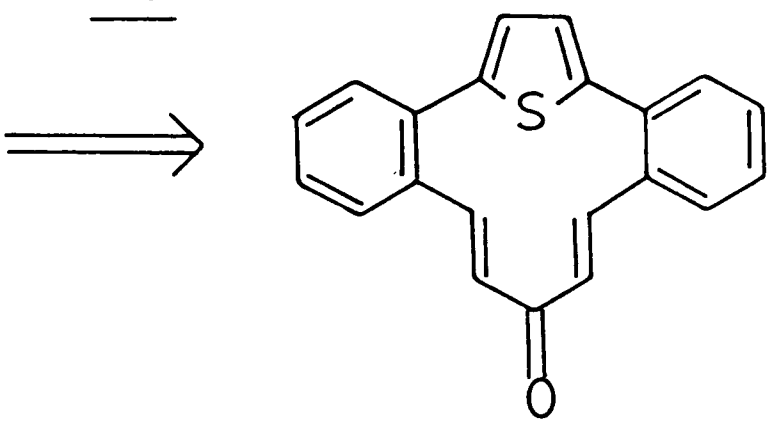


195

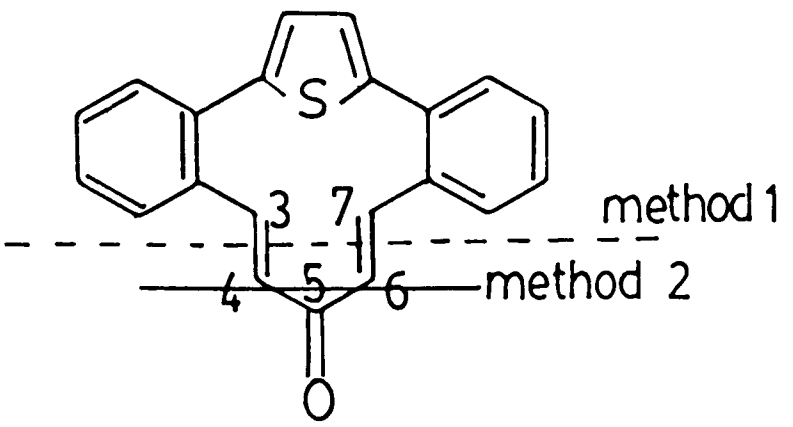
Since symmetrically substituted thiophenes are synthetically more accessible than non-symmetrical ones, the obvious approach would be to add the appropriate missing carbon fragments to the acyclic 2,5-symmetrically substituted thiophene precursors. Two possible disconnections are:

Method 1

Dissect along the double bond between C_3-C_4 and C_6-C_7 in (195) (dotted line) and the 3-C fragment (C_4, C_5 and C_6) was added.

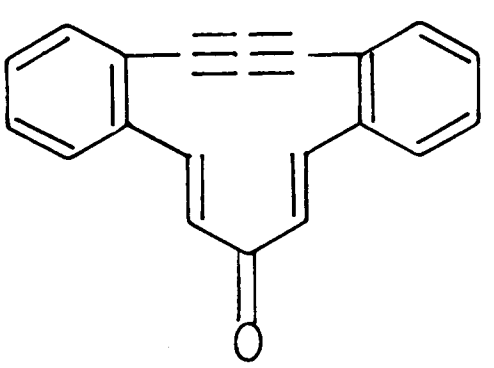
Method 2

Based on symmetry consideration, the alternative disconnection will be along C_4-C_5 and C_5-C_6, leaving C_5 as the missing fragment (solid line).



195

Alternatively, as 1,4-butadiyne can be a precursor of a thiophene ring, 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127) could be the immediate precursor for (195).



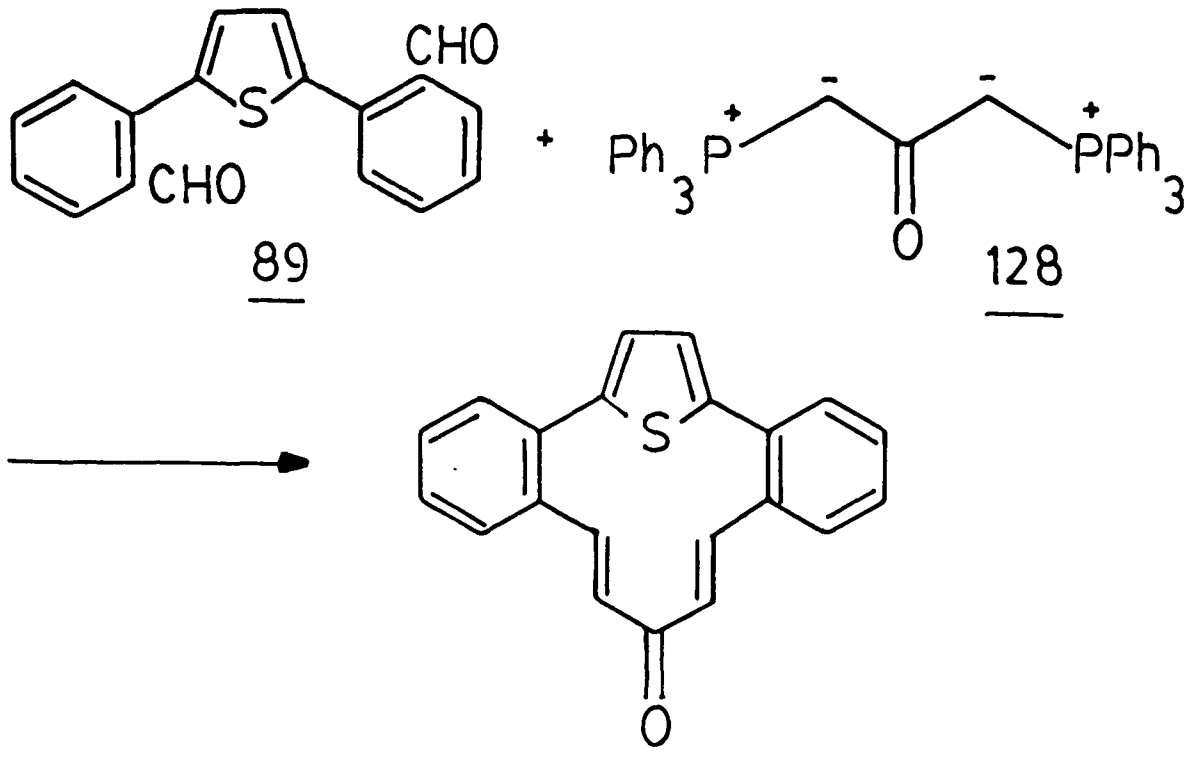
127

4.2 Results and discussions

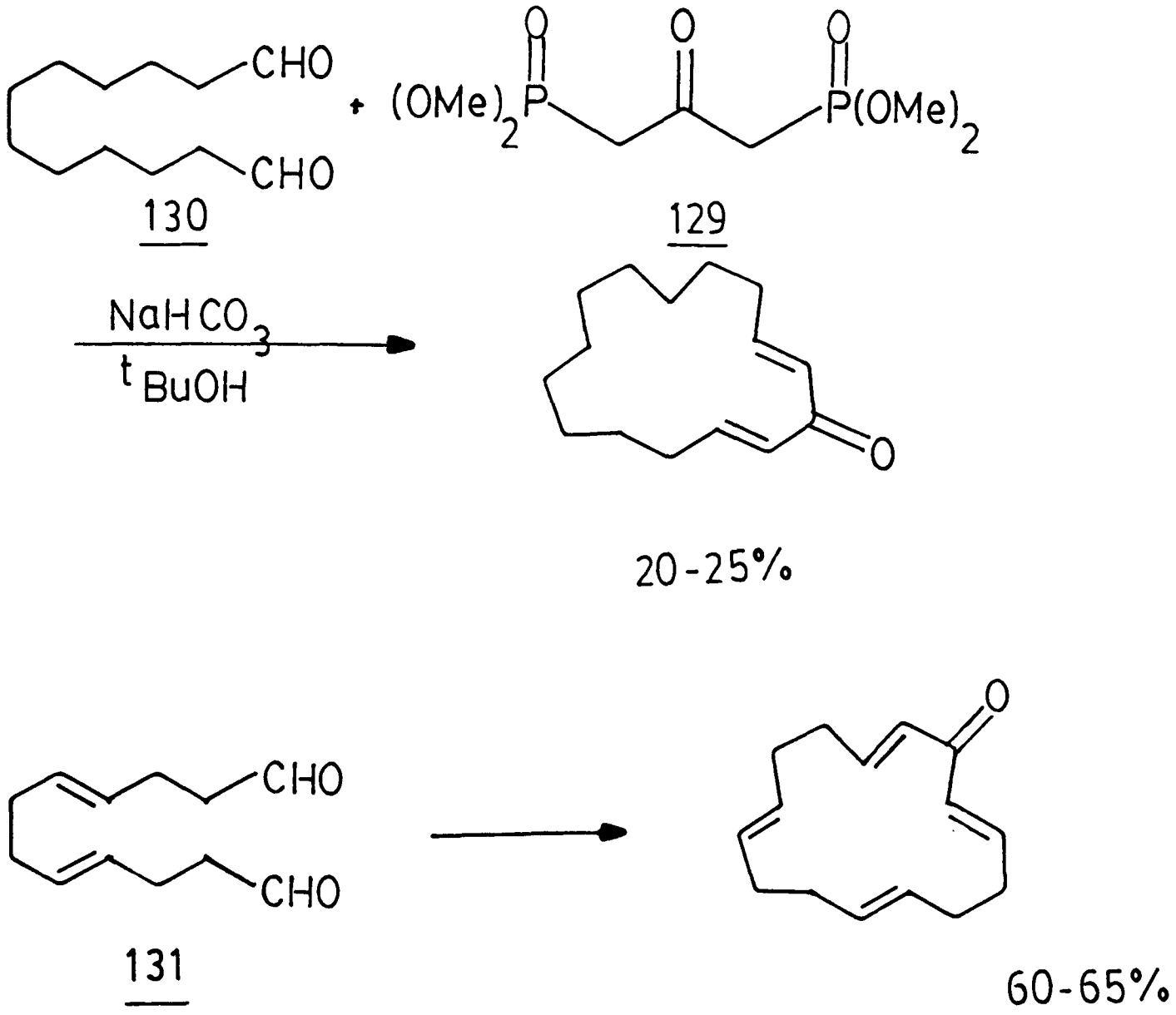
Method 1

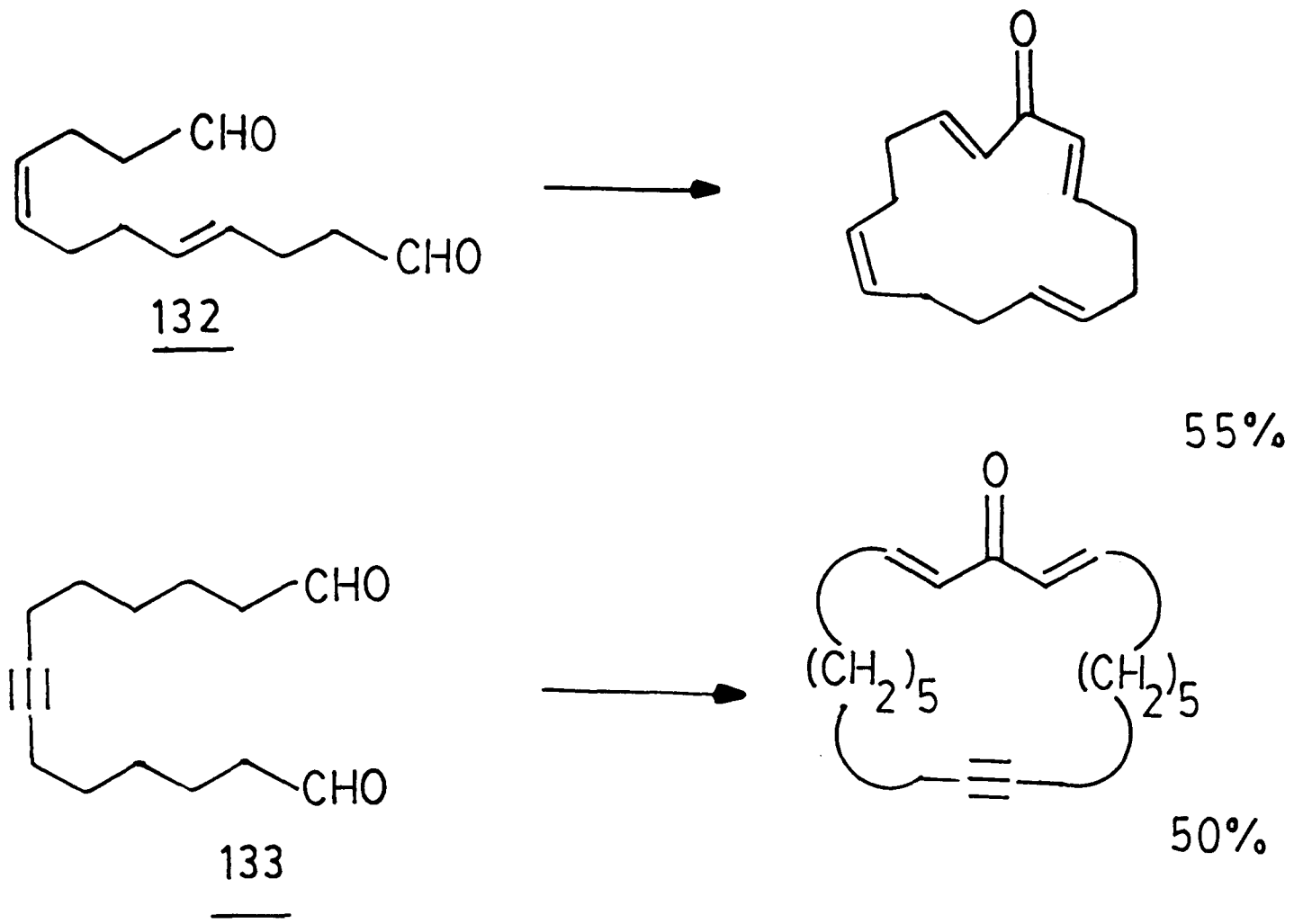
Introduction

The set of double bonds (between C_3-C_4 and C_6-C_7) in (195) suggests that they may be constructed by the Wittig reaction. Olefination of 2,5-bis(2-formylphenyl)thiophene (89) with acetone-1,3-bis-phosphorane (128), which react with carbonyl compounds,[98] should give (195).



Using the Horner-Emmons modification of the Wittig reaction, Büchi et al[99] successfully prepared fifteen and seventeen member macrocyclic ketones from the corresponding twelve and fourteen aliphatic α,ω-dialdehyde viz.,





According to the rigid group principle,[85,100] the less flexible dialdehydes {(131)-(133)} were expected to undergo cycloolefination more efficiently than the corresponding saturated analogue (130). This was indeed found to be the case, as shown by the increase in yield as the unsaturation increases.

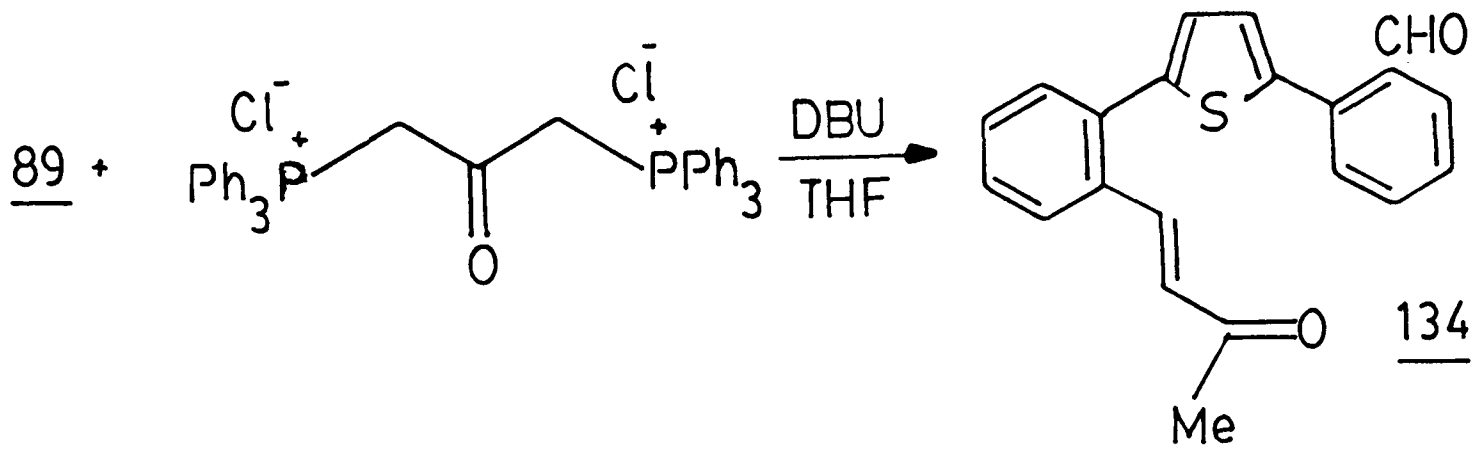
The rigid dialdehyde (89) should therefore undergo cycloolefination readily.

Results

Although no macrocyclic dienone has been prepared from the bisphosphorane (128), its ready availability made it an attractive alternative to the less available phosphonate analogue (129).

When the dialdehyde (89) in DMSO was stirred with the bisphosphorane (128), prepared[101] from acetone-1,3-bis(triphenylphosphonium)

chloride[98a] and DBU, no reaction occurred. However, by refluxing in THF for 20 h, the mono-olefin (134) was formed in 24%, together with 36% recovery of the starting dialdehyde.

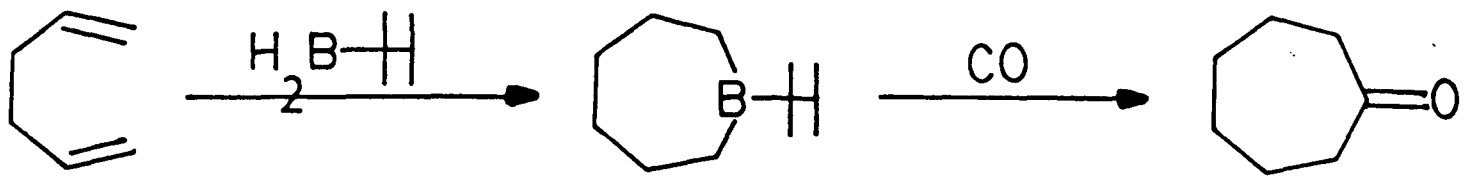


Unfortunately, prolonged reaction time (30 h) and higher temperature (Ca. 90°C) led to no improvement and no sign of the expected dienone (126) was detected.

Method 2

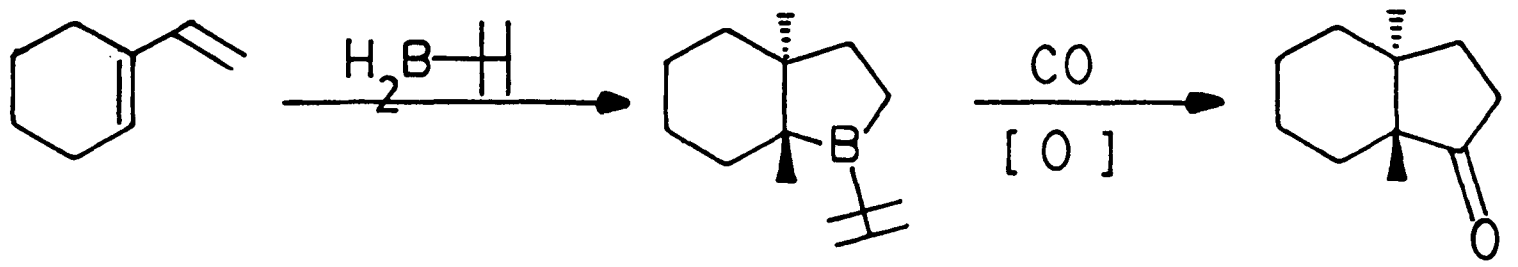
Introduction

In 1967 Brown et al[102] reported a general procedure for preparing cyclic ketones via carbonylation of thexylborane derivatives. Such derivatives are readily prepared from thexylborane and dienes viz.,

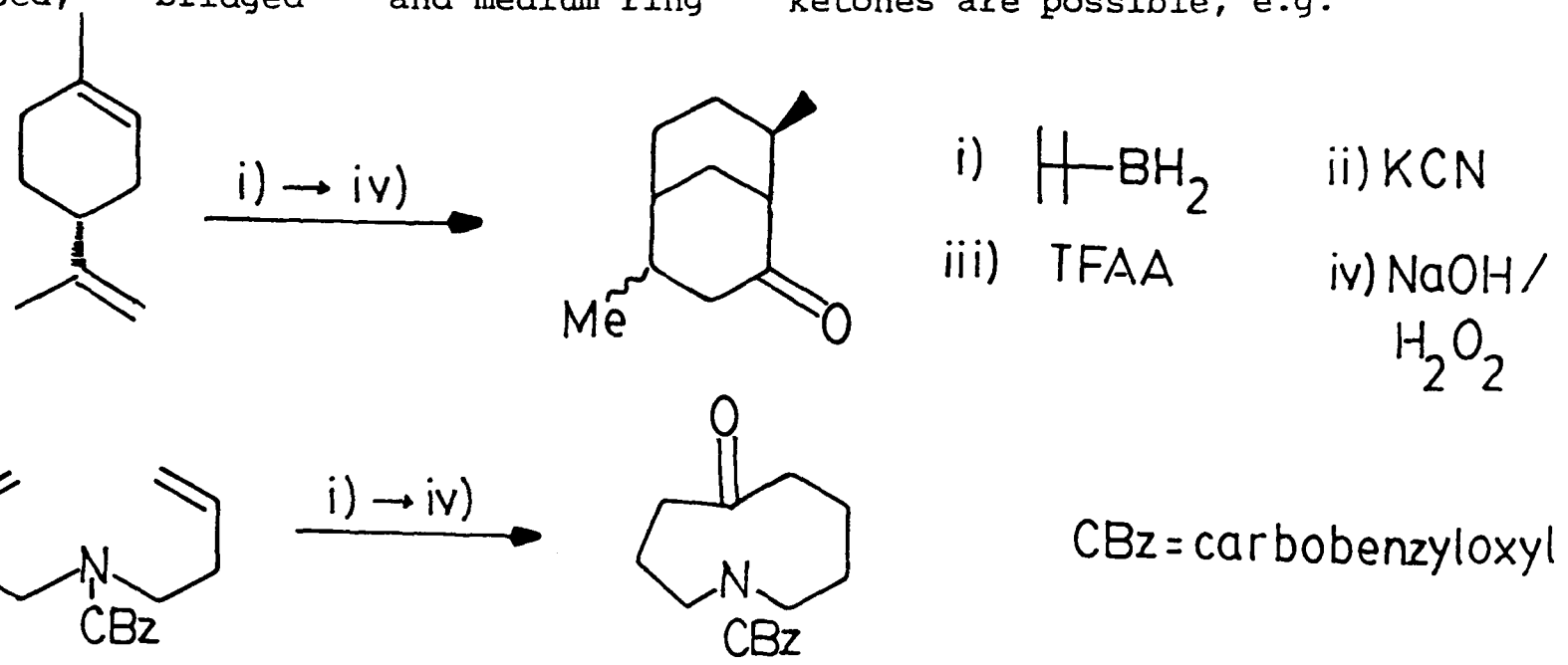


65%

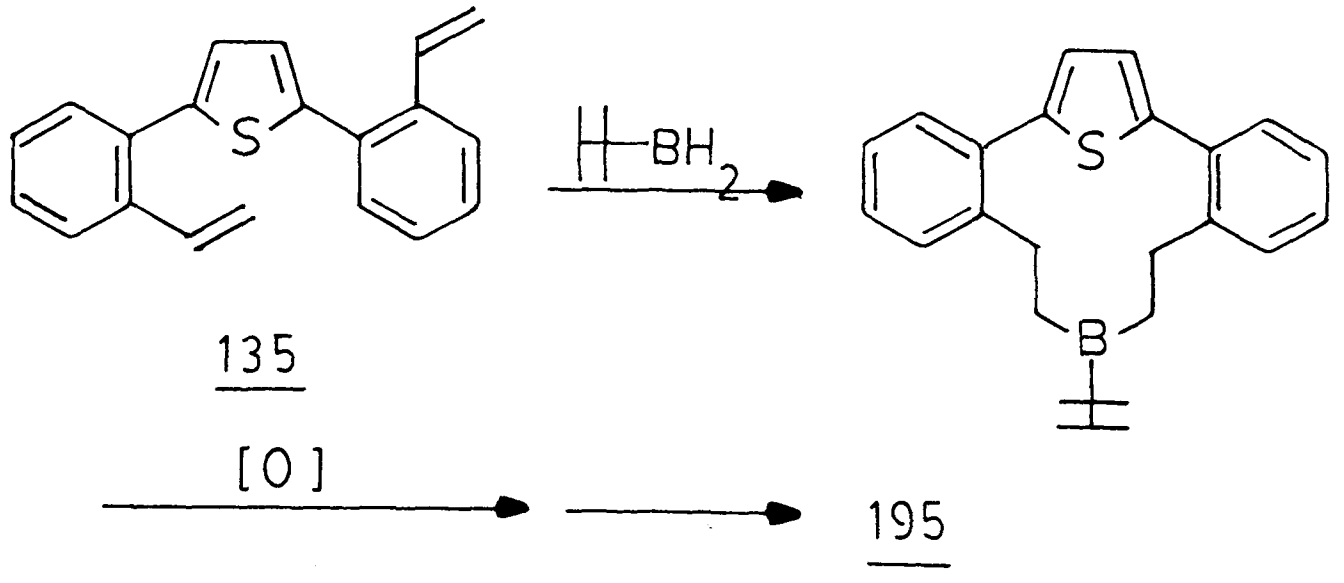
Such reactions are especially useful for annelation,[103] e.g.



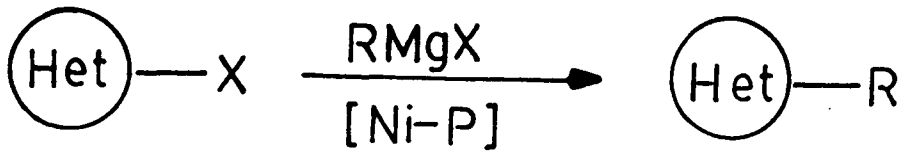
Later Pelter et al[104] developed the cyanoborate process, which employs the isoelectronic cyanide ion for carbon monoxide. Annelation to fused,[105] bridged[106] and medium ring[107] ketones are possible, e.g.



Thus, if the cyanoborate is used to introduce C-5 in (195), 2,5-bis(2-ethenylphenyl)thiophene (135) will be required.

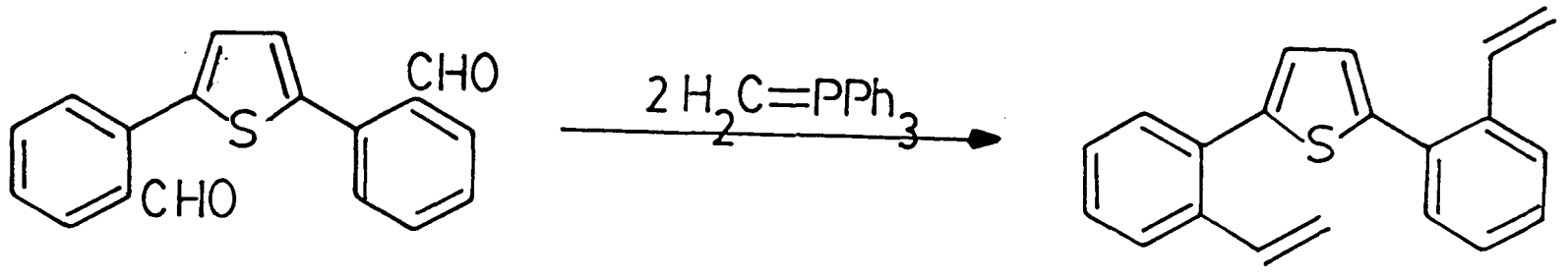


Certain nickel-phosphine complexes,[108] e.g. dichloro{1,3-bis-(diphenylphosphino)propane}nickel(II) {$Ni(dppp)_2Cl_2$} exhibit extremely high catalytic activity for the selective cross-coupling of Grignard reagents with aryl, alkenyl and heterocyclic halides.[109,78]



Thus it seemed possible to prepare (135) in one step when the appropriate Grignard reagent and halothiophenes were used.

Finally a double Wittig reaction on 2,5-bis(2-formylphenyl)-thiophene (89) using triphenylphosphonium methylide might lead to an alternative synthesis of (135).



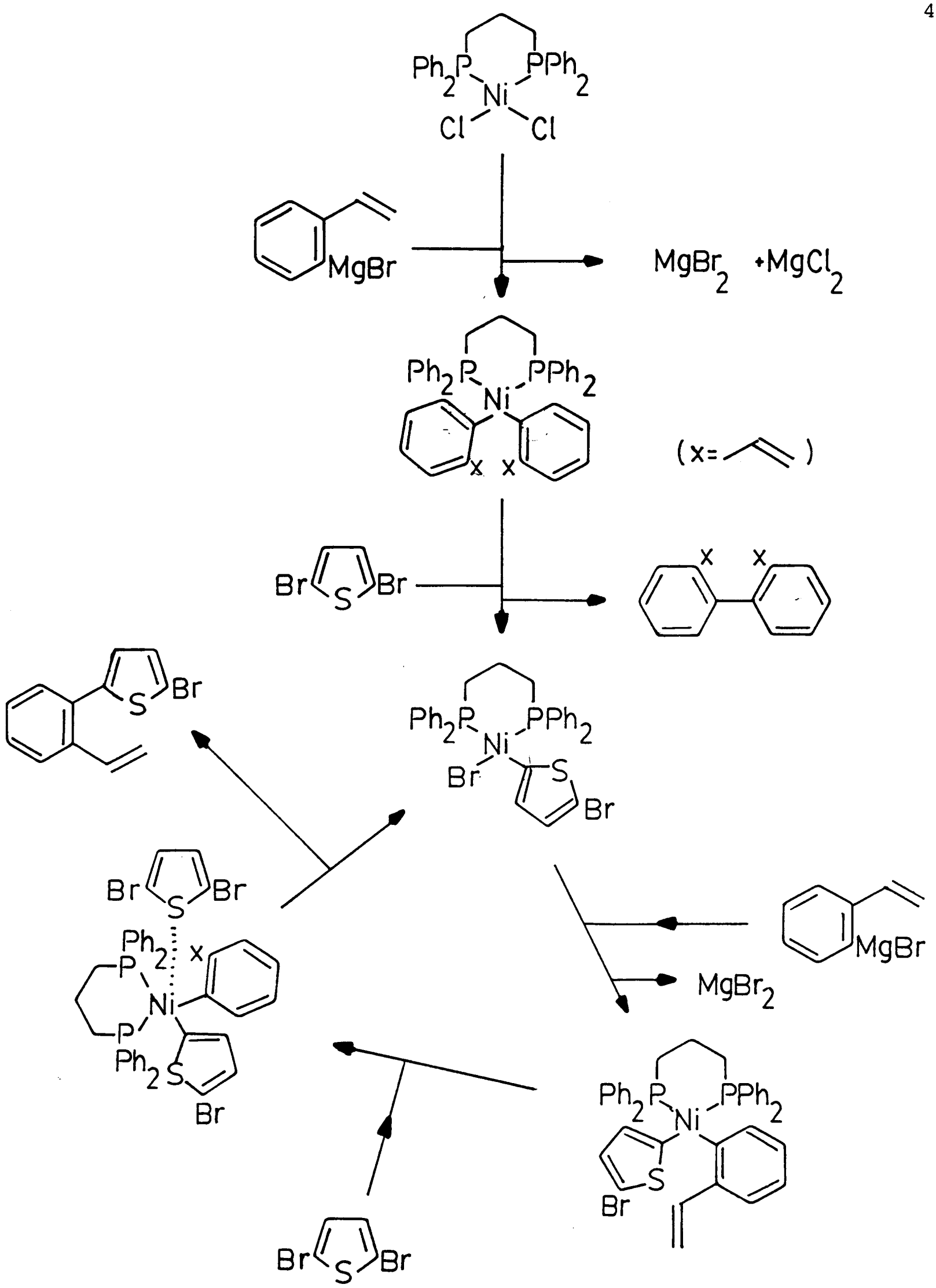
89 135

Results

When 2-styrylphenylmagnesium bromide was allowed to react with 2,5-dibromothiophene and Ni{(dppp)Cl_2} in THF under the conditions reported[108a,108d,78] for 12 h, a complex mixture of products resulted. TLC{SiO_2;Et_2O-PE(1:9)} examination revealed 3 major and 2 minor constituents (Rf=0.63, 0.50, 0.38, 0.58 and 0.30, which were coloured purple, green, yellow, blue and yellow respectively). Careful chromatography (SiO_2, 3%Et_2O-PE), followed by preparative TLC (SiO_2, 10%Et_2O-PE) allowed separation of the three major components, the structure of which were deduced from their ^1H NMR and MS spectra and combustion analysis. The first spot (Rf 0.63) was the desired 2,5-bis(2-ethenylphenyl)thiophene (9.3%), confirmed by comparing with

an authentic sample prepared by an alternative route. The second spot (Rf 0.50) was 2,2'-styrylbiphenyl (8.7%) resulting from the self-coupling of 2-styrylphenylmagnesium bromide. The remaining spot (Rf 0.38) was probably bis-2,2'-(5,5'-O-styrylphenyl)thiophene, which could arise from the self-coupling of the mono cross-coupled product (see scheme 2). A considerable amount of polar material was also obtained, which was presumably poly-coupled material and which was not investigated further. Variation of the reaction time (4-12 h) and solvent (ether) led to no improvement. Although Kumada's[78] preparation of 2,5-diphenylthiophene (from phenylmagnesium bromide, 2,5-dibromothiophene and Ni(dppp)Cl_2) was reproduced by us, under the same condition 2-methyl and 2-styrylphenylmagnesium halides gave complex mixtures of products. This subtle difference in reactivity of the 2- and un-substituted phenyl Grignard reagent could be due to steric and electronic factors. It may be worth noting that although many examples using 4- or 3,4-substituted phenylmagnesium halides were cited in Kumada's work,[45] none possessed a 2-substituent. Unfortunately, the instability of 2,5-dimagnesiothiophene halides in solution[110] precludes its use for coupling with 2-bromostyrene.

It has been reported that certain zerovalent palladium is an effective catalyst for stereoselective cross-coupling of $C(Sp^2)$ halides with Grignard reagents.[49,92,111] Thus, Kumada et al[45] prepared 2,5-diarylthiophene from the corresponding 2,5-dihalothiophene and arylmagnesium bromide using tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) as catalyst, while Murahashi et al[92] coupled 2-lithiothiophene and vinyl halides using the same catalyst.

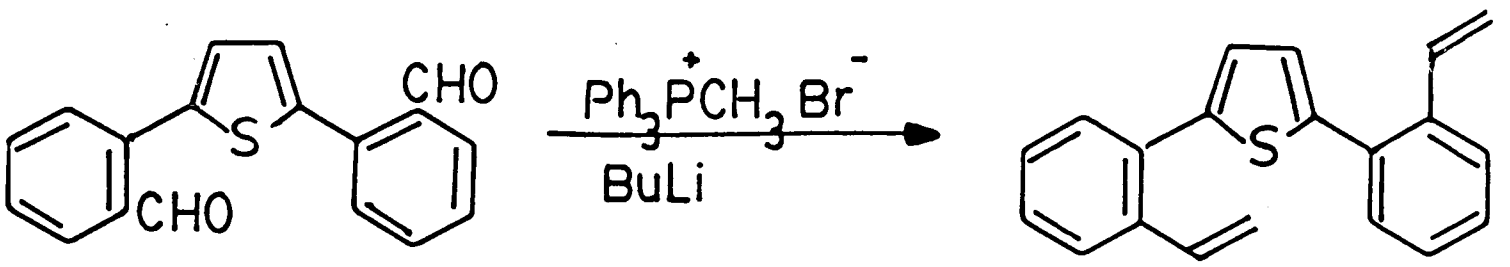

Ph2P PPh2
Ni
Cl Cl
MgBr
MgBr2 +MgCl2
Ph2P PPh2
Ni
x x
(x=)
Br S Br
x x
Ph2P PPh2
Ni
Br S
Br
Br S Br
Ph2P PPh2
Ni
P
Ph2 S
Br
x
MgBr
MgBr2
Ph2P PPh2
Ni
S
Br
Br S Br

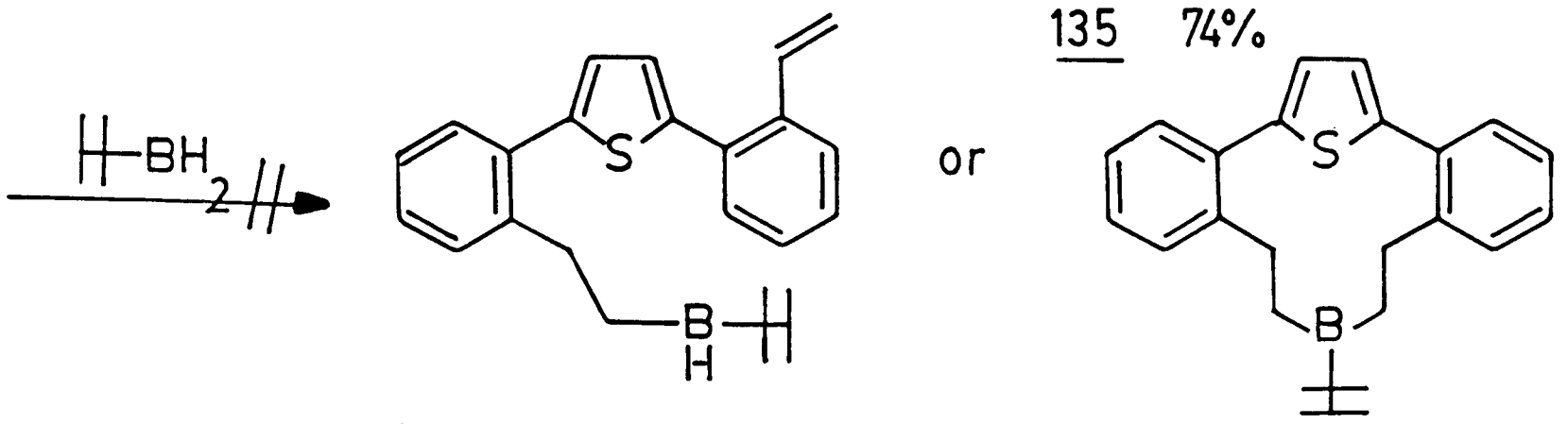
SCHEME 2

When 2-bromostyrene was treated with 2,5-dilithiothiopene, generated from 2,5-dibromothiophene and n-butyl lithium, with $Pd(PPh_3)_4$, only 2,5-dibutylthiophene, identified from its spectra, and 2-bromostyrene were isolated after chromatography. The 2,5-dibutylthiophene could have arisen from 2,5-dibromothiophene and n-butyl bromide, formed by halogen exchanged between 2,5-dibromothiophene and n-butyl lithium. Tert-Butyl lithium[112] has been used to circumvent such problems. Using 2 equivalents with an aryl bromide, the aryl lithium reagent was formed and the resulting tert-butyl bromide was dehalogenated rapidly by the second equivalent. Surprisingly, when 2-bromostyrene or 2-iodotoluene was allowed to react with 2,5-dilithiothiophene (generated from 2,5-dibromothiophene and 2 moles excess of tert-butyl lithium), with $Pd(PPh_3)_4$, under the conditions reported, no reaction occurred.

Based on the results obtained so far, it seems that 2,5-di(2-substituted phenyl)thiophenes cannot be made by direct coupling. The other approach involving olefination of 2,5-bis(2-formylphenyl)thiophene (89) with triphenylphosphonium methylide was investigated.

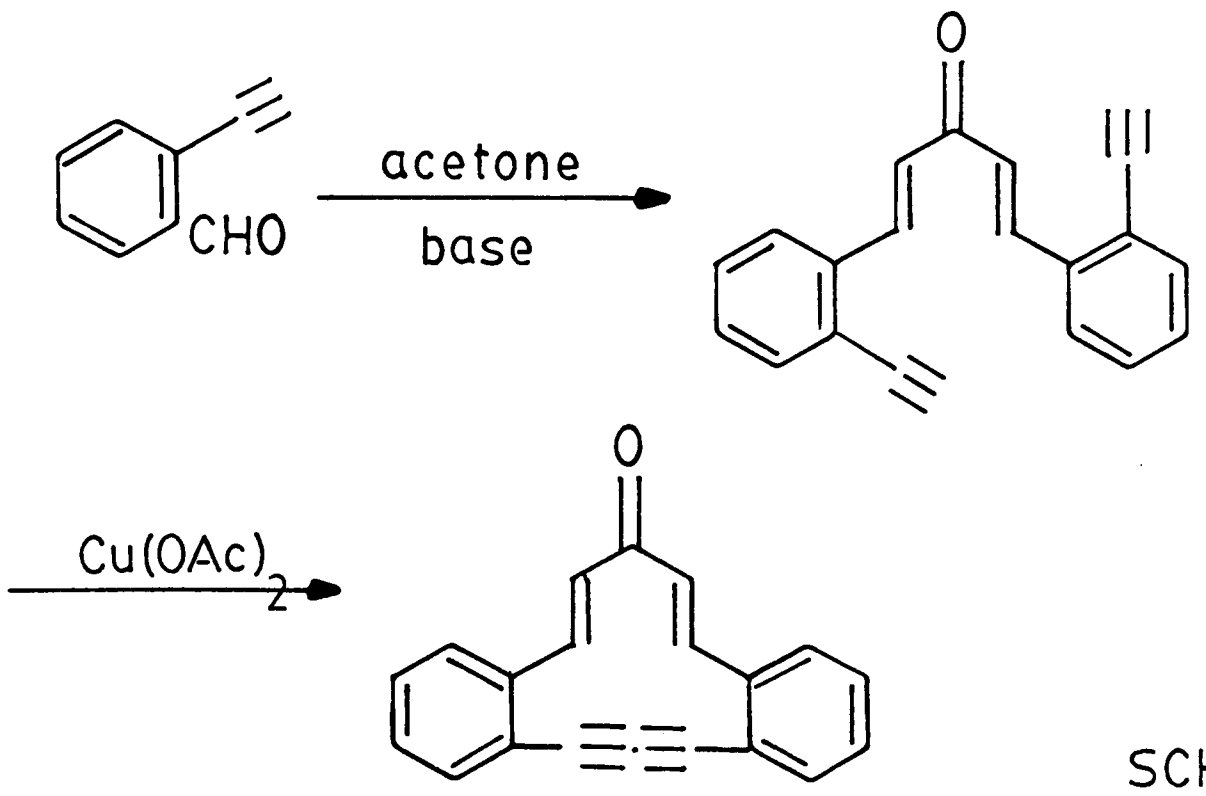
As expected, 2,5-bis(2-formylphenyl)thiophene (89) underwent olefination smoothly with triphenylphosphonium methylide at $0^{o}C$ to give 2,5-bis(2-styrylphenyl)thiophene (135). Disappointingly, when (135) (1 equivalent) was added to 1 equivalent of thexylborane[113] at room temperature, under high dilution condition, only the styrene was recovered. That was quite unexpected, since styrene can undergo hydroboration easily.[114]





As attempts to join the appendages of a 2,5-disubstituted thiophene together to form a thiophenophane had failed, the synthesis of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127), the possible immediate precursor for (126), became our next objective.

In 1977, Ojima et al[115] reported, giving no experimental details, the synthesis of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127) from 2-ethynylbenzaldehyde (scheme 3), which itself was synthesized by an eight step procedure from 2-(2-aminoethyl)benzaldehyde.[116] Recently, Austin et al[76] reported a facile two steps synthesis of 2-ethynylbenzaldehyde from the readily available 2-bromobenzaldehyde. A combination of these procedures was expected to give an easy synthesis of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127).

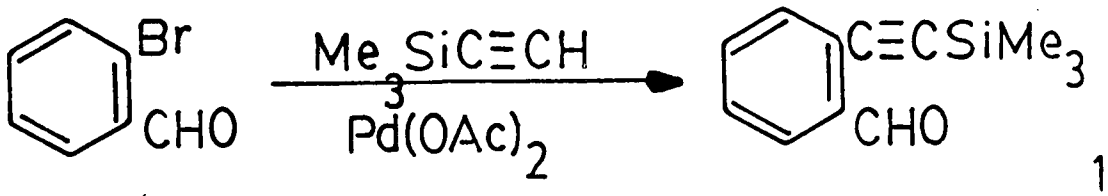


SCHEME 3

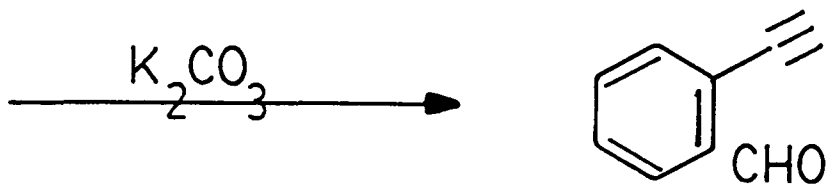
127

Results

The facile synthesis of 2-ethynylbenzaldehyde reported by Austin et al[76] involves a palladium-catalyzed coupling between 2-bromobenzaldehyde and ethynyltrimethylsilane to give (137) which on deprotection with potassium carbonate gave 2-ethynylbenzaldehyde (138).



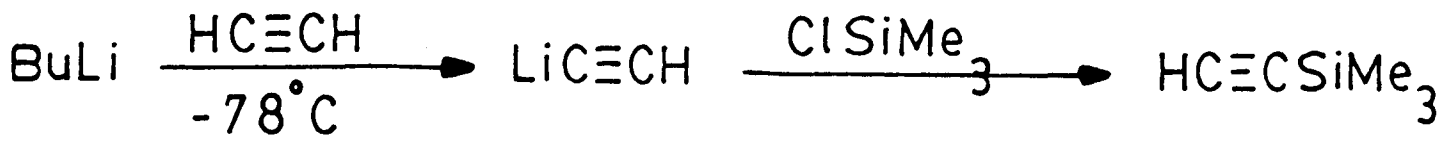
137



138

The only disadvantage is the use of pure ethynyltrimethylsilane, which is both expensive and tedious to prepare. The literature preparations from chlorotrimethylsilane and sodium acetylide[117] or ethynyl magnesium bromide[118] did not give the reported (Ca. 30%) yield, and an alternative synthesis was sought.

Midland[119] prepared monolithium acetylide at -78°C and demonstrated that it could be trapped by various electrophiles at that temperature. Following this, chlorotrimethylsilane was treated with lithium acetylide, generated *in situ* at -78°C from *n*-butyl lithium and acetylene in THF, and gave a solution containing 75-85% of the ethynyltrimethylsilane.



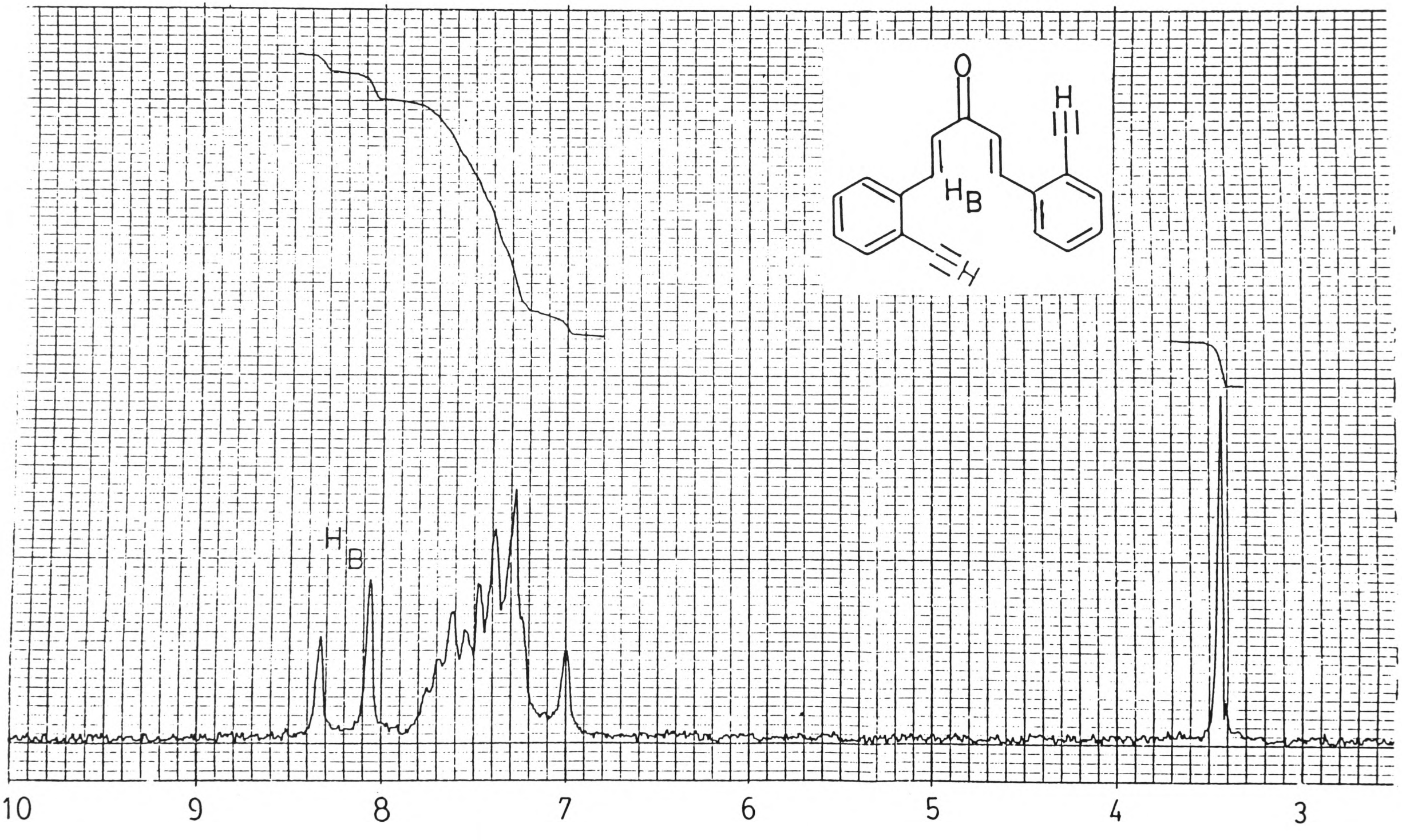
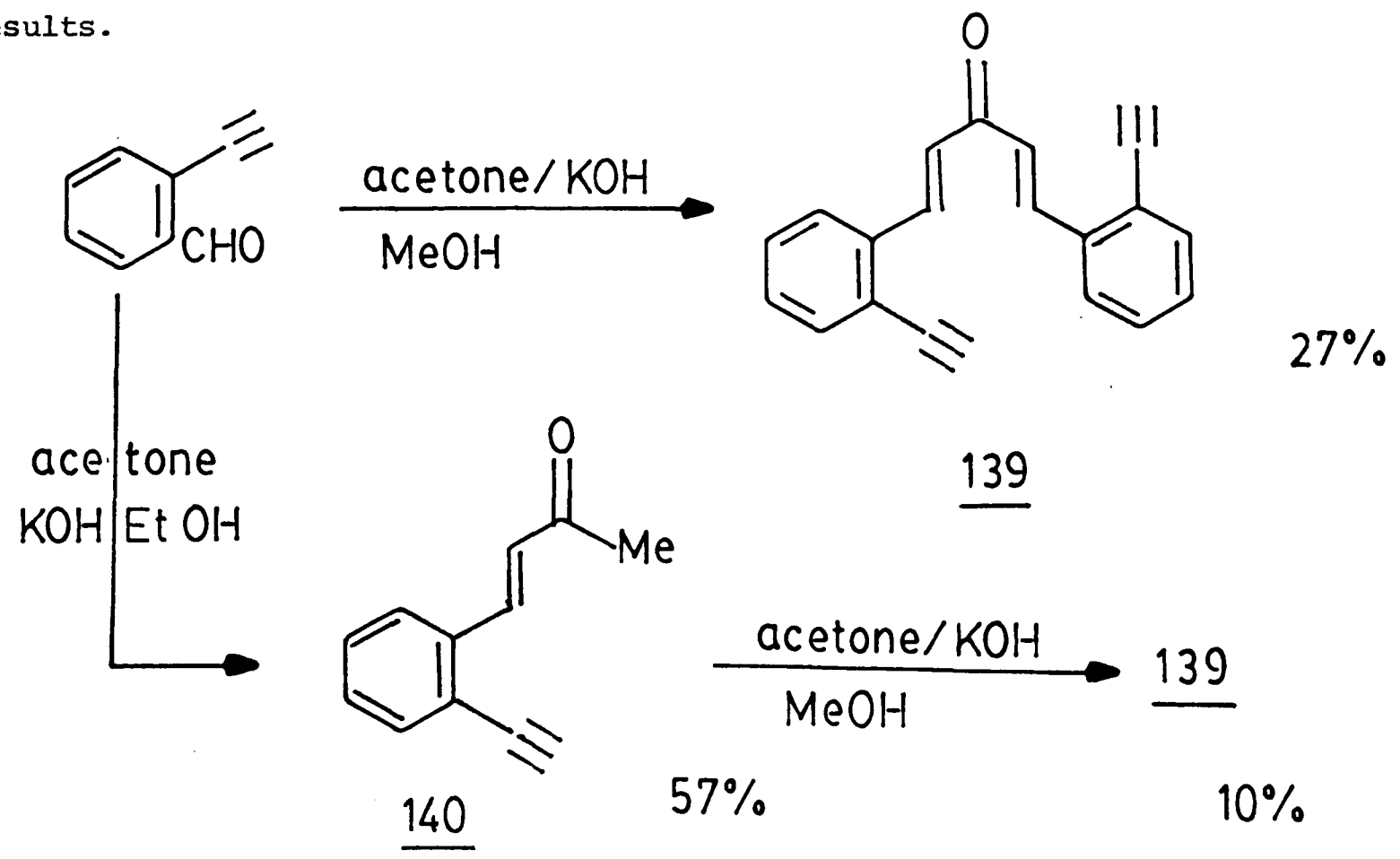


diagram 1 ^{1}H NMR(60MHz) of (139)

This solution was treated with 2-bromobenzaldehyde, in the presence of palladium(II)acetate and triethylamine, under the conditions reported,[76] and gave a 91% yield of distilled 2-{(trimethylsilyl)ethynyl} benzaldehyde (137). The use of ethynyltrimethylsilane, conveniently prepared *in situ* in dilute solution in THF-hexane, does not appear to have been reported before. As noted by Austin *et al*,[76] the quality of triethylamine was very critical. Triethylamine obtained from Fluka gave satisfactory and reproducible results, but that from Aldrich or BDH did not. Desilylation was affected by anhydrous potassium carbonate in methanol as reported[76] or by potassium fluoride in DMF. Although both methods gave comparable yields, the latter was much preferred since 2-ethynylbenzaldehyde is extremely base sensitive, especially above Ca. 40°C. In one trial, when the methanol was being removed, the residual potassium carbonate presumably caused an explosive decomposition.

Treating 2-ethynylbenzaldehyde with half a mole of acetone in methanol-ether and 0.25 mole of potassium hydroxide gave the dienone (139) (diagram 1) in 27% yield, more base gave only polymers. Carrying out the reaction in two stages (scheme 4), as described,[96] gave much poorer results.



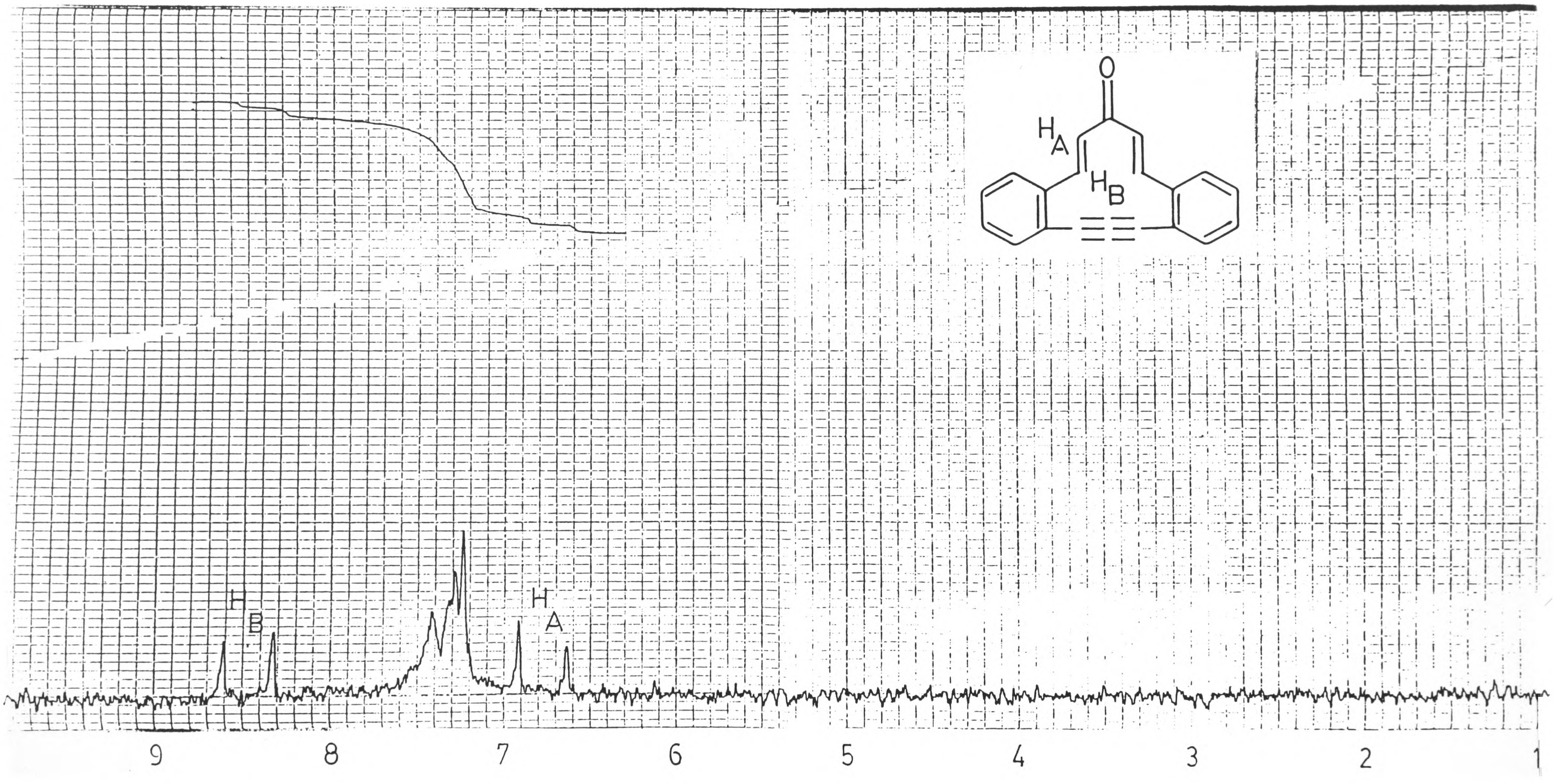
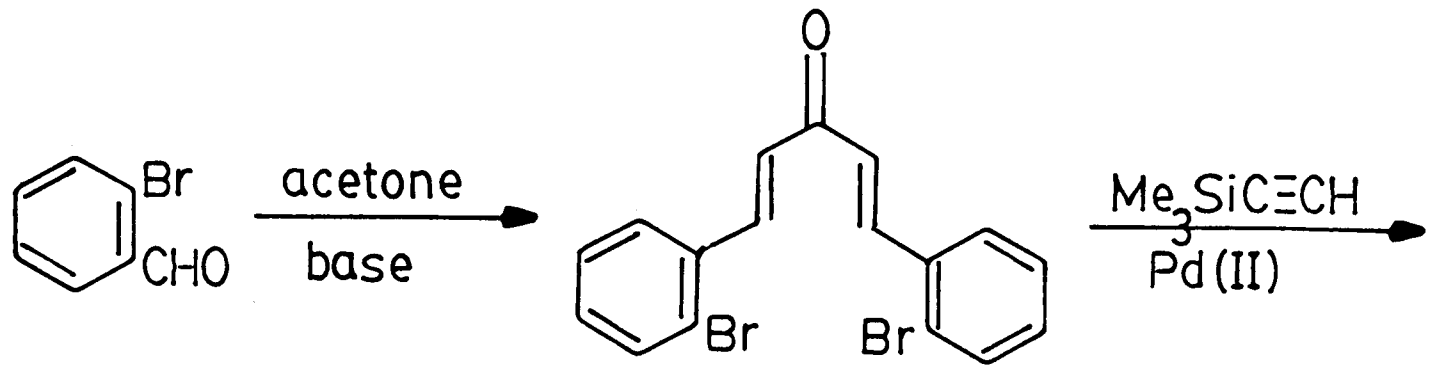
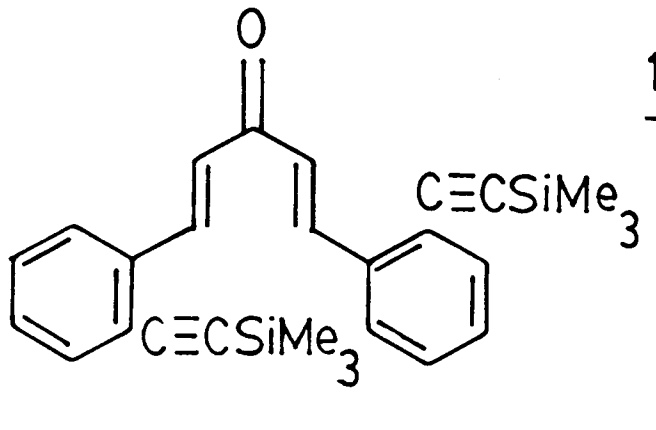


diagram 2 ^{1}H NMR (60MHz) of (127)

Attempts were also made to induce cross-coupling between ethynyltrimethylsilane and 1,5-bis(2-bromophenyl)penta-1,4-dien-3-one (141), readily prepared from 2-bromobenzaldehyde and acetone, to give 1,5-bis{(2-trimethylsilyl)ethynylphenyl}penta-1,4-dien-3-one (142), which on desilylation should give (139).



141

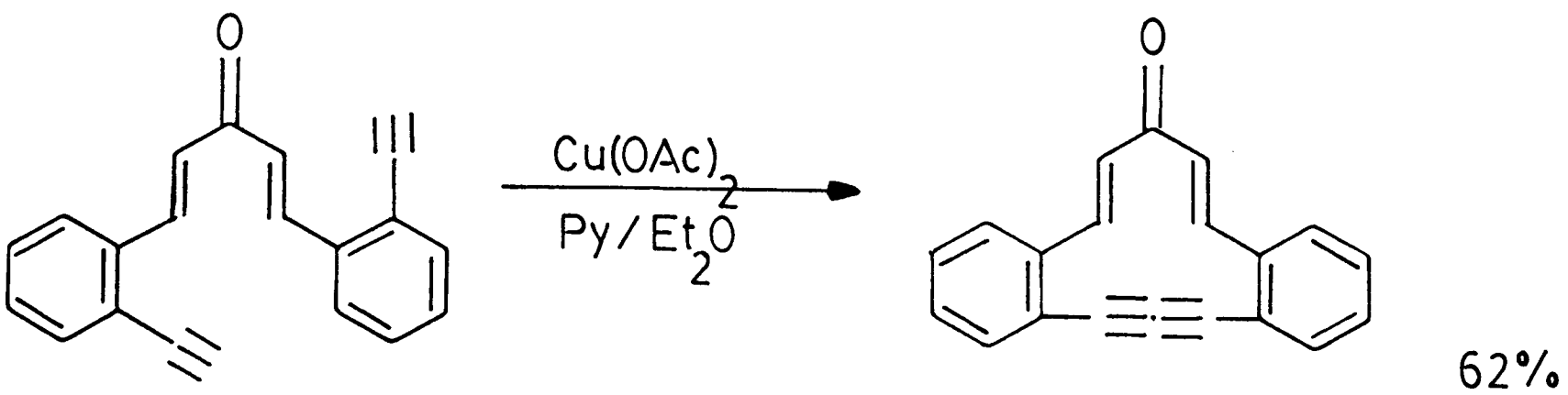


139

142

Unfortunately, at most a 5% yield of (142) was obtained under various reaction conditions and solvent systems.

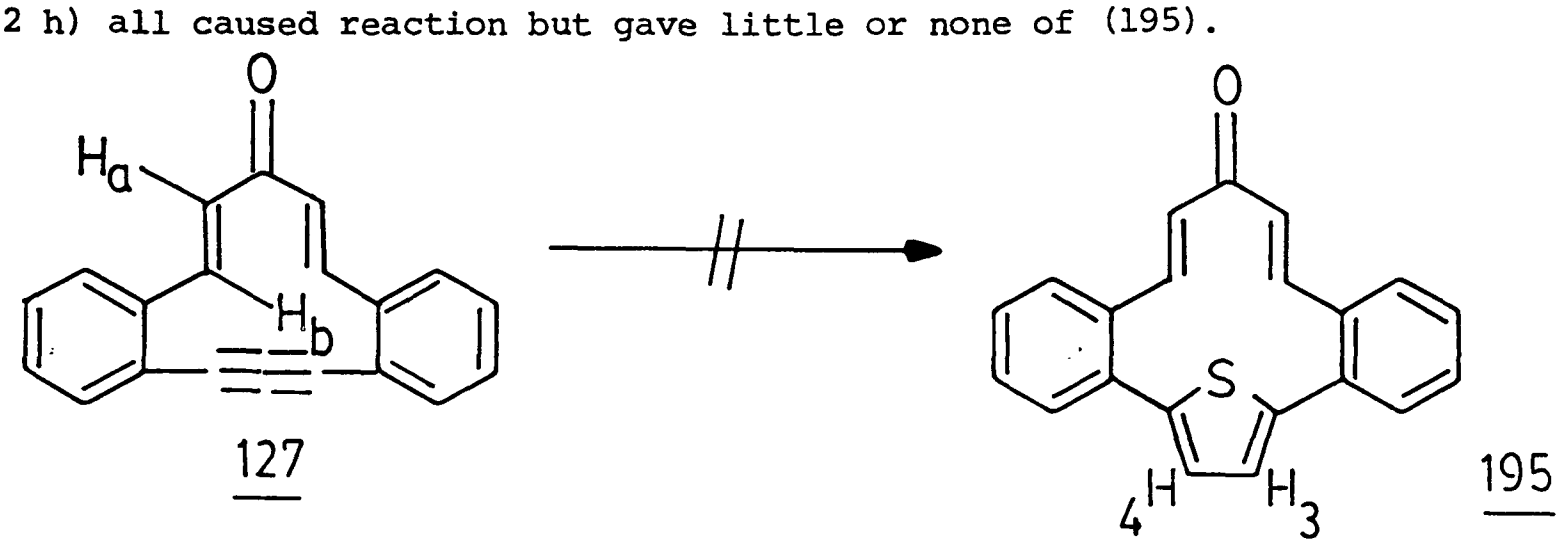
Oxidative coupling of (139) under conditions suggested by the work of Sondheimer et al[96] gave the desired 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127), which had similar physical and spectroscopic data (diagram 2) as that reported by Ojima et al.[115]



139

127

With (127) in hand, efforts were then directed to convert its diyne moiety into a thiophene ring. No reaction was caused by sodium sulphide in a water/CH_2Cl_2 system (room temperature, 20 h), while sodium sulphide nonahydrate in refluxing methanol[120] (16 h), sodium sulphide nonahydrate and potassium hydroxide in aqueous DMSO[121] (room temperature, 2 h), hydrogen sulphide and sodium ethoxide in refluxing ethanol[22] (½ h), hydrogen sulphide and DBU in CH_2Cl_2 (room temperature, 2 h) all caused reaction but gave little or none of (195).



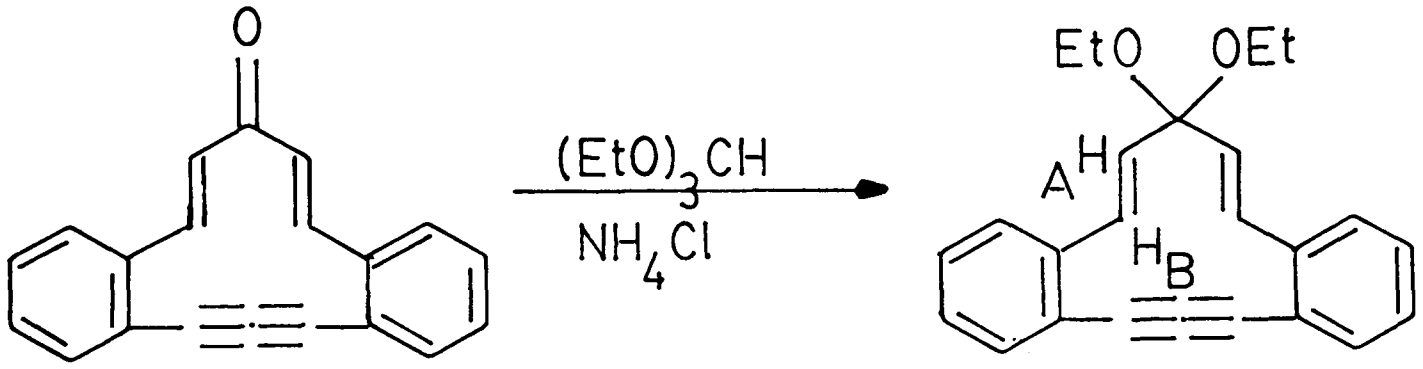
127 195

In all these cases, the ^1H NMR spectra of the products showed a broad hump between δ 7.00-8.00, with no sign of the thiophene protons H_3 and H_4 in (195), expected as a singlet at around δ 6.80-7.00. The doublets due to H_A and H_B of (127), centered at δ 6.78 and δ 8.48, had disappeared, indicating addition to the olefinic bonds. Further evidence of the saturation of the double and triple bonds in (127) was provided by the disappearance of the acetylenic absorption at 2180 cm^{-1} and the shift of the carbonyl absorption from 1660 to 1710 cm^{-1}. No clear deduction could be made from the mass spectra. Though the exact nature was not certain, the substances were probably polysulphides.

If hydrogen sulphide is to be added regiospecifically across the diyne in (127) to form the thiophene ring, the reactivity of the

activated double bonds in (127) must be suppressed, either by protection of the carbonyl group or the double bonds themselves.

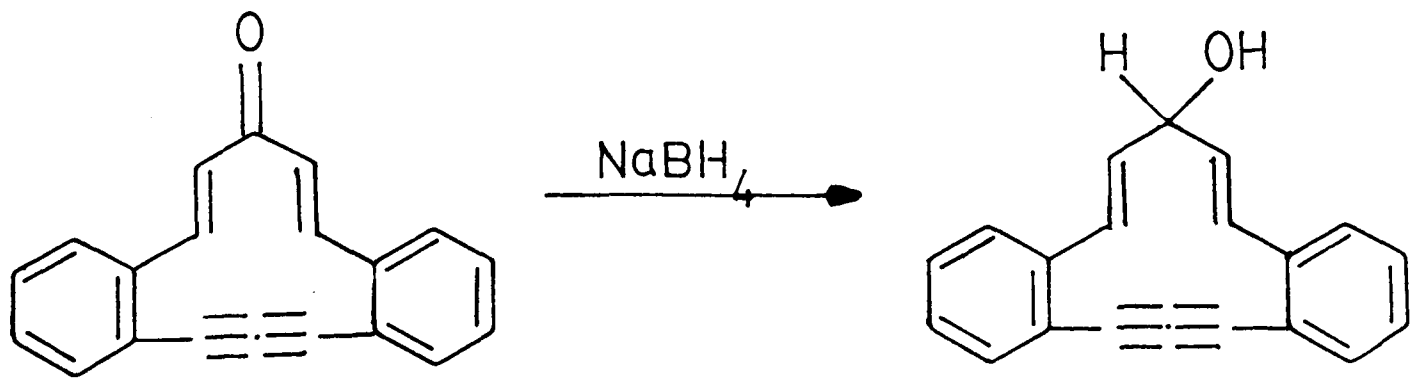
Diethyl acetal preparation was unsatisfactory. When triethyl orthoformate was stirred with (127) and a catalytic amount of ammonium chloride[122] for 72 h at RT, starting materials were recovered. After 5 h refluxing, less than 10% of the expected diethyl acetal (143) was formed, while prolonged refluxing (16 h) gave only 20% of (143) and decomposition of (127).



143

The formation of (143) was detected by ^{1}H NMR. H_A now resonates at 6.92 (d, J 15.3 Hz) and H_B at 5.55 (d, J 15.3 Hz), as expected from the disappearance of the carbonyl group. The rest of the spectrum fitted the remaining ethoxy and phenyl resonances. Further characterization was not attempted.

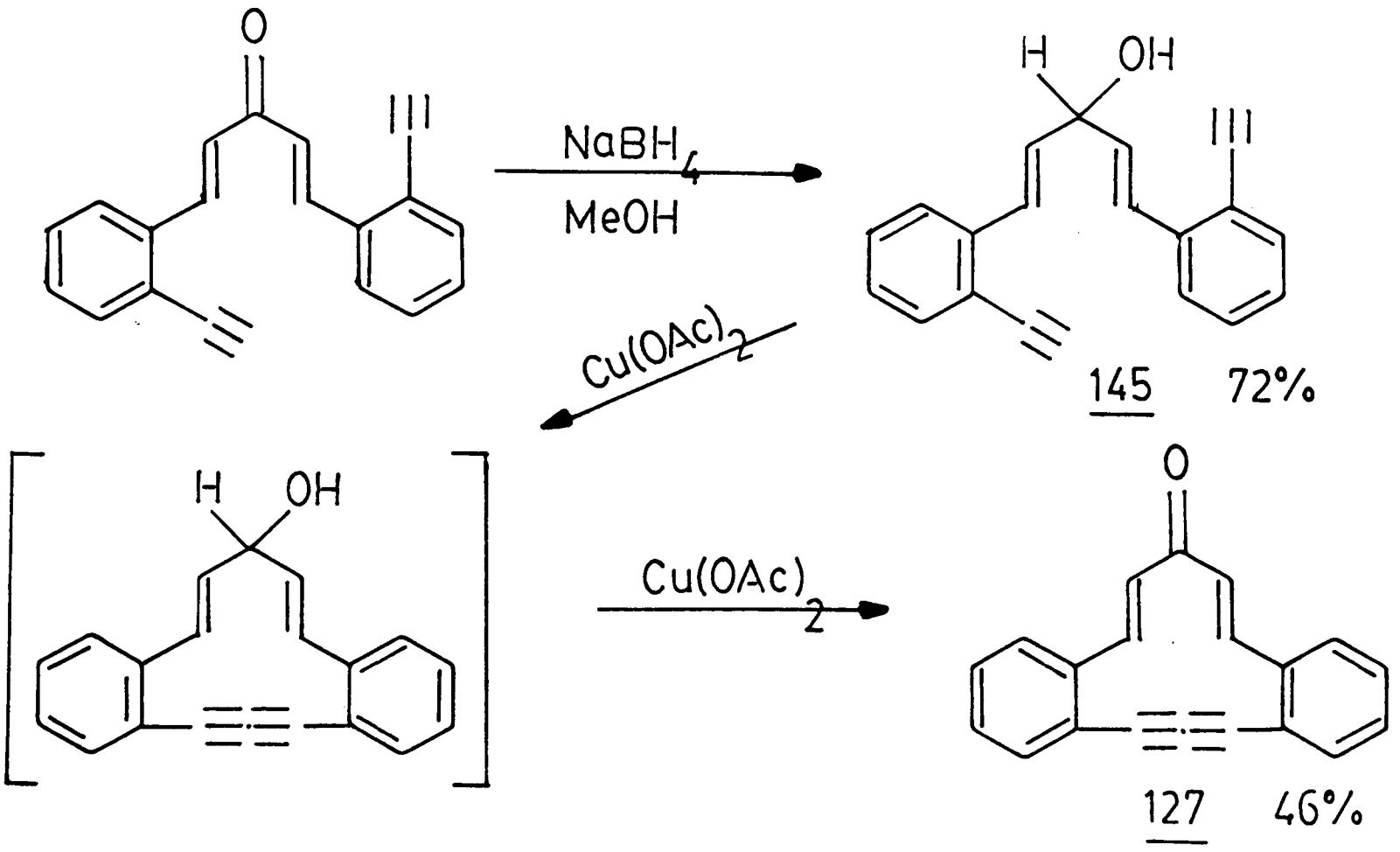
Ojima et al[123] reported, giving no experimental details, the synthesis of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-ol (144) in 91% yield from its corresponding ketone (127) by sodium borohydride reduction. The alcohol (144) could be regarded as the protected ketone (127).



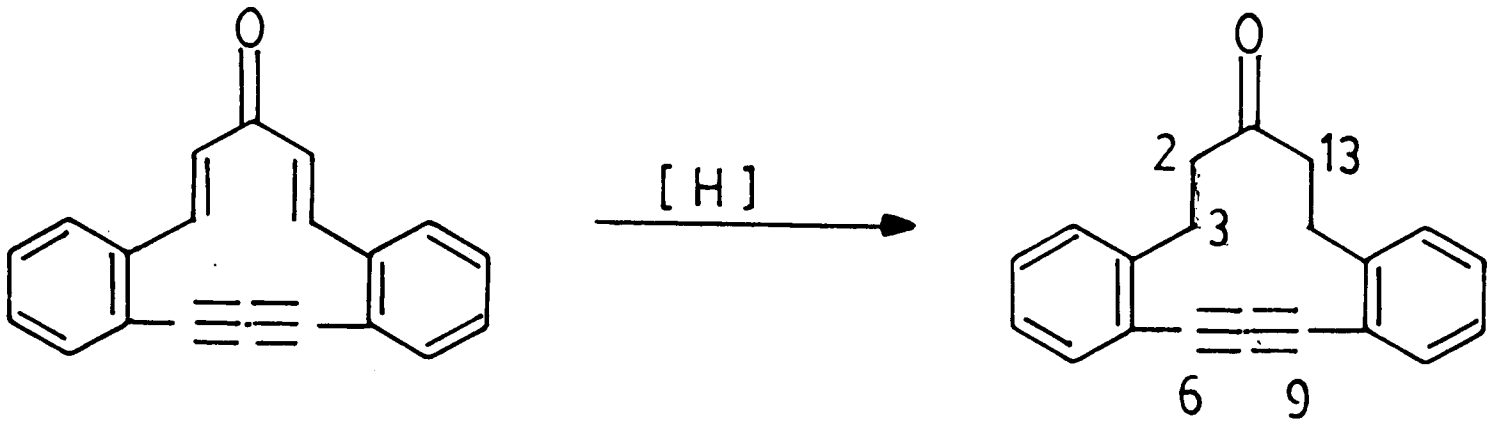
144

Reduction of the dienone (127) was carried out as reported[123] in ether with ethanolic sodium borohydride and after chromatography on a column of SiO_2, TLC indicated at least 6 components were present. ^1H NMR (300 MHz) of the eluent showed a very complex spectrum and the alcohol (144) was present in a relatively small proportion, longer reaction time (16 h) and other solvent systems led to no improvement.

One alternative is to reduce the acyclic dienone (139) down to the alcohol before ring closure by oxidative dimerization. Surprisingly, contrary to Ojima's report[123] again, reduction of the acyclic dienone (139) proceeded smoothly in 3 h to give a high yield of the corresponding alcohol (145), instead of requiring 20 h and giving a poor yield.[123] Nevertheless, the spectroscopic data for (145) were similar to that reported by Ojima.[123] Unfortunately, intramolecular oxidative dimerization of (145) gave only (127) as the product.



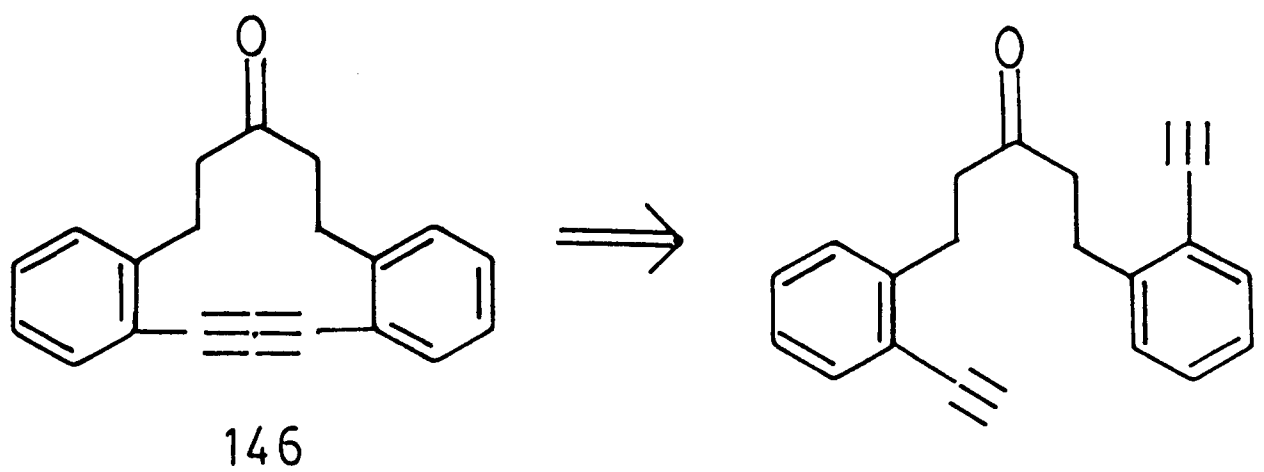
Selective protection of the double bonds in the presence of the triple bonds was now considered.



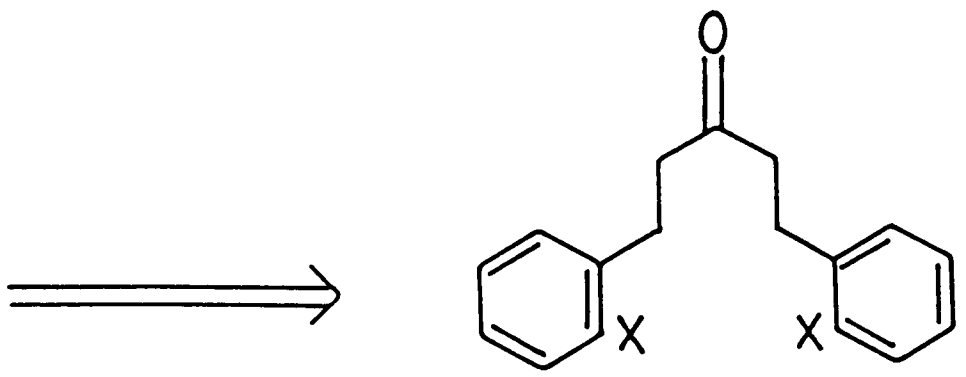
146

A number of reagents, ranging from the classical sodium in liquid ammonia (Birch reduction),[124] amalgamated zinc in hydrochloric acid (Clemmenson reduction),[125] to the more recent ones like n-butyl tin hydride,[126,127] tris(triphenylphosphine)rhodium(I)chloride (Wilkinson's catalyst),[128] hydriodo iron carbonyl complexes,[129] potassium tri-secbutylborohydride(K-Selectride),[130] hydrosilane rhodium(I) complexes,[131] various Cu(I)H complexes[132] and cyanoborohydride,[133] are known to effect reduction of conjugated ketones to the corresponding saturated derivatives, but none of them is selective enough to cause conjugate reduction without attacking the triple bond. The desired 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-one (146) must therefore be synthesized in such a way that the C_2-C_3 and C_{12}-C_{13} bonds are saturated before the triple bonds (C_6, C_7, C_8 and C_9) are introduced.

This could be done by ethynyltrimethylsilane coupling with an aryl halide[76] such as (147), followed by desilylation and coupling to (146).

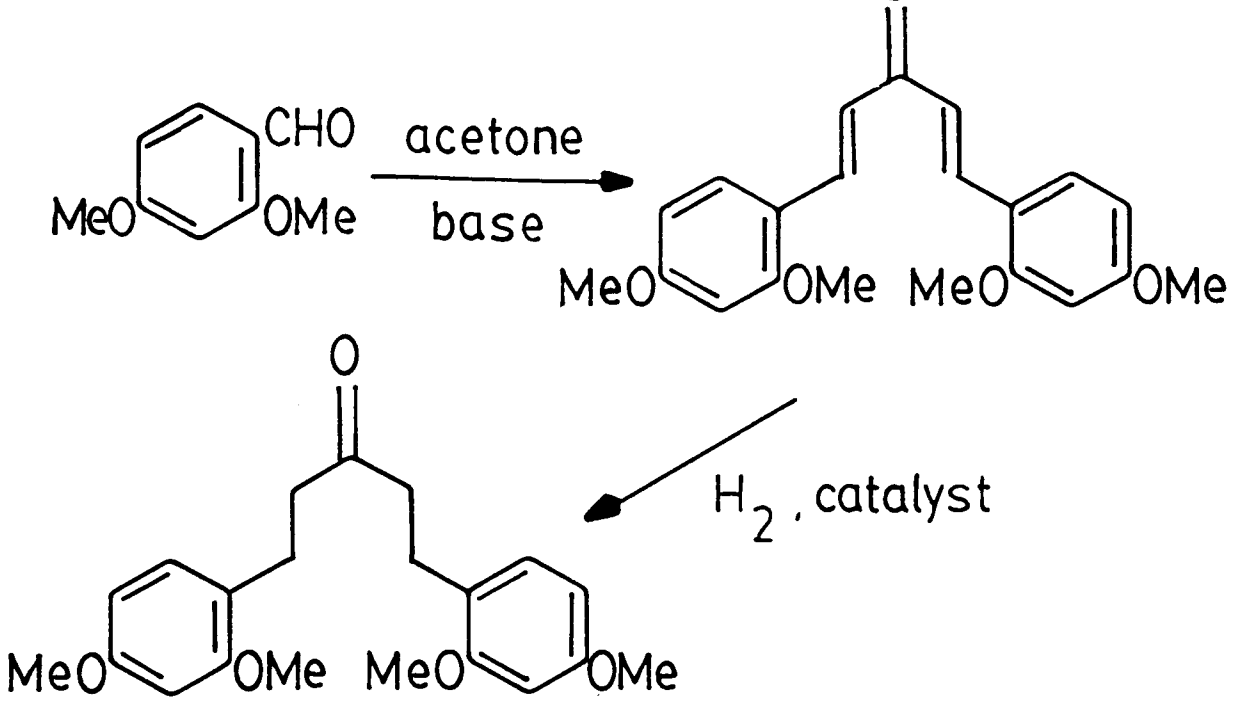


146

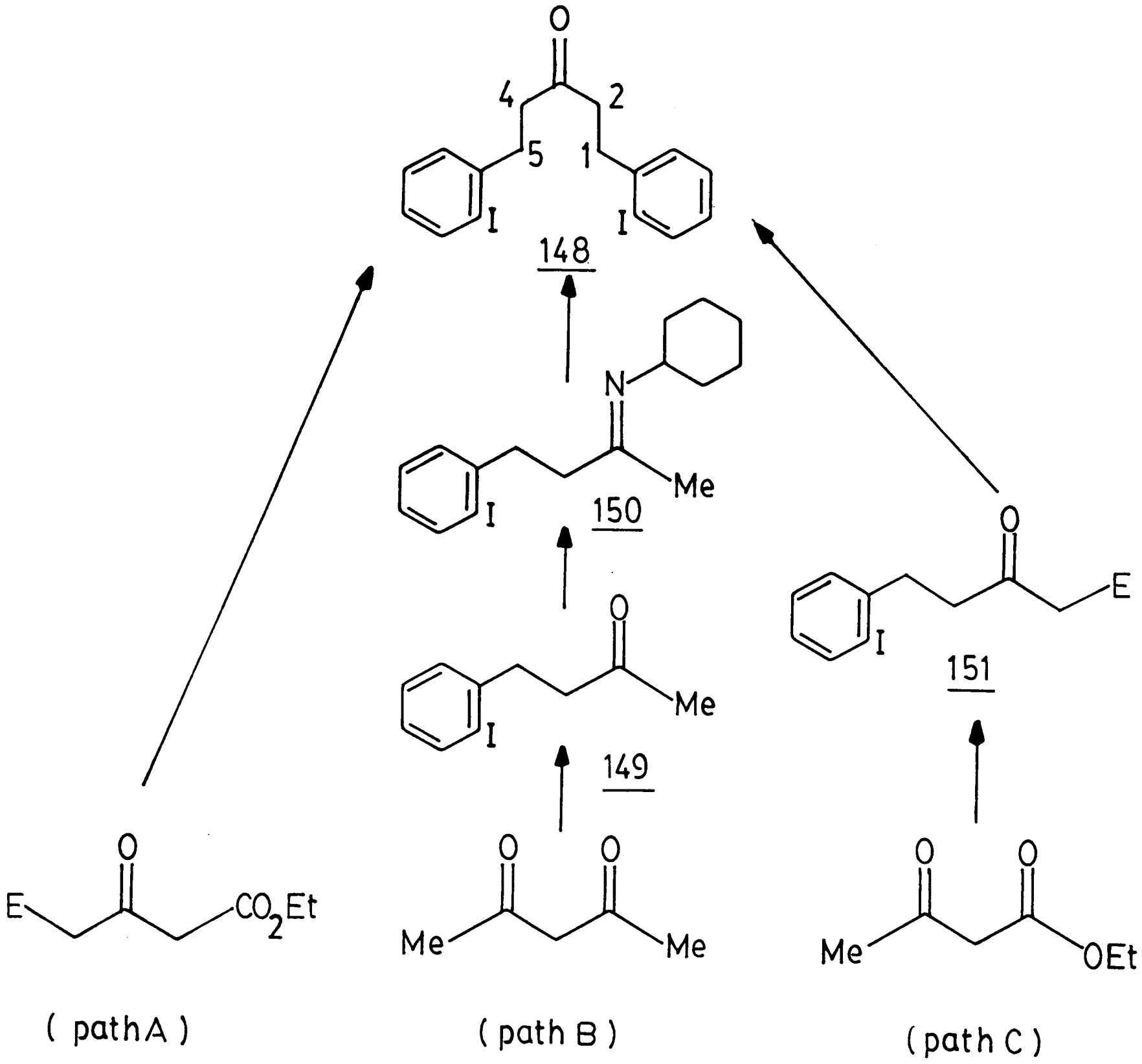


147
148, X = I

Since electron-withdrawing (activating) groups are absent in (147), the diiodo (148, x=I) compound must be used.[76,134,135] 1,5-Di(2-substituted phenyl)pentan-3-ones (147) are usually prepared by catalytic hydrogenation of the corresponding dibenzalacetone, obtained from acetone and the 2-substituted benzaldehyde, e.g.



As aryl iodides are easily hydrogenolysed routes avoiding reductive methods were first examined. 2-Iodobenzyl bromide is easily available and the routes outlined on scheme 5 were investigated.

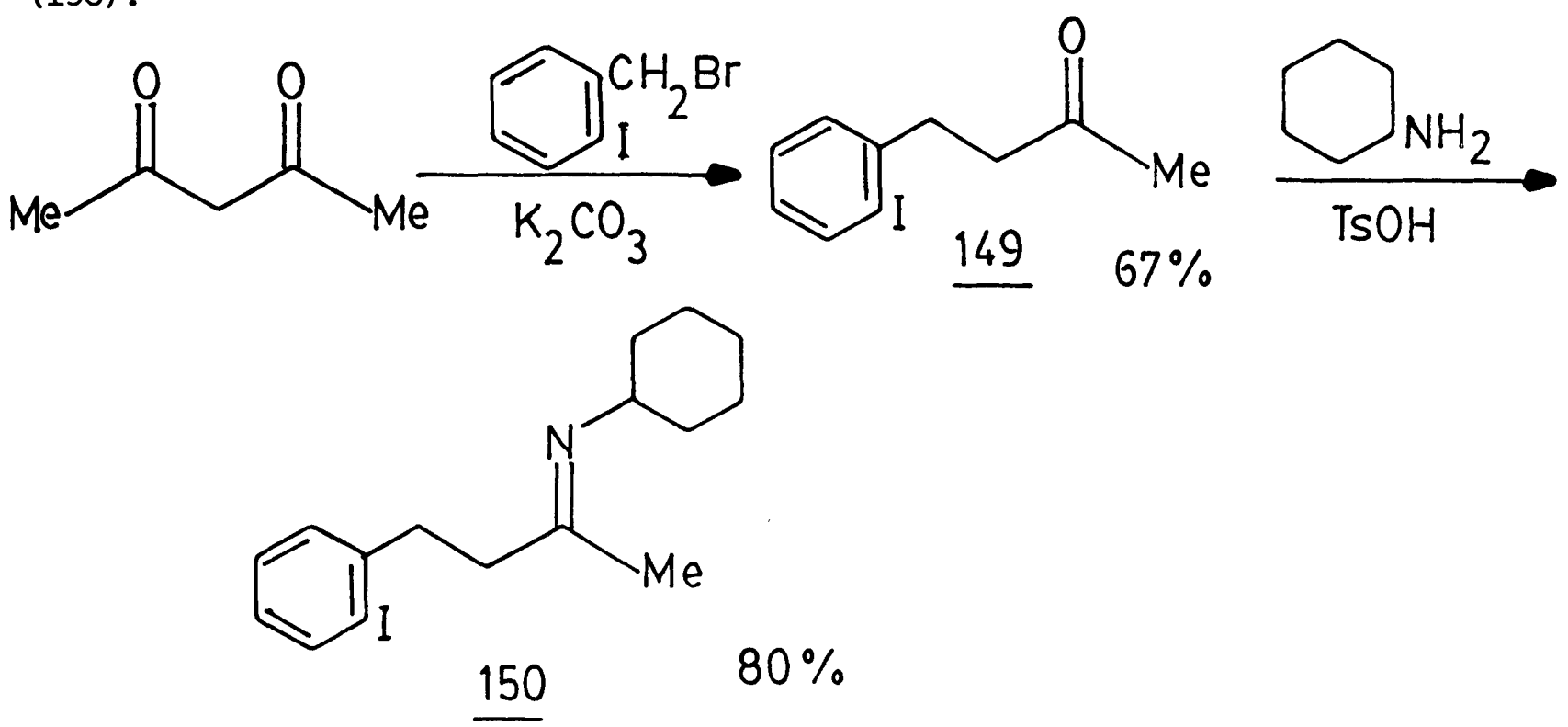


SCHEME 5

Alkylation of diethyl 1,3-acetonedicarboxylate (1 equivalent) with 2-iodobenzyl bromide (2 equivalents) (scheme 5, path A) in the

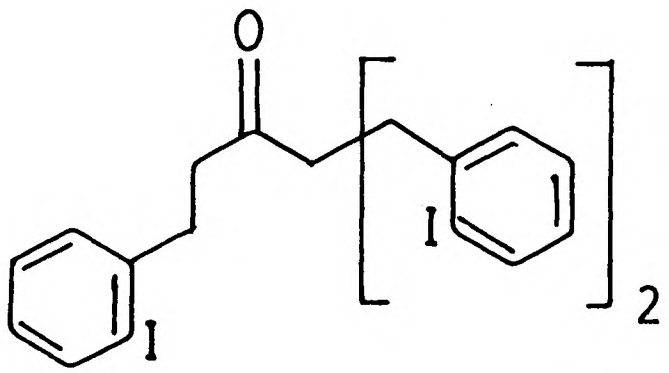
presence of sodium ethoxide or potassium tert-butoxide under various conditions gave unresolvable mixtures of di- and poly-alkylated products.

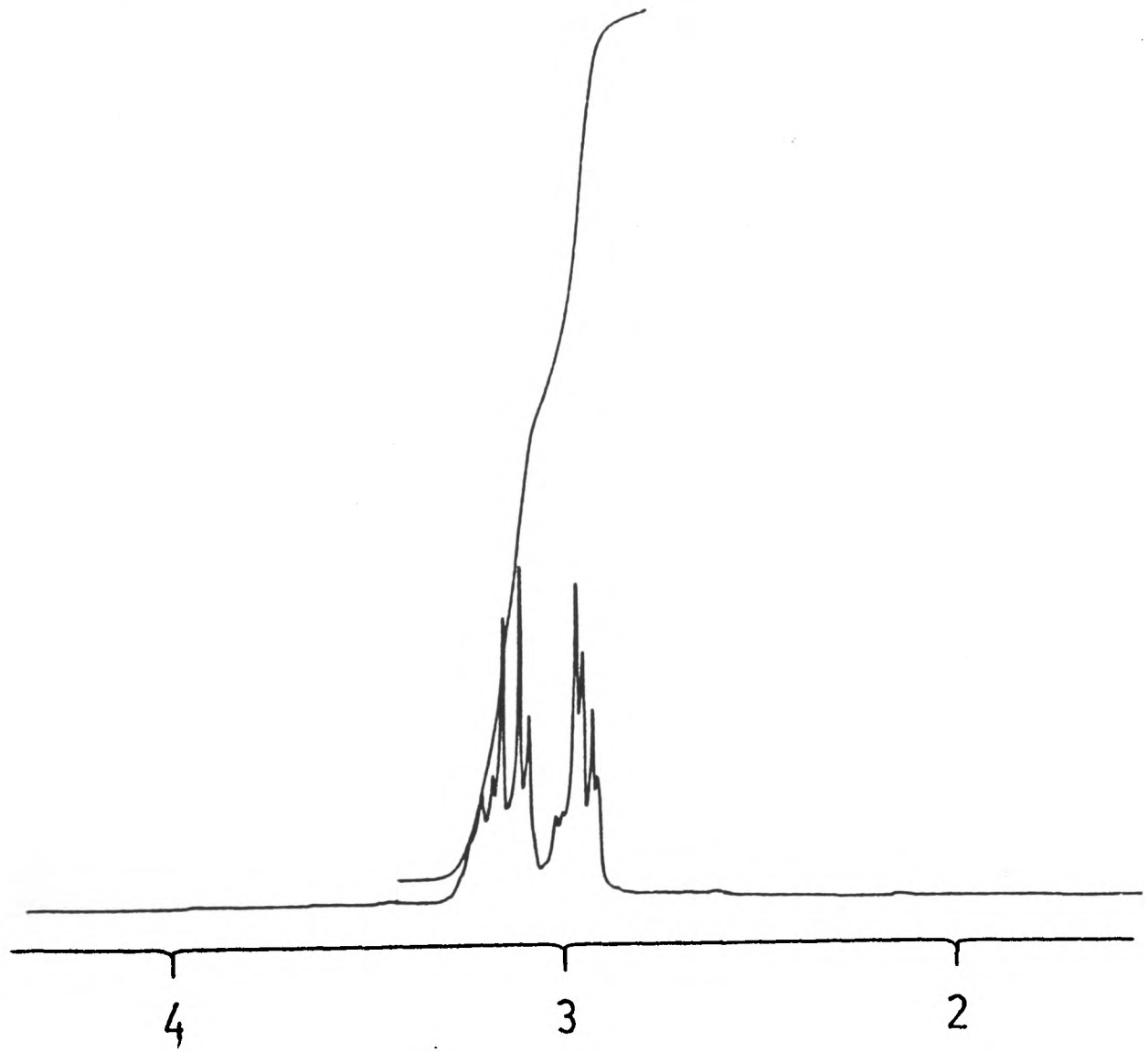
In 1976, Pearce et al[136] reported that ketimines undergo selective monoalkylation, especially when the ketone is unsymmetrical, the new group entering on the least hindered side.[137] With that in mind, it was found that 2,4-pentanedione, modifying the literature procedure,[138] gave 4-(2-iodophenyl)-2-butanone (149) and the corresponding ketimine (150).[136]



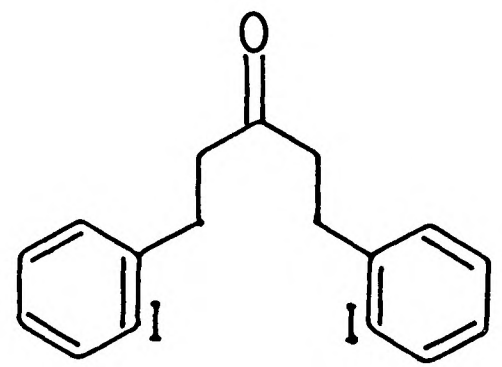
Alkylation of the ketimine (150) with 2-iodobenzyl bromide, employing ethylmagnesium bromide as the base for 20 h as described[136] gave a mixture of mainly starting materials and the expected 3-pentanone (148). Increasing the reaction time to 3 days caused no improvement and the mixture could not be separated easily.

Starting from ethyl acetoacetate dianion, which alkylates selectively at the γ-position,[139] ethyl 5-(2-iodophenyl)-3-ketopentanoate (151) was synthesized and identified from its ^{1}H NMR and mass spectra.



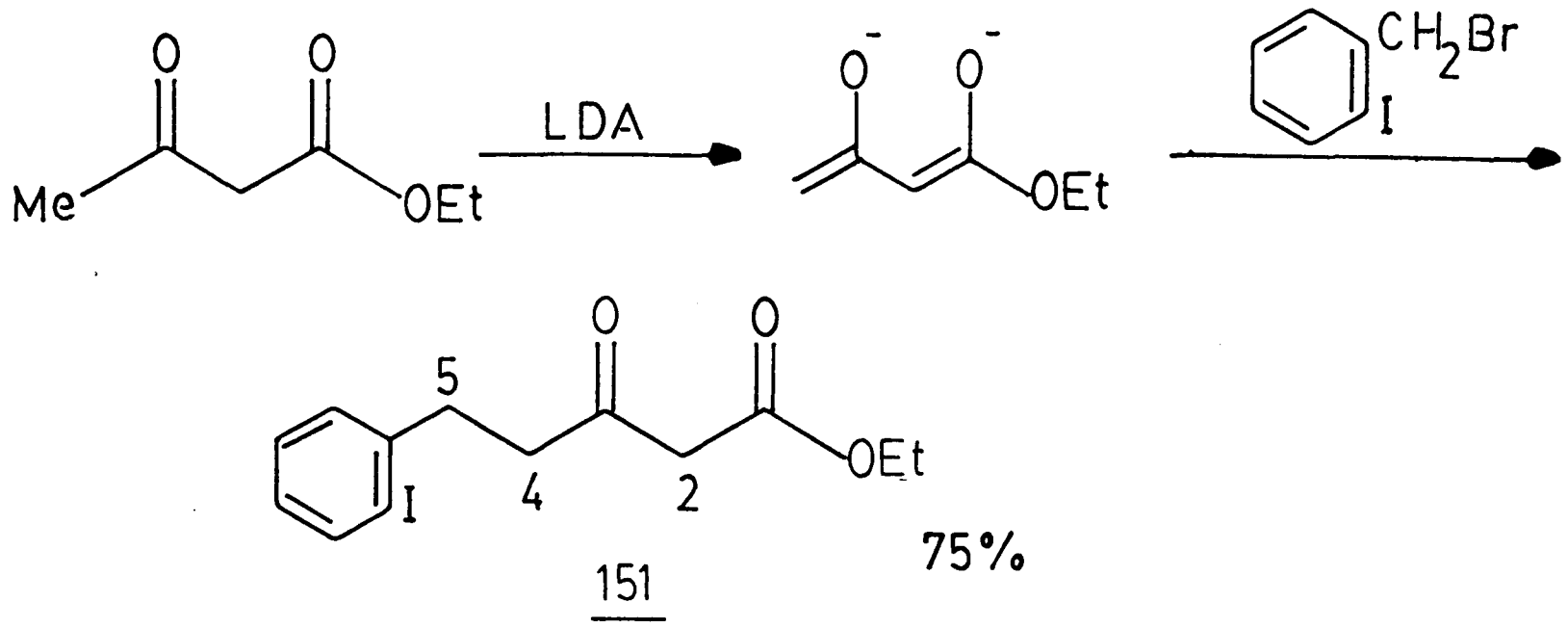


^{1}H NMR(300MHz) of(152)



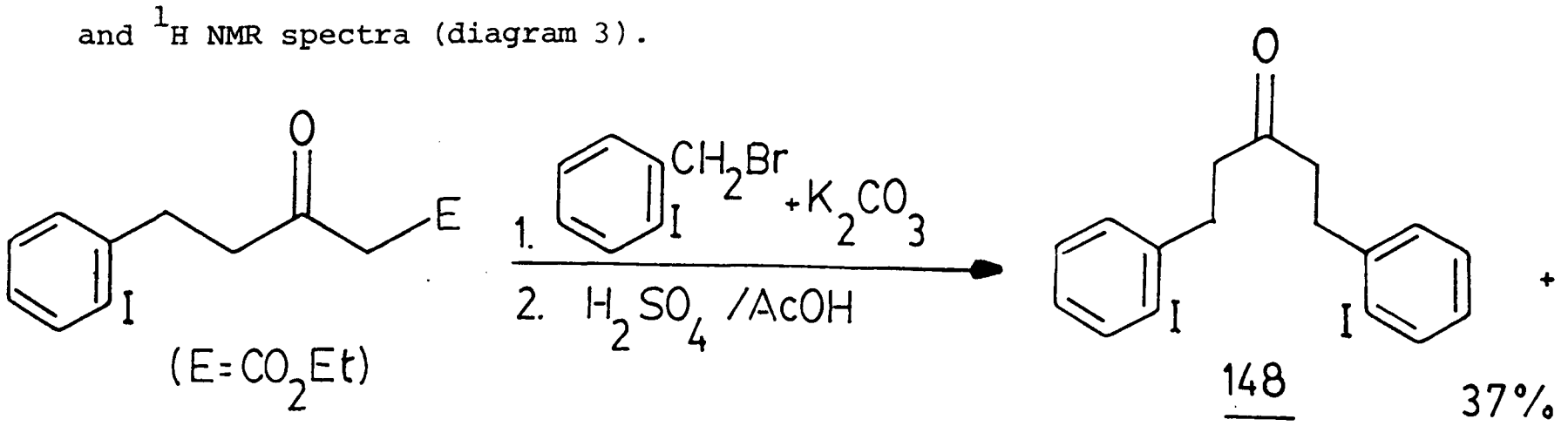
^{1}H NMR(300MHz) of (148)

diagram 3

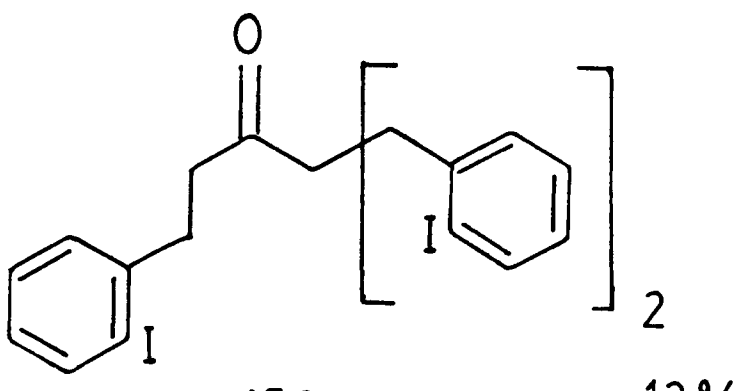


151

Attempts to purify (151) by distillation failed, but nevertheless the crude keto-ester was alkylated successively with 2-iodobenzyl bromide at C_2. Although a number of bases have been employed for the generation of the anion from β-keto esters,[140] we found that refluxing an equi-molar mixture of (151) and anhydrous potassium carbonate[141] in acetone gave the best results. After acid hydrolysis (to minimize retro-Claisen condensation)[142] and decarboxylation, two crystalline products were isolated. They were identified unequivocally as 1,5-di (2-iodophenyl)pentan-3-one (148) and 2-(2-iodophenylmethyl)-1,5-di(2-iodophenyl)pentan-3-one (152) from their analytical data, mass and ^1H NMR spectra (diagram 3).



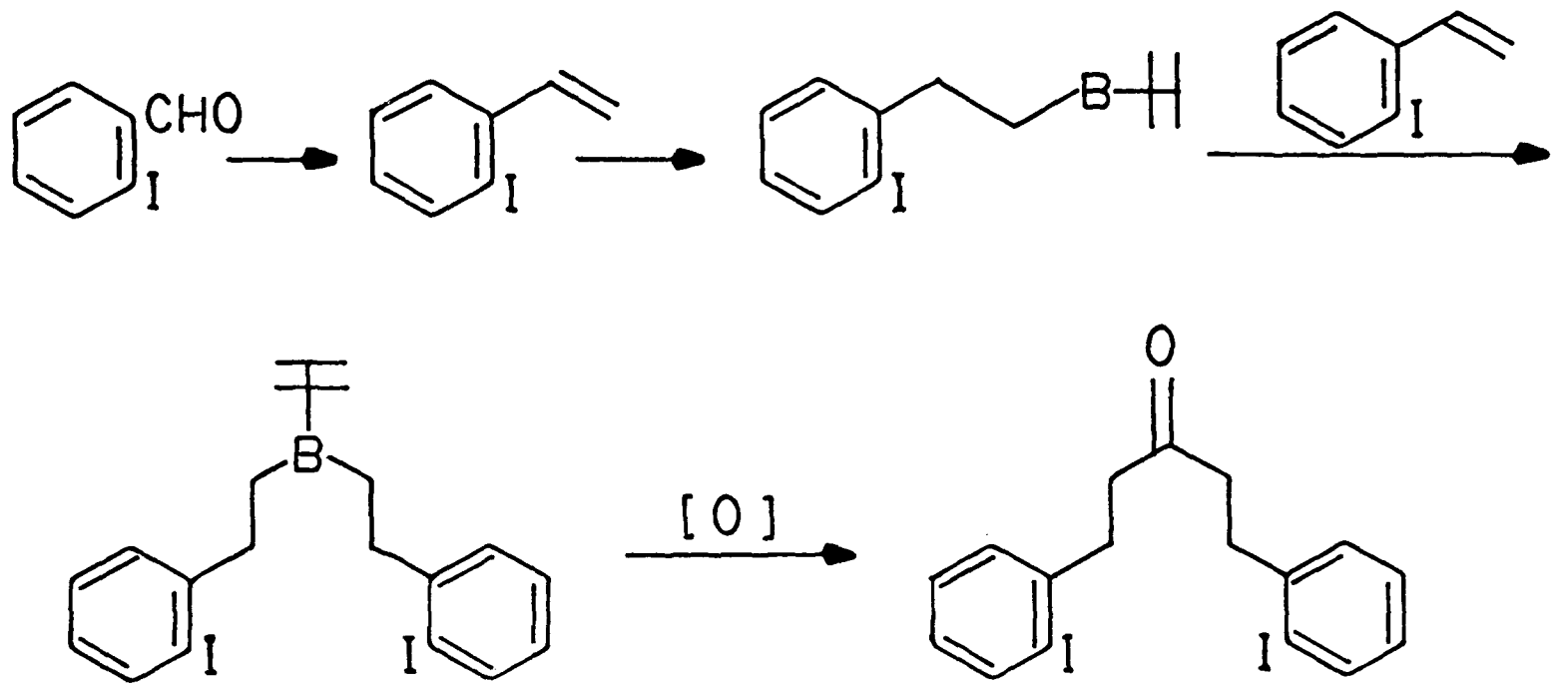
148 37%



152 13%

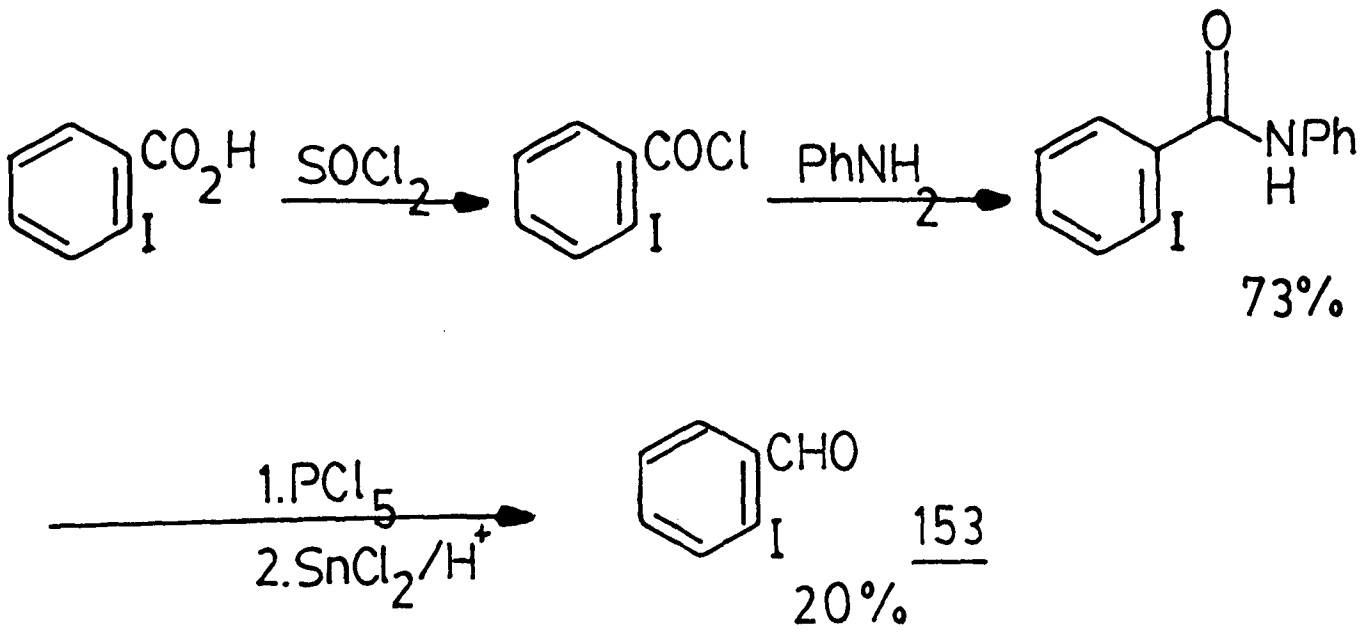
Unfortunately, attempts to eliminate the formation of (152) were unsuccessful. Though (148) was made by this route, the low yield was not satisfactory for a multistage synthesis.

A completely different approach to (148) could be based on Pelter's modification of Brown's ketone synthesis, and this requires 2-iodobenzaldehyde as the starting point.



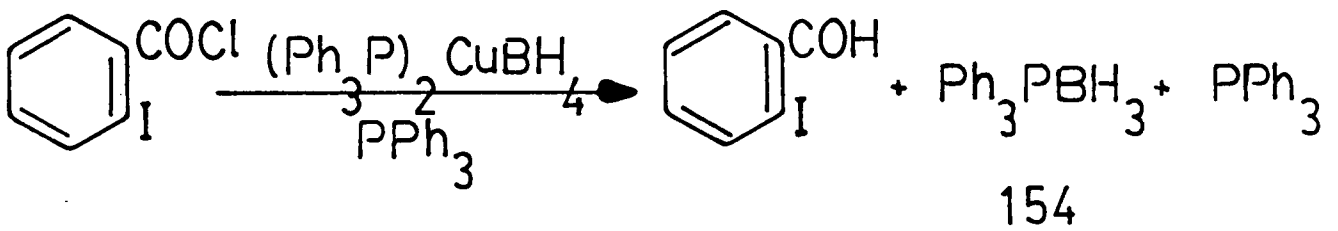
148

Two syntheses of 2-iodobenzaldehyde are known in the literature. The first involved the reaction between 2-iodobenzanilide, phosphorous pentachloride and stannous chloride in ethereal hydrogen chloride,[143] while the second was an inconvenient oxidation of 2-iodobenzyl alcohol with dinitrogen tetroxide[145] which was not examined. Although 2-iodobenzanilide was obtained easily, only a 20% conversion to 2-iodobenzaldehyde was achieved instead of the 60% claimed.[143]



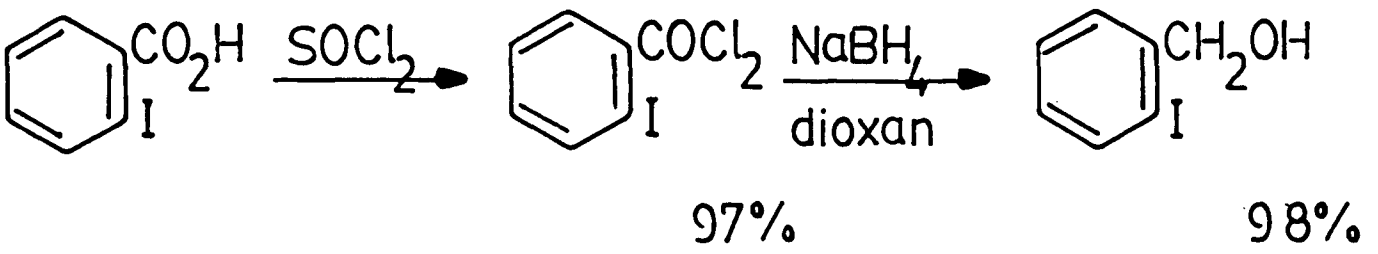
153

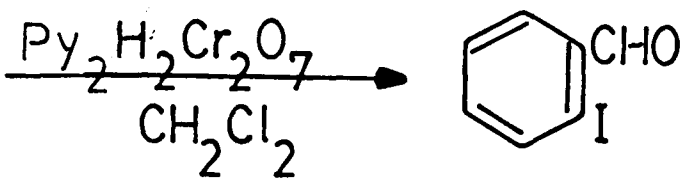
Of the various procedures employed for the direct reduction of acid chlorides to aldehydes, namely catalytic hydrogenation,[145] lithium aluminium tri-tert-butoxyhydride[146] at low temperatures, hydridoirontetracarbonyl anion,[147] bis(triphenylphosphine)copper(I) tetrahydroborate[148] and tributyl tin hydride,[149] only bis(triphenylphosphine)copper(I) tetrahydroborate seemed worth examining as the others would be affected by the steric hinderance caused by the iodine atom which could also be reduced out. The reduction of 2-iodobenzoyl chloride by bis(triphenylphosphine)copper(I) tetrahydroborate gave the aldehyde in 55-68% yield but large scale reductions using stoichiometric amount of the complex involved a very large physical bulk of the reagent, which proved difficult to handle and on several occasions, separation of triphenylphosphineborane (154) from 2-iodobenzaldehyde proved difficult.



154

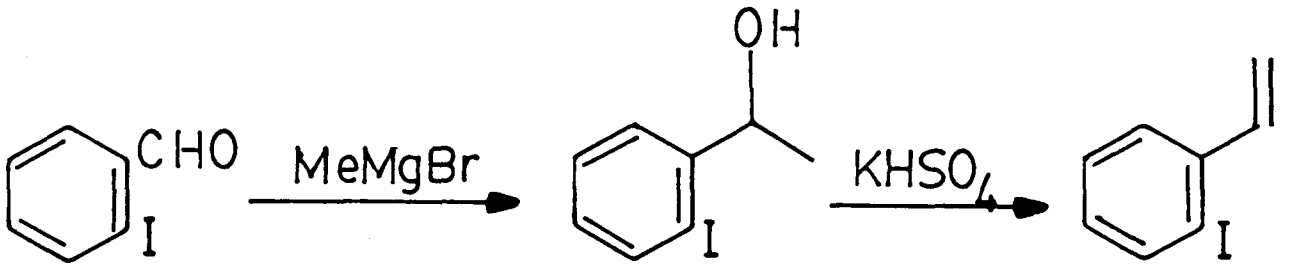
Reduction of 2-iodobenzoyl chloride to 2-iodobenzyl alcohol (155) by sodium borohydride in dioxane,[150] followed by oxidation with pyridinium dichromate[151] in CH_2Cl_2 proved to be a very satisfactory synthesis of 2-iodobenzaldehyde, so two new methods[152,153] involving modified sodium borohydride for the reduction of acid chlorides to aldehydes were not examined.





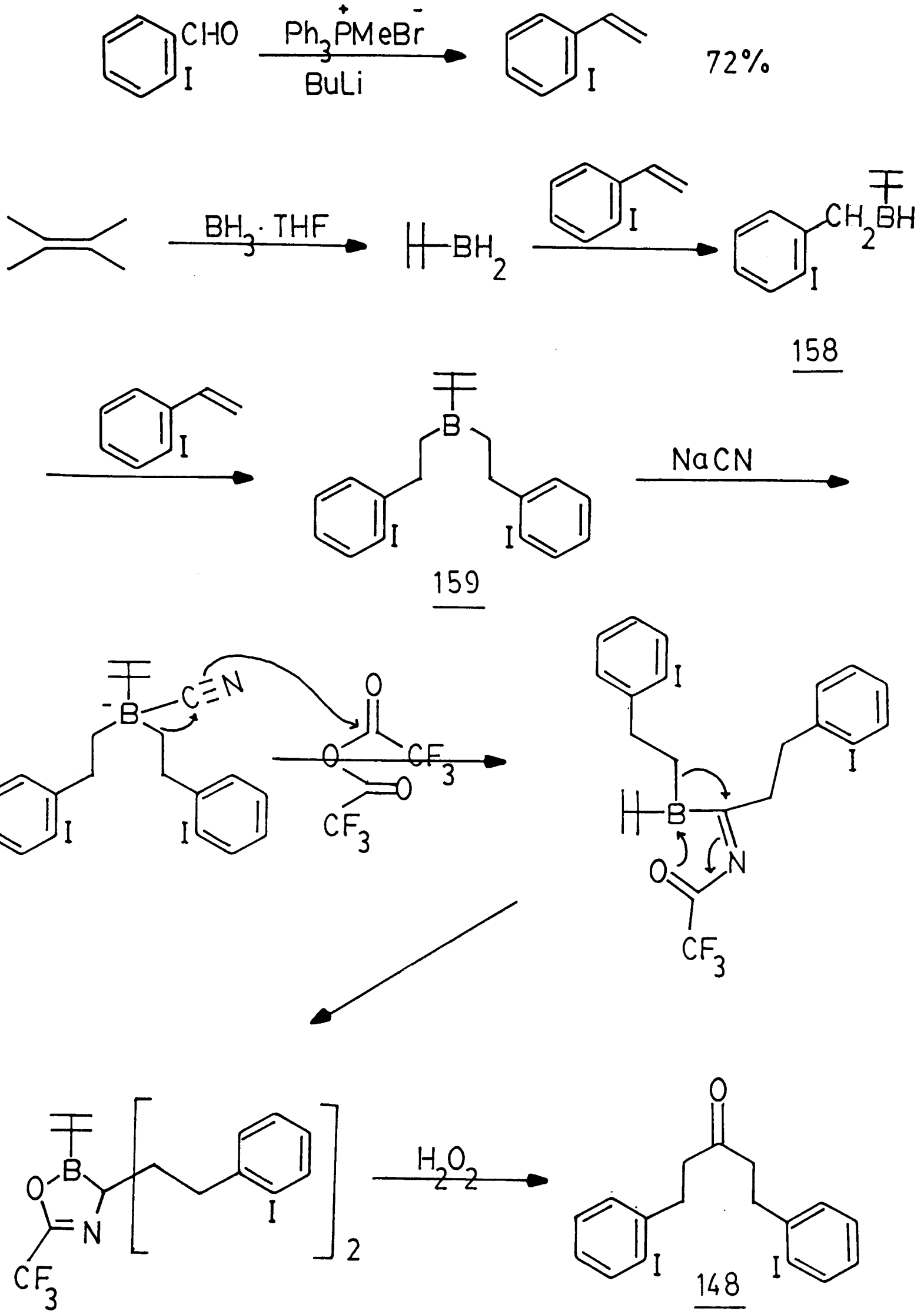
153 76%

The only literature preparation[154] of 2-iodostyrene was based on the dehydration of 2-iodophenylmethylcarbinol (156), itself prepared from 2-iodobenzaldehyde and methylmagnesium bromide, by potassium hydrogen sulphate, a method similar to that used for other halo-substituted styrenes.[155]



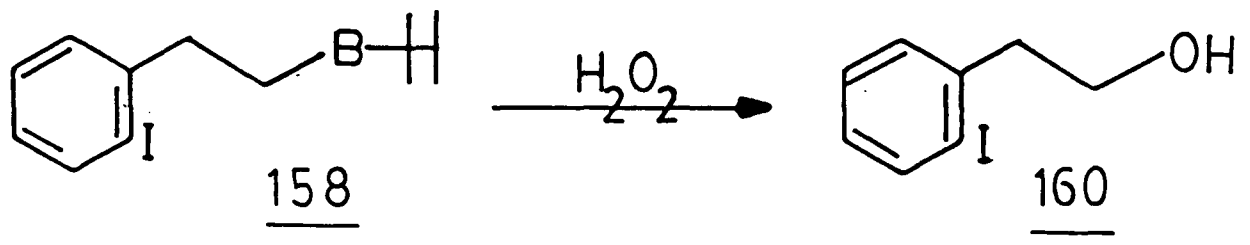
156 157

Using a modified procedure,[157] a Wittig reaction converted 2-iodobenzaldehyde smoothly into 2-iodostyrene. Hydroboration of 2-iodostyrene with thexyl borane[113] was carried out under the condition reported.[105a,157] The thexyl derivative (158) was treated with sodium cyanide,[104,105a] followed by trifluoroacetic anhydride and hydrogen peroxide (scheme 6).


CHO
I
Ph3PMeBr
BuLi
72%
BH3 · THF
BH2
CH2BH
158
159
NaCN
CN
CF3
H2O2
148

SCHEME 6

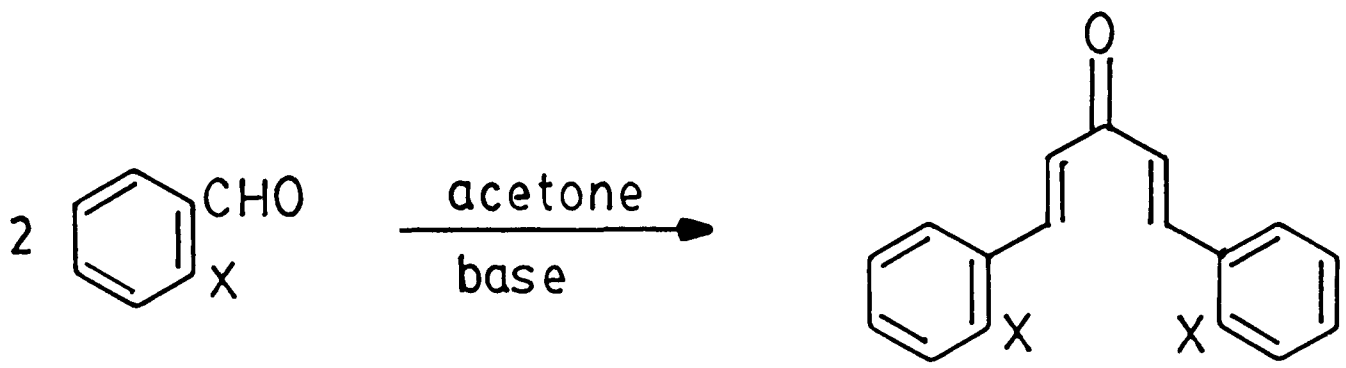
Careful chromatography of the product on SiO_2 gave unreacted 2-iodostyrene (10.7%), 1,5-di(2-iodophenyl)pentan-3-one (56%) and 2-(2-iodophenyl)ethanol (160) (15.3%). The last presumably arose from the oxidation of the monothexyl derivative (158).



158 160

The 1,5-di(2-iodophenyl)pentan-3-one thus obtained had essentially the same spectroscopic data (^{1}H NMR, IR and MS) as that synthesized by the previous route. However, it was obtained as a light yellow viscous oil, instead of colourless prisms, and could not be induced to crystallise. This was attributed to residual impurities containing boron which were very difficult to remove. The 2-(2-iodophenyl)ethanol was identified by its ^{1}H NMR spectrum, which showed 2 sets of triplets (δ 2.90 and δ 3.75) for the methylene units and an exchangeable proton (δ 2.40) and aromatic signals. Changing the reaction condition did not improve the situation and the higher yield of a less pure product obtained by this more laborious route made the synthesis less attractive than the previous one (p.62).

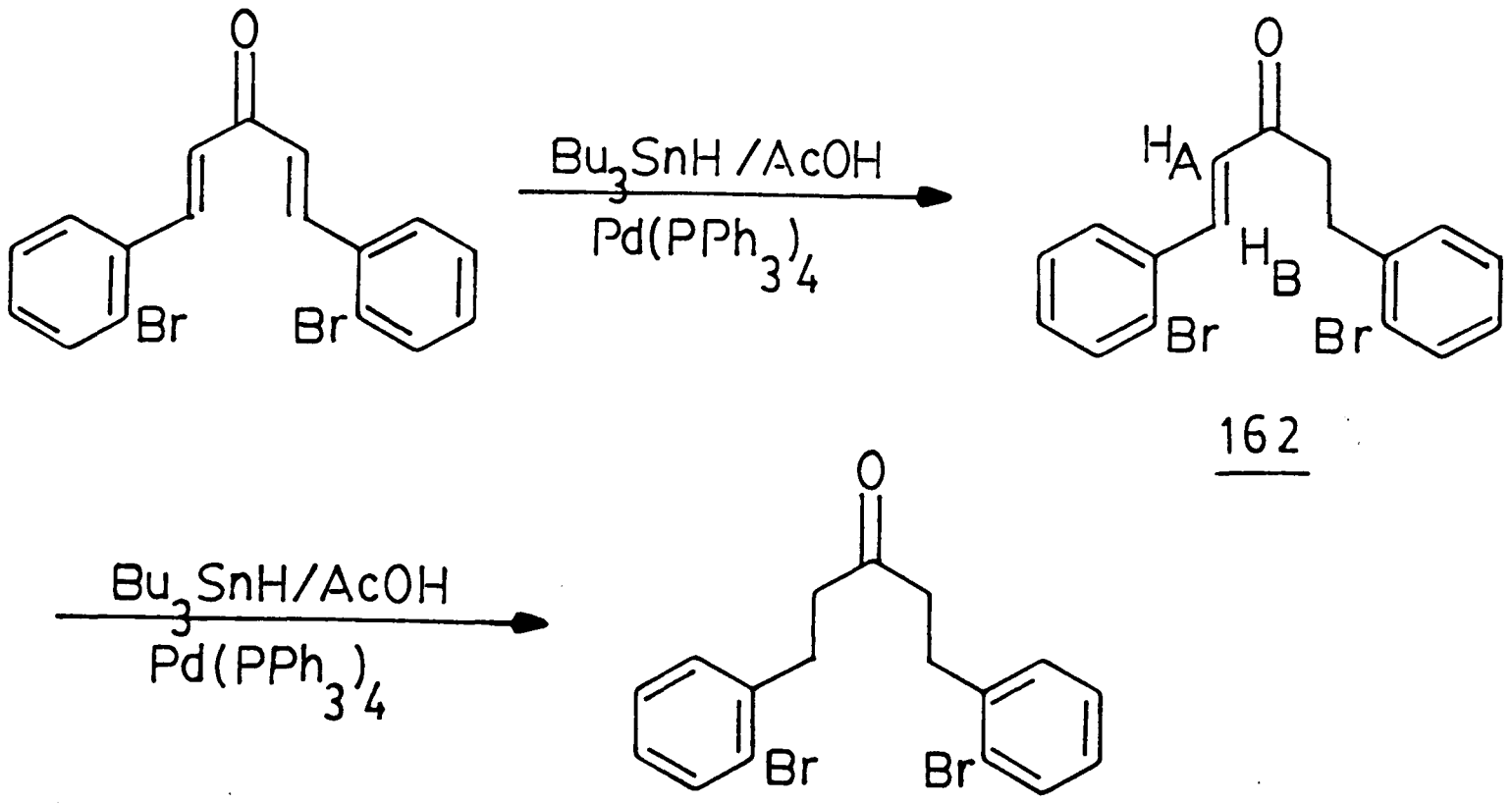
The availability of 2-halobenzaldehydes and their easy conversion to the corresponding dienones with acetone and base suggested an investigation of the conjugate reduction of (141) and (161), hydrogenation methods having been excluded earlier (p.64) for (161).



141 X = Br

142 X = I

1,5-Bis(2-bromophenyl)penta-1,4-dien-3-one (160) was synthesized[159] and treated with n-butyl tin hydride (2.4 equivalent), tetrakis-(triphenylphosphine)palladium(0) (2 mols %), acetic acid (2.1 equivalents) in benzene using standard conditions.[126] Reduction to the saturated analogue (163) detected by the changes in the ^{1}H NMR spectra took place.

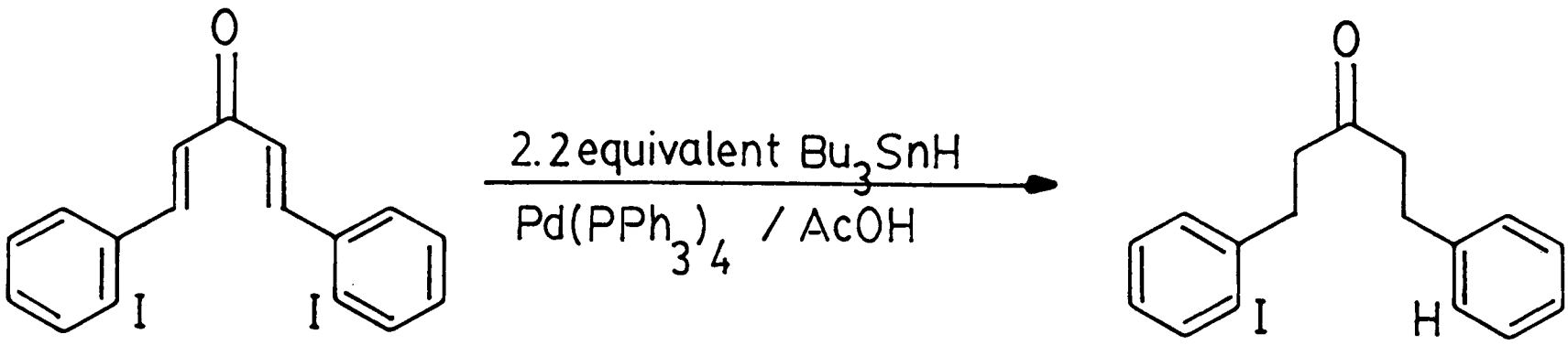


162

163

Examining the ^{1}H NMR of the reaction mixture after 10 min revealed that the 'semi-saturated' dienone (162) was present. The methylene groups appeared almost at δ 3.05 as a broad singlet and the olefinic protons HA (δ 6.55) and HB (δ 7.90) appeared as doublets, showing that stepwise reduction was taking place. No attempts were made to isolate and characterise this intermediate.

Encouraged by these results, 1,5-di(2-iodophenyl)pentan-3-one (161) was reduced under identical conditions and after 20 min reaction was complete. Chromatography afforded a viscous yellow oil, the ^{1}H NMR spectrum of which showed two groups of protons δ 2.50-3.10 and δ 6.70-7.75 in a 8:9 ratio. The mass spectrum showed the molecular ion at m/e 364 and the IR spectrum showed λmax 1710 cm^{-1} corresponding to a saturated ketone. One of the iodine atoms in (148) had been cleaved off to form (164).



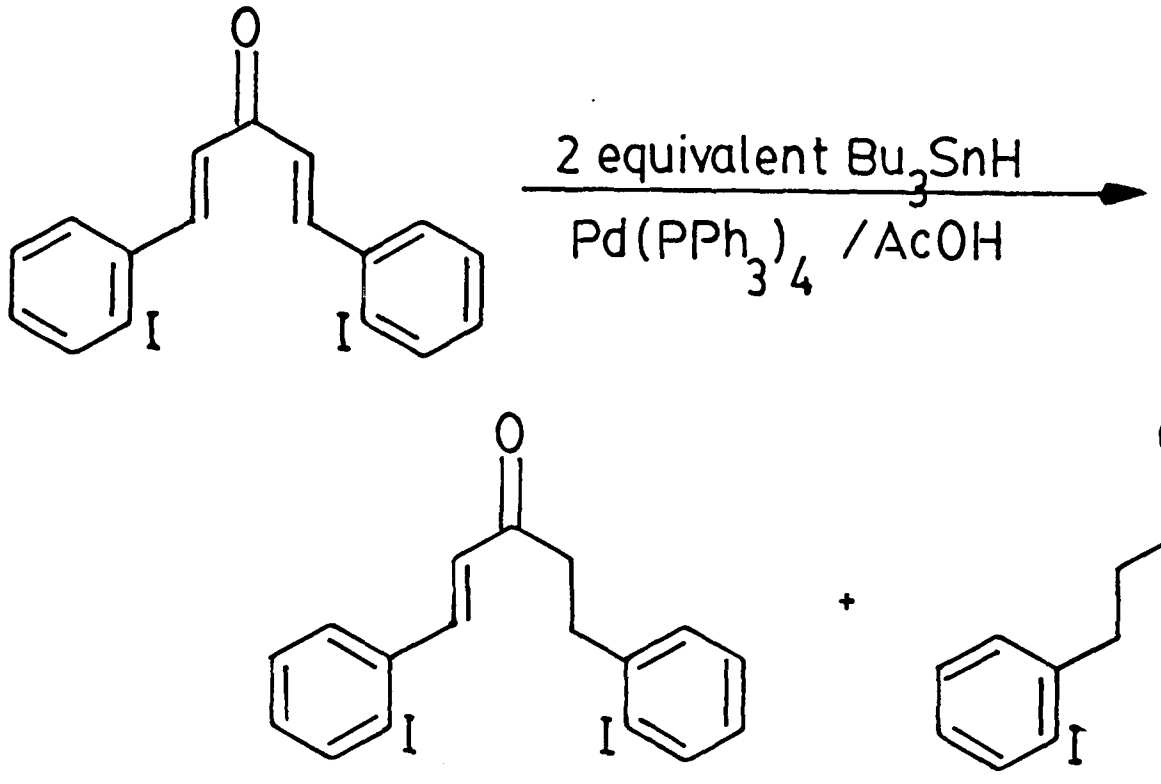
161 164

Guibe et al[149c] reported that at the end of such reduction, decomposition of the excess butyltin hydride usually occurred.

$$Bu_3SnH \xrightarrow{Pd(PPh_3)_4} Bu_3SnSnBu_3 + H_2$$

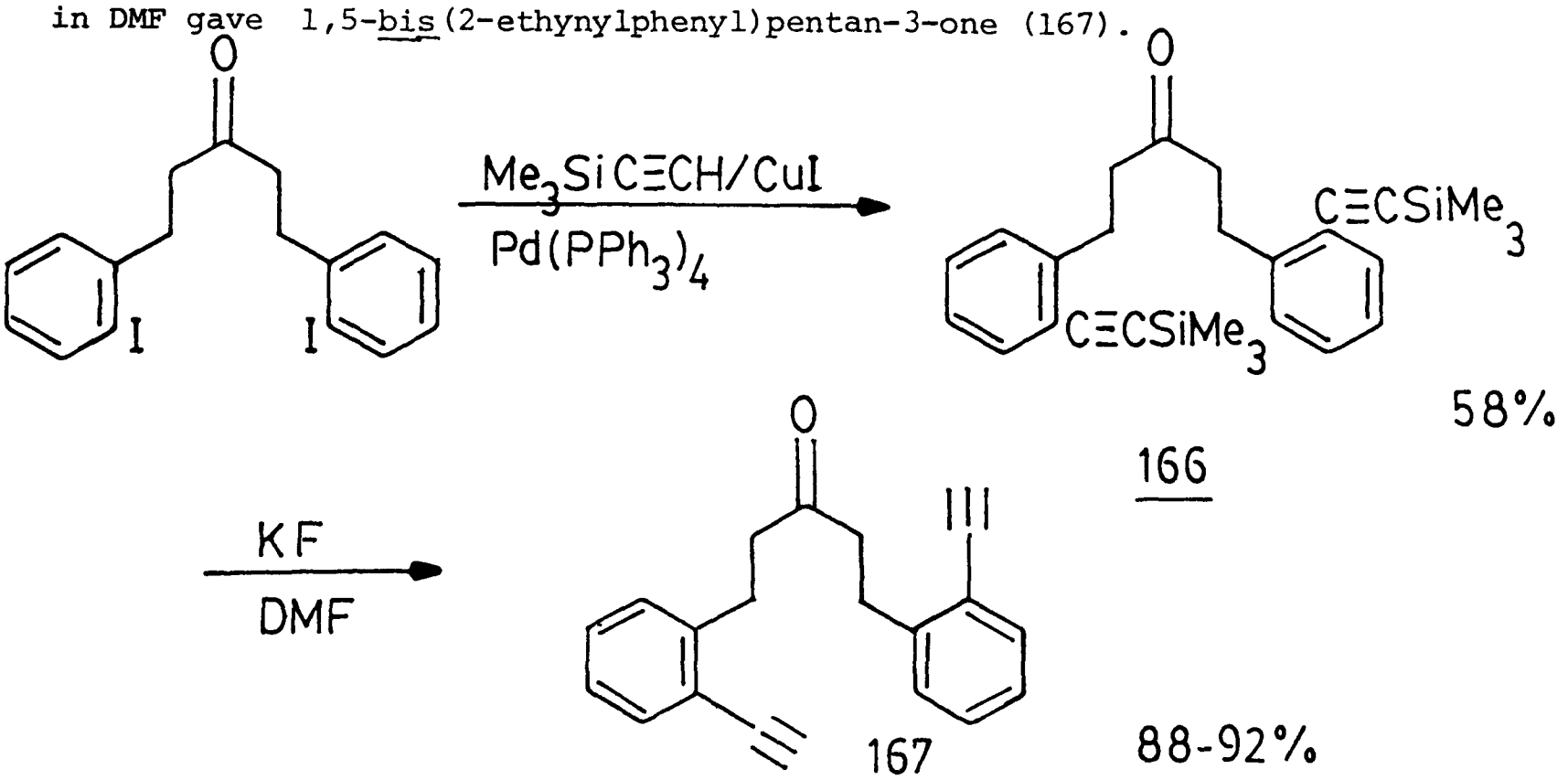
Thus, it is possible that the iodine atom in (164) was hydrogenolysed by the liberated hydrogen. However, we cannot omit the

possibility of direct displacement of the iodine atom by butyltin hydride, as reported by House et al.[159] After reducing the amount of butyltin hydride to exactly 2 equivalents, ^{1}H NMR showed that a roughly 1:1 mixture of (148) and (165) was formed.



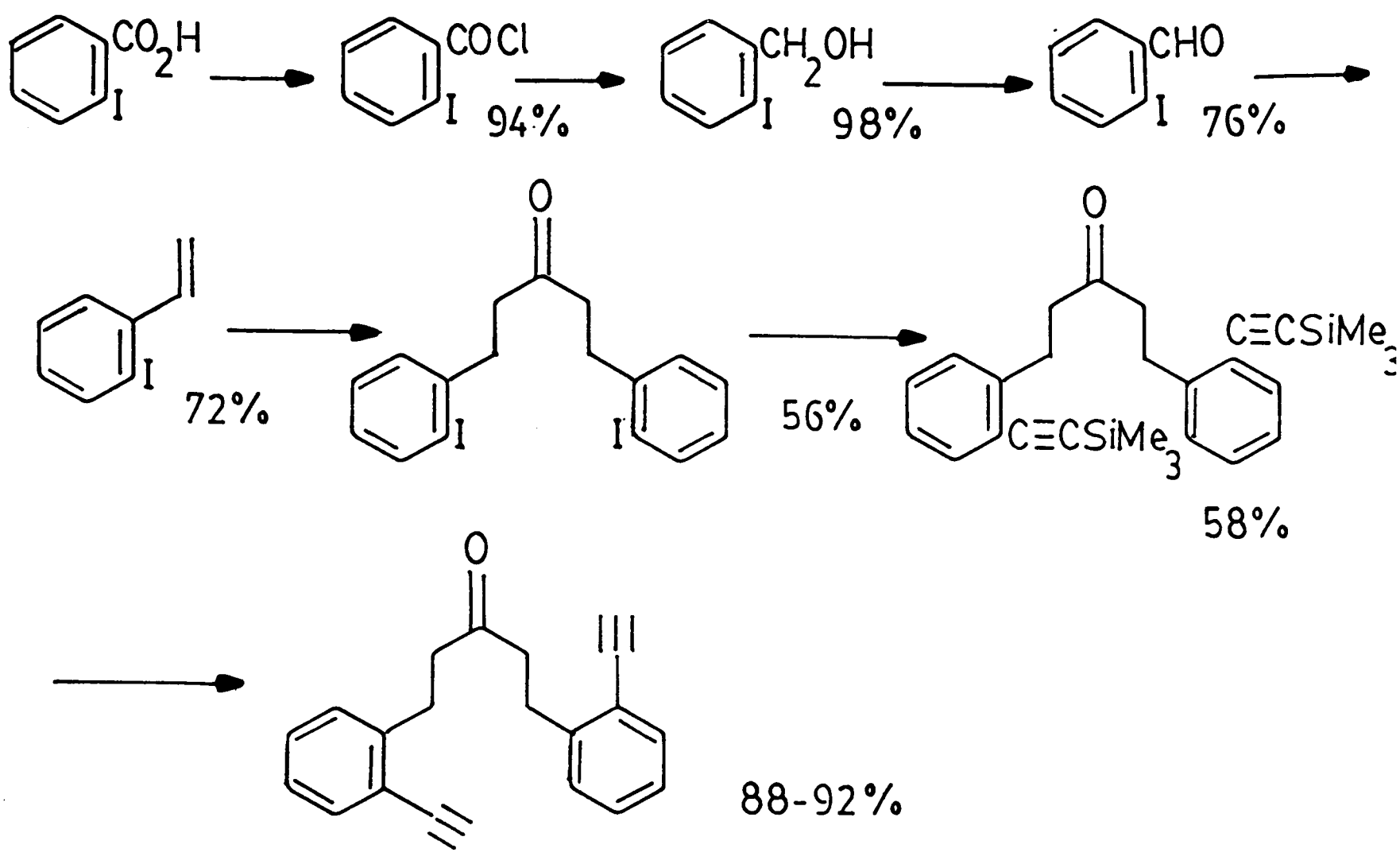
	165		148
ca.	50%	:	50%

1,5-di(2-iodophenyl)pentan-3-one (148) was now coupled with ethynyltrimethylsilane in THF/hexane in the presence of $Pd(PPh_3)_4$, copper(I)iodide and triethylamine. The hoped for bis-ethynylsilylated derivative (166) was formed and on desilylation with potassium fluoride in DMF gave 1,5-bis(2-ethynylphenyl)pentan-3-one (167).

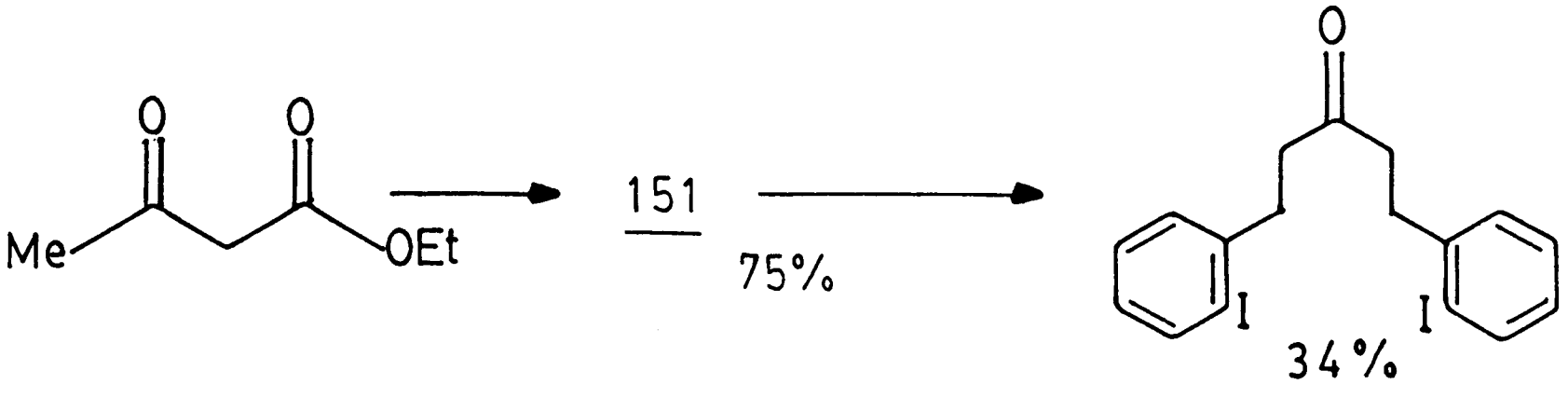


It is interesting to note that by replacing the iodine atom in (148) with the ethynyltrimethylsilyl group, the low field doublet (J 8 Hz) for the 3' aromatic proton moved upfield into the aromatic multiplet. The size of this doublet was used to measure the extent of the coupling.

The synthetic scheme is now summarised:



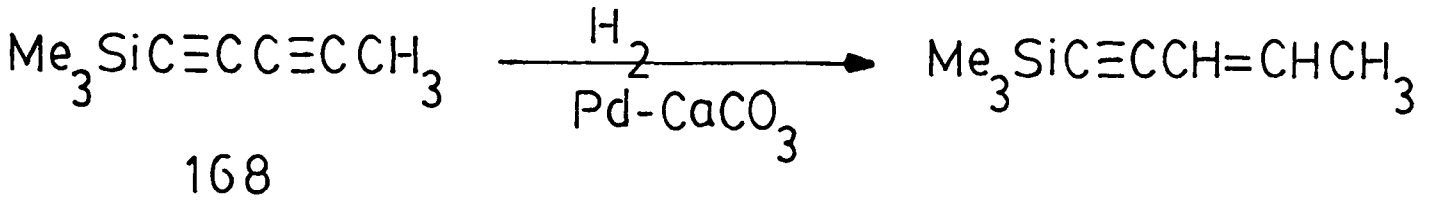
SCHEME 7



SCHEME 8

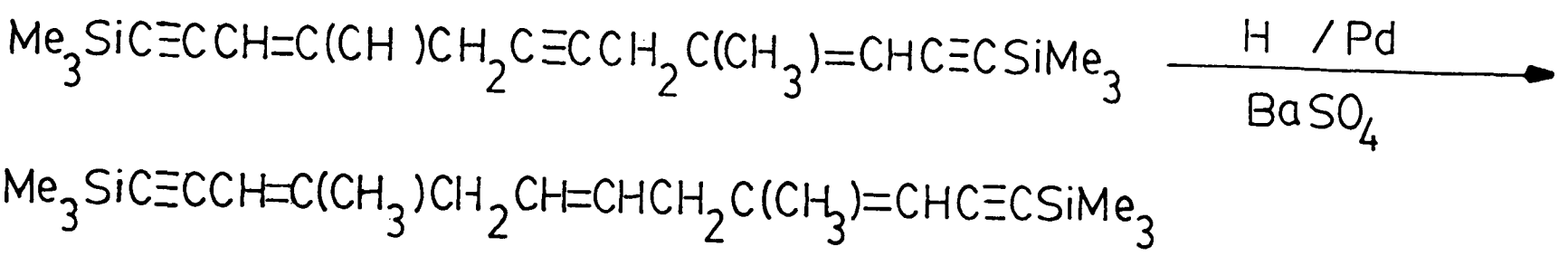
The low yield of 1,5-bis(2-iodophenyl)pentan-3-one (148) affected the overall yield of (167) greatly. It therefore seemed a good idea to avoid the intermediacy of (148) in the synthesis of (167). This would require the insertion of the ethynyl group at an earlier stage, leading to the complication of reducing a conjugate ketone while leaving the ethynyl group intact.

In 1964, Shakhovskoi et al[160] found that a triple bond attached to a silicon atom is not reduced when 1,3-pentadiynyltrimethylsilane (168) is treated with palladium on calcium carbonate.

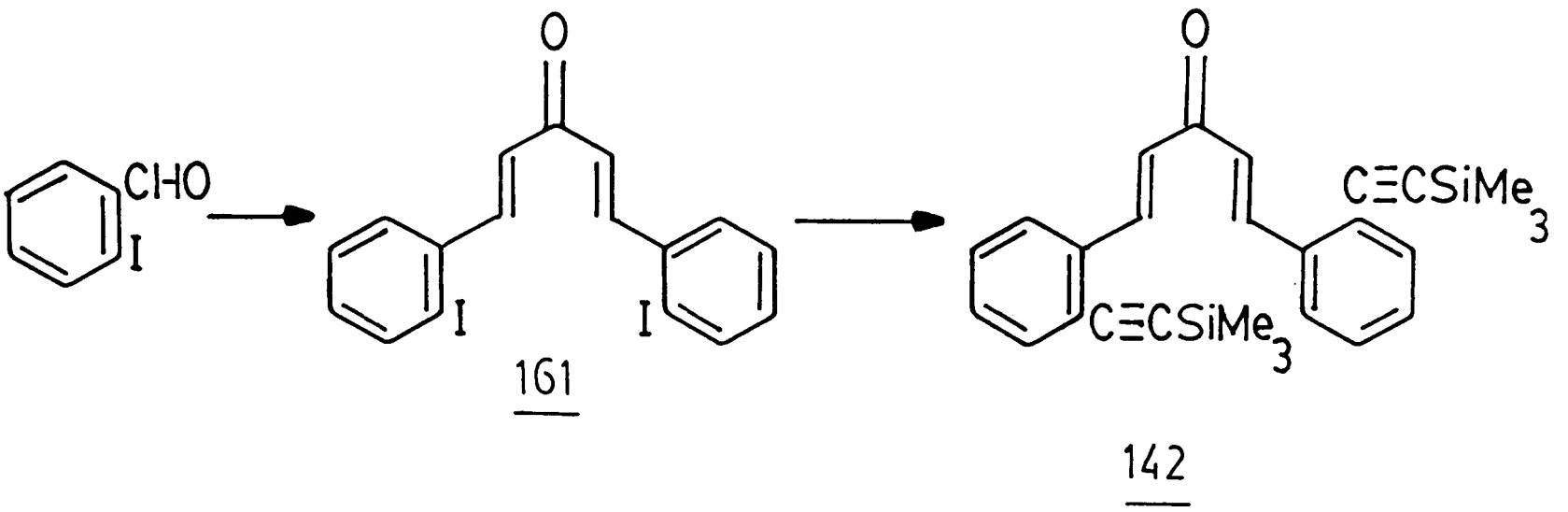


168

Later, Schmidt et al[161] reported a similar finding.

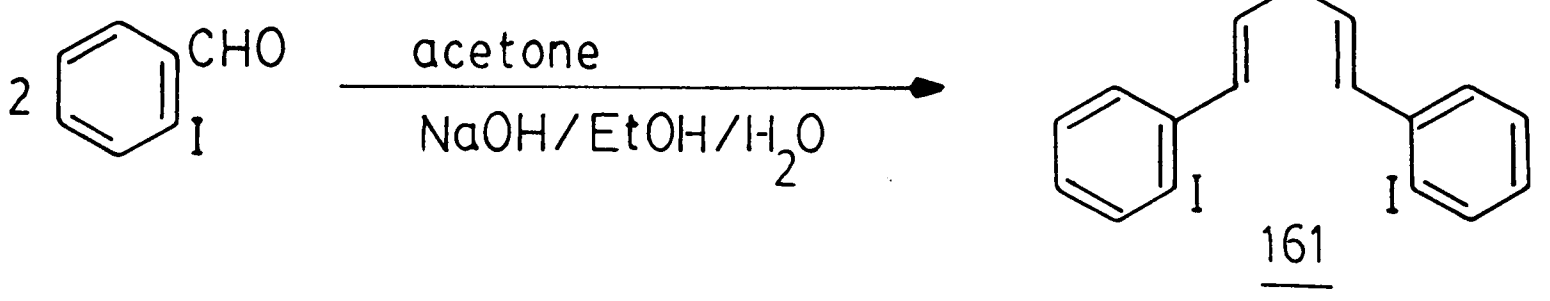


As n-butyltin hydride, in the presence of $Pd(PPh_3)_4$ and acetic acid, can affect conjugate reduction of the dienone systems of (160) and (161), it is not unreasonable to suspect that this reagent might effect conjugate reduction of the enone system of (142), while leaving the trimethylsilylated triple bond intact. The new synthetic scheme would be:



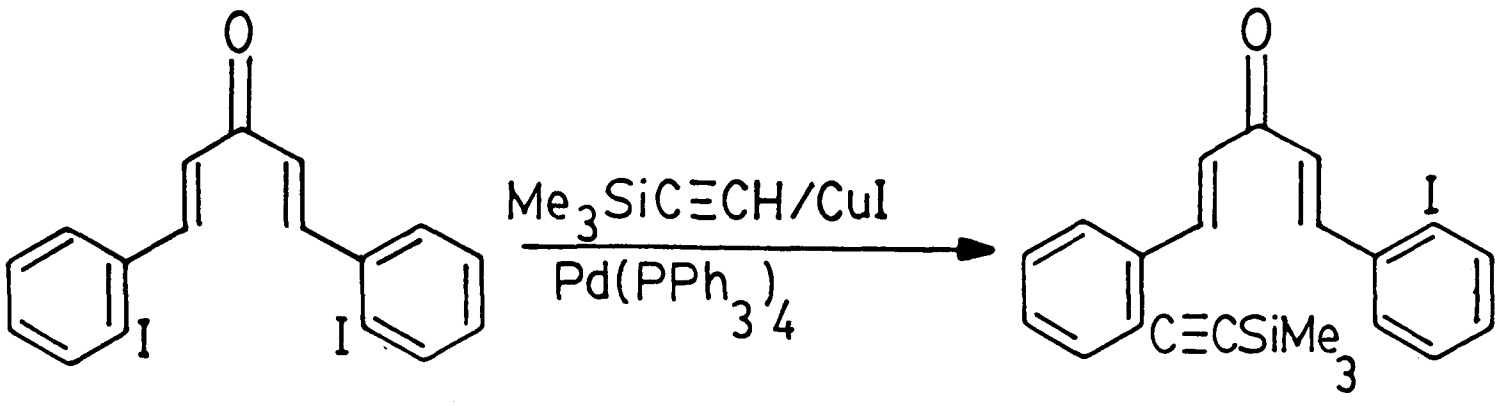
161 142 166 167

By condensing 2-iodobenzaldehyde with acetone under similar conditions reported for dibenzalacetone,[158] 1,5-bis(2-iodophenyl)-penta-1,4-dien-3-one (161) was obtained in 75% yield.

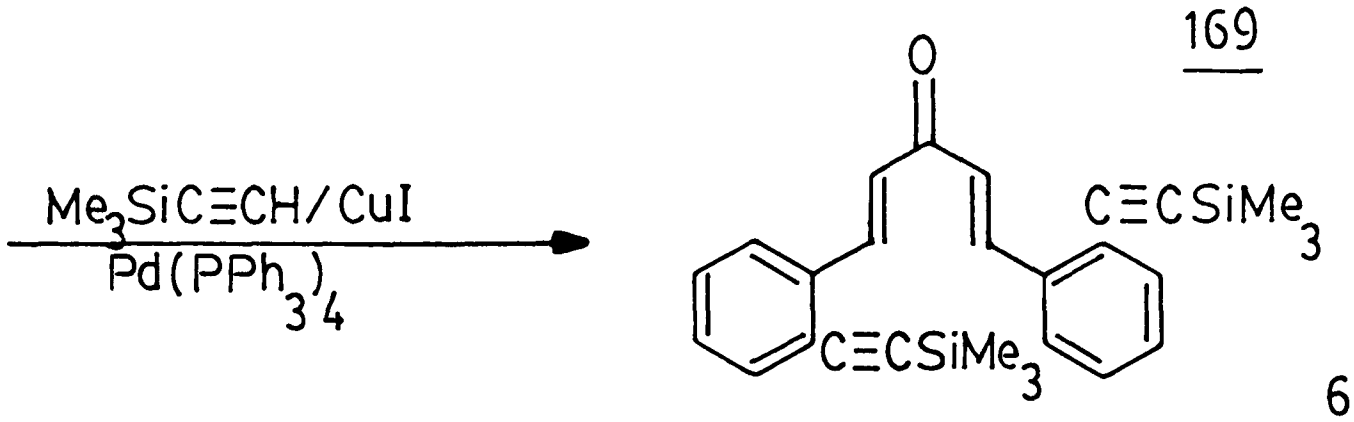


161

Subsequent coupling of (161) with ethynyltrimethylsilane (as a solution in THF/hexane), in the presence of $Pd(PPh_3)_4$, copper(I)iodide, triethylamine and xylene (as cosolvent) gave 1,5-bis{2-(trimethylsilyl)-ethynylphenyl}penta-1,4-dien-3-one (142).



169

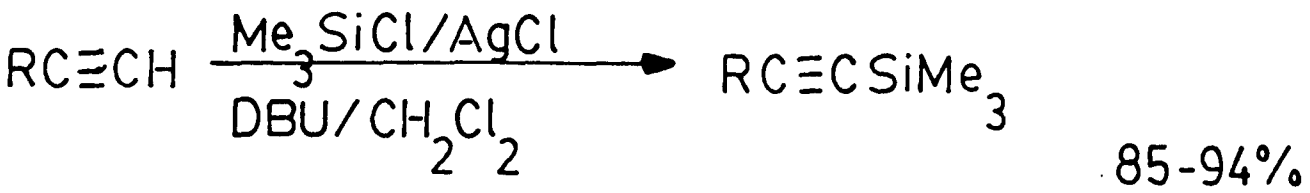


63% overall

142

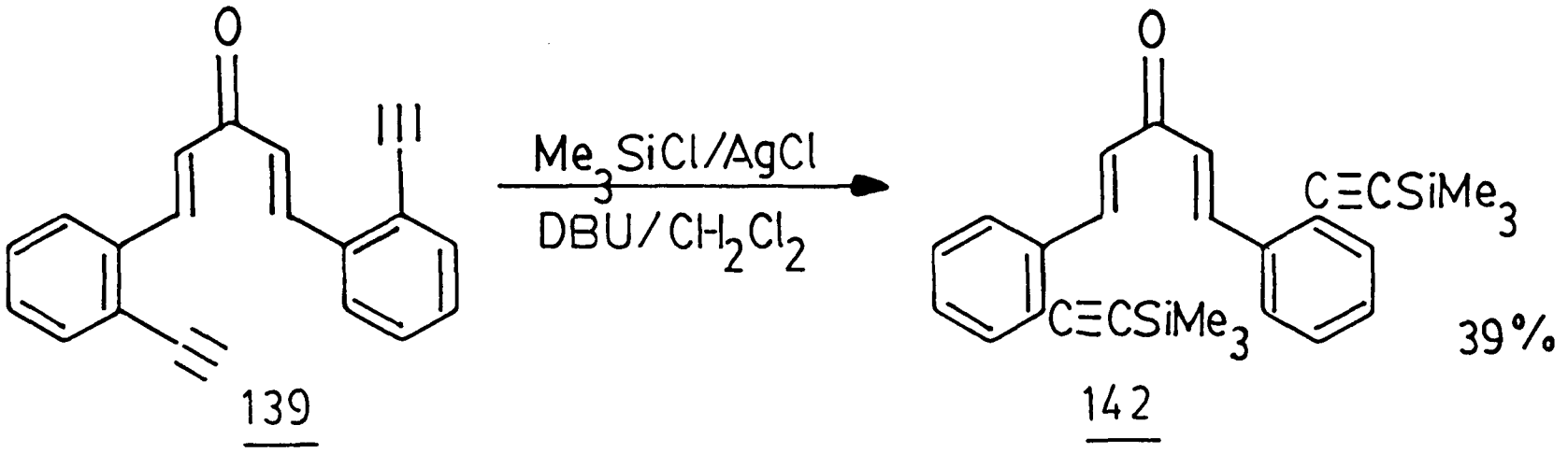
Monitoring the reaction by TLC (SiO_2, Et_2O/PE, 3:7) revealed 3 components (Rf=0.29, 0.42 and 0.50) after 3 h refluxing, and after 7 h, only the spot with Rf 0.50 remained. Apparently the first spot (Rf=0.29) is the starting material (29), the third spot (Rf=0.50) is the product (142), while the remaining one (Rf=0.42) is probably (169), showing that the coupling is stepwise.

Recently Yamaguchi et al[162] reported mild conditions would effect the trimethylsilylation of terminal acetylenes,



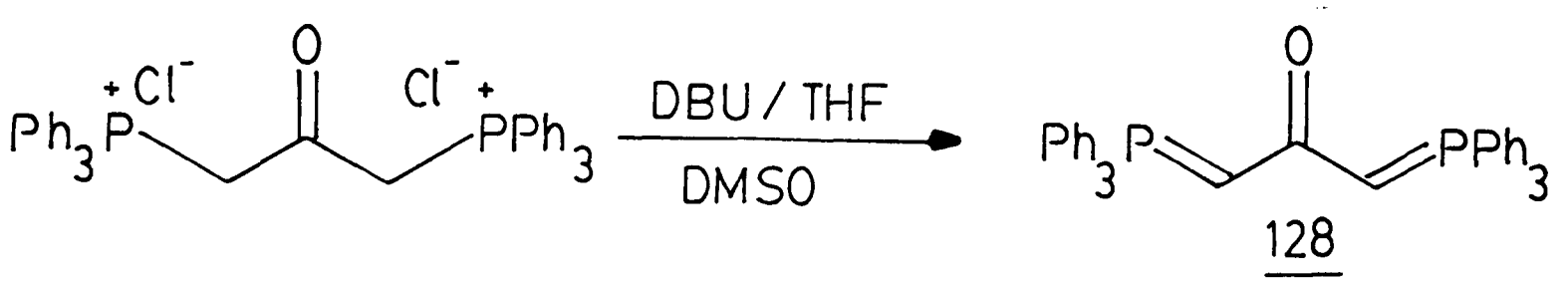
85-94%

Tempted by the high yield, the above reaction was tried on (139), as an alternative approach to (142), but only 39% was obtained.

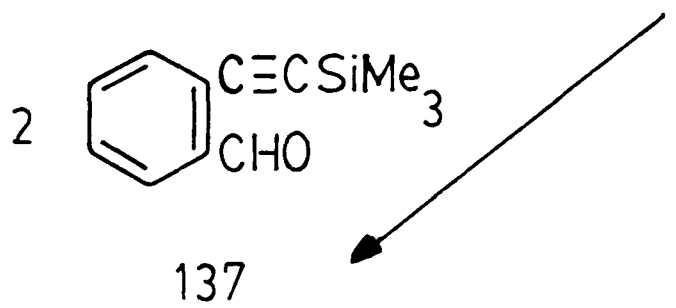


139 142

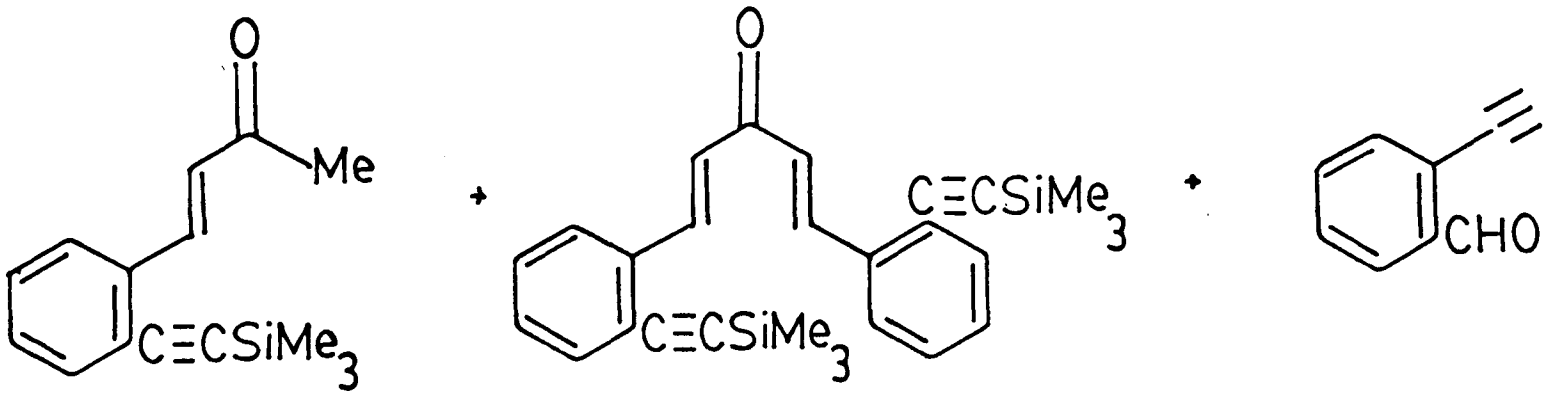
Similarly, a bis-Wittig reaction between 2-(trimethylsilyl)-ethynylbenzaldehyde (137) and the bis-phosphorane (128), prepared from acetone-1,3-bis(triphenylphosphonium)chloride[98a] and DBU, was equally frustrating. Thus, under various conditions and different solvents, complex mixtures of products including desilylated ones, were obtained.



128

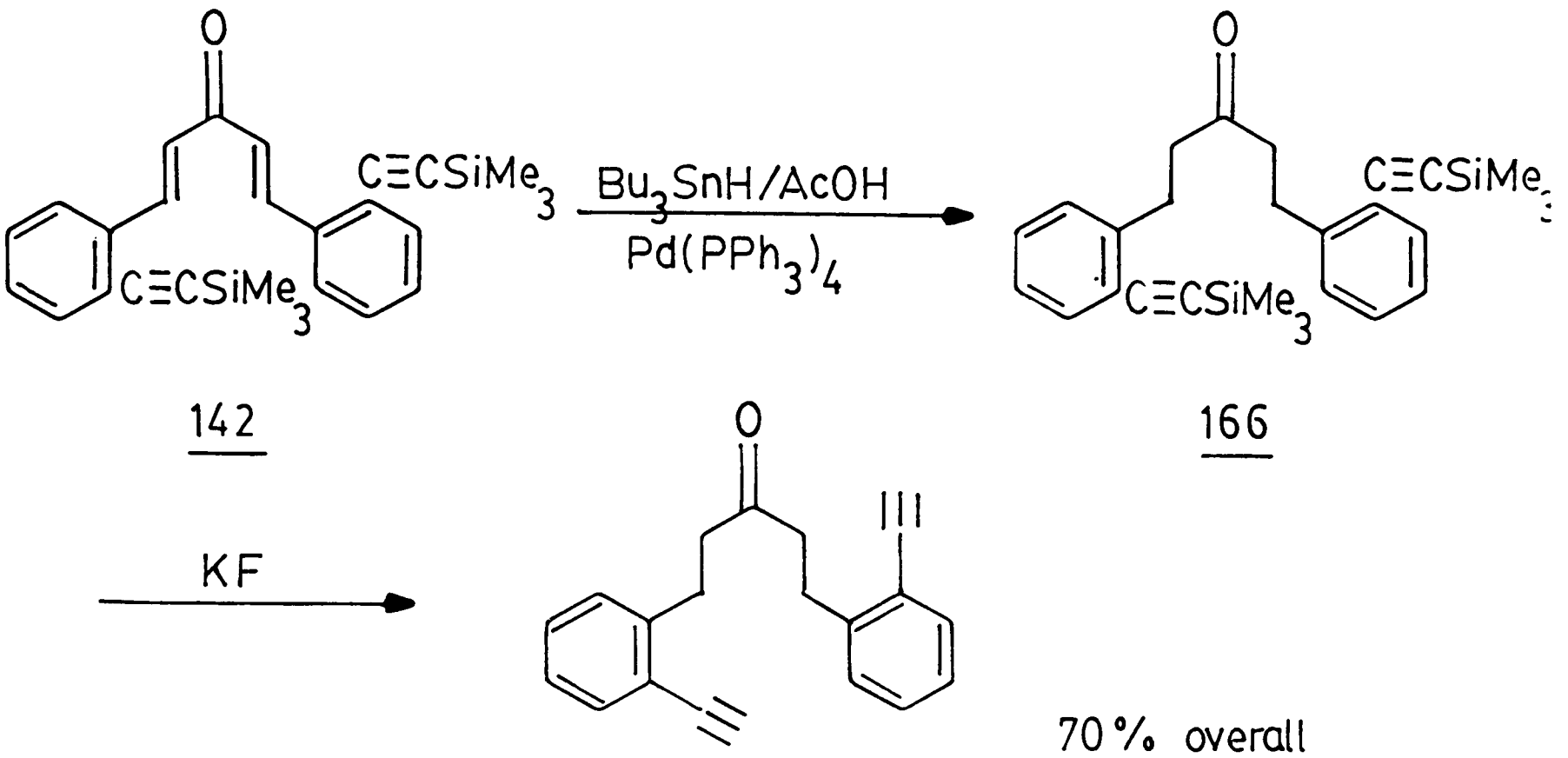


137



(+ desilylated analogues)

Conjugated reduction of (142) was carried out under the general conditions reported.[126] By using 2.4 equivalents of n-butyltin hydride to 1 equivalent of (168), reduction was complete within 20 min at RT. After flash chromatography on alumina, (166) thus obtained was desilylated by potassium fluoride in DMF to give 1,5-bis(2-ethynyl-phenyl)pentan-3-one (167).



142 → 166 → 167

So, the prediction that a trimethylsilylated acetylene is inert under the normal conditions used for conjugate reduction by n-butyltin hydride was realized! A methodology hitherto unknown in the literature.

Examination of the reaction mixture after 3 min by TLC revealed that apart from the starting material (142), 2 spots (Rf=0.15 and 0.25) were present and after 20 min, only the one with Rf=0.25 was left, suggesting that stepwise reduction was taking place.

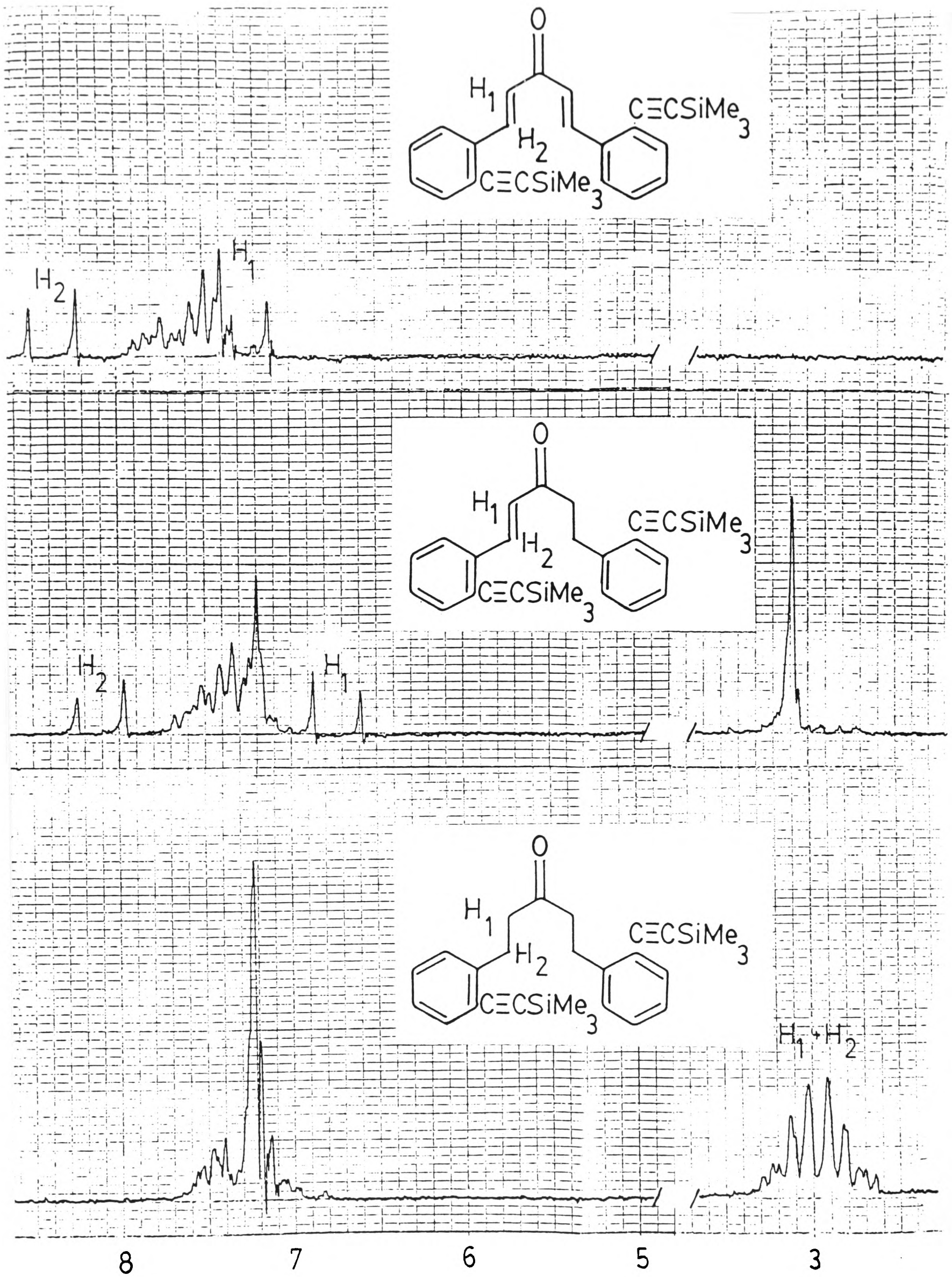
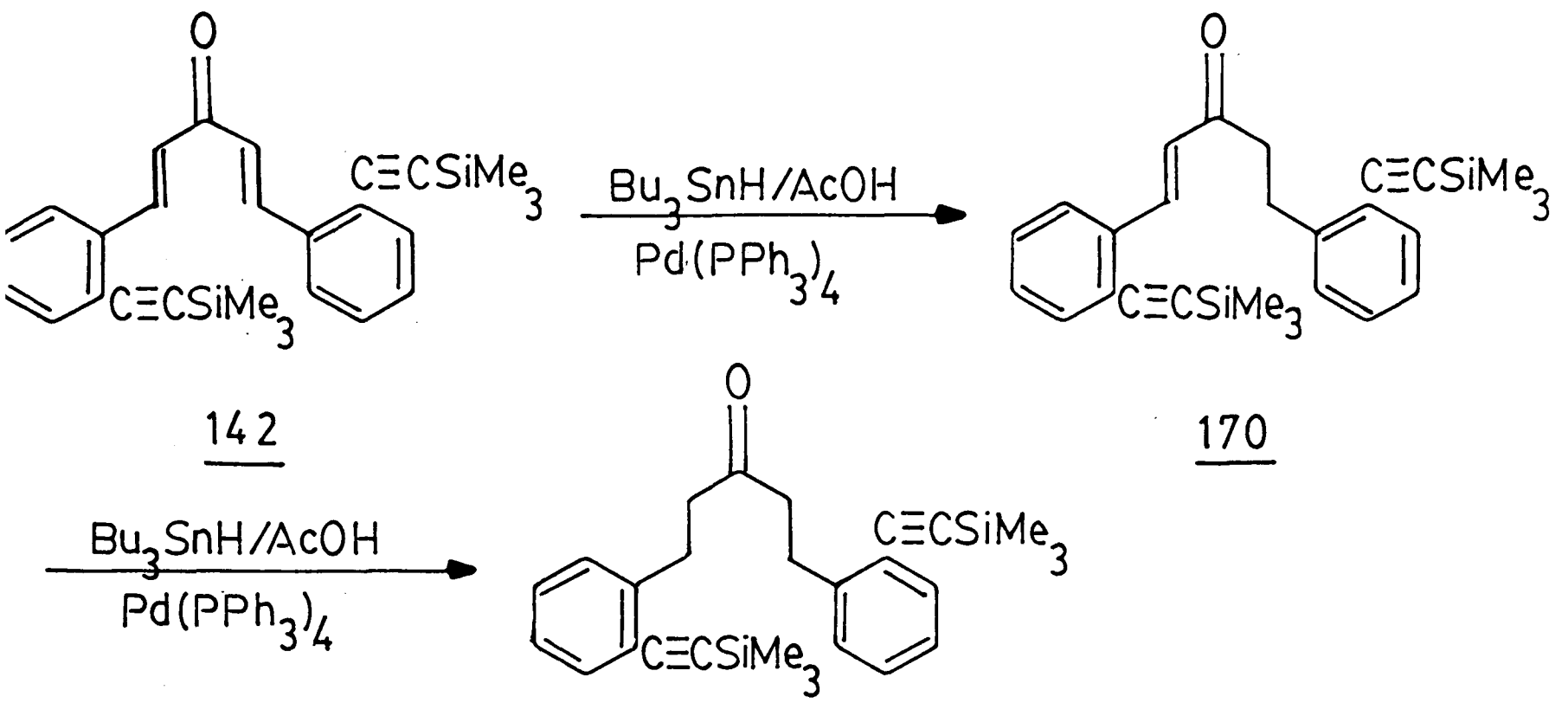


diagram 4 ^{1}H NMR(60MHz) of (142),(170) and(166)



In order to prove this, 1 equivalent of n-butyltin hydride was allowed to react with (142), under identical conditions as before. After 20 min, the reaction was quenched and ^{1}H NMR examination of the crude reaction product showed that it was essentially (170), contaminated by traces of (166). Recrystallization gave 1,5-bis{2-(trimethylsilyl)ethynylphenyl}1-penten-3-one (170) as colourless prisms in 85% yield, and it was initially identified from its ^{1}H NMR spectrum. The methylene protons appeared as a broad singlet (δ 3.10), the olefinic protons H_1 (δ 6.72) and H_2 (δ 8.10) as doublets J 16.7 Hz, while in (166) the corresponding sets of protons appeared as a symmetrical multiplet between δ 2.50-3.20 (diagram 4); MS (m/e 428 for M^+); IR 1665 cm^{-1} (νc=O).

Compound	λmax (EtOH) nm		
(142)	324.5 (31030)	251 (29638)	225 (19593)
(170)	292 (5438)	249 (13936)	203 (8667)

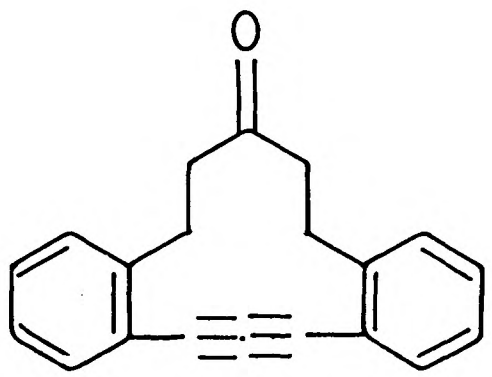


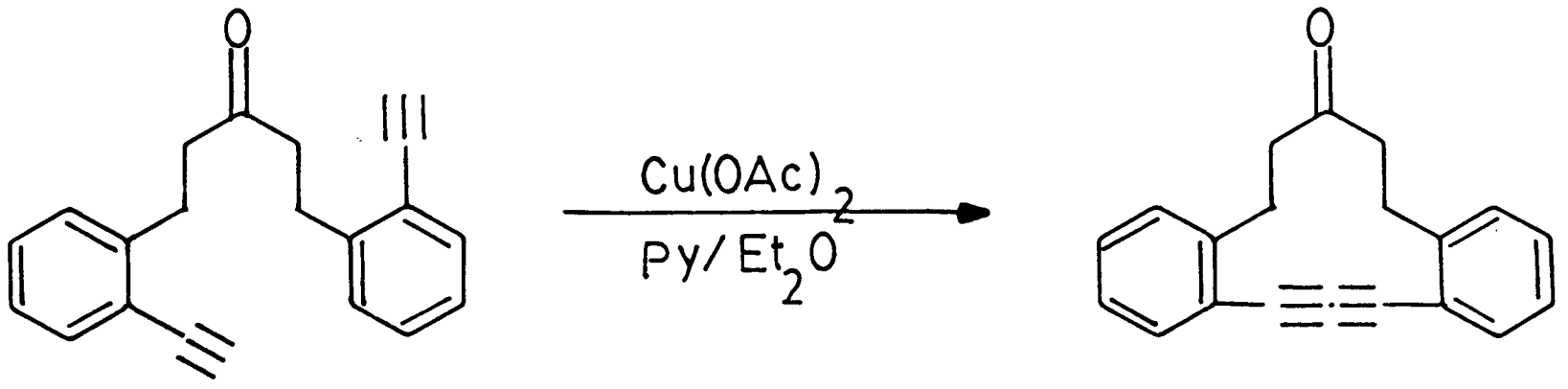
diagram 5 ^{1}H NMR(300MHz) of (171)

The remaining double bond in (170) was readily reduced by a further equivalent of n-butyltin hydride under identical conditions to give (166) in 80% yield.

As compared to the original route, this new approach to (166) is undoubtedly superior. Not only the yield of (167) is nearly double, but the reaction time involved is reduced considerably.

Intramolecular oxidative coupling of (167) initially gave problems. Very slow addition of (167) to the slurry of anhydrous copper acetate, hence a longer reaction time, gave very low yield of (171) presumably due to the instability of (171) under those conditions. Attempts to scale the reaction up sixfold led to a threefold decrease in yield, while freshly distilled and very carefully dried solvents enhanced the overall yield.

By adopting the condition suggested by Sondheimer et al[96] and with all the precautions taken, intramolecular oxidative coupling of (167) to 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-one (171), the first example of a partially saturated dibenzo{13}annulenone was effected in 77% yield, after recrystallization.



171

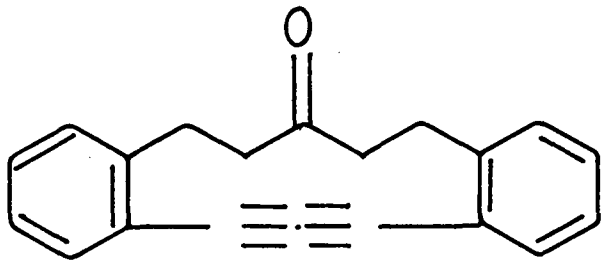
The ^{1}H NMR (diagram 5) and ^{13}C NMR spectra show the expected resonances. The carbonyl absorption in the IR (1695 cm^{-1}) is slightly lower than that expected. The UV spectrum shows much more fine structure than

its fully unsaturated analogue (127),[115] and addition of perchloric acid gave the corresponding protonated carbonyl species.

Table 1

Compound	λmax(EtOH) nm
(127)	- - - 284, 298, - - - - 379, 468
(171)	200, 219.5, 277, 288, 295.5, 309.5, 317, 332, 339, - -
(171)+$HClO_4$	201.5, 221, 227, 292, 297.5, 311.5, 319, 331, 341, - -

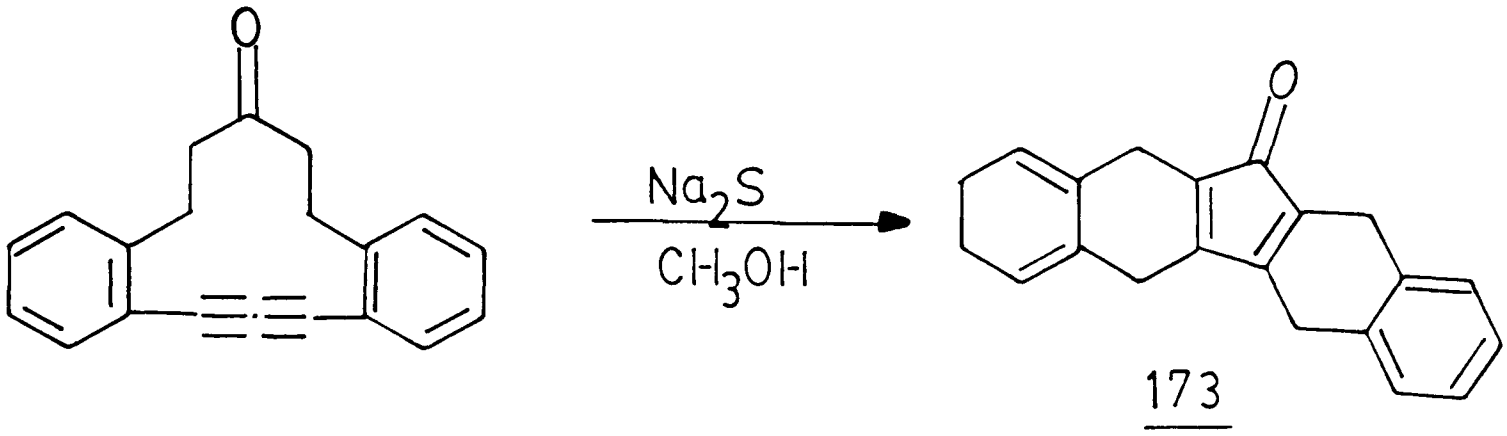
A Dreiding model of (171) shows clearly a 'bowed' diacetylene linkage.



171

Refluxing (171) with 4 equivalents of sodium sulphide in methanol did not result in the expected {9}(2,5)thiophenophane (172). The ^1H NMR spectrum showed 2 groups of broad singlets at δ 3.11 and 3.83 and aromatic signals, with the integration suggesting a ratio of 1:1:2. The original carbonyl absorption of (171) at 1695 cm^{-1} disappeared and was replaced by one at 1602 cm^{-1}. The MS gave m/e 284 for M^+, while the UV spectrum showed λmax at 370 nm. Combustion analysis suggested an empirical formula of $C_{21}H_{16}O$, assuming that no sulphur was incorporated into (171) during the reaction. Since the empirical formula $C_{21}H_{16}O$ (MW=284) is not only consistent with that observed in the MS, but also the same as that of (171), obviously intramolecular rearrangement had taken place. Based on the above data and symmetry

consideration, structure (173) rather than (174) and (175) is tentatively assigned to the product. Sodium sulphide could be acting as the basic catalyst for the proposed prototropic shift. Recalling that in the intramolecular oxidative dimerization of 1,2-bis(2-ethynylphenyl)ethane (108) using copper acetate, the strained intermediate macrocyclic enol acetate underwent transannular fusion to form a more stable tetracyclic structure, a parallel could probably be drawn for the present situation. Similar transannular cyclization has been reported by Raphael et al[163] in the case of the strained tetrayne (176) which on hydrogenation gave the pentacyclic hydrocarbon (177).



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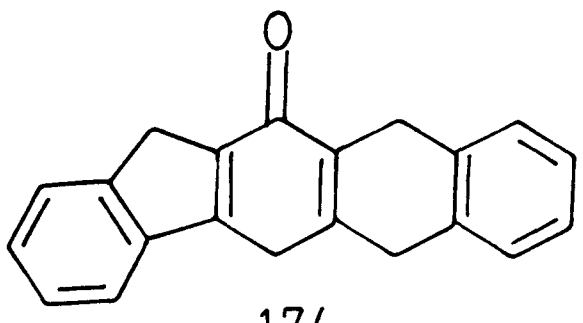

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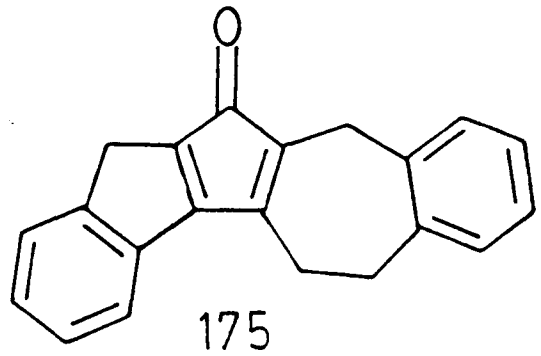

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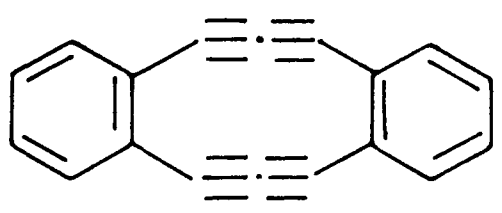

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177

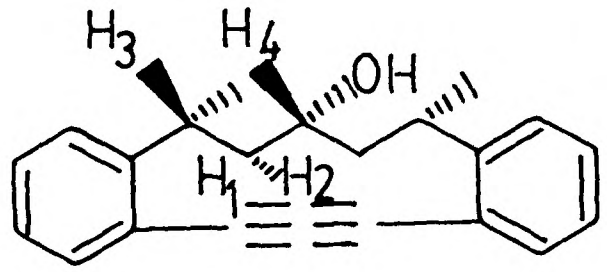
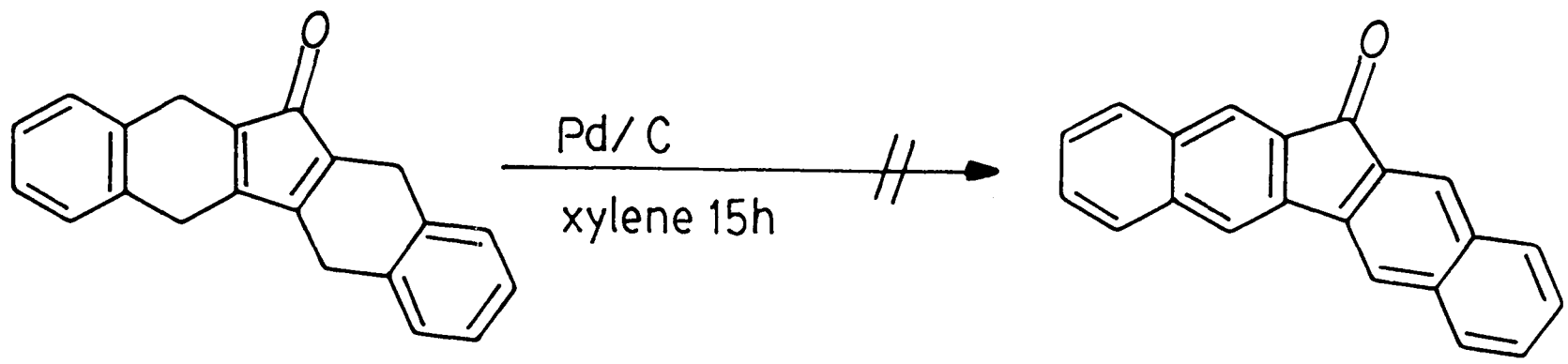


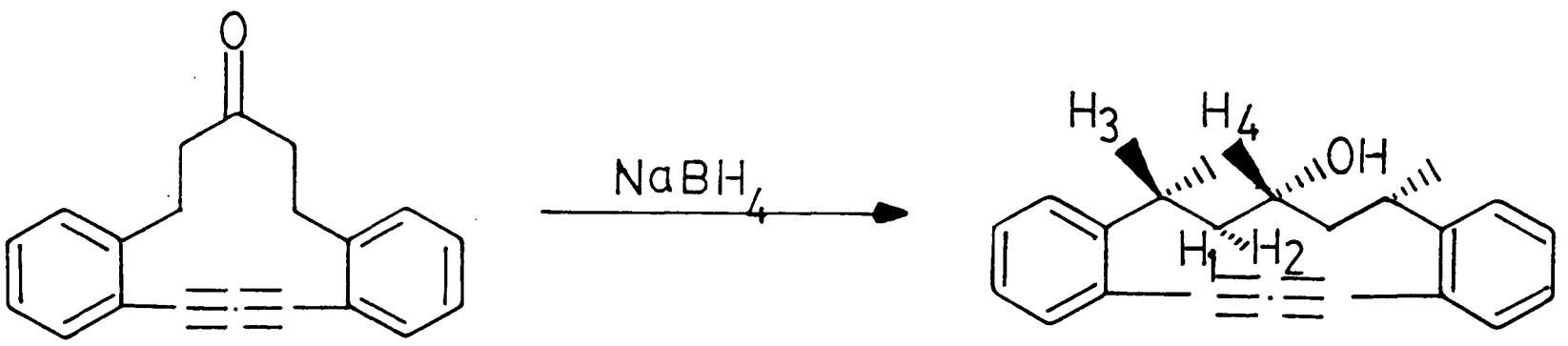
diagram 6 ^{1}H NMR(300MHz) of (179)

Attempted dehydrogenation of (173) to the fully conjugated analogue (178), by 15 h refluxing in xylene under N_2 with palladium on charcoal, was unsuccessful and essentially starting material was recovered.



173 178

One simple way to avoid the complications caused by the protons α to the carbonyl group is to reduce the latter down to an alcohol. Unlike its fully unsaturated analogue (127), (171) was readily reduced by sodium borohydride to the corresponding alcohol (179).



179 94%

Structure of (179) was clearly established from its analysis and ^{1}H NMR spectra (diagram 6). The most important features of ^{1}H NMR spectra were the sets of protons H_1 and H_2. Since the H_1 protons are closer to the plane above the diacetylene linkage, they resonate at a lower field than H_2 (δ 2.17 and δ 1.83 respectively). The hydroxy proton was observed to couple with H_4 and appeared as a doublet at δ 1.58.

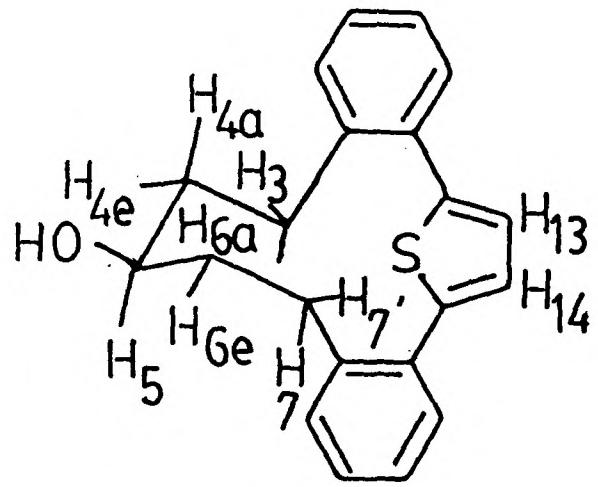
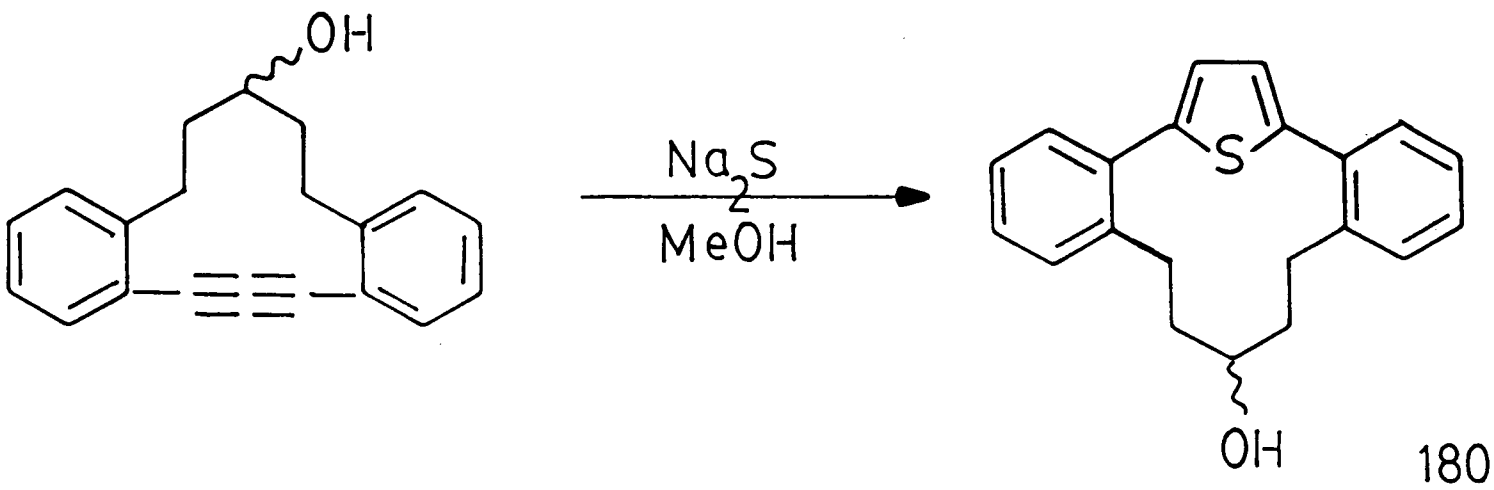


diagram 7 ^{1}H NMR(300MHz) of (180)

Like (171), a Dreiding model of (179) showed the 'bowed' diacetylene linkage.

Refluxing (179) with 4 moles of sodium sulphide nonahydrate in methanol followed by chromatography over silica afforded 1,2,8,9-dibenzo-5-hydroxy{9}(2,5)thiophenophane (180) as yellow prisms. (180) represents the first member of a class of hitherto unknown dibenzo-fused thiophenophane.



180 29%

The structure of (180) was firmly established from spectroscopic data and combustion analysis. The ^{1}H NMR (300 MHz) spectrum showed the thiophene protons (H_{13}, H_{14}) as a singlet (δ 6.93), indicating the symmetrical nature of the molecule H_5 (δ 3.78) appeared as a triple triplet on expansion, J 9+2 Hz. Assuming coupling with the adjacent methylene groups this suggests dihedral angles of 162° and 59° respectively which are consistent with coupling to H_{4a} (H_{6a}) and H_{4e} (H_{6e}) respectively (diagram 7). The benzylic protons appear as a broad multiplet (δ=2.60), the hydroxy proton at δ 1.42 and the aromatic protons between δ 7.28 to 7.55. The remaining H_4 and H_6 appeared as two groups at δ 1.58 and 1.82. With increasing concentrations of the shift reagent $Eu(fod)_3$, the group at δ 1.58 was observed to move downfield faster than the one at δ 1.82. Based on the report that in cis-4-tert-butylcyclohexanol, where the OH group is axial, the H_{4e} and

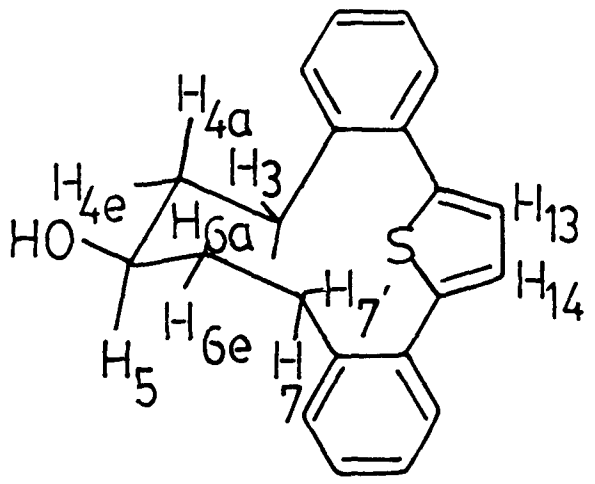
H_{6e} equatorial protons experienced a greater chemical shift than the corresponding H_{4a} and H_{6a} axial protons, in the presence of the same concentrations of $Eu(thd)_3$,[164] the group at δ 1.58 is tentatively assigned to H_{4e} and H_{6e} and the remaining one (δ 1.82) to $H_{4a}+H_{6a}$.

The UV of (180) is different from those of 2,5-diphenylthiophene and p-terphenyl by a blue shift, and this indicates that the aromatic rings substend different average angles to each other in the three compounds. A Dreiding model shows that the aliphatic chain in (180) still adopts a chair conformation and having the least gauche interaction when the thiophene ring and the benzene rings are coplanar or otherwise.

Table 2

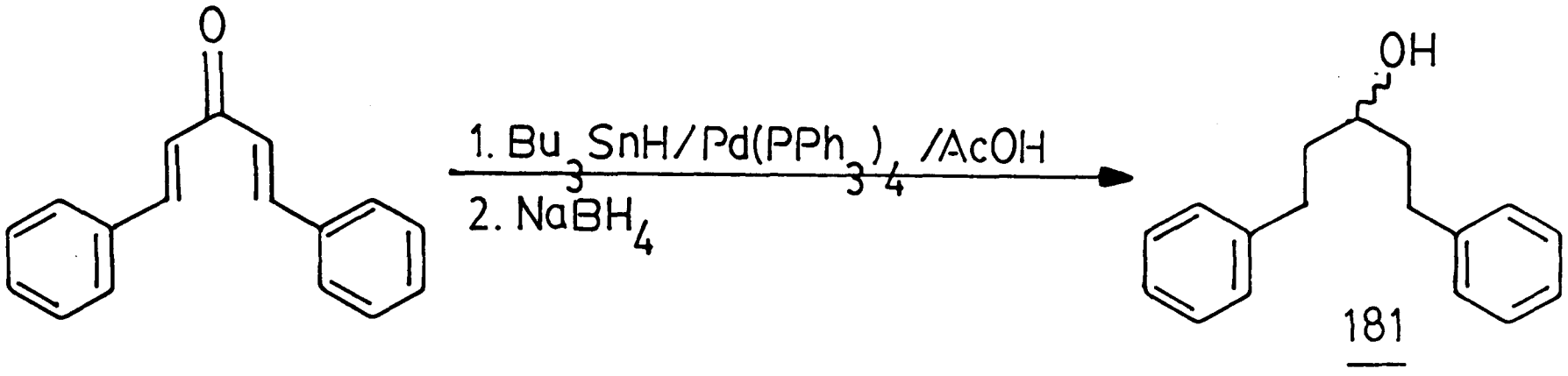
λmax (log εmax) (solvent=ethanol)

(180)	196 (4.41)	-	227 (4.02)	332 (3.39)
2,5-diphenylthiophene	202 (4.35)	229 (3.96)	325 (4.31)	-
p-terphenyl	-	-	279 (4.47)	-



MS of (180) shows some unusual features. The EI spectrum had M^+ as the base peak, which is very unusual for a secondary alcohol, while $(M-H_2O)^+$ was less than 5%. Under similar conditions, the molecular ion

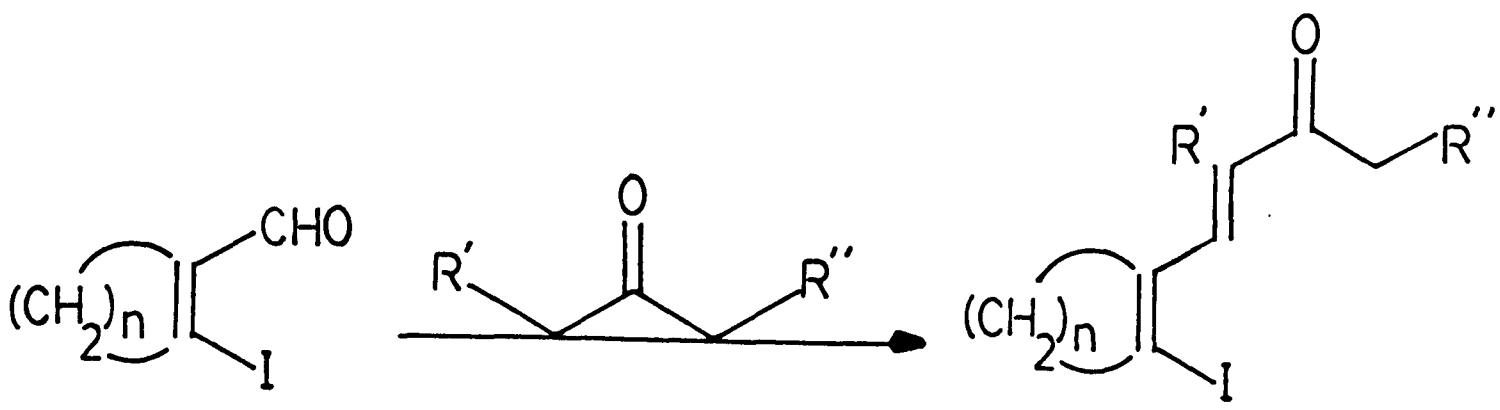
of 1,7-diphenylheptan-4-ol (181) was not observed and the $(M-H_2O)^+$ peak was approximately 20% of the base peak.



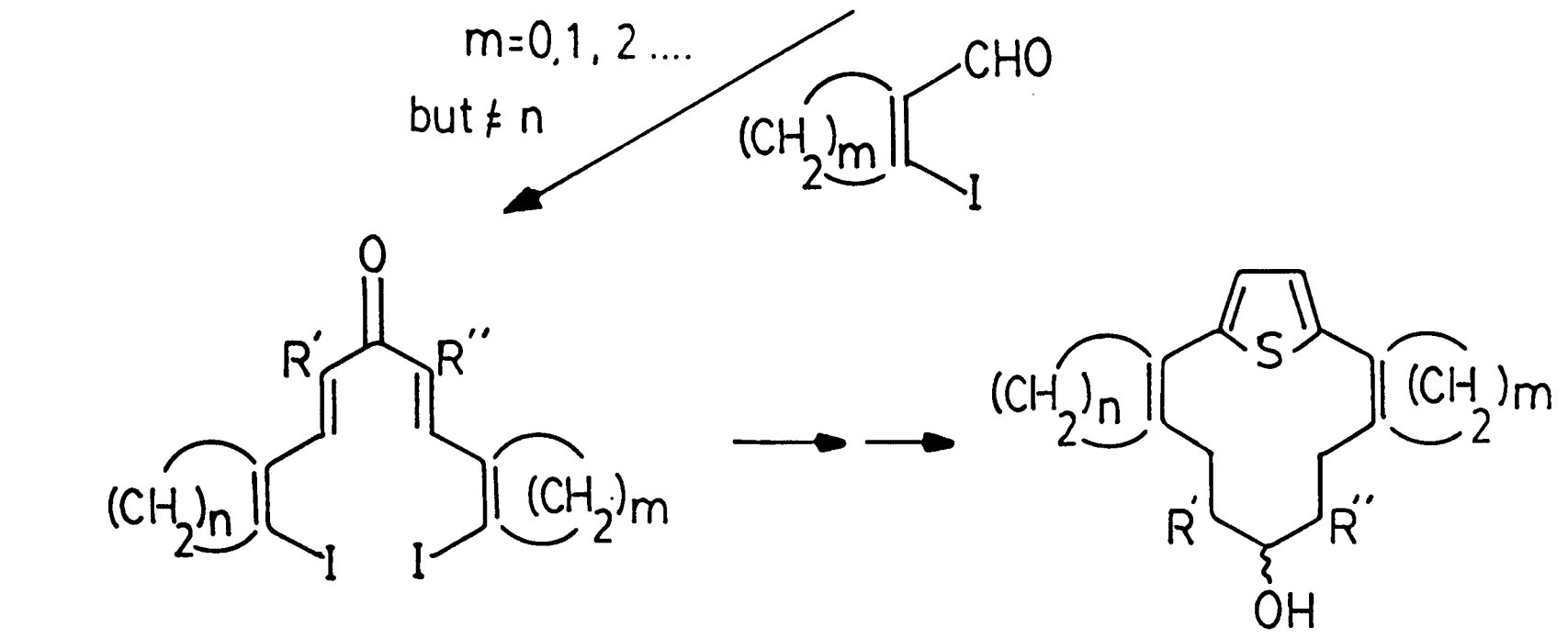
It is worth mentioning that in the attempted conversion of (179) to (180), using hydrogen sulphide and sodium ethoxide in ethanol instead of sodium sulphide in methanol, addition of EtOH across the diyne in (179) occurred as the major reaction, as shown by the ^1H NMR and MS of the products.

The scheme developed for the synthesis of (180) could have wide application. It depends particularly on the ability of the acetylene group to undergo oxidative coupling and on the conversion of the resulting diacetylene to a thiophene. Asymmetrical macrocycles of the same ring size, and with larger ring, as well as (182) might be synthesized (scheme 9).

A) asymmetrical ones

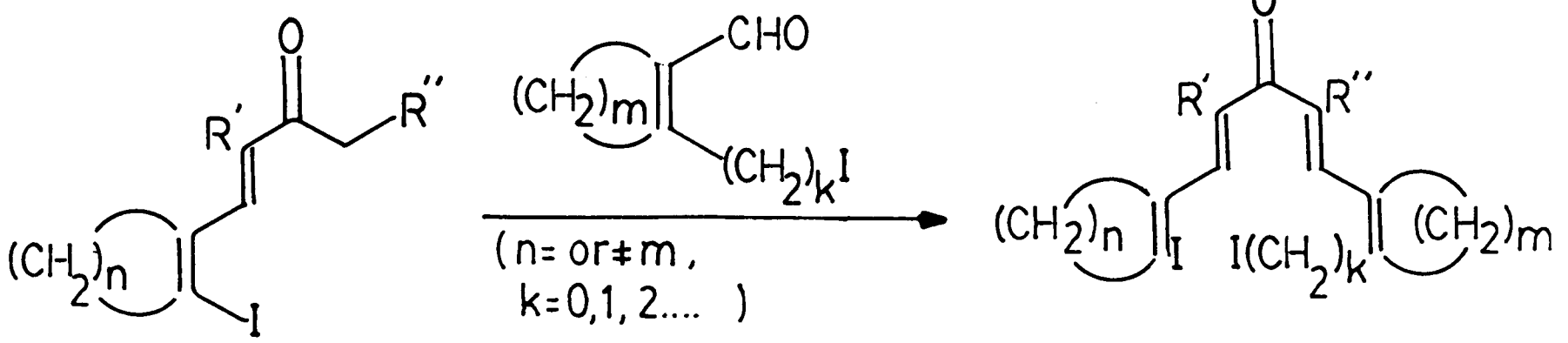


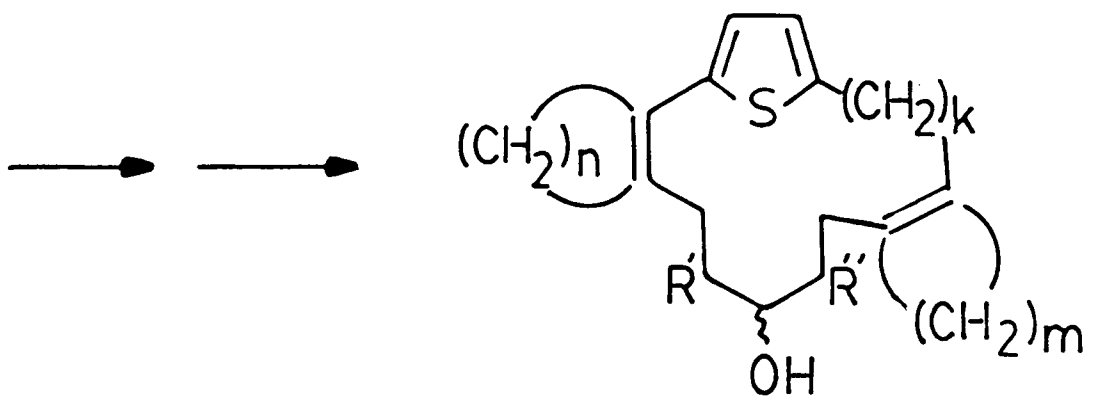
n = 0, 1, 2 .....



182 m=n=0 and R=R'=H

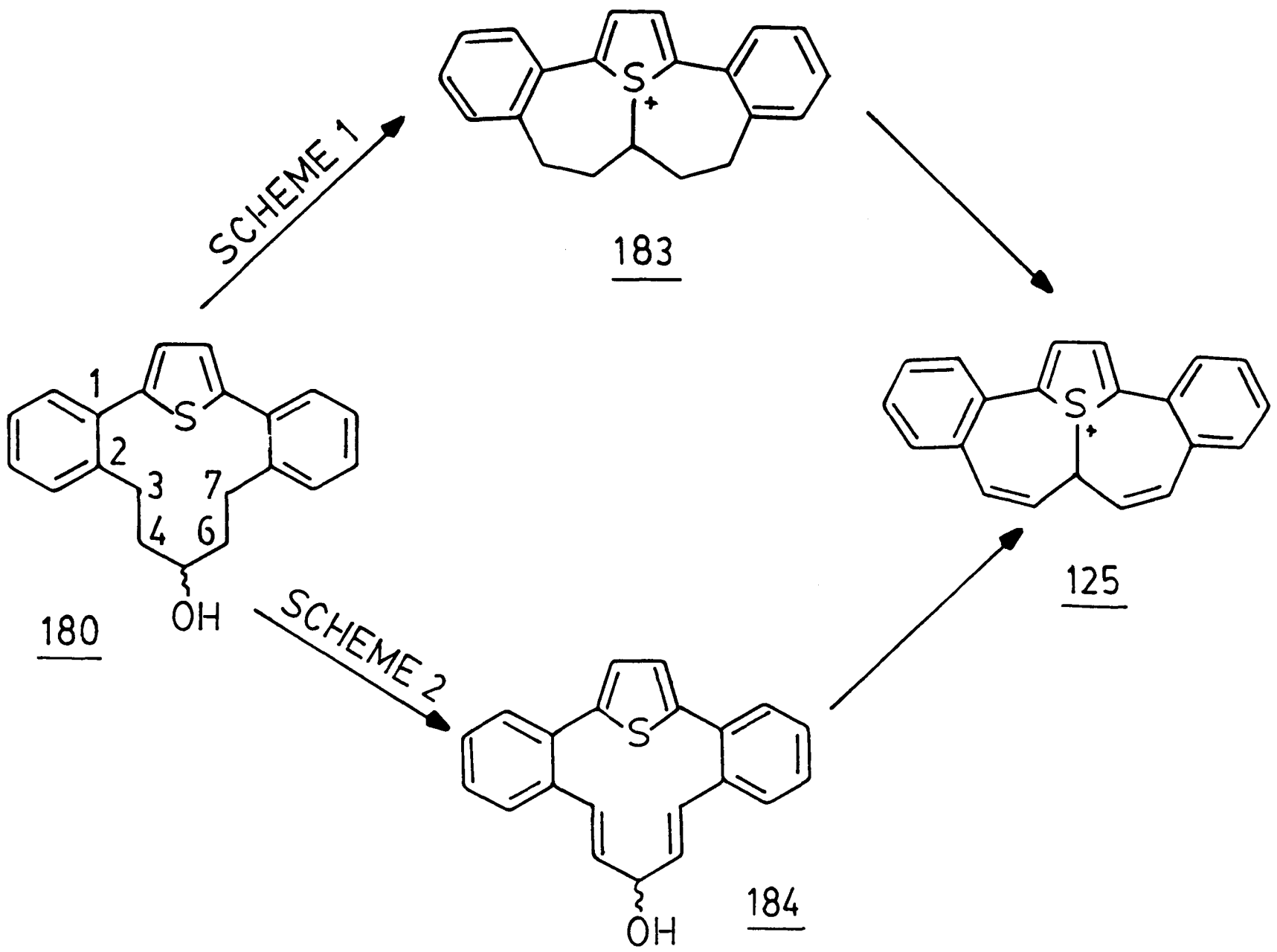
B) other ring sizes





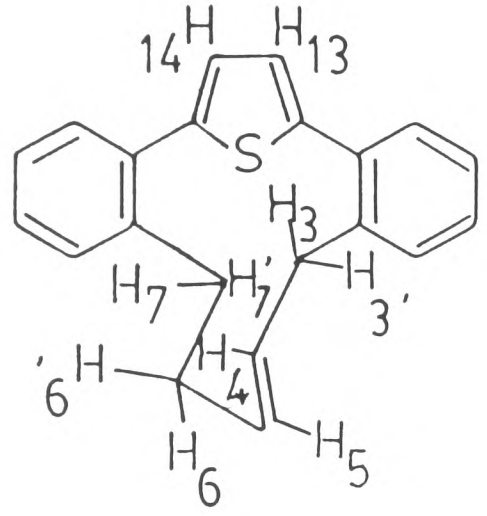
SCHEME 9

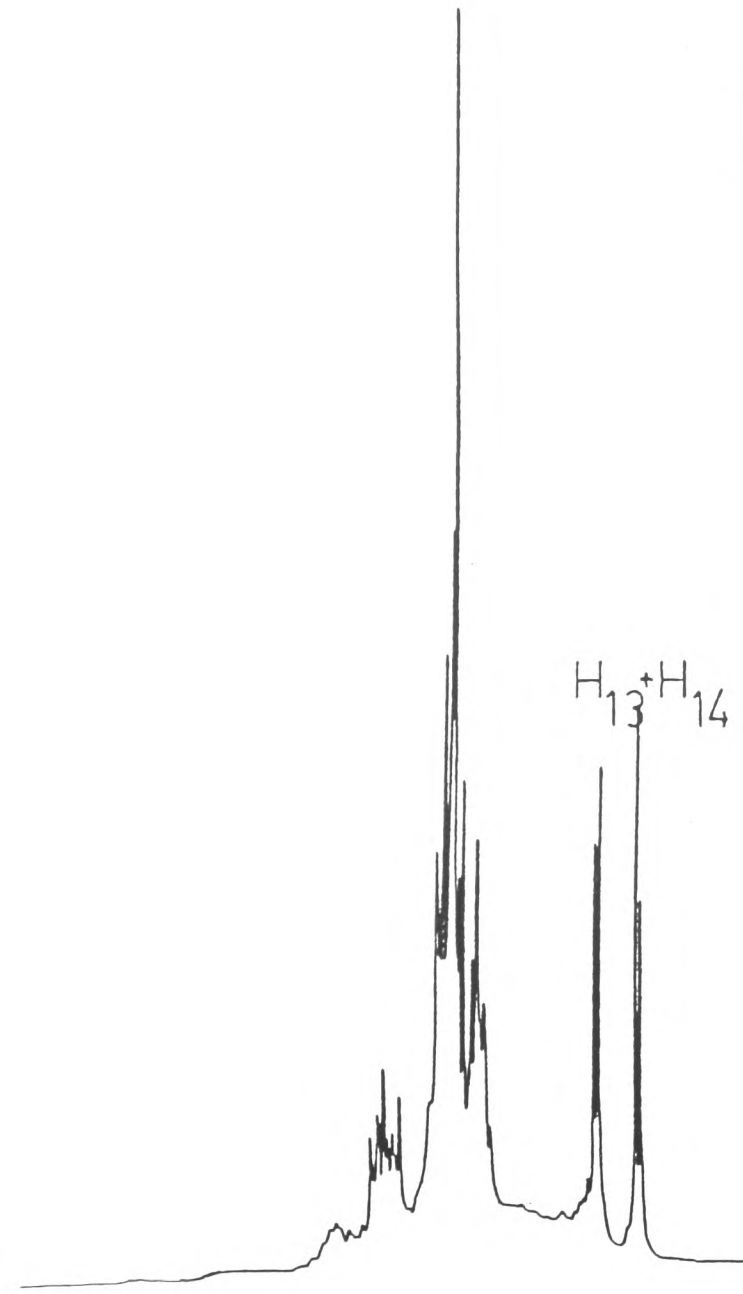
Depending on whether bond formation between the sulphur and C_5 or the introduction of unsaturation between C_3-C_4 and C_6-C_7 in (180) is carried out first, two schemes (I and II) are possible for the conversion of (180) to (125).

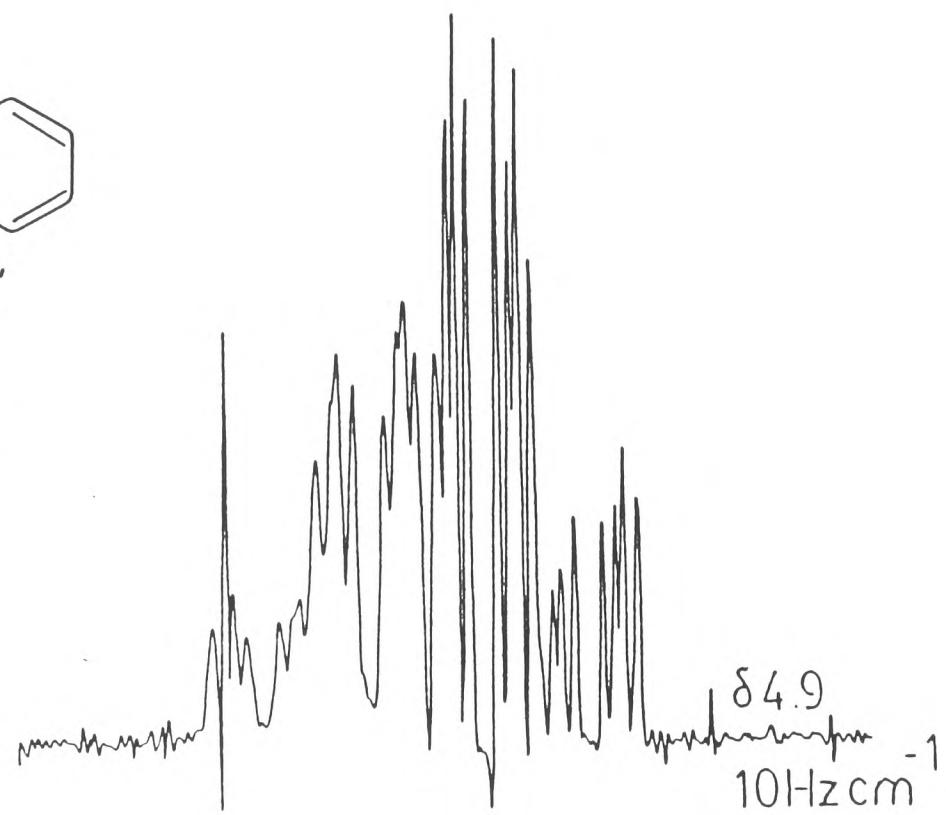


As shown clearly in the Dreiding model, the flexibility incurred in the methylene groups in (180) enables C_5 to come in closer proximity to the sulphur than its unsaturated analogue (184). Thus, scheme I was investigated first.

In order to facilitate bond formation to occur between the sulphur and C_5 in (180), the triflate derivative (185) was chosen. Alkylation of sulphur by alkyl triflates has been described recently.[165] Treating (180) with triflic anhydride under the general conditions reported,[165,166] using sodium carbonate as base, firstly at -40°C then at room temperature, followed by worked up and careful chromatography







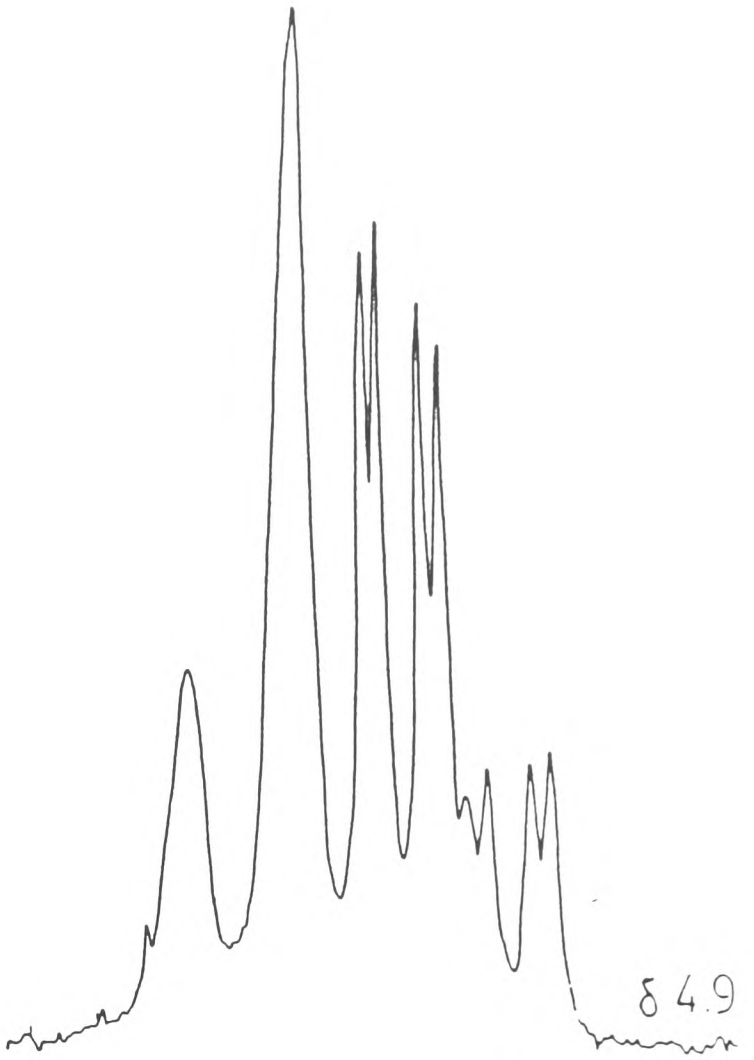
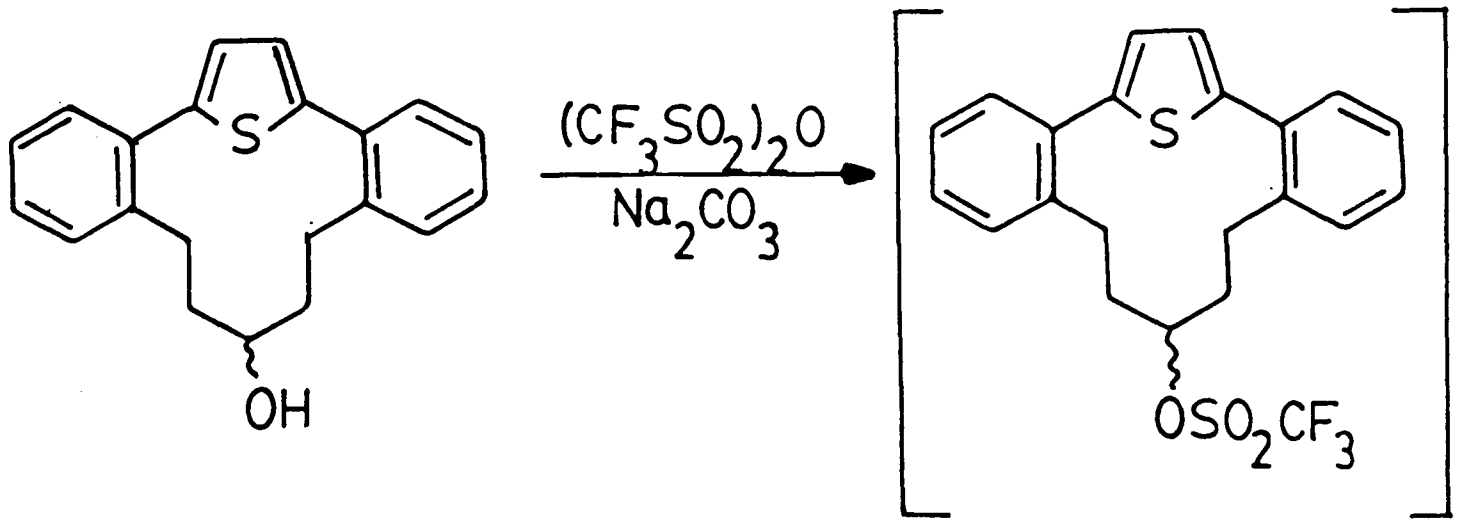
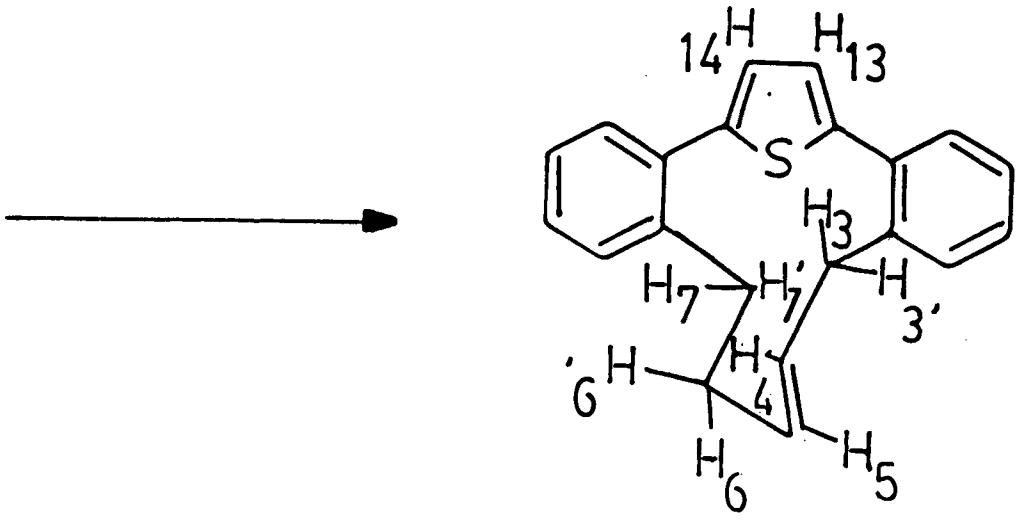


diagram 8 ^{1}H NMR(300MHz) of (186)

on silica gave back (180) (Rf=0.21 19% recovery) and a brown oil (Rf=0.60), which was identified unequivocally as 1,2,8,9-dibenzo-{9}(2,5)thiophenoph-4-ene (186) from its ^{1}H NMR and MS. The ^{1}H NMR (300 MHz) spectrum (diagram 8) showed the thiophene protons (H_{13}, H_{14}) as a double doublet (δ 6.84 and 6.95, $\underline{J}$=3.75 Hz), indicating the unsymmetrical nature of the molecule. H_3 (δ 3.20) appeared as a broad doublet ($\underline{J}$ 15 Hz) while H_3' as a double doublet centered at δ 3.32 ($\underline{J}$ 15 Hz + 10 Hz). Assuming coupling with the adjacent olefinic proton H_4 this suggests dihedral angles of Ca. 180° and 90° between H_4-H_3' and H_4-H_3 respectively. H_4 and H_5 appeared as a very complex multiplet centered at δ 4.92, while H_6+H_6' and H_7+H_7' appeared at δ 1.65 and 2.92 respectively as broad humps. On decoupling H_3 and H_3' (at δ 3.30), the very complex multiplet for H_4 and H_5 collapsed into a broad doublet and 2 sets of double doublets, assigned tentatively to H_4 and H_5 respectively. H_4 coupled to H_5 ($\underline{J}$ 15Hz) and weakly to H_6/H_6', thus appearing as a broad doublet. H_5 coupled to H_4 ($\underline{J}$ 15Hz) and was further split by H_6 and H_6'. The observed $\underline{J}H_5H_6$ (10Hz) and $\underline{J}H_5H_6$' (3 Hz) suggests dihedral angles of 180° and 51.6° between H_5-H_6 and H_5-H_6 respectively. The remaining aromatic protons resonated between δ 7.16-7.50 as a multiplet. MS gave m/e 302 for M^+, consistent with the suggested molecular formula for (186).



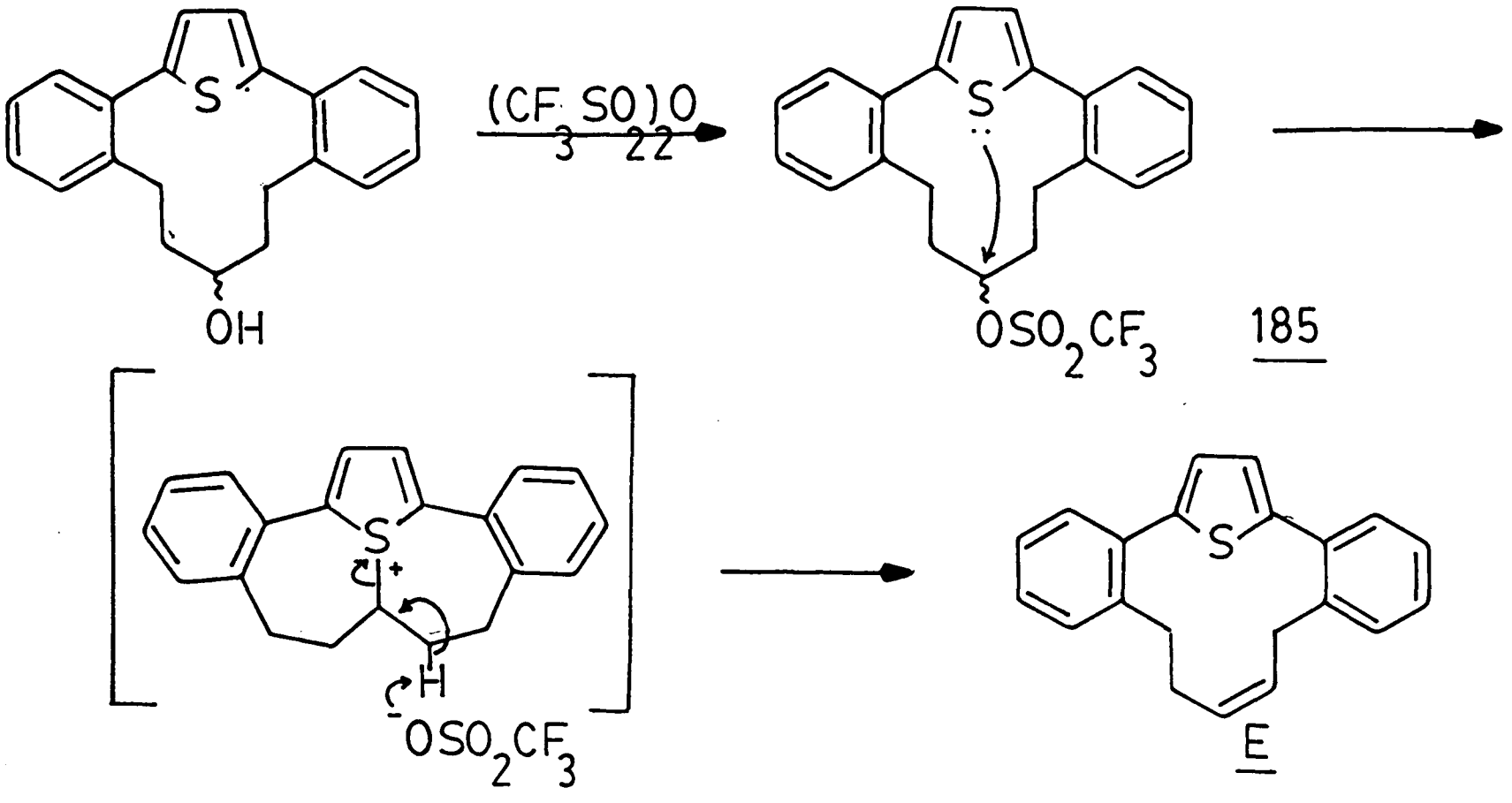
185



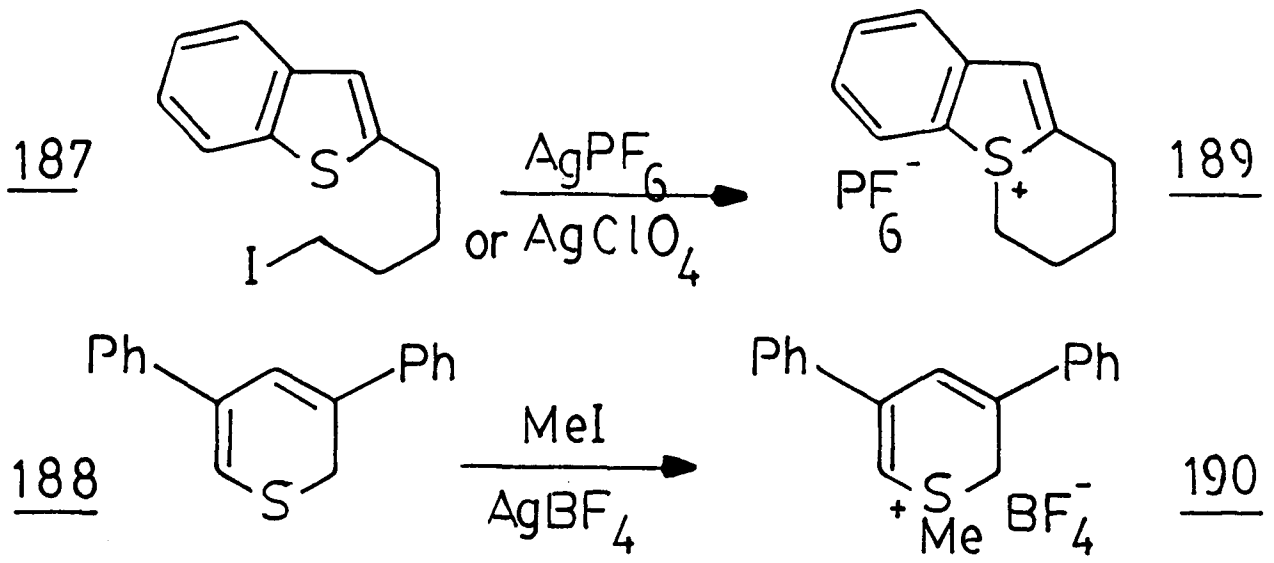
186

A Dreiding model shows clearly that in (186) unlike the starting alcohol (180), only one of the phenyl groups is in plane with the thiophene ring, while the other one is roughly at right angles to it. The dihedral angles among the various protons H_3, H_3', H_4, H_5, H_6, H_6', H_7 and H_7' are in consistent with the observed data from ^1H NMR.

In order to prove whether the decomposition of the triflate (180) to (186) occurred <u>in situ</u> or during subsequent worked up, the reaction was monitored by ^1H NMR using a variable temperature probe between -40^oC and $+40^oC$. Since the thiophene protons in (180) changed from a singlet to a double doublet in (186), this resonance was chosen as the yardstick for indicating the extent of reaction. To start with, the thiophene protons of (180) appeared as a singlet at δ 6.93 ($CDCl_3$, probe temp -40^oC). On addition of triflic anhydride, followed by increasing the probe temperature slowly, the singlet started to collapse to a multiplet at -20^oC and became a double doublet completely at $+20^oC$, showing that conversion to (186) was completed <u>in situ</u>.- Since no base had been added, it is not unreasonable to assume that neighbouring group participation, involving the sulphur lone pair, is involved in such a rapid decomposition (Ca. within 20 min) of the triflate (185), with the pentacyclic thiophenium salt (183) as the possible intermediate.

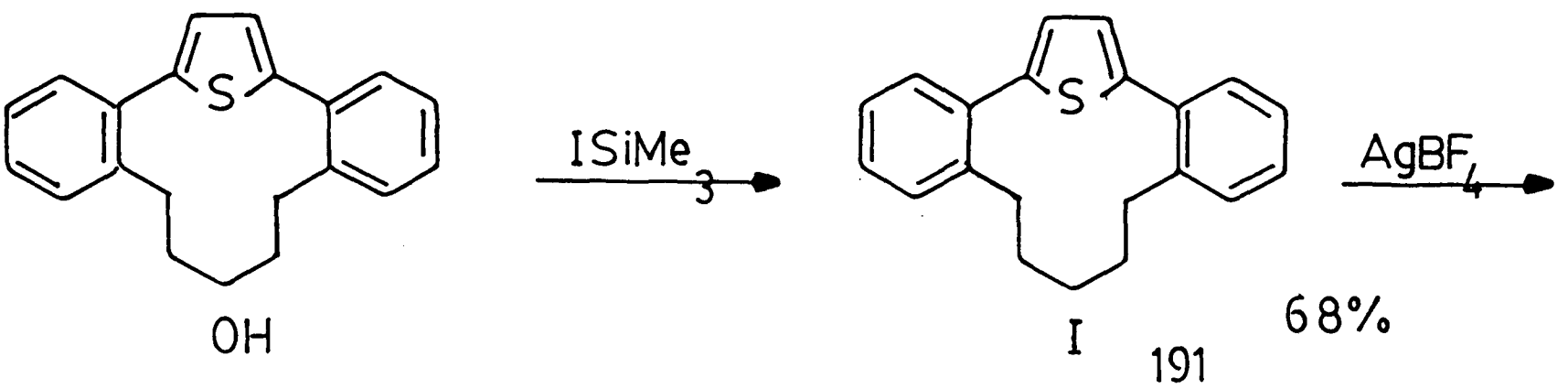


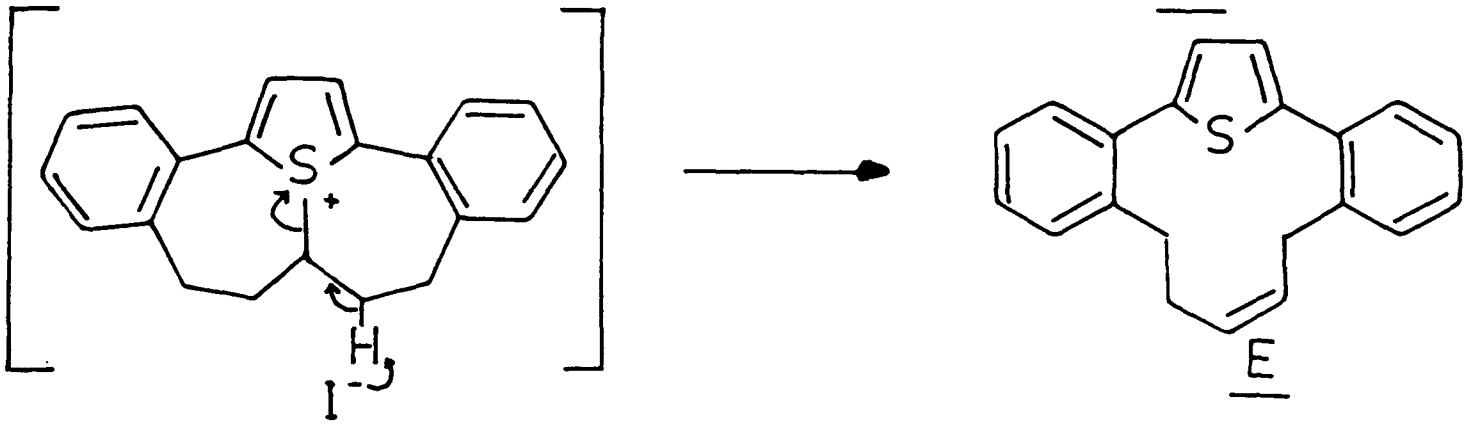
The other leaving group that is frequently employed in the synthesis of sulphonium salts is iodide. Thus, treating the iodo-compounds (187) and (188) with a silver salt, the corresponding sulphonium salts (189) and (190) were prepared.[3,167]



Thus converting (180) to the corresponding iodo-derivative and subsequent treatment with a silver salt may constitute a possible route to (183).

Reacting (180) with iodotrimethylsilane under the reported condition[168] gave the corresponding iodo-derivative (191). Subsequent treatment with silver tetrafluoroborate in 1,2-dichloroethane followed by worked up and chromatography on silica afforded an oil, which was identified unequivocally as (186) from the ^{1}H NMR spectrum, MS and TLC. The pentacyclic thiophenium salt (183) may again be involved.



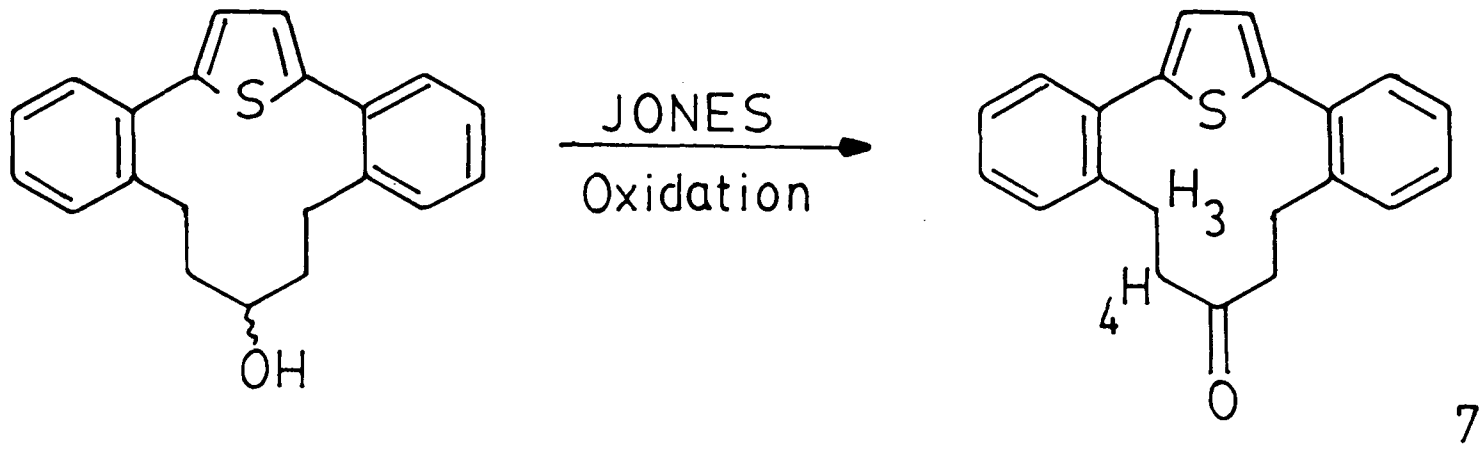


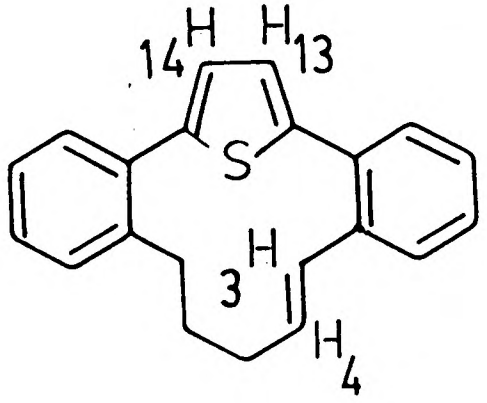
183 186

Since carbenes are far more reactive than carbonium ions, it was thought that if a carbene is generated at C_5 of (180), trapping by the sulphur might occur before or at a comparable rate to olefin formation. Trapping of the sulphur lone pair with carbene is well-known and has been reported.[169] Carbene formation should easily be accomplished by the Bamford-Stevens reaction.[170]

Jones oxidation of (180) gave the corresponding ketone (172),

whose structure was firmly established from its spectra and combustion analysis. Subsequent experiments revealed that direct oxidation of the crude alcohol (180) gave a better yield. As symmetry is restored in (180), H_3 and H_4 now appeared as two symmetrical groups centered at δ 2.44 and 2.96 in the ^1H NMR spectrum. Subsequent condensation with p-toluene sulphonylhydrazine gave the corresponding hydrazone (192), which on reacting with excess lithium diisopropylamide gave a mixture of alkenes (186), (193) and (194). Presumably the latter arose from carbonium rearrangement of the former.





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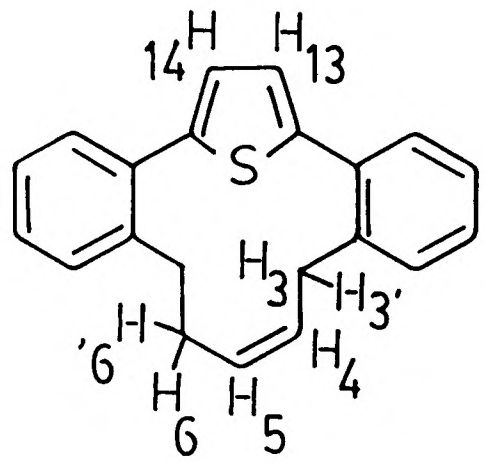

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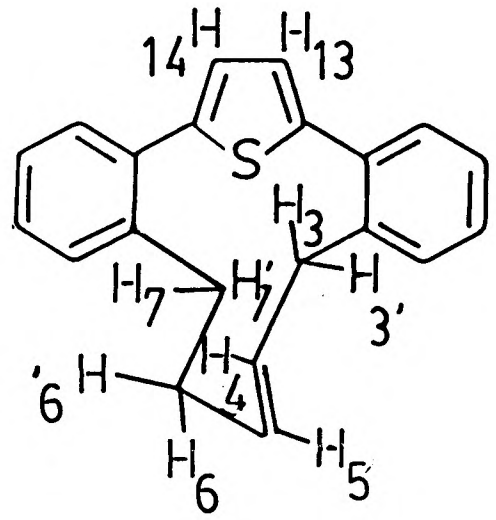


186

irradiate at δ 3.2

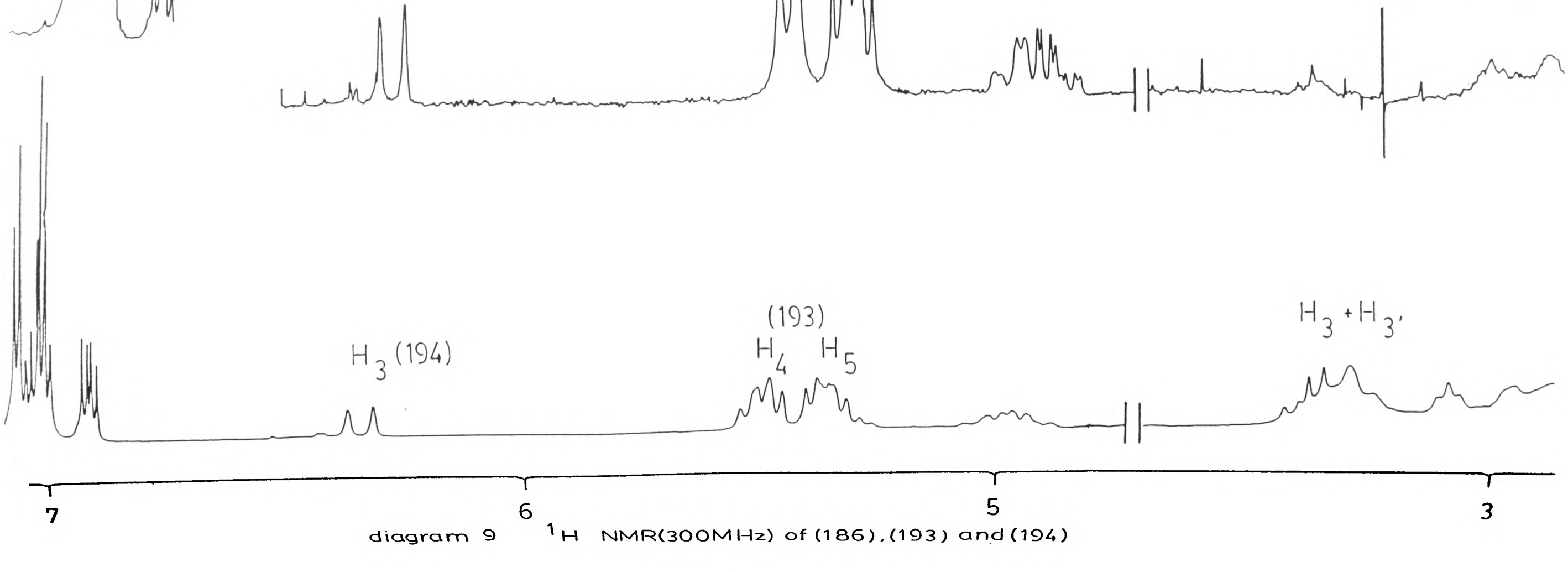
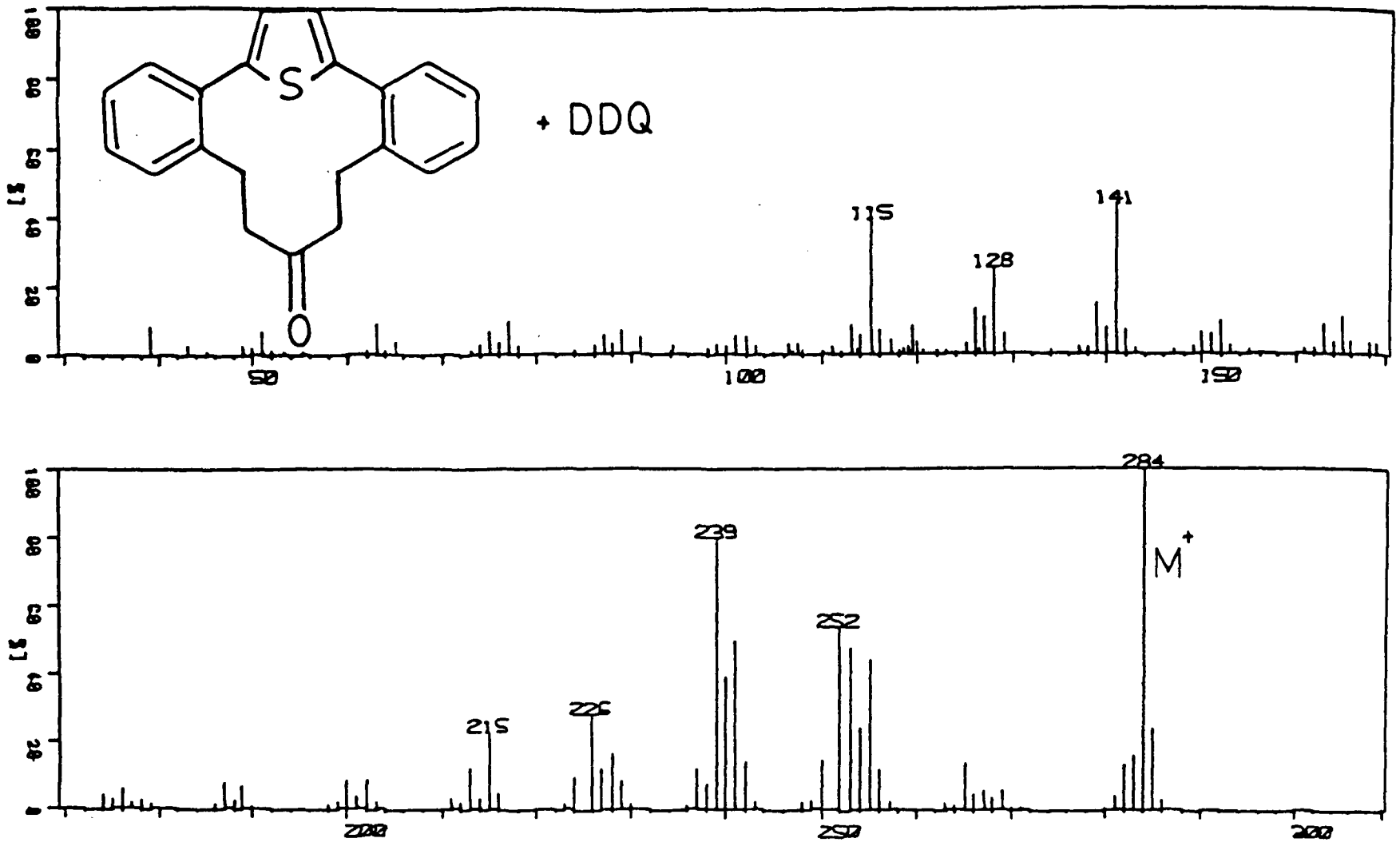


diagram 9 ^{1}H NMR(300MHz) of (186), (193) and (194)

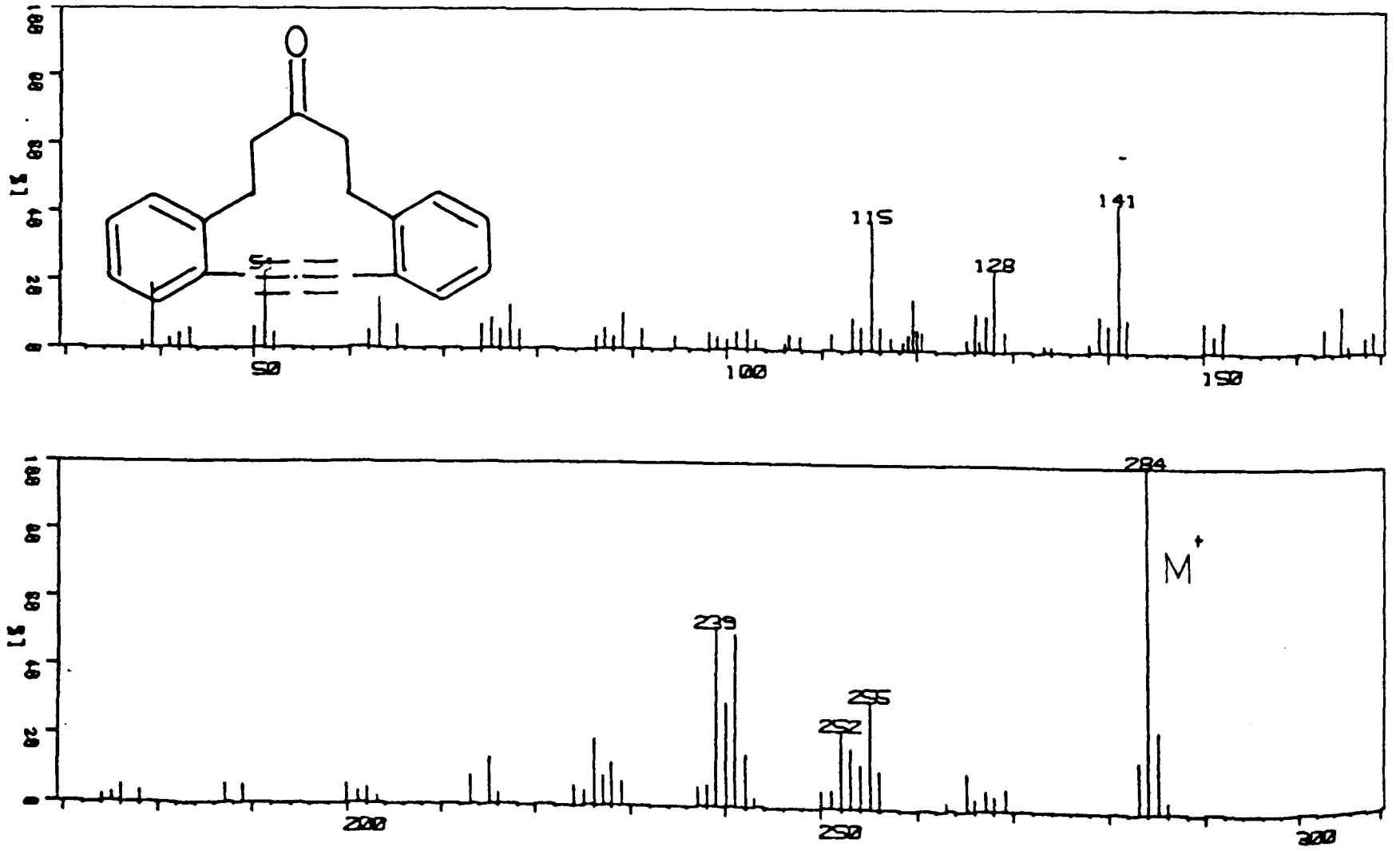
The structures of these alkenes were established from their ^{1}H NMR spectra and MS. MS gave m/e=302 for M^+, suggesting the isomeric nature of the products. The ^{1}H NMR (300 MHz) spectrum of (193) (diagram 9). showed the thiophene protons (H_{13}, H_{14}) as a double doublet (δ 6.89, 6.99, $\underline{J}$ 3.75 Hz), H_3 and H_3' appeared as a broad multiplet at δ 3.20, while H_4 and H_5 as two very complex multiplets centered at δ 5.22 and δ 5.35 respectively. On decoupling H_3 and H_3' (at δ 3.20), the multiplet for H_4 collapsed into a doublet ($\underline{J}H_4,H_5$ 10Hz), while that for H_5 became two sets of triplet ($\underline{J}H_5,H_4$ 10Hz; $\underline{J}H_5H_6=\underline{J}H_5H_6$' 7.5 Hz). The observed $\underline{J}H_5H_6$ and $\underline{J}H_5H_6$' (7.5 Hz) suggests dihedral angle of 16.9° between H_5-H_6 and H_5-H_6'. As for (194), the thiophene protons (H_{13},H_{14}) appeared as a double doublet (δ 7.00, δ 7.06, $\underline{J}$ 3.75 Hz), H_3 as a doublet (δ 6.35, $\underline{J}$ 16.3 Hz), and H_4 was hidden under the multiplet at δ 5.22. Finally (186) was identified by comparing with that obtained previously.

It becomes apparent that scheme II, i.e. introduction of unsaturation between C_3-C_4 and C_6-C_7 in (180) first before forming the S-C_5 bond, should represent a more feasible route, if the complication caused by olefin formation is to be avoided. The ketone (172), instead of the alcohol (180), was chosen as the starting point on the assumption that many methods would be available for converting it to the corresponding α,β unsaturated analogue which could then be converted to the carbene.

However, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[172] tetrachloro-$\underline{o}$-benzoquinone ($\underline{o}$-chloranil),[173] did not dehydrogenate (172) to the corresponding α-β unsaturated analogue (195) and instead a highly unexpected elimination of hydrogen sulphide took place

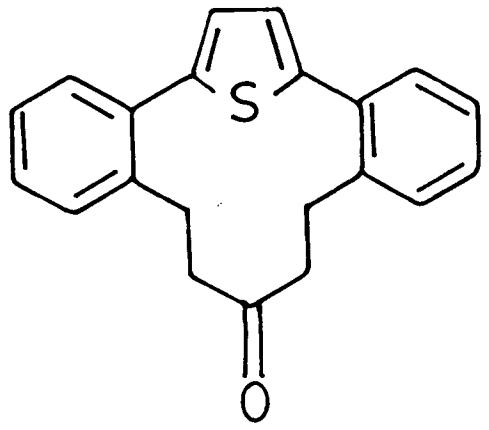


MS of (147) + DDQ



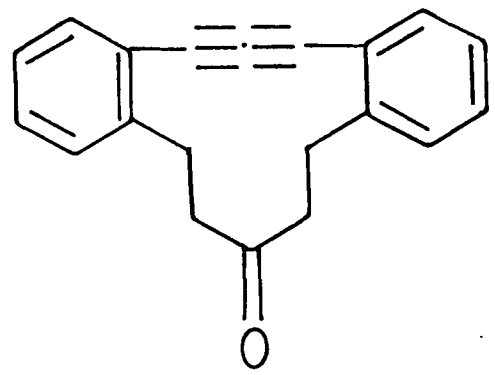
MS of (171)

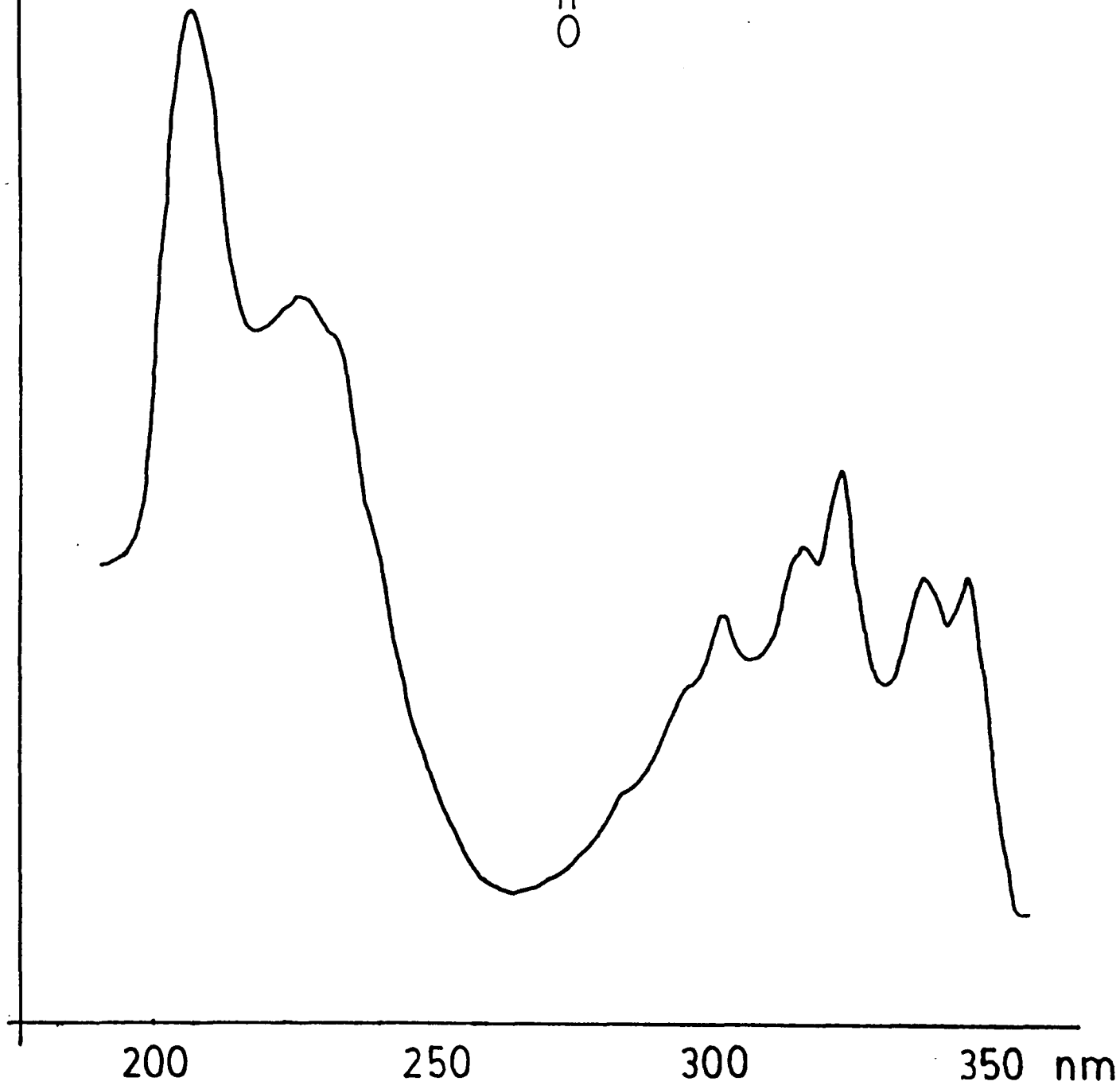
diagram 10



+ DDQ

UV of (147) + DDQ

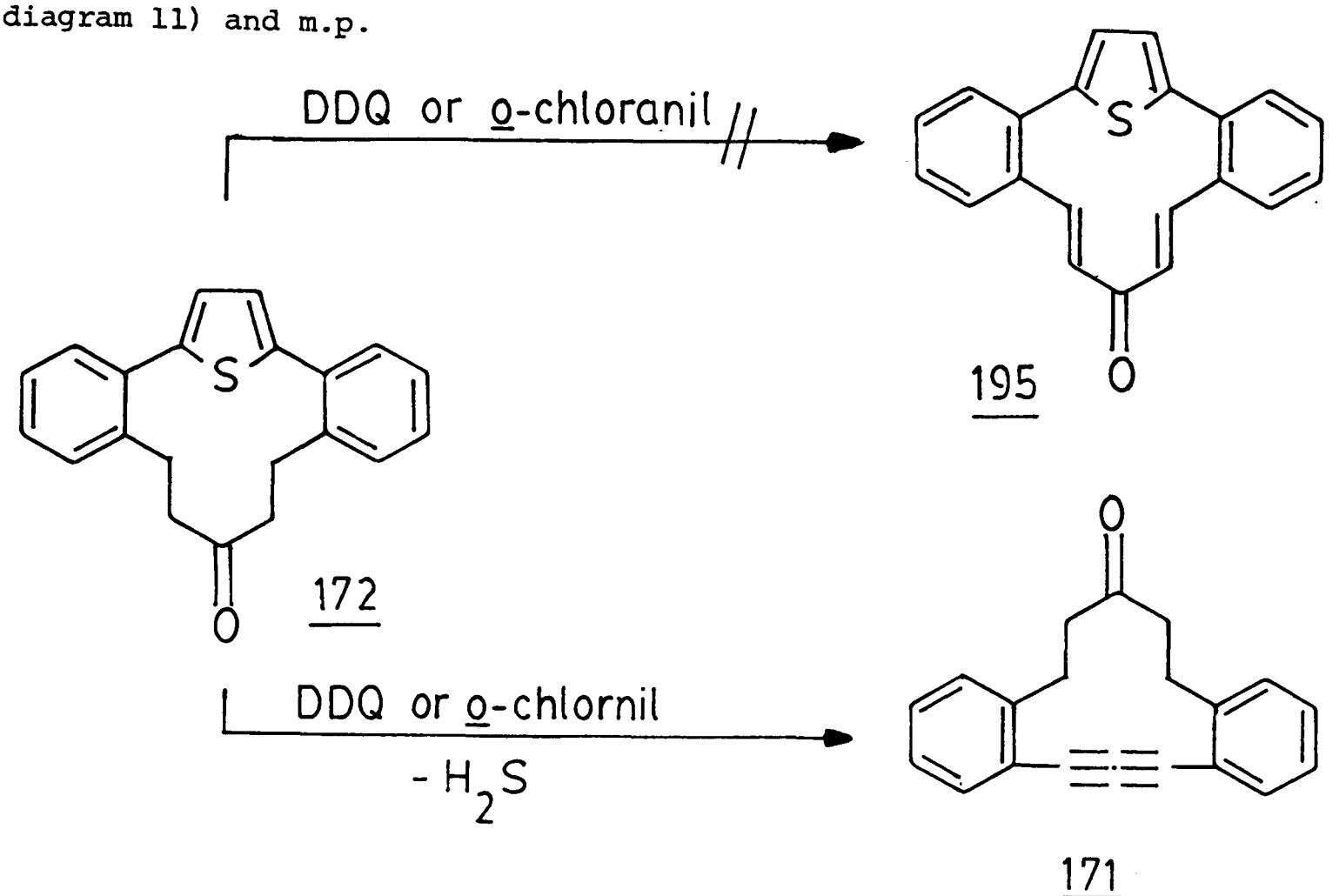




UV of (171)

diagram 11

giving back (171)!, as shown by ^{1}H NMR, MS (diagram 10), IR, UV (diagram 11) and m.p.

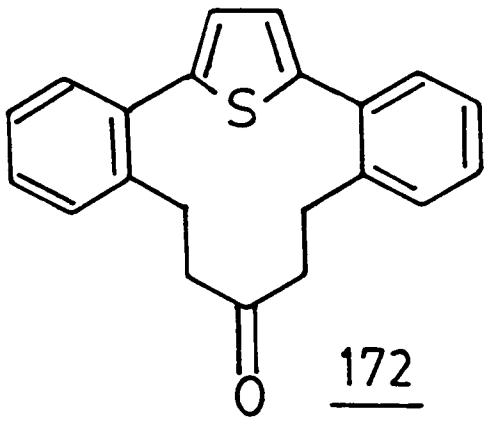


However, under similar conditions, neither DDQ nor o-chloranil can eliminate hydrogen sulphide from 2,5-diphenylthiophene and 2,5-bis(2-bromophenyl)thiophene (97).

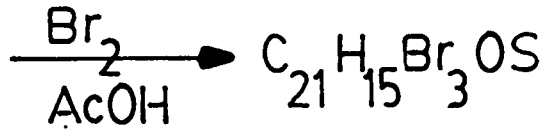
With palladium(II)chloride,[173] in boiling tert-butanol and hydrochloric acid, no sign of dehydrogenation was shown, while with benzeneseleninic anhydride[174] only polymeric products, apart from diphenyl diselenide were obtained.

Finally, bromination and subsequent dehydrobromination of (172) was investigated. Bromination of (172) with bromine in acetic acid replaced three hydrogen atoms by bromine, as shown by the MS. Subsequent treatment of the bromo-derivative (196) with DBN gave an oil (197), whose molecular ion corresponds to an elimination of one bromine atom and a hydrogen sulphide molecule from (196). No

sign of the expected dienone (195) or the corresponding mono-bromo derivative was detected. Furthermore, bromination of (171) did not give any (197) and MS suggested that addition of four bromine atoms had occurred.



172



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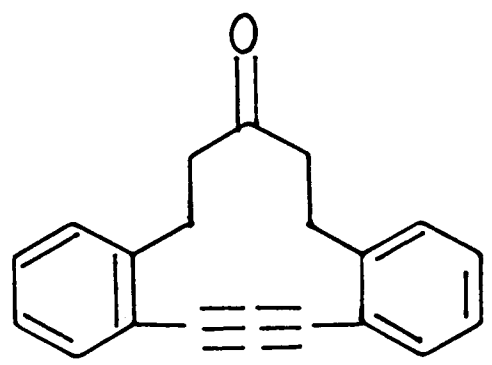
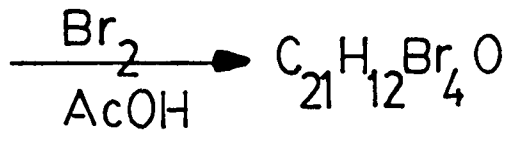
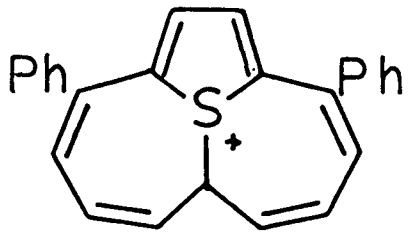
197



171

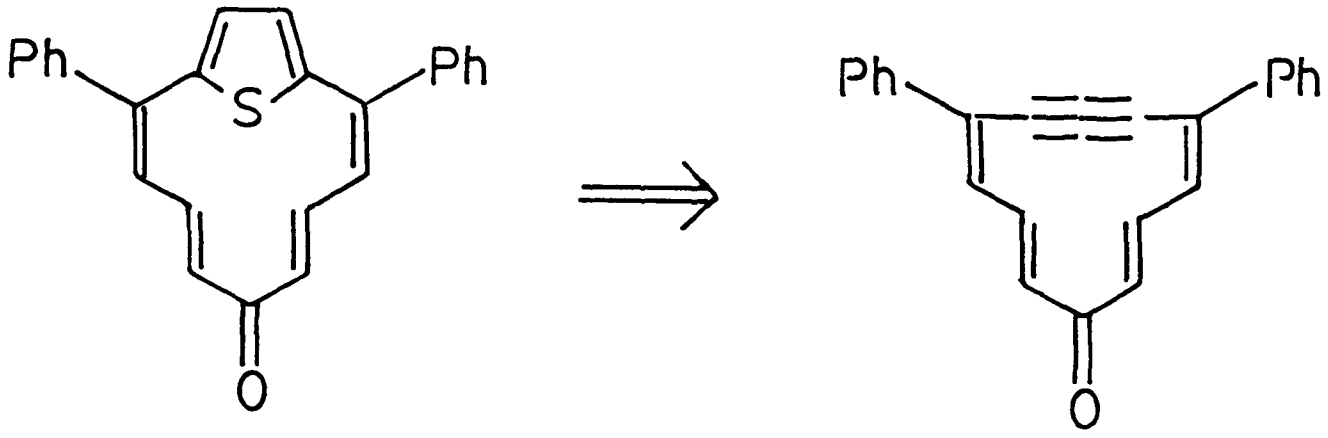


Part B



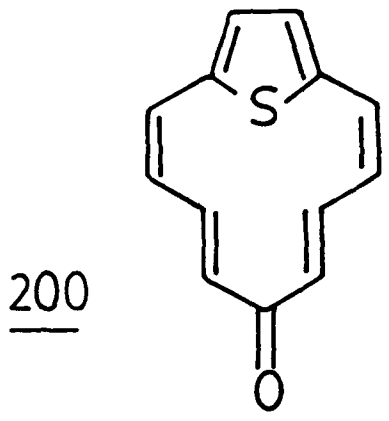
4.3 Introduction and synthetic planning

During the early part of work on the synthesis of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127), a similar system 5,10-diphenyl-2,4,10,12-cyclotridecatetraene-6,8-diyn-1-one (199) was investigated, on the assumption that the synthesis of 5-keto-1,3,6,8-tetraene-{9}(2,5)-thiophenophene (198) might be possible on the basis of a similar strategy, viz.

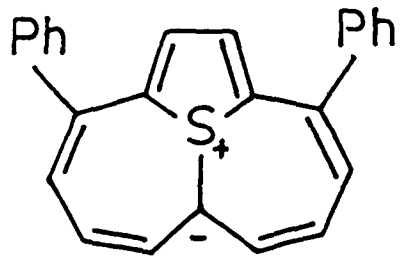


198 199

It was expected that (199) would be more easy to handle than (200) because of the phenyl groups and that these groups might assist resonance stabilisation in the final synthesis aim (201).



200

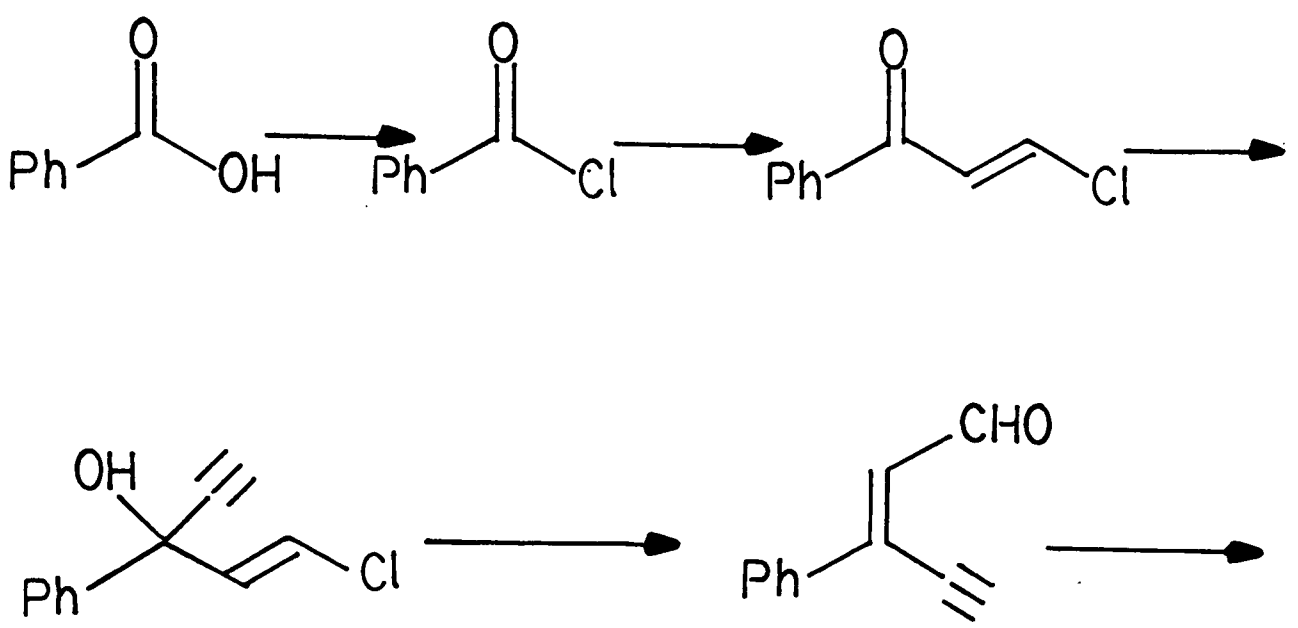


201

Synthetic planning

In 1977, Sondheimer et al[96] reported the synthesis of 5,10-dimethyl-2,4,10,12-cyclotridecatetraene-6,8-diyn-1-one (202), which is the same

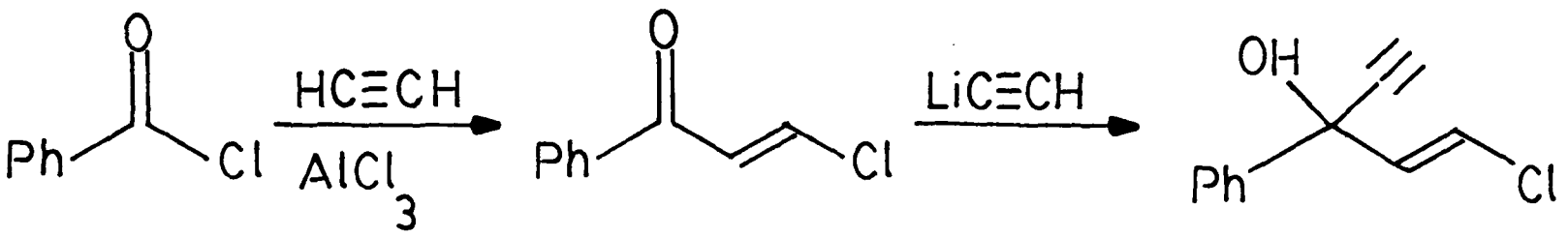
as (201) except that methyl groups replace our desired phenyl groups. Thus, the same synthesis, appropriately modified, should give (201):



SCHEME 10

4.4 Result and discussions

Based on a modified procedure of Pappalardo et al,[175] Friedel-Crafts acylation of acetylene with benzoyl chloride gave β-chlorovinyl phenyl ketone (203) in 45% yield; longer reaction times and freshly purified starting materials gave no improvement. Although vinyl chloride, instead of acetylene, gives[176] a 83% yield of (203) the toxicity of this reagent precluded its use.

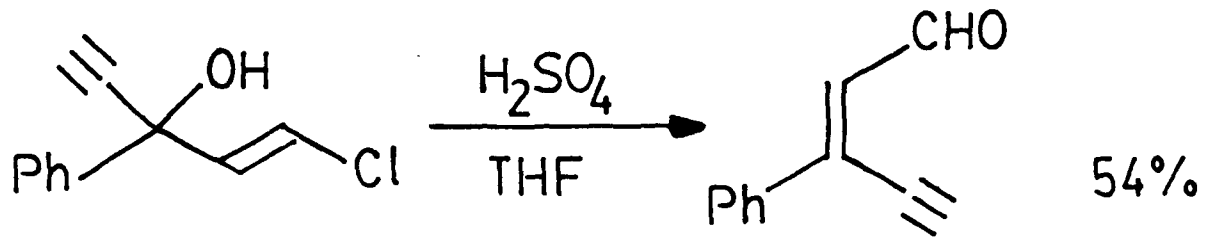


203 204 40%

Addition of lithium acetylide to (203) gave 1-chloro-3-phenyl-1-penten-4-yn-3-ol (204). Several trials revealed that lithium acetylide, prepared from acetylene and n-butyl lithium as reported by Midland[119] gave a higher yield of (204) than that prepared from lithium in liquid ammonia.

Despite careful temperature control, spontaneous explosive decomposition always occurred during the distillation of (204), and this may account for the low yields compared with those claimed.[176]

Anionotropic rearrangement of (204) by acid treatment yielded 3-phenyl-2-penten-4-ynal (205).

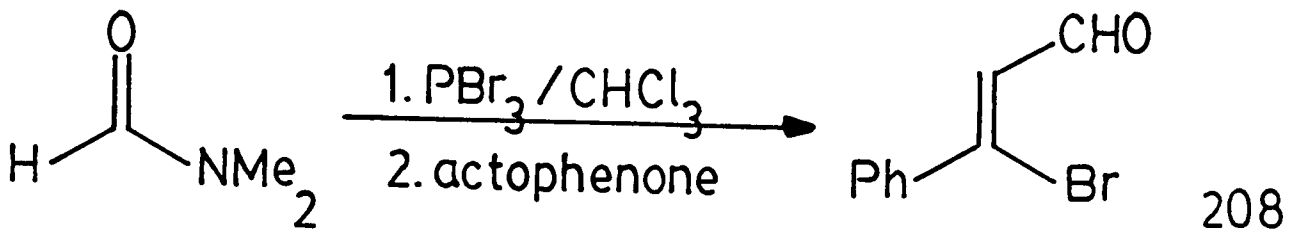


54%

205

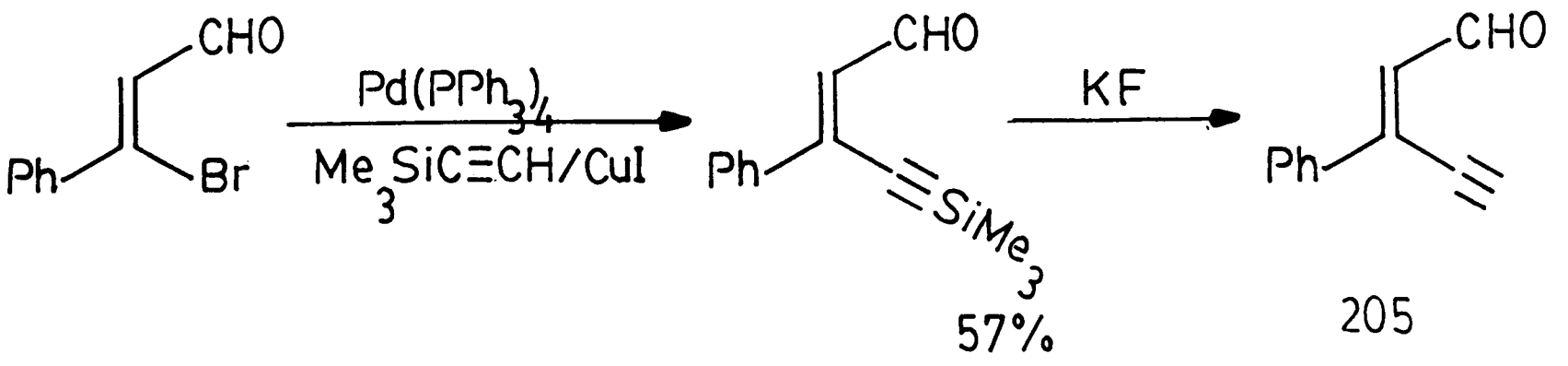
The overall yield of (205) from benzoyl chloride was only 9.7%, so a better synthesis was sought. As ethynyltrimethylsilane, in the presence of a palladium catalyst, can undergo stereospecific coupling with a vinyl bromide or iodide,[134,135a,177] 3-bromo-3-phenylpropen-1-al (208) might behave similarly, and subsequent desilylation should give (205).

Following Holy's procedure,[178] 3-bromo-3-phenylpropen-1-al (208) was obtained in 23% yield.



208

Attempts to attain the reported yield (45%) were unsuccessful. Nevertheless, 3-bromo-3-phenylpropen-1-al (208) coupled smoothly with ethynyltrimethylsilane, in the presence of $Pd(PPh_3)_4$ and copper(I)iodide, to give 3-phenyl-5-trimethylsilylpent-2-ene-4-yn-1-al (209) in 57% after purification. The structure of (209) was clearly established from its spectroscopic data. Due to its hygroscopic nature satisfactory analytical data could not be obtained and partial hydrolysis to the aldehyde (205) also occurred. Desilylation of (209) by potassium fluoride in DMF gave (205), identical with the previous sample, in nearly quantitative yield.



209

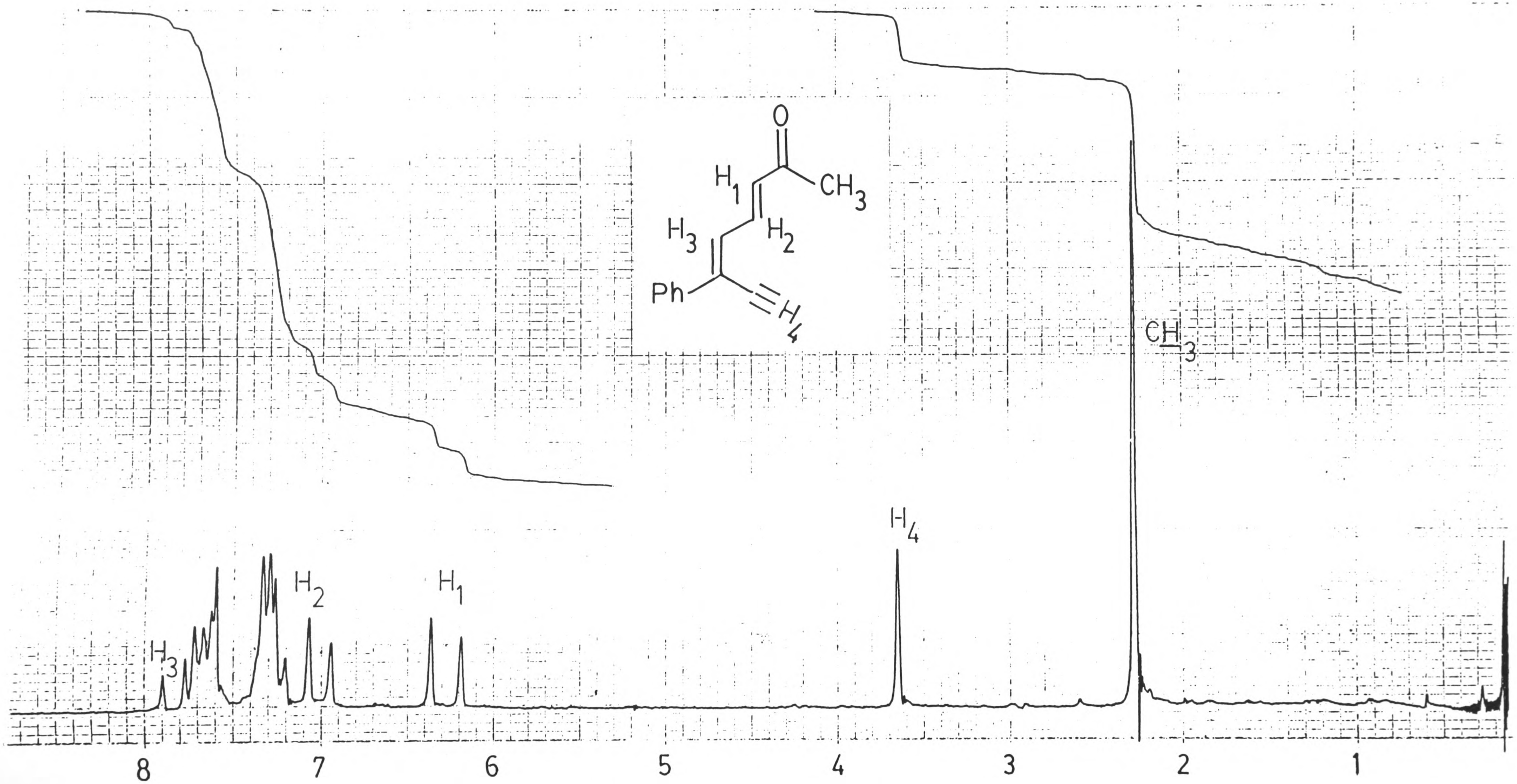
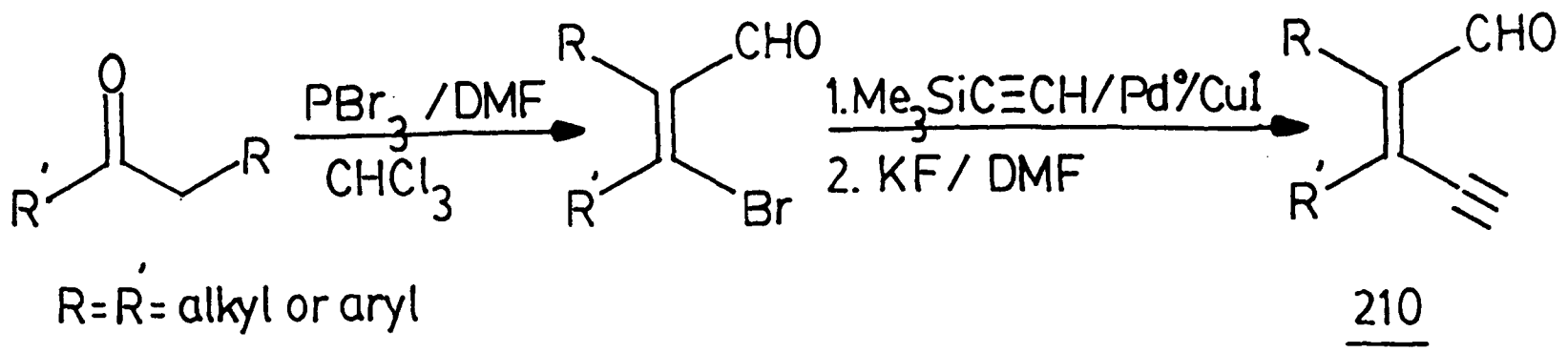


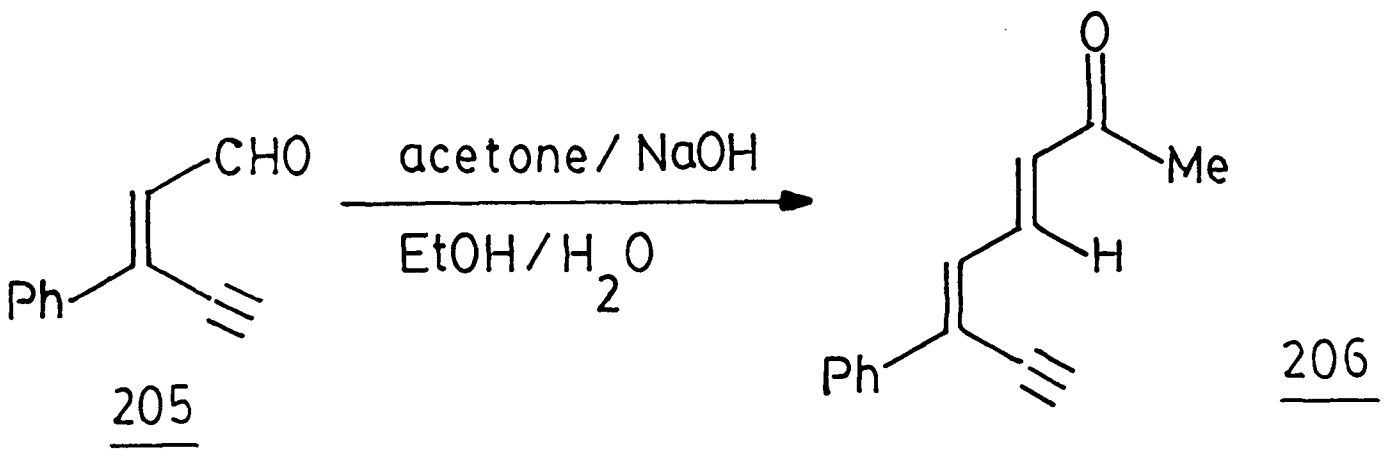
diagram 12 ^{1}H NMR(90MHz) of (206)

Although the increase in overall yield of (205) by this new route was not great, the easier laboratory operations still made it attractive. The method represents a general approach to any aldehyde of type (210) (scheme 11).



SCHEME 11

Aldol condensations between 3-phenyl-2-penten-4-ynal (205) and acetone, under conditions suggested by Nakagawa et al,[176] gave 67% of 6-phenyl-3,5-octadien-7-yn-2-one (206); Sondheimer's[96] condition gave only 35%.



The ^{1}H NMR spectrum of (206) showed the expected three spin system and coupling constants (diagram 12).

Further aldol condensation between (205) and 3-phenyl-2-penten-4-ynal (206) under conditions used by Sondheimer et al[96] gave 3,11-diphenyl-3,5,8,10-tridecatetraene-1,12-diyn-7-one (207),

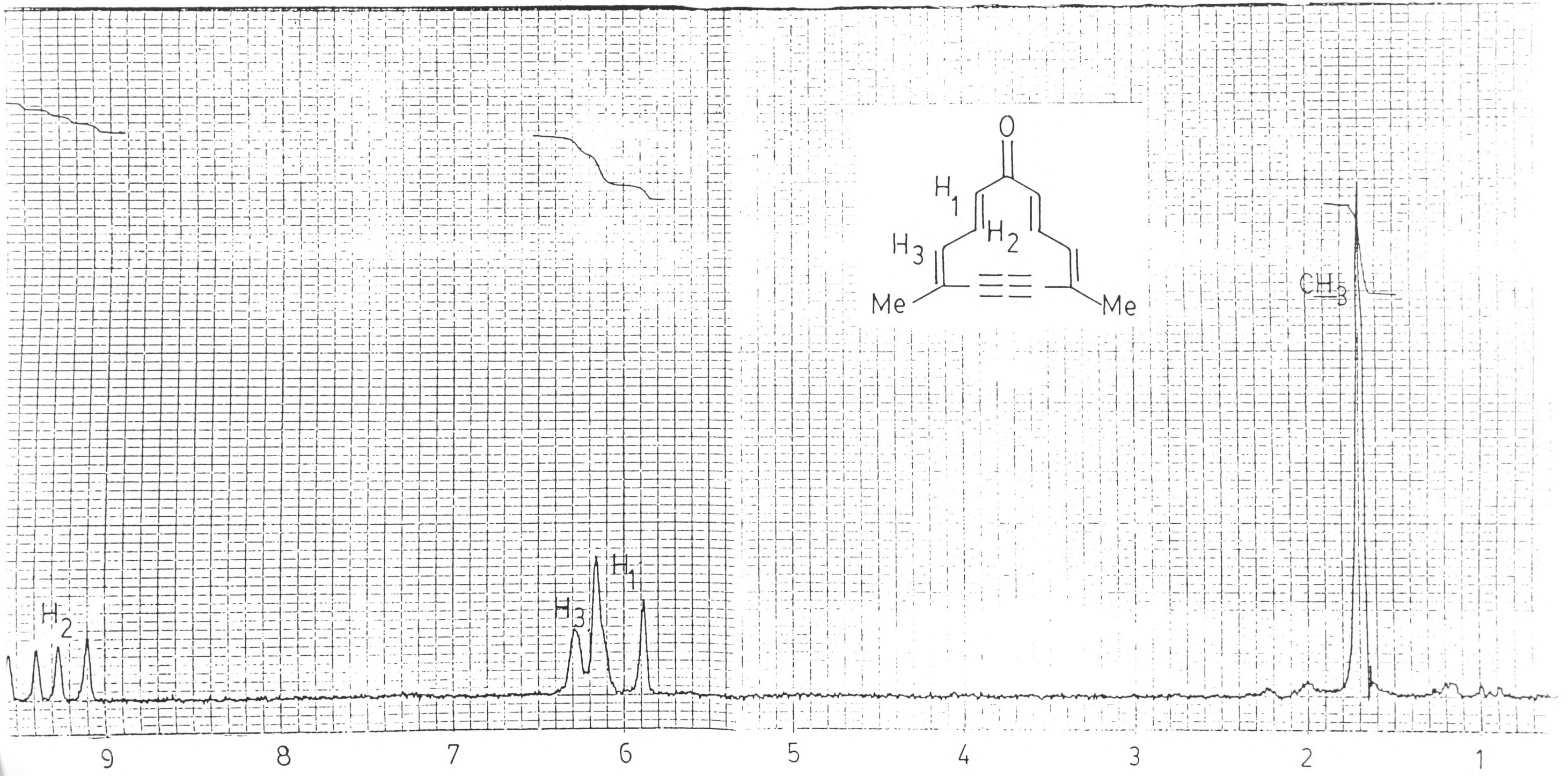


diagram 13a ^{1}H NMR(60MHz) of (202)

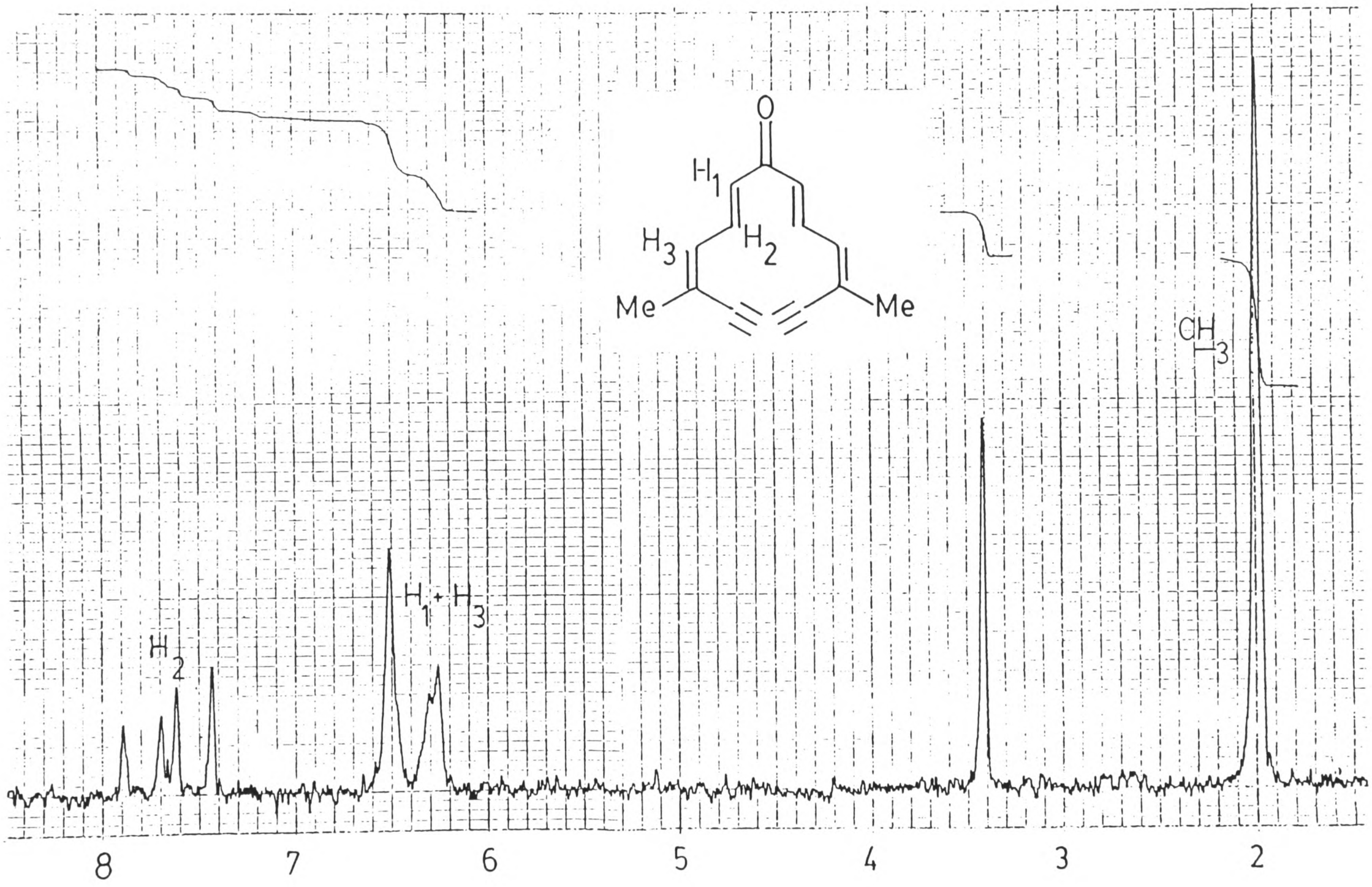
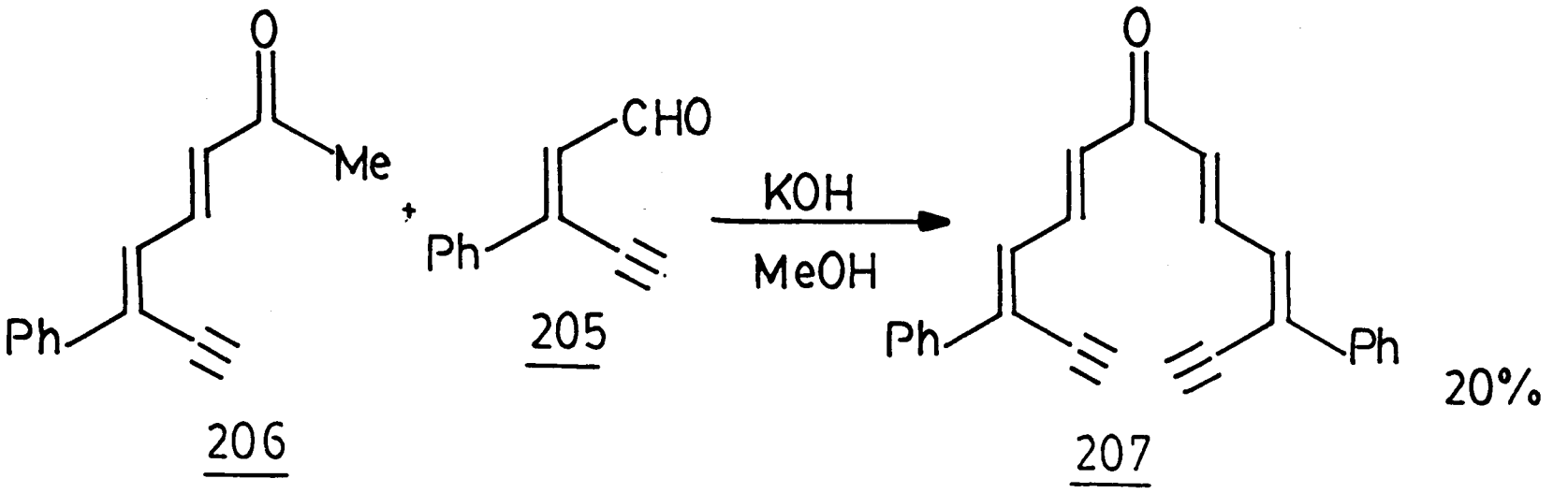
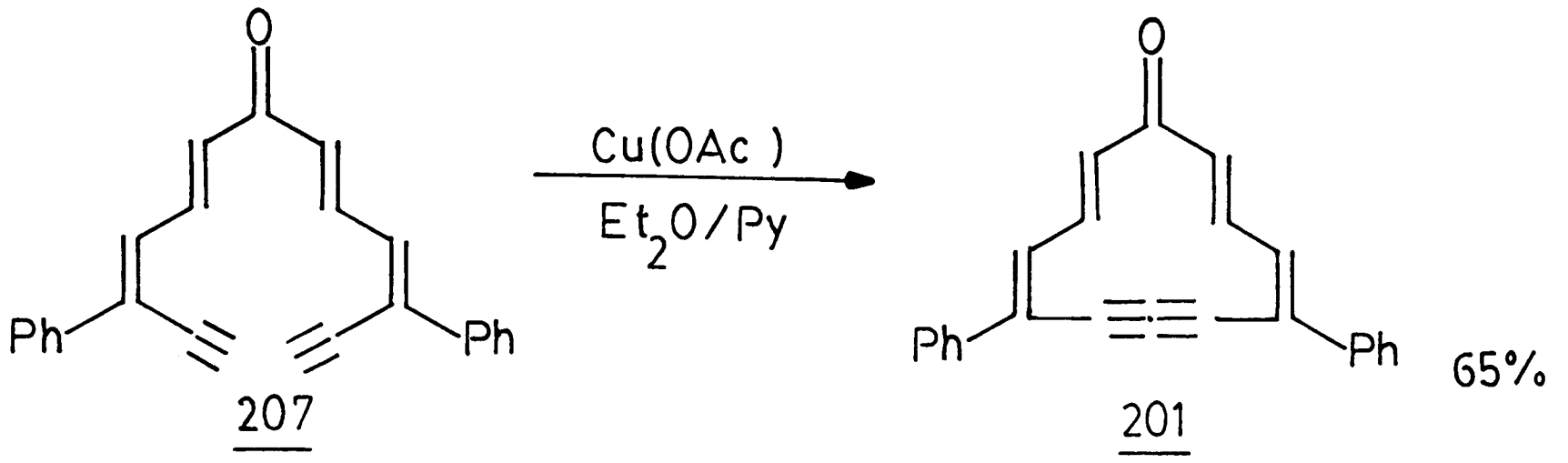


diagram 13 ^{1}H NMR(60MHz) of 3,11-dimethyl-3,5,8,10-tridecatetraene-1,12-diyn-7-one

identified from its spectra (diagram 14) and analysis.



Intramolecular oxidative coupling of (207) under the conditions reported[96] gave 5,10-diphenyl-2,4-10,12-cyclotridecatetraene-6,8-diyn-1-one (201) as deep red needles.



The structure of (201) was firmly established from its ^{1}H NMR (diagram 15) spectrum. Apart from the aromatic signals (δ 7.35), H_1 resonates at δ 6.10 (d, $\underline{J}H_1H_2$ 16.7 Hz), H_2 at 9.84 (dd, $\underline{J}H_1H_2$ 16.7 Hz, $\underline{J}H_2H_3$ 9.75 Hz) and H_3 at 6.90 (d, $\underline{J}H_2H_3$ 9.75 Hz). Comparison of the chemical shifts of the various protons of (201) with those of the corresponding acyclic model (207) (see Table 3), indicates that (201) is weakly paratropic, as might be expected of a 12π electron system. This follows from the fact that essentially all the outer protons in (201) resonate at higher field than the corresponding protons in (207), whereas the inner protons in (201) resonate at lower field. This is in accord with that reported by Sondheimer *et al.*[96]

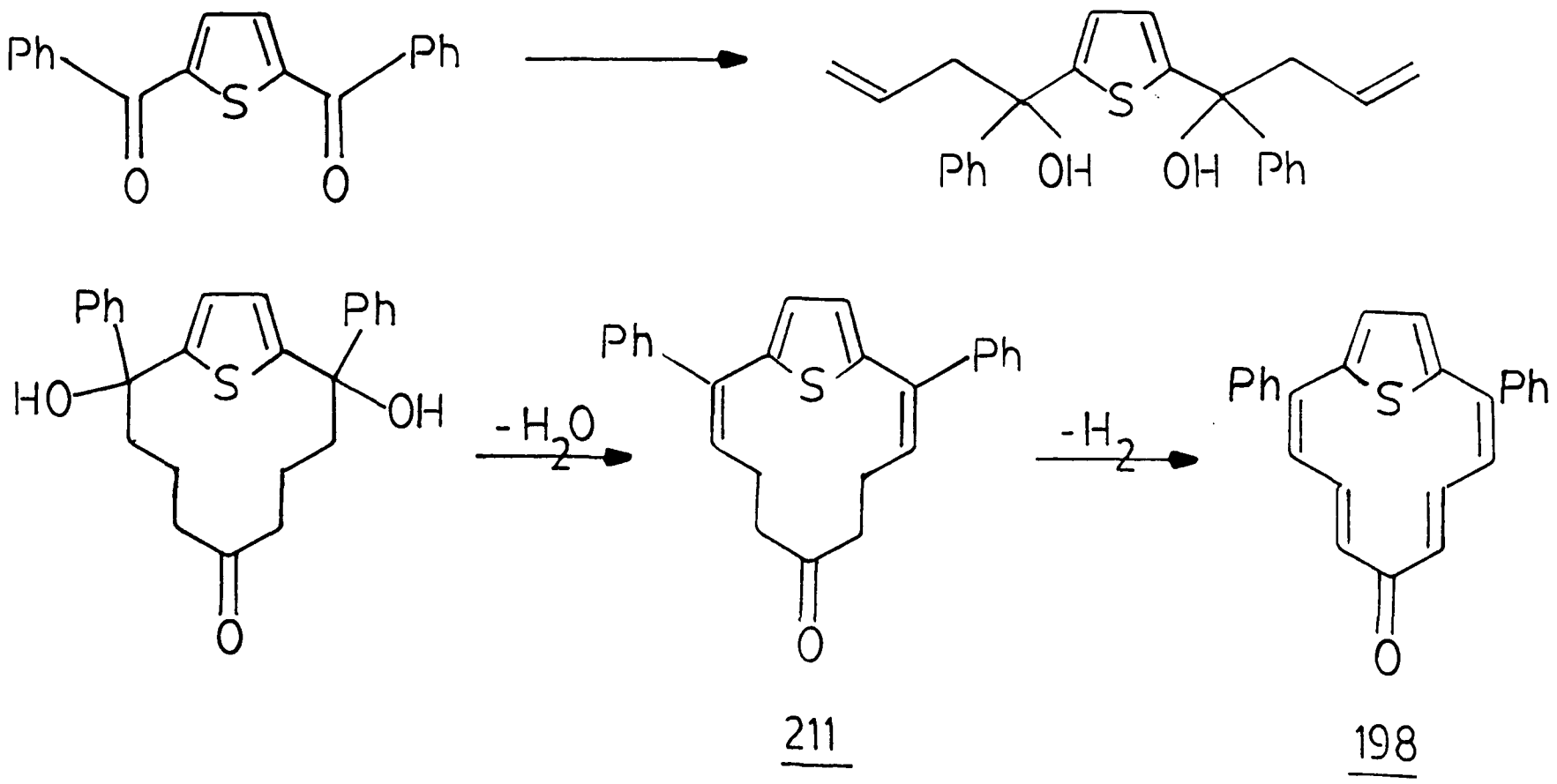
Table 3

	(207)		(201)	
	δ (ppm)	J (Hz)	δ (ppm)	J (Hz)
H_1	6.65	15.3	6.10	16.7
H_2	7.98	15.3+11.3	9.84	16.7+9.75
H_3	7.10	11.3	6.90	9.75

As for comparison, the dimethyl analogue of (201), i.e. (202), was also synthesized[96] and its ^1H NMR spectrum is shown in diagram 13a.

At this point it was discovered that it was impossible to convert (127) to the thiophene derivative, and as (201) was so similar the synthetic work along this route was halted.

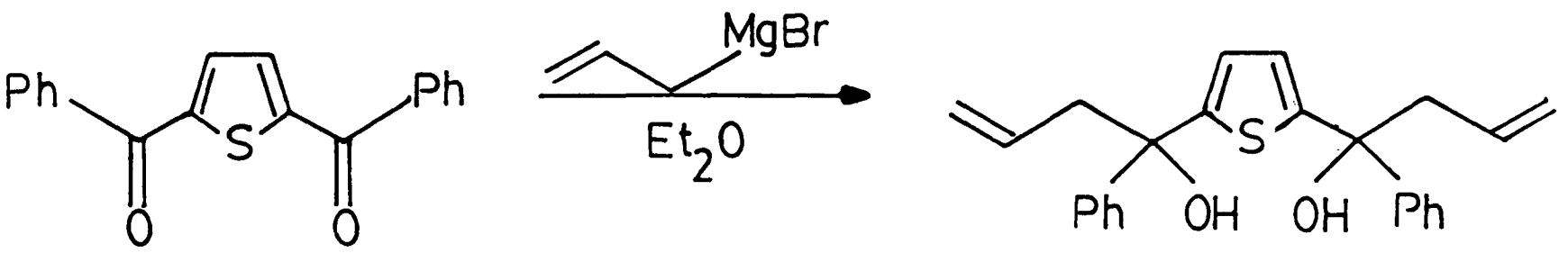
Finally, a completely different approach to the synthesis of 5-keto-1,8-diene-{9}(2,5)thiophenophene (211), a precursor of the fully unsaturated analogue of (198), was tried. The scheme chosen was as follows:



211

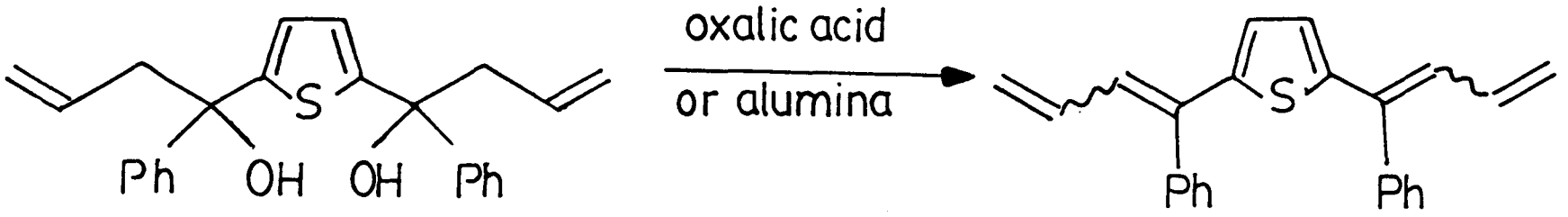
198

Addition of allyl magnesium bromide to 2,5-dibenzoylthiophene in ether gave the diol (212).



212 81%

Attempts to purify (212) by high vacuum distillation caused extensive polymerization, which can readily be explained by the ease of formation of two tertiary carbonium ion centres α to the thiophene ring. This observation was further exemplified by the ease of dehydration of (212) to the conjugated diene (213) using oxalic acid or grade (I) Al_2O_3.

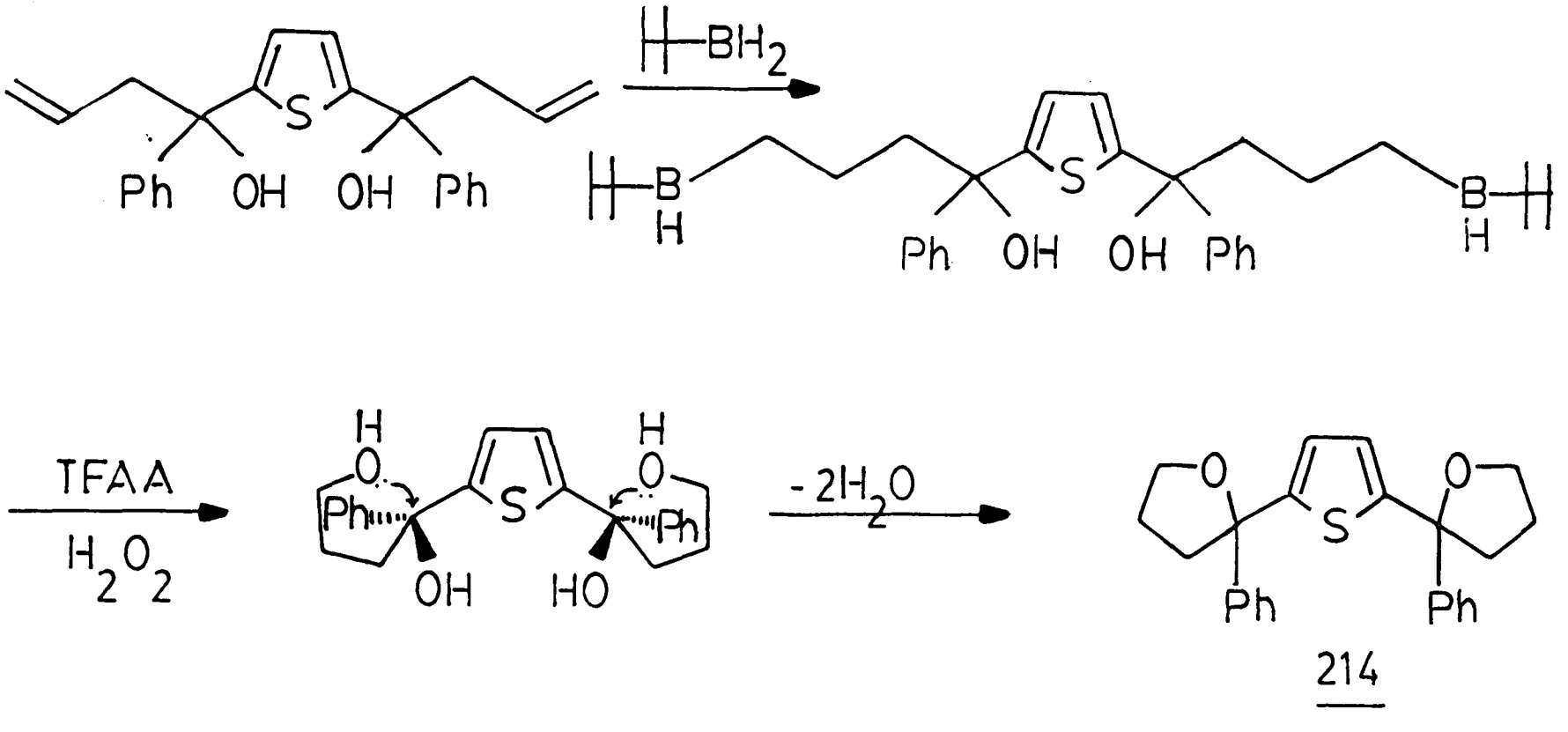


212 213

Hydroboration of (212) was carried out under the general conditions reported.[105a] Cyanidation of the thexyl derivative using sodium cyanide,[104] followed by trifluoroacetic anhydride, oxidative work up and chromatography over silica afforded white needles.

The mass spectrum and combustion data suggested a molecular composition of $C_{24}H_{24}SO_2$. The ^1H NMR spectrum suggested a symmetrical molecule showing four-proton multiplets at δ 1.70-2.25 and 2.25-2.70, a two-proton multiplet at δ 6.48 and ten aromatic protons (δ 7.30, s). The IR spectrum showed no carbonyl absorption and a band at 1050 cm^{-1} suggestive of an aliphatic ether. Structure (214) is consistent with

these data could be formed as indicated.

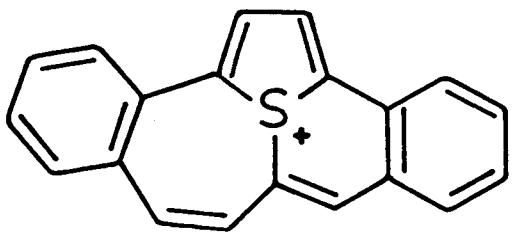


214

No further work was done along this line.

Chapter 5

Attempted synthesis of 13c-thioniabenzo{e}naphth{ij}azulene (126) and 3,9-diphenyl-9b-thioniacyclohept{cd}indene (245).



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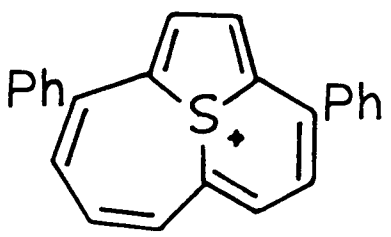
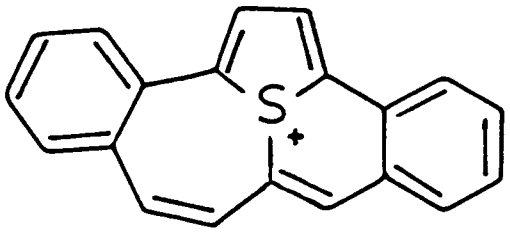
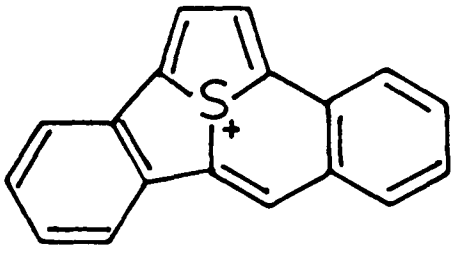


245

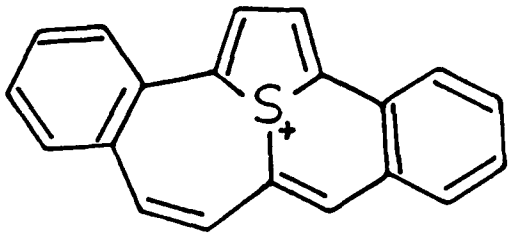
Part A



5.1 Synthetic planning

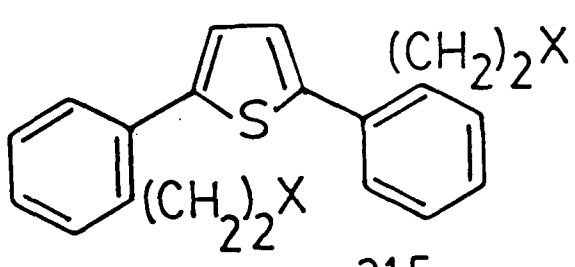


16

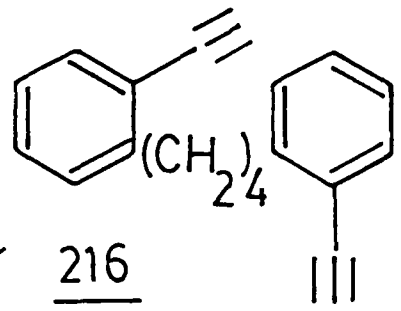


126

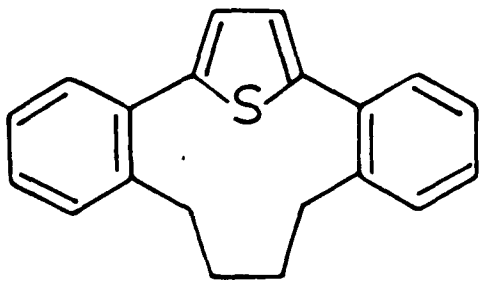
Since (126) and (16) are structurally similar, the strategies used previously for the attempted synthesis of (16) should be equally applicable here. In theory, either closing the appendages of the appropriate 2-substituted 2,5-diphenylthiophene (215) (method B), or intramolecular oxidative coupling of the acyclic diacetylene (216) (method A), followed by addition of H_2S or equivalent should provide the basic skeleton of the dibenzo-fused{8}(2,5)thiophenophane (217).



215



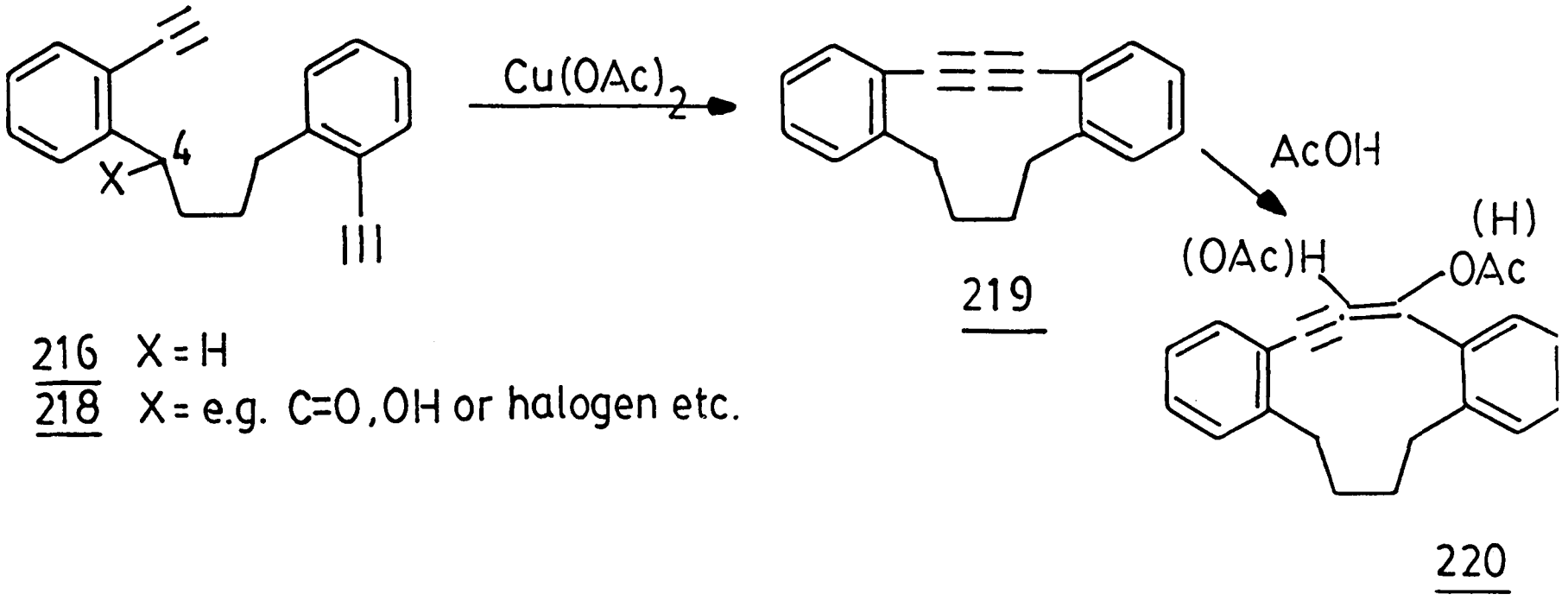
216



217

Introducing functionalization at C_4, or providing it at an earlier stage in the synthesis of a substituted (216), such as (218), seemed difficult. At the ring formation stage giving the butadiyne type (219) significant strain would be introduced implying that acetic acid

addition to the (220) type might occur.

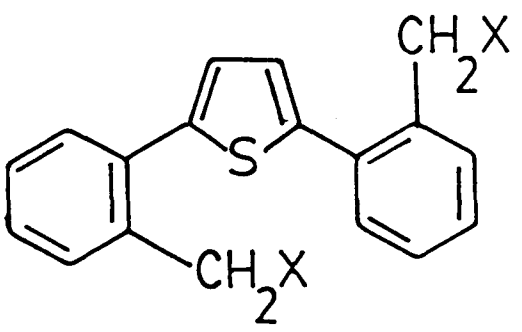


216 X = H
218 X = e.g. C=O, OH or halogen etc.

219

220

Method (B) was therefore first examined as a general approach to (217). In order to try the acyloin condensation or McMurray's titanium coupling as the methodology for ring closure, the diester (221) or the dialdehyde (222) was required.



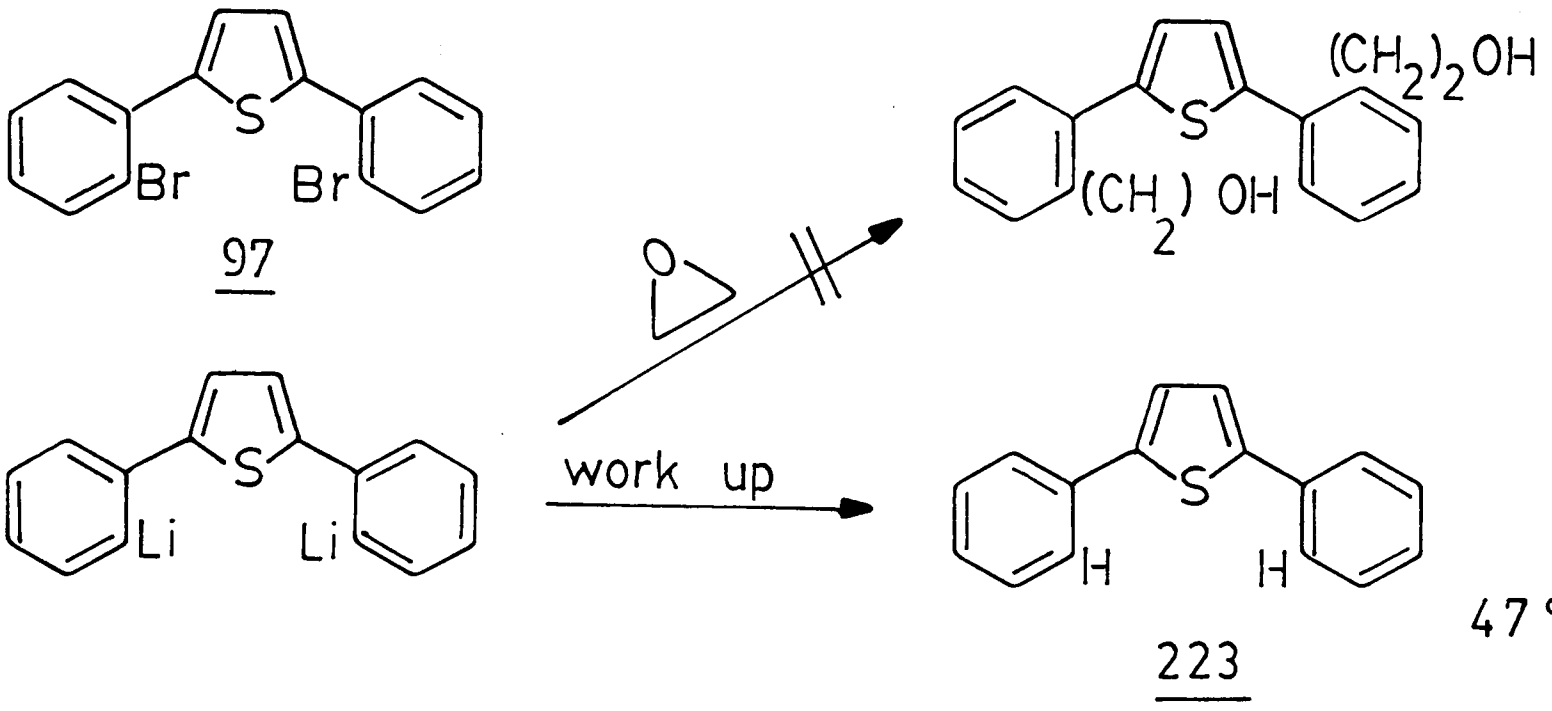
221 X = CO_2R
222 X = CHO

However, the acidity of the benzylic protons in (221) would make the acyloin condensation unfavourable, thus leaving the titanium coupling as the better possibility.

5.2 Results and discussions

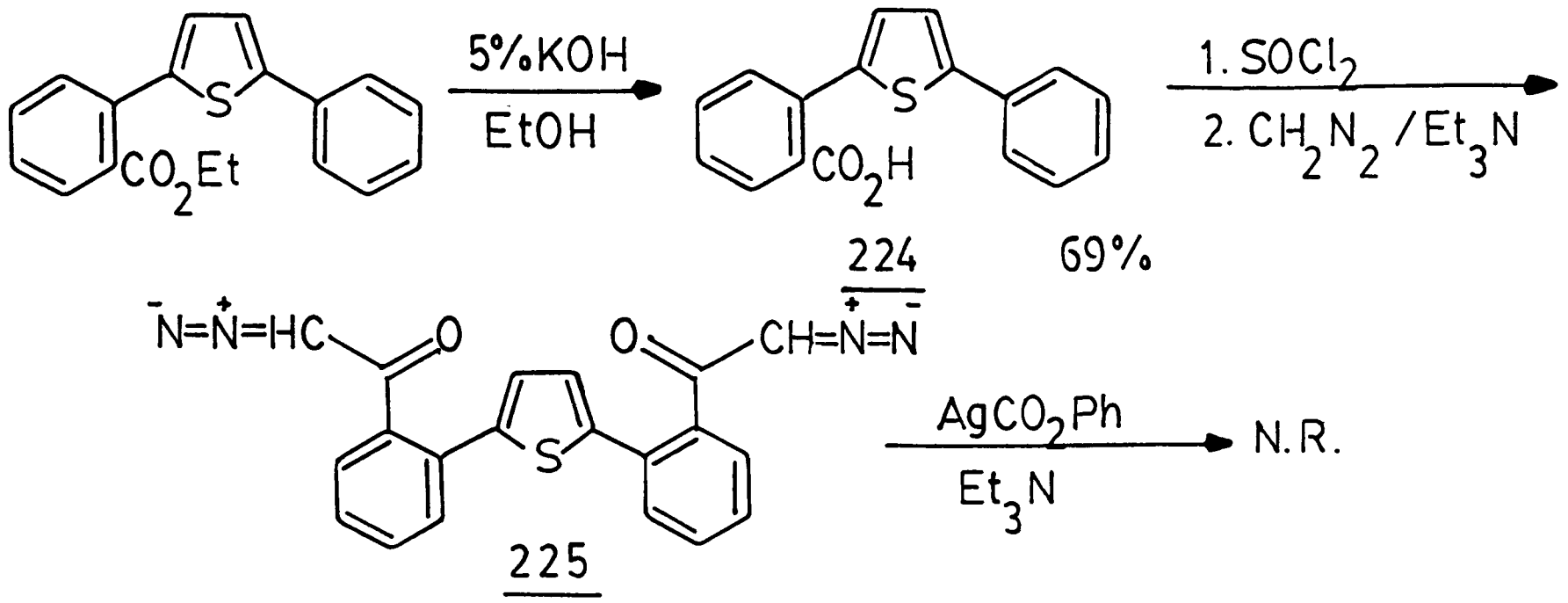
Metallation of 2,5-di(2-bromophenyl)thiophene (97), followed by trapping with ethylene oxide should provide the desired carbon chain and subsequent controlled oxidation should give the dialdehyde (222).

Trapping 2,5-di(2-lithiophenyl)thiophene, generated from 2,5-di(2-bromophenyl)thiophene and n-butyl lithium at -70°C, with excess dried ethylene oxide afforded yellow crystals, which were identified as (223) from its spectra. Unfortunately, this unexpected result was reproduced on several trials, every precaution being taken to exclude water.

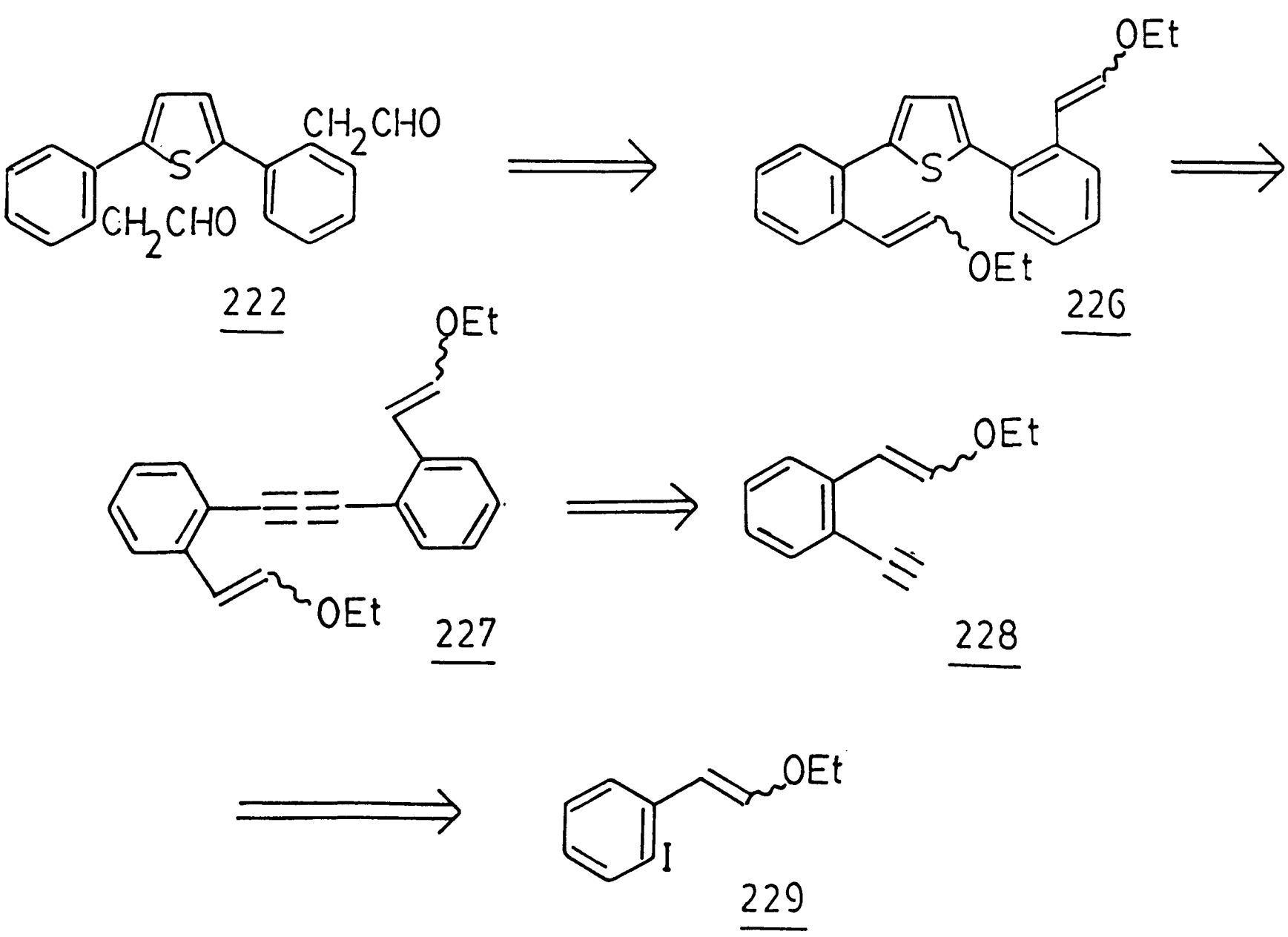


Another well-established procedure for extending by a one-carbon fragment is the Arndt-Eistert reaction. Thus, starting from the previously synthesized 2,5-bis(2-ethoxycarbonylphenyl)thiophene (81), saponification followed by a double Arndt-Eistert reaction should give the 2-carbon homologue diester (221). Saponification of (81) with 5% ethanolic KOH gave the diacid (224). Unfortunately, subsequent reaction with thionyl chloride and diazomethane gave only 16.6% yield

of the diazoketone (225), and attempted Wolff rearrangement of the diazoketone (225) under the conditions suggested gave back only (225).

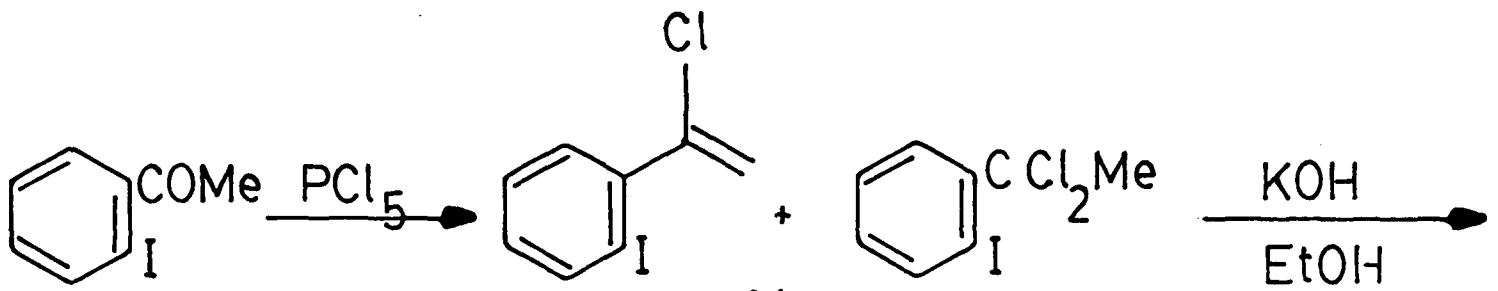


It is well known that vinyl ethers are masked aldehydes; thus, a simple retrosynthesis on (222) is shown:



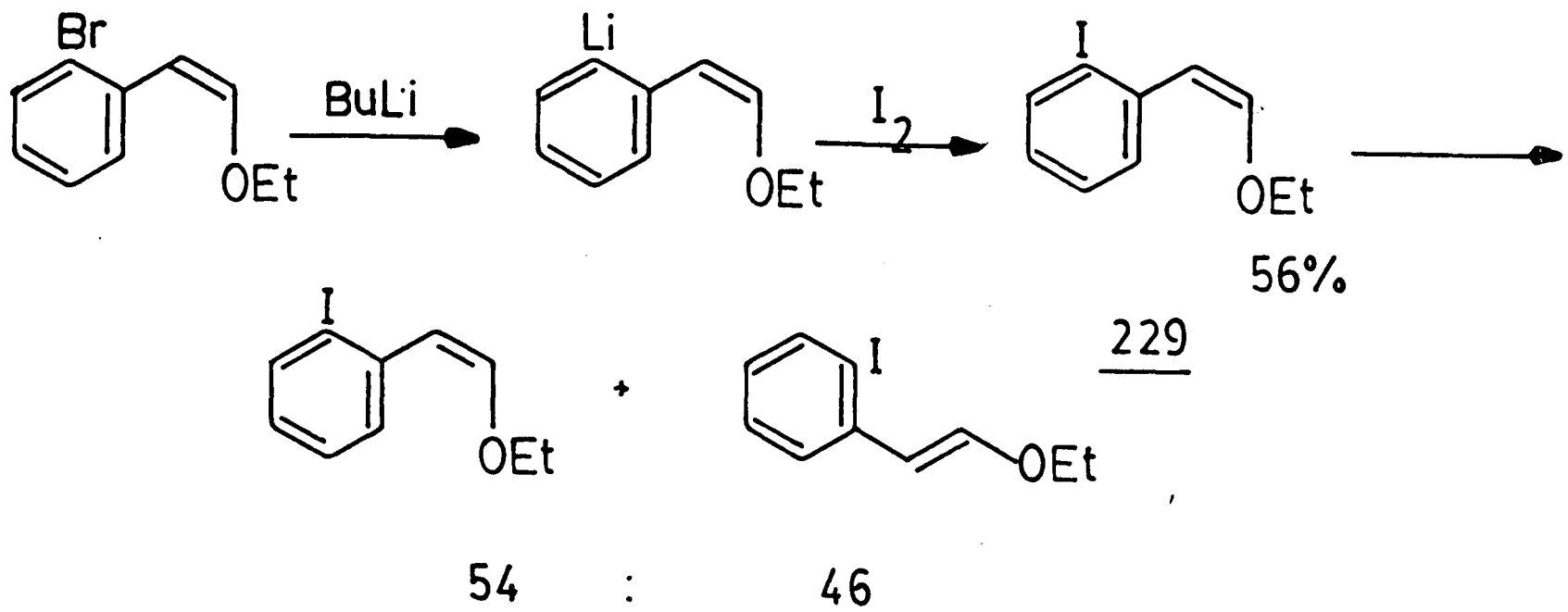
Recalling that Z-(2-bromophenyl)ethoxyethene (94) is the only isolable product when a mixture of 1-(2-bromophenyl)-1-chloroethene (91) and 2-bromo-1,1-dichloroethylbenzene (92) were allowed to react with alcoholic potash for Ca. 15 h, a similar approach should give Z-(2-iodophenyl)ethoxyethene (229).

Refluxing a mixture of 1-(2-iodophenyl)-1-chloroethene (230) and 2-iodo-1,1-dichloroethylbenzene (231), prepared from 2-iodoacetophenone[88] and phosphorous pentachloride, with ethanolic potassium hydroxide for 3 h gave only 2-iodophenylacetylene (232) and 1-(2-iodophenyl)-1-chloroethene (230). No sign of Z-(2-iodophenyl)-ethoxyethene (229) was detected.



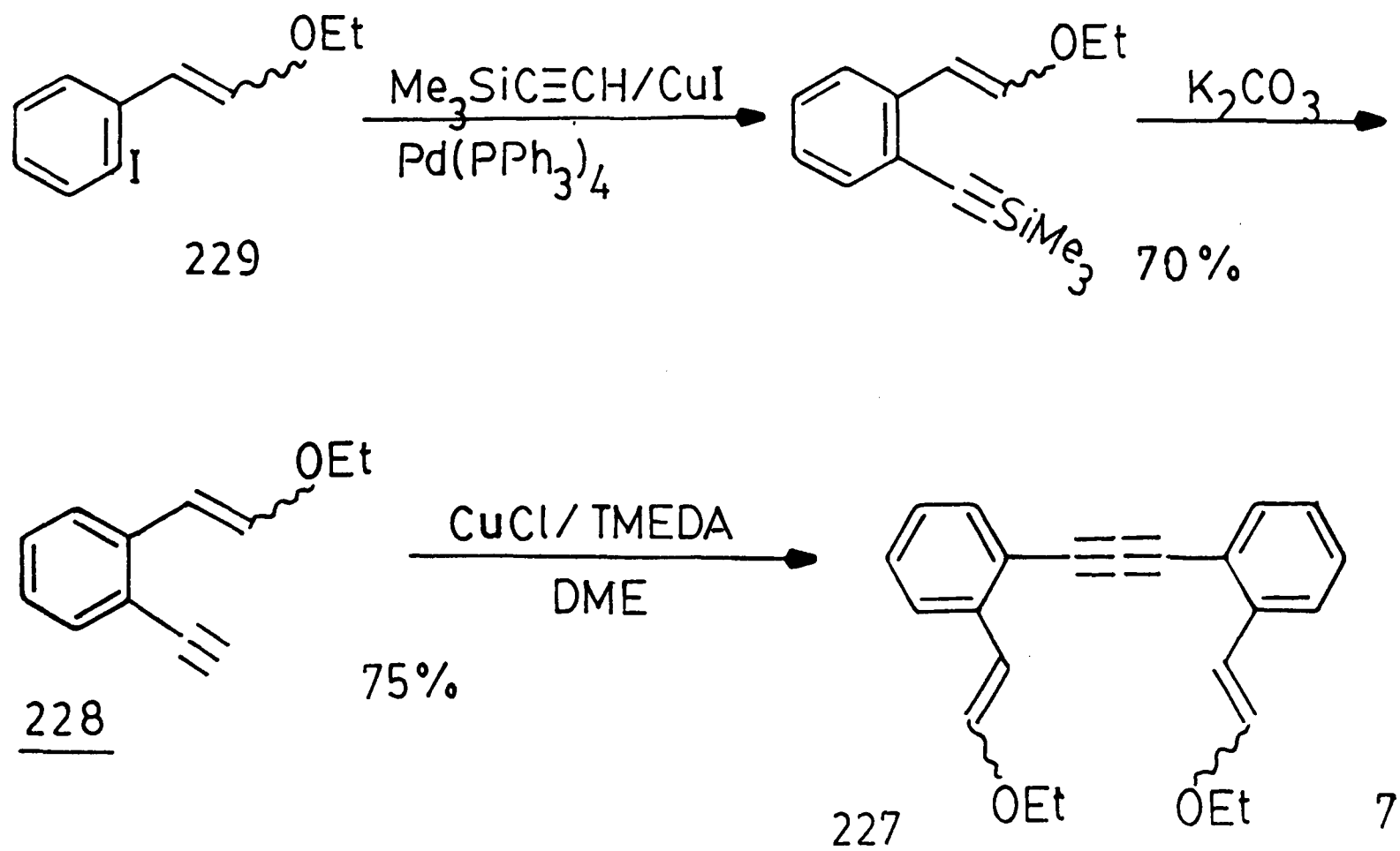
One simple way to overcome the problem is to synthesise Z-(2-bromophenyl)ethoxyethene (94) and subsequent halogen exchange, via the lithio-derivative, with iodine.

Z-(2-Bromophenyl)ethoxyethene (94) was synthesized as described earlier. Subsequent lithation with n-butyl lithium, followed by trapping with iodine, gave the expected Z-(2-iodophenyl)ethoxyethene (229).



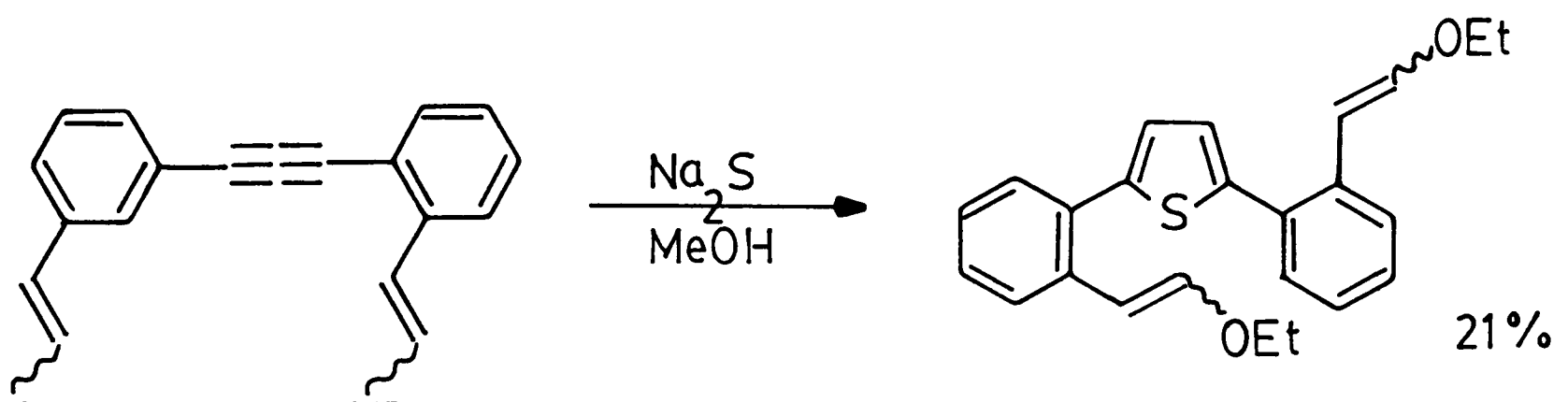
^{1}H NMR spectrum of the crude reaction product showed the Z-configuration of the double bond was retained. However, on purifying (229) by high-vacuum distillation it isomerized to a mixture of Z and E isomers in a ratio of 54:46 as shown by ^{1}H NMR.

Coupling with ethynyltrimethylsilane under the usual conditions[76] followed by desilylation gave a mixture of the expected Z and E-(2-ethynylphenyl)ethoxyethene (228). Though purification by distillation was unsuccessful, the crude mixture was oxidatively coupled, using Hünig's procedure, to the diacetylene (227).



On storage, the more stable E,E isomer of (227) crystallized out, which was characterized fully by ^{1}H NMR, MS and combustion analysis.

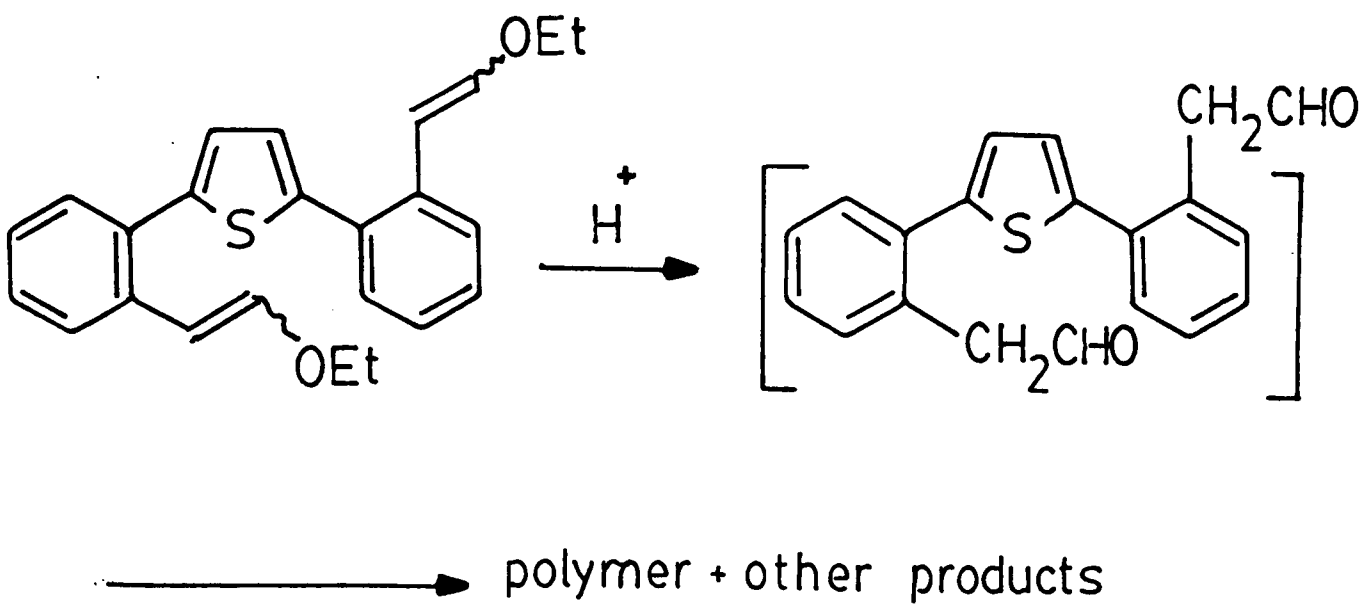
Conversion of (227) to the corresponding thiophene (226) was effected by sodium sulphide in refluxing methanol.[22] After 16 h refluxing, chromatography on SiO_2 afforded an oil, which was a roughly 1:1 mixture of (227) and the expected thiophene (226), which could not be separated. Prolonged refluxing for 48 h gave only a slight increase in yield.



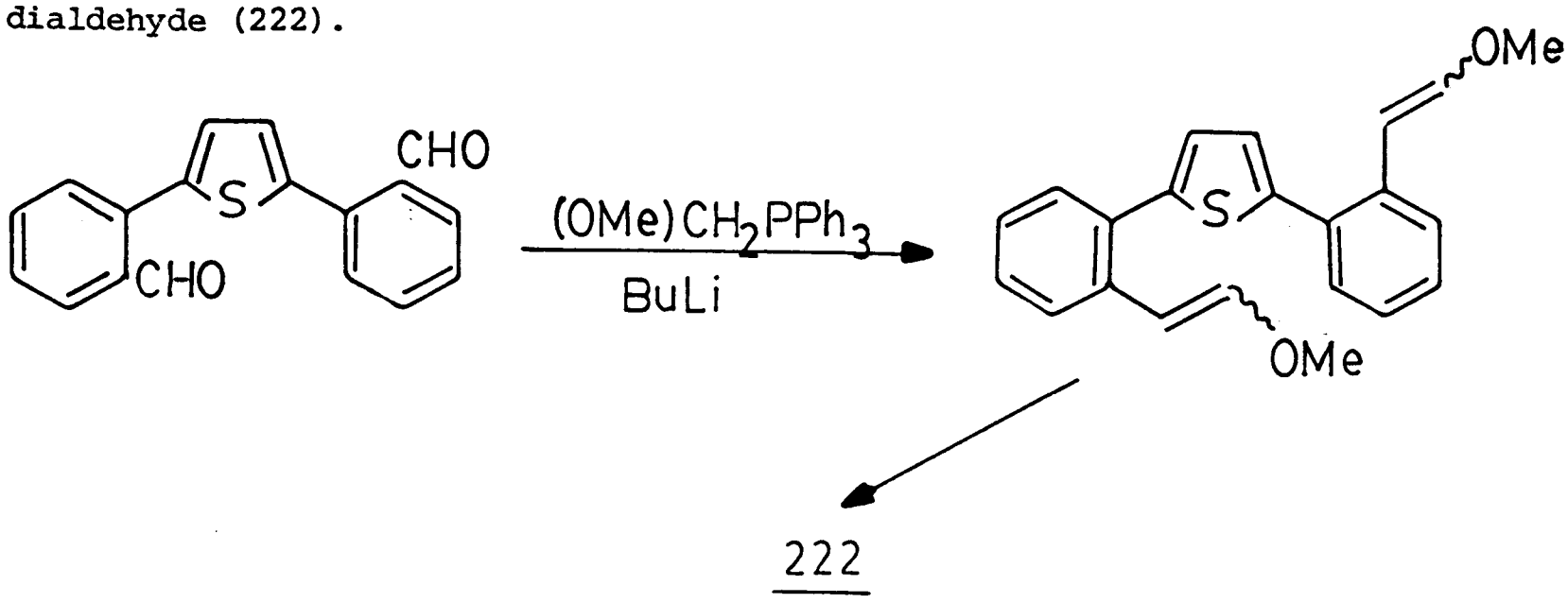
227 226

Nevertheless, the structure of (226) was firmly established from its ^{1}H NMR spectrum and MS. The thiophene protons appeared as a singlet at δ 7.05, while MS gave 376 for M^+.

The vinyl ether (226) was essentially stable to 1 M HCl for 1 h but 6 M HCl caused decomposition to an oil and a highly crystalline material. The latter was insoluble in water and only slightly soluble in boiling DMSO. ^{1}H NMR examination even at 110°C showed no signal; presumably the solid was polymeric. The ^{1}H NMR spectrum of the oil showed only a small aldehyde signal, compared to the large aromatic ones, suggesting that the dialdehyde (222) was formed but underwent further reaction.

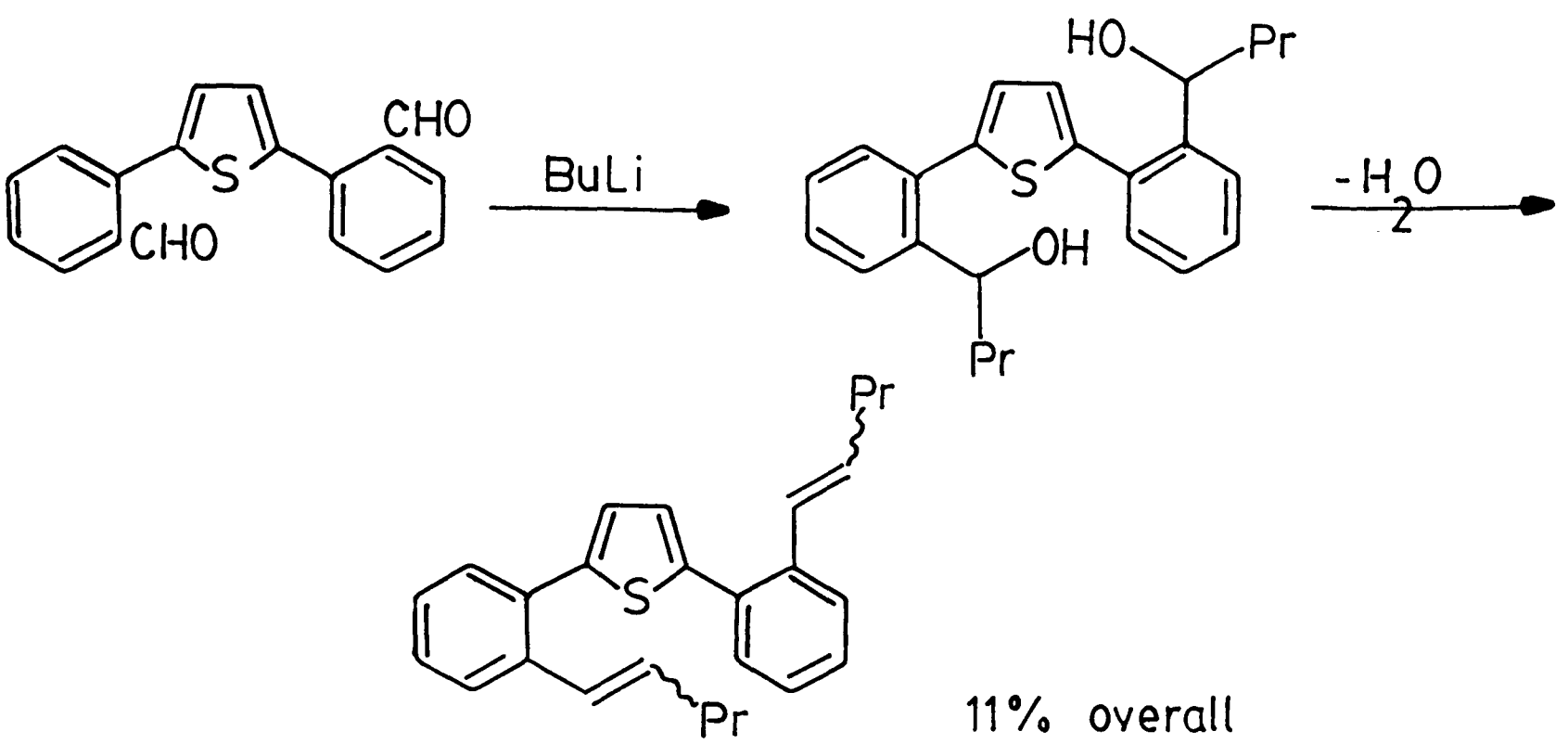


The following reaction was tested as an alternative route to the dialdehyde (222).



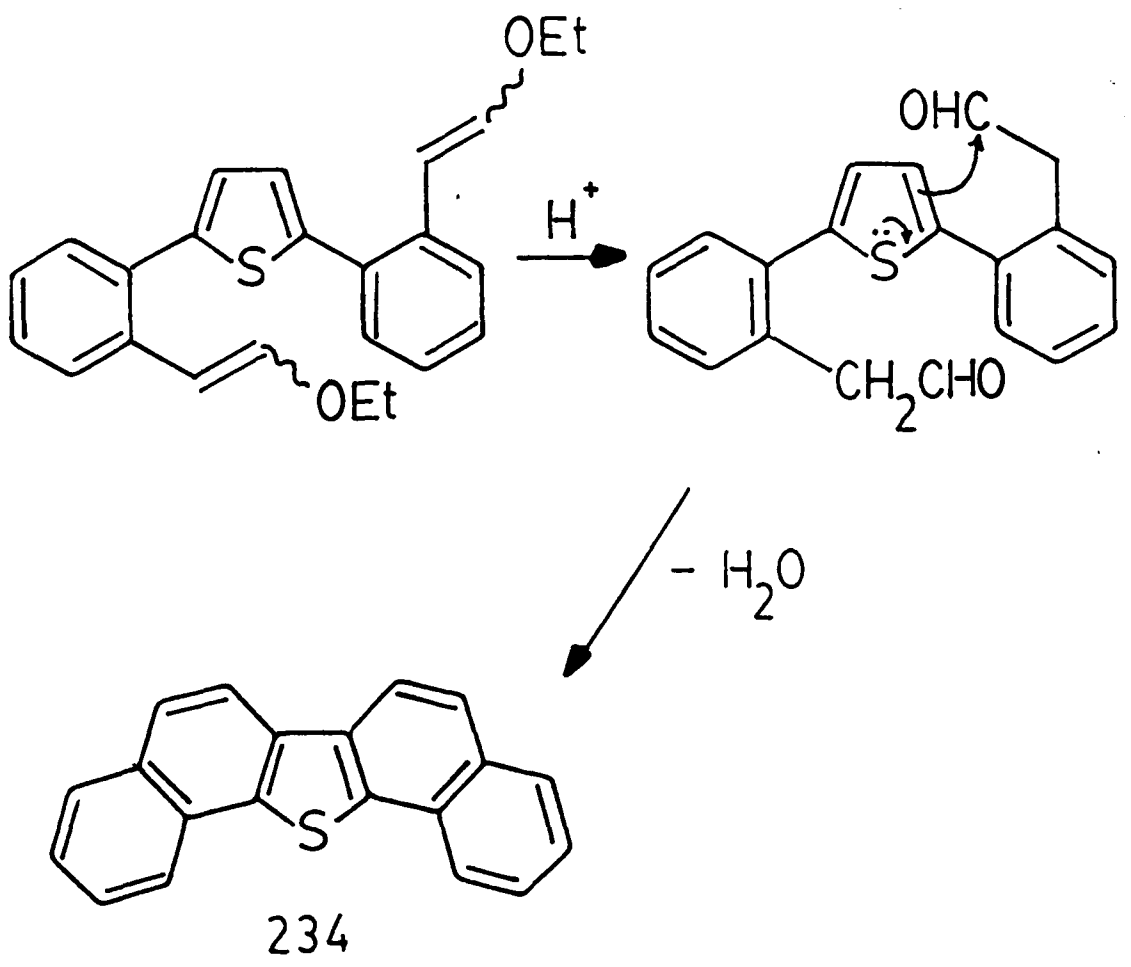
222

Reacting a mixture of (89) and 3 equivalents of methoxymethinephosphorane, generated from n-butyl lithium and (methoxymethyl)-triphenylphosphonium chloride at $0^{o}C$, followed by acid hydrolysis and careful chromatography on SiO_2 (10% Et_2O-PE) afforded two compounds. The first one (Rf=0.79) which was identified unequivocally as a mixture of Z,E-isomers of 2,5-bis{2-(pent-2-enyl)phenyl}thiophene (233) from its ^{1}H NMR and MS, arose apparently from the addition of n-butyl lithium to (89) followed by dehydration.



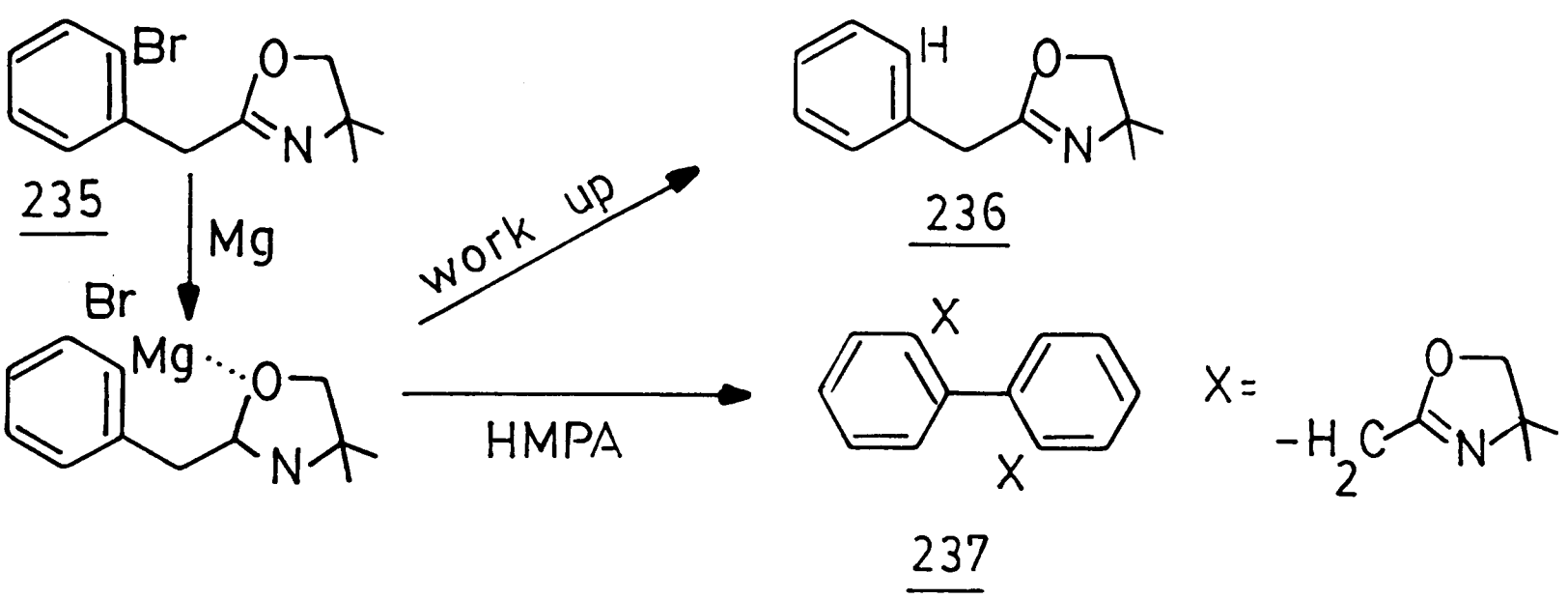
233

The second product (Rf=0.72) was isolated in only 5% yield as pale yellow crystals after recrystallization from PE. ^{1}H NMR spectrum showed only aromatic protons, IR gave no carbonyl absorption, while MS gave m/e 284 for M^{+}. The compound was dinaphtho{2,1-b:1',2'-d} thiophene (234), which could be formed from electrophilic closure followed by dehydration.

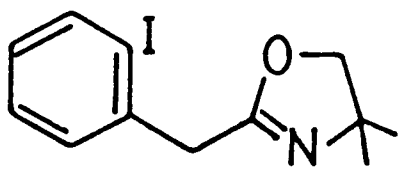


234

Equally frustrating were the results obtained from the attempted coupling of 2,5-dibromothiophene with the Grignard reagents derived from 4,4-dimethyl-2-(2-halobenzyl)oxazolines. 4,4-Dimethyl-2-(2-magnesiobenzyl)oxazoline, prepared from the corresponding bromide (235) and magnesium, with 2,5-dibromothiophene, in the presence of $Ni(dppp)Cl_2$, under the conditions reported[108d] gave only 4,4-dimethyl-2-benzyloxazoline (236). When HMPA was added as a co-solvent, only 2,2'-bis{3-(4,4-dimethyl-oxazolino)methyl}biphenyl (237) was formed. Both (236) and (237) were identified from their ^1H NMR and MS.

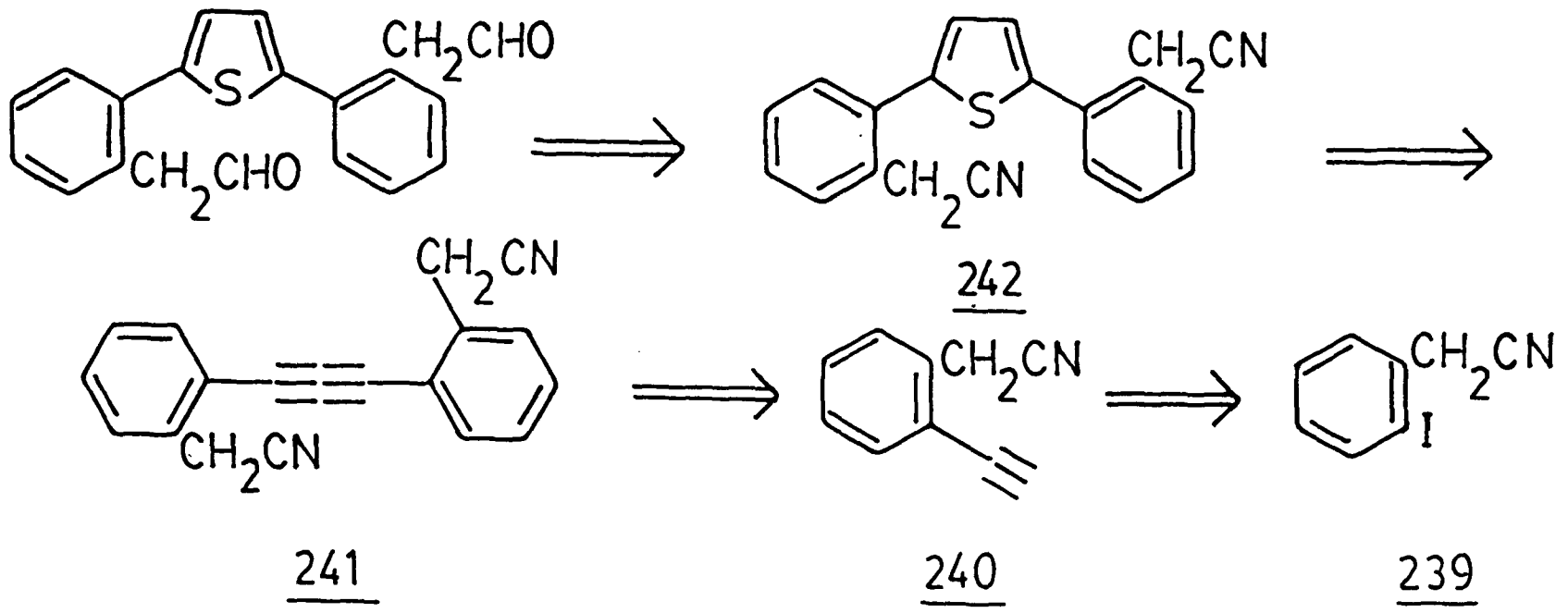


Surprisingly, by using 4,4-dimethyl-2-(2-iodobenzyl)oxazoline (238) instead, no reaction occurred!

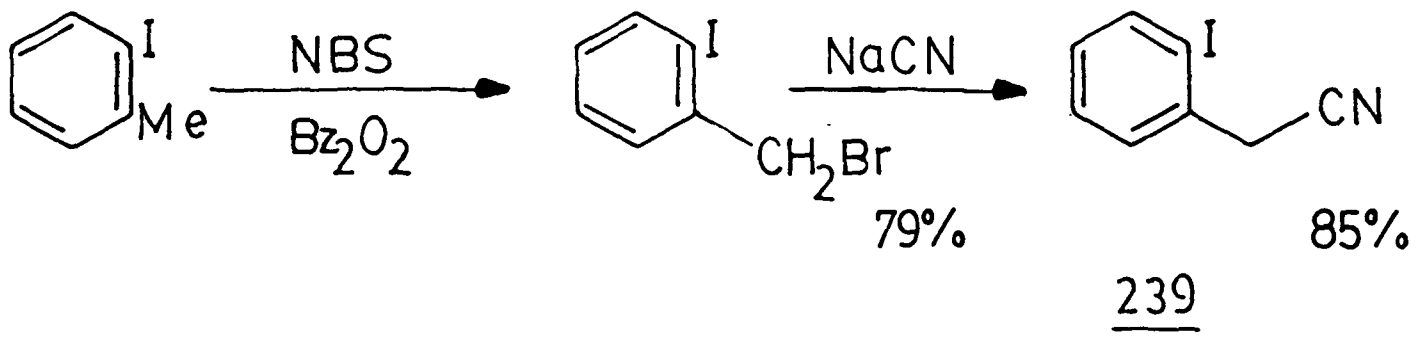


238

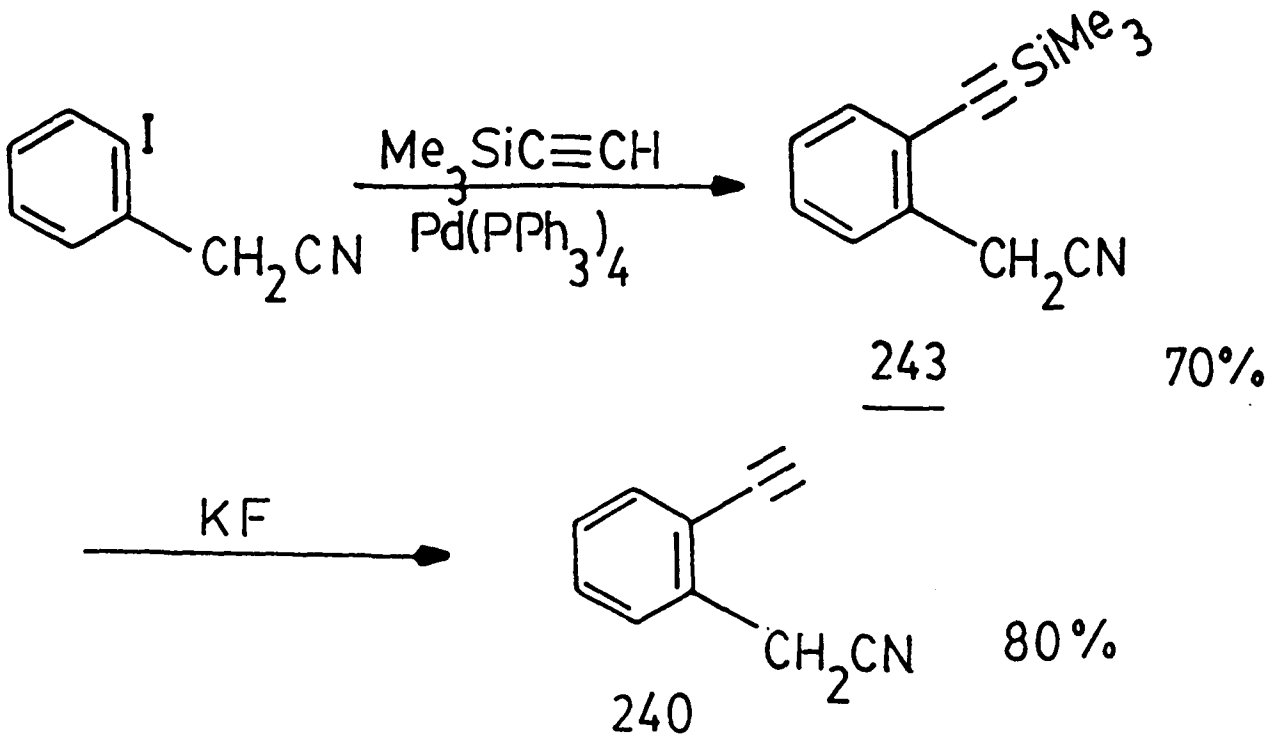
Another functional group equivalent to an aldehyde is a nitrile.[180] Thus, the synthesis of the dialdehyde (222) could start from (239).



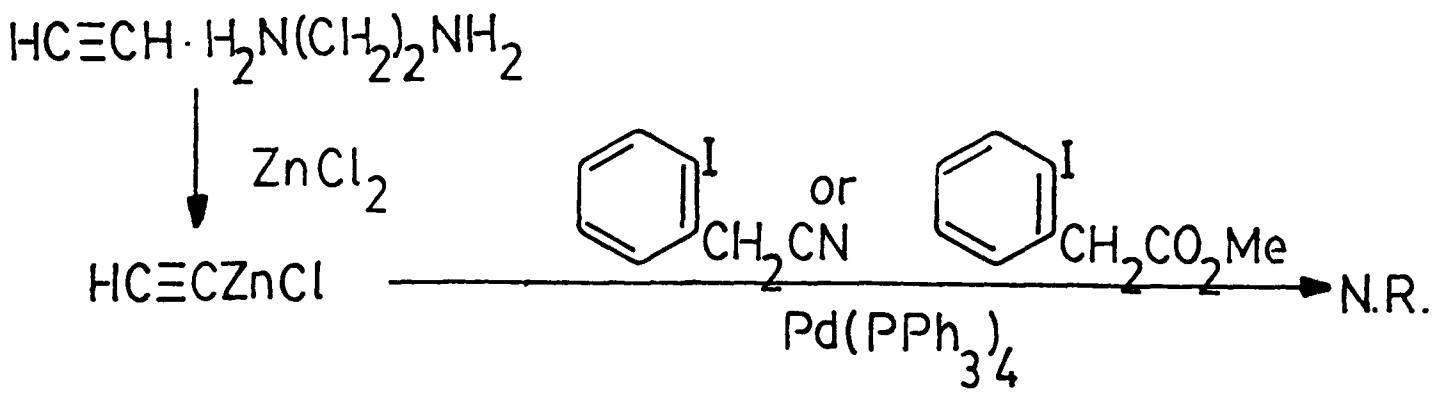
Starting from 2-iodotoluene, free radical bromination by N-bromosuccinimide,[181] followed by cyanide displacement,[182] gave 2-iodobenzyl cyanide (239).



Coupling between (239) and ethynyltrimethylsilane, using palladium(II)acetate as catalyst and under conditions reported[76] gave no reaction. However, by adding a catalytic amount of copper(I)iodide and using $Pd(PPh_3)_4$ instead, (239) underwent coupling smoothly to give 2-{(trimethylsilyl)ethynyl}benzyl cyanide (243). Subsequent desilylation gave the expected 2-ethynylbenzyl cyanide (240).

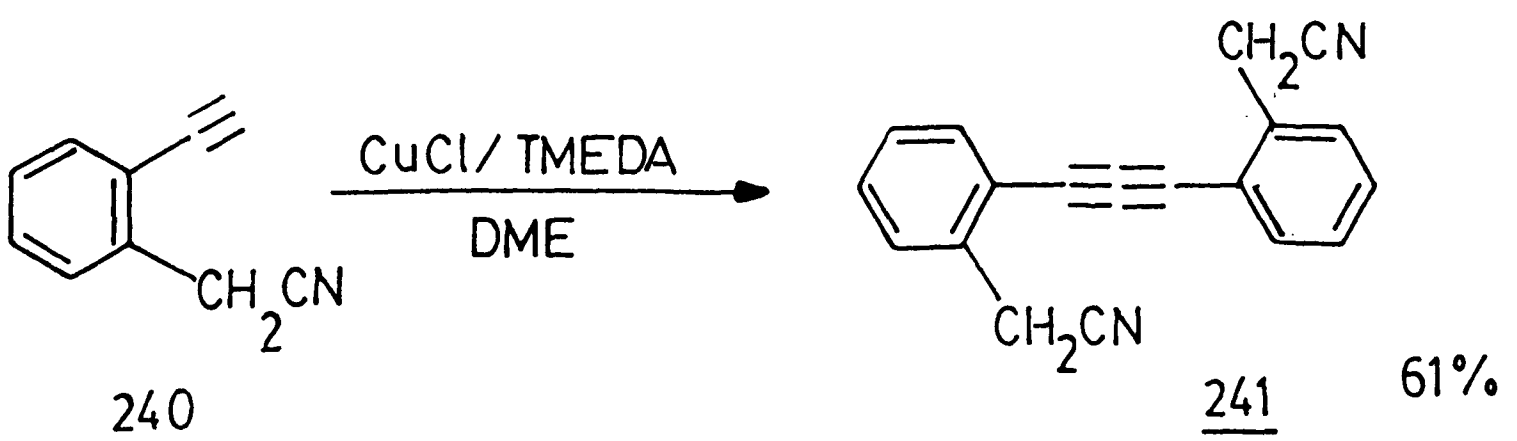


It is worth mentioning that 2-bromobenzyl cyanide gave only 34% of the coupled product under similar conditions. Attempts to adopt the literature report[183] on the use of ethynylzinc chloride (244), generated *in situ* from the commercially available ethynyllithium-ethylenediamine complex and anhydrous zinc chloride, instead of ethynyltrimethylsilane for coupling failed. Thus, reacting a mixture of 2-iodobenzyl cyanide or methyl 2-iodophenylacetate with ethynyl zinc chloride under the conditions reported[183] gave back only starting materials.



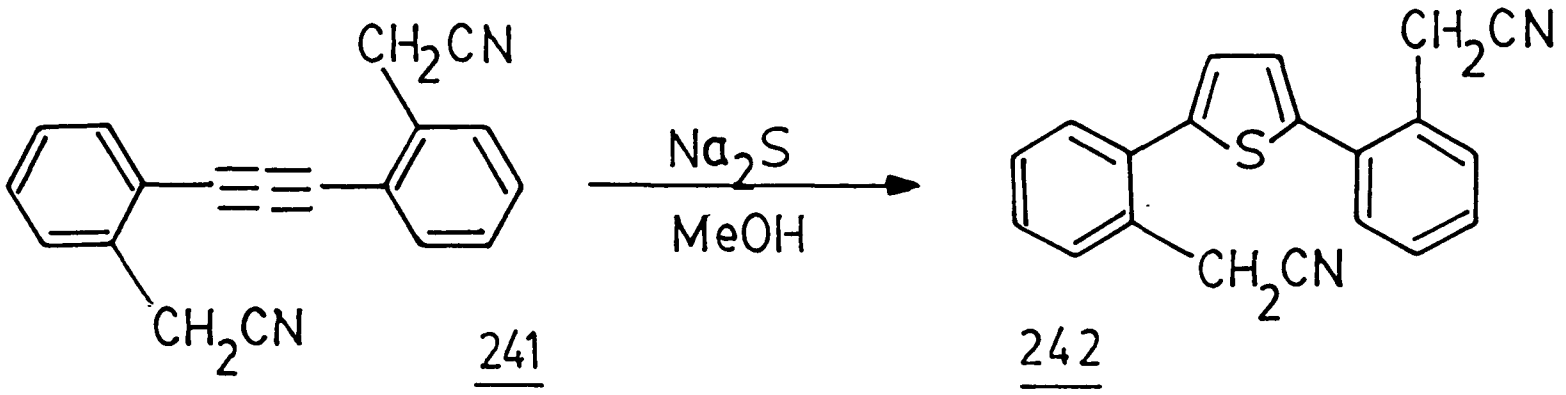
244

Intermolecular oxidative coupling of (240), using Hünig's[75] method gave the diacetylene (241).



240 241

Conversion of the diacetylene (241) into the substituted thiophene (242) was effected by sodium sulphide in refluxing methanol,[22] while ethanolic sodium hydroxide and hydrogen sulphide[68] only led to extensive polymerization, which also occurred when the reaction was scaled up from 3 to 10 mmol.

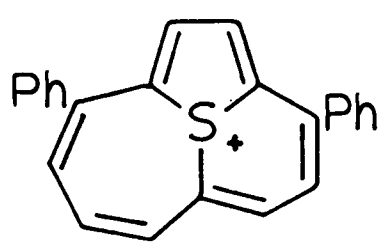


241 242

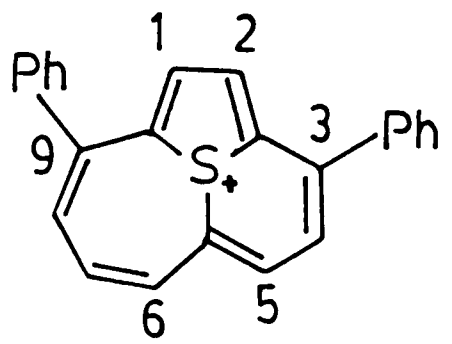
The structure of (242) was firmly established from its spectroscopic and combustion analysis data. Though the yield obtained by the above route to (242) is not great, however, (242) represents the first example in the literature of a 2,5-diphenylthiophene having a 2-carbon fragment as the substituent.

Due to the shortage of time, the above synthetic scheme was terminated at (242).

Part B

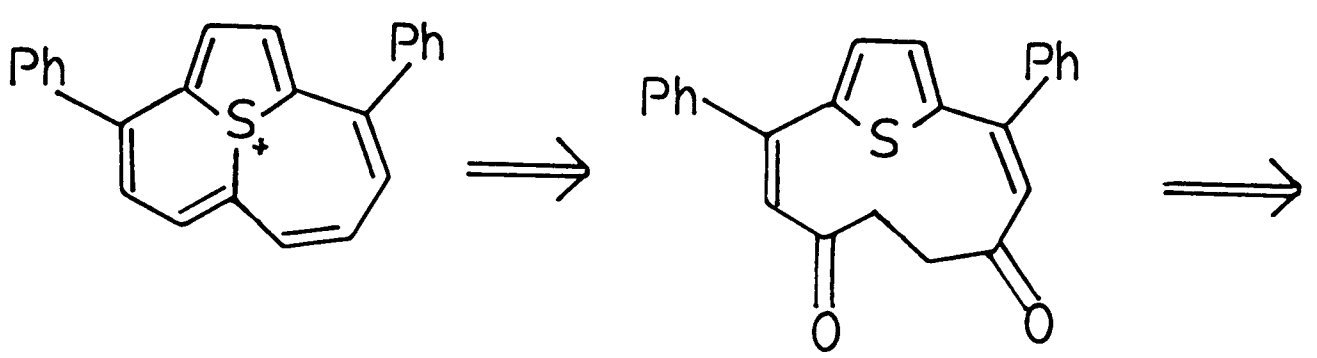


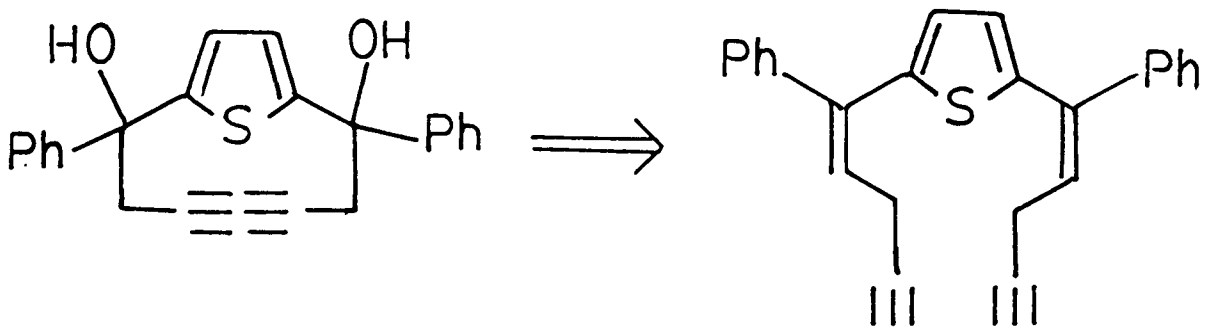
In the initial stage of the attempted synthesis of (126), the preparation of (245) was also investigated.



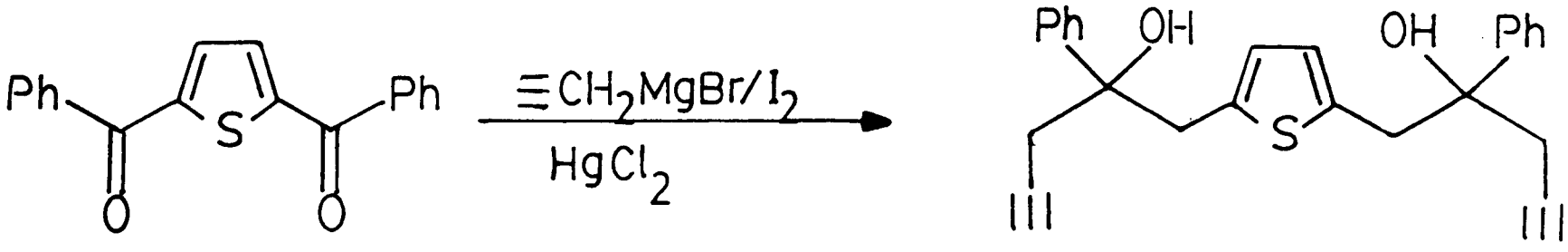
245

Intramolecular oxidative coupling was chosen as the means of constructing the C_5-C_6 bond viz:





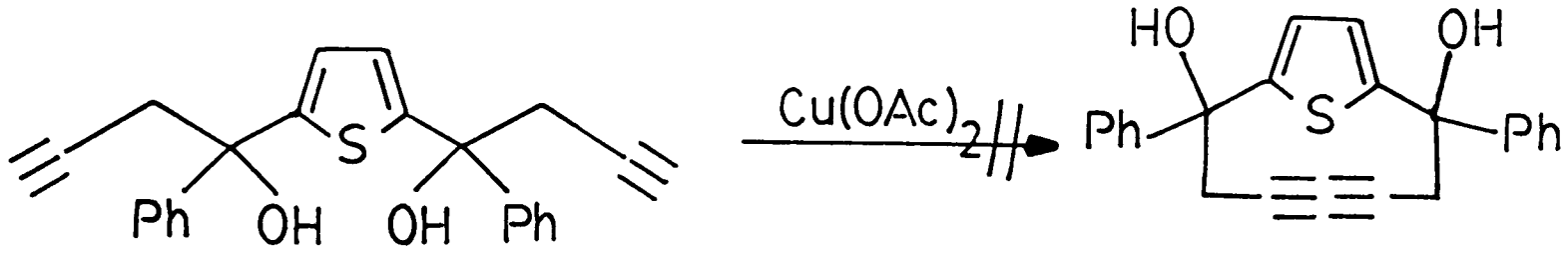
Addition of propargyl magnesium bromide to 2,5-dibenzoylthiophene, in the presence of a small quantity of mercury(II)chloride and iodine, gave the diol (246).



246

Attempts to purify (246) by high vacuum distillation caused extensive polymerization. Nevertheless, (246) was characterized fully by spectroscopic data.

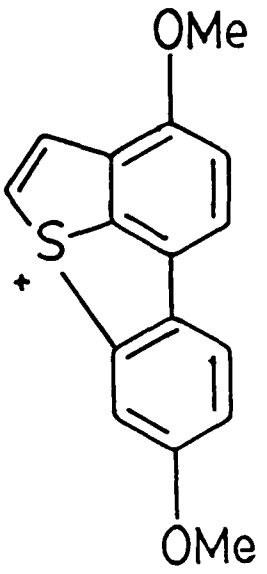
Intramolecular oxidative coupling of (246), using copper(II)acetate, under the general reported conditions, gave no sign of the expected diyn (247) and instead a compound, whose structure could not be assigned unambiguously from the available data, was obtained.



247

Chapter 6

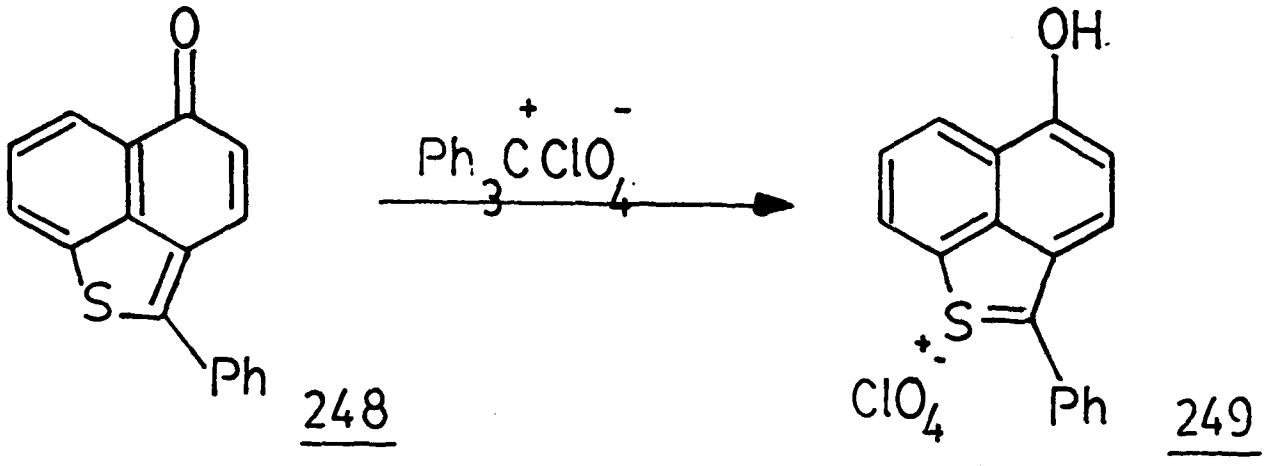
Attempted synthesis of 3,8-dimethoxy-9b-thioniacyclopenta{jk}fluorene (254).



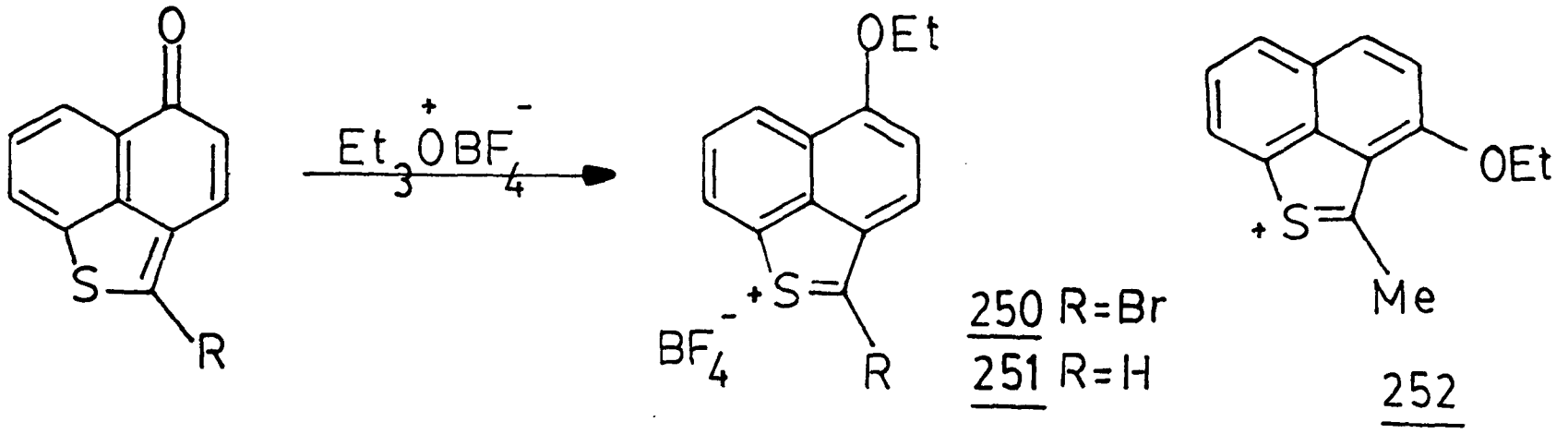
254

6.1 Introduction and Synthetic Planning

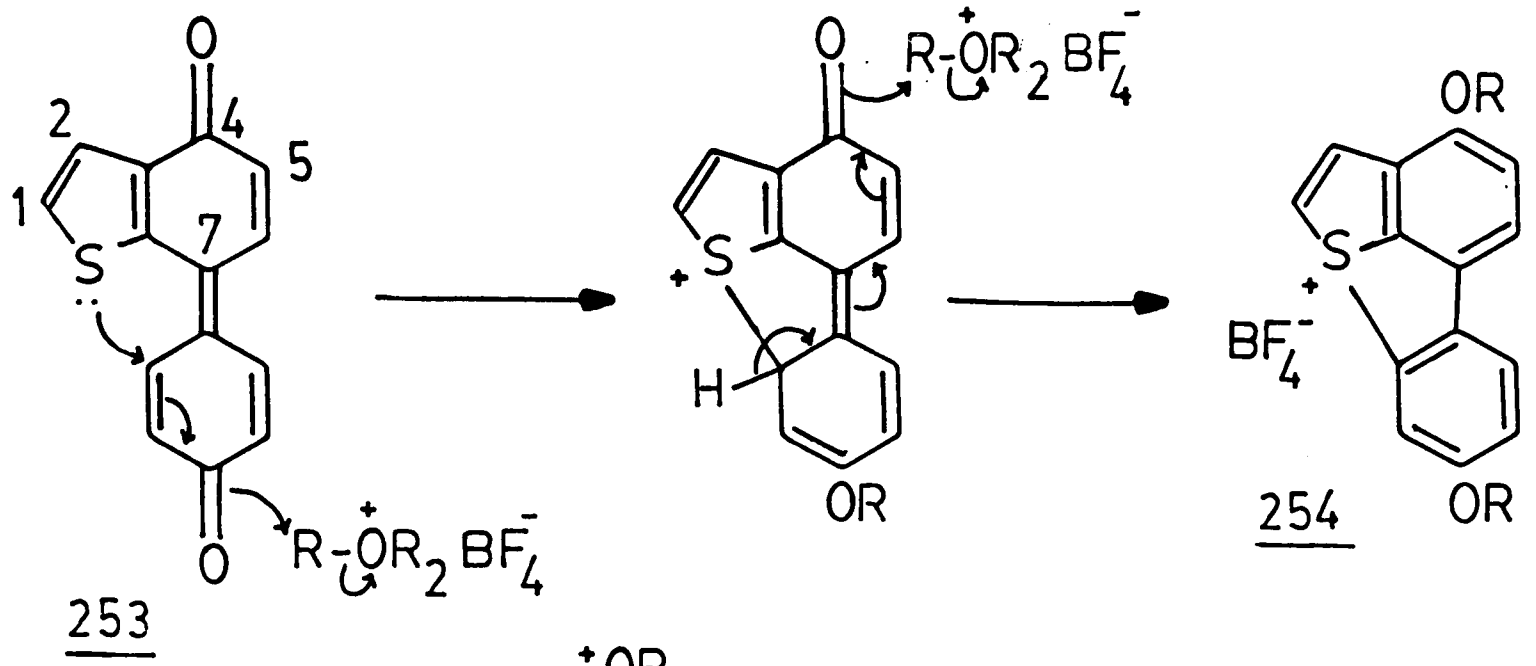
In 1966, Hawthorne et al[184] reported the first synthesis of naphtho{1,8-b,c}-thienylium perchlorate (249) from the corresponding naphtho{1,8-b,c}thiophene (248).

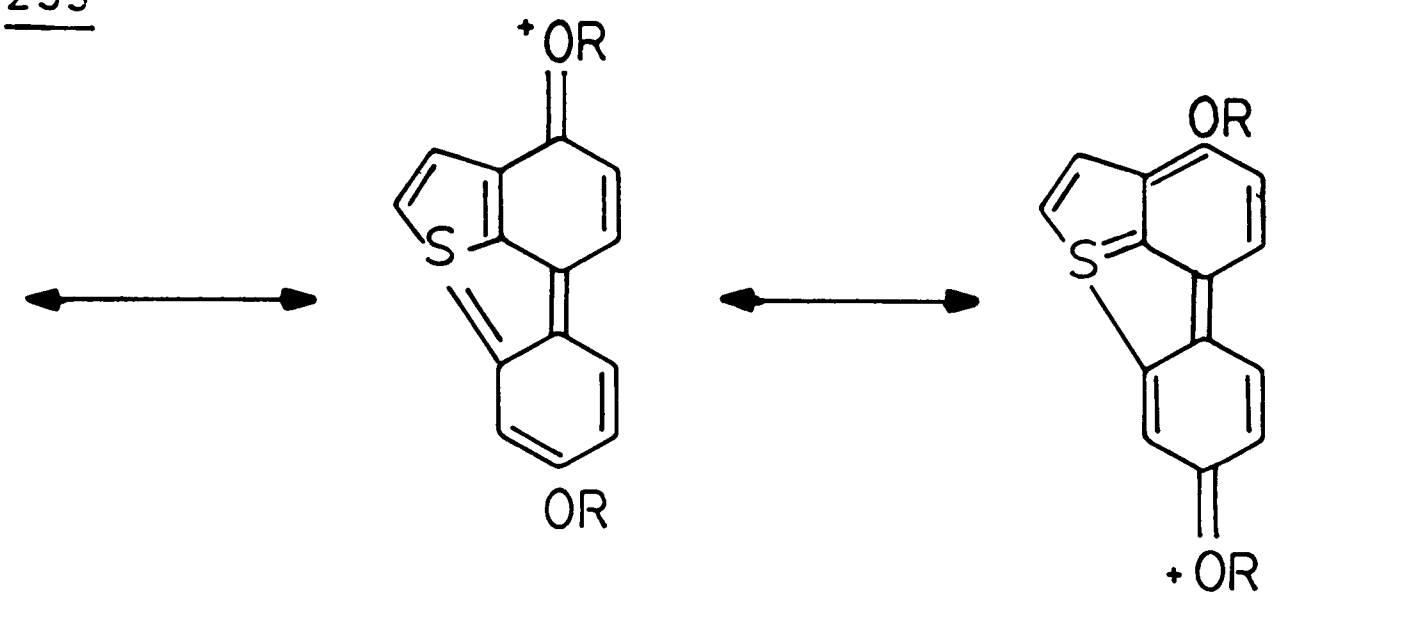


Ever since, other similar systems (250),[185] (251),[186] and (252)[187], which are now collectively known as thiapseudophenalenium salts,[187] appeared.



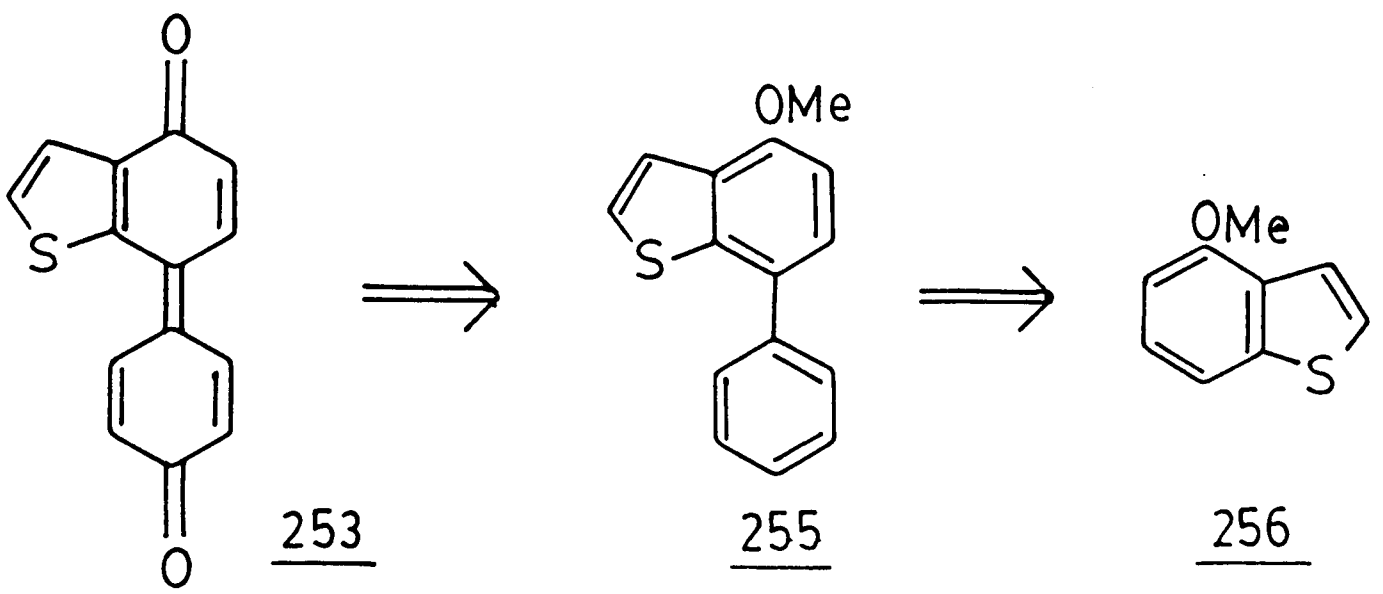
The participation of the sulphur lone pair in the above reactions led us to speculate that via a similar mechanism, (253) might undergo an intramolecular ring closure to the benzothiophenium salt (254). Structure (254) can be highly stabilized by resonance, which should assist its formation.





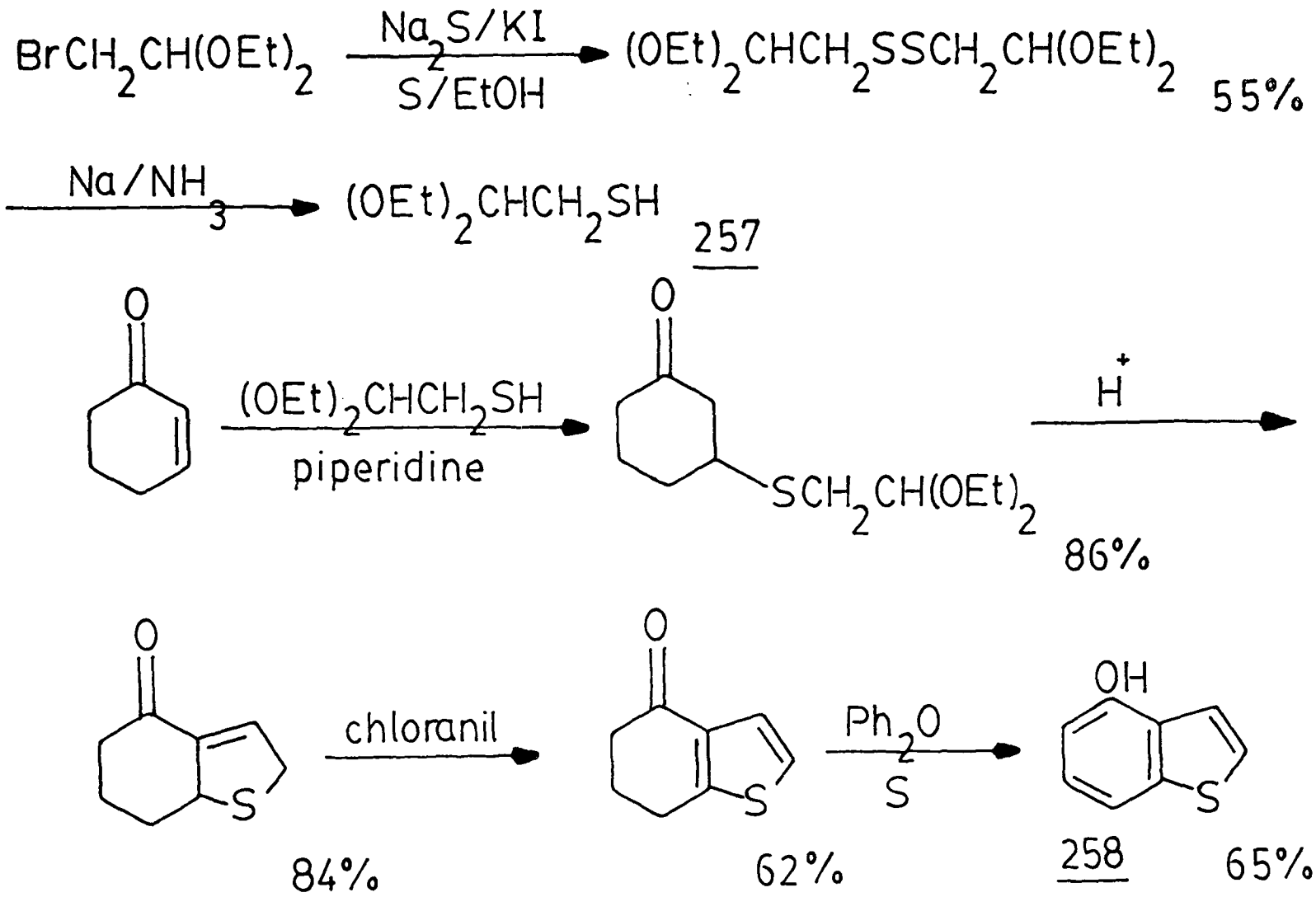
The bonds from the S atom could have to be coplanar, as in (249)-(252), contrasting to the case of the S-alkylthiophenium salts.

Since structure (253) can be regarded as a derivative of 4-methoxybenzo{b}thiophene (255) and if we assumed that the phenyl group in C_7 is to be introduced later, the synthesis of (253) simply becomes that of 4-methoxy-benzo{b}thiophene (256).

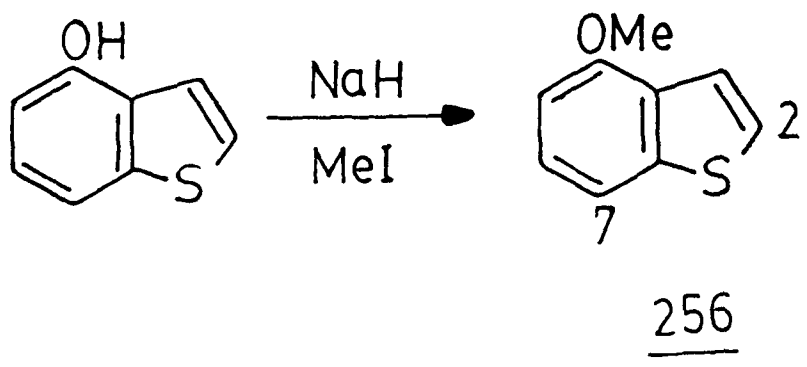


6.2 Results and discussions

Following Napier's reported procedure[188] and via a 4 stage synthesis starting from mercaptoacetaldehyde diethylacetal[189] (257), 4-hydroxybenzo{b}-thiophene (258) was obtained.



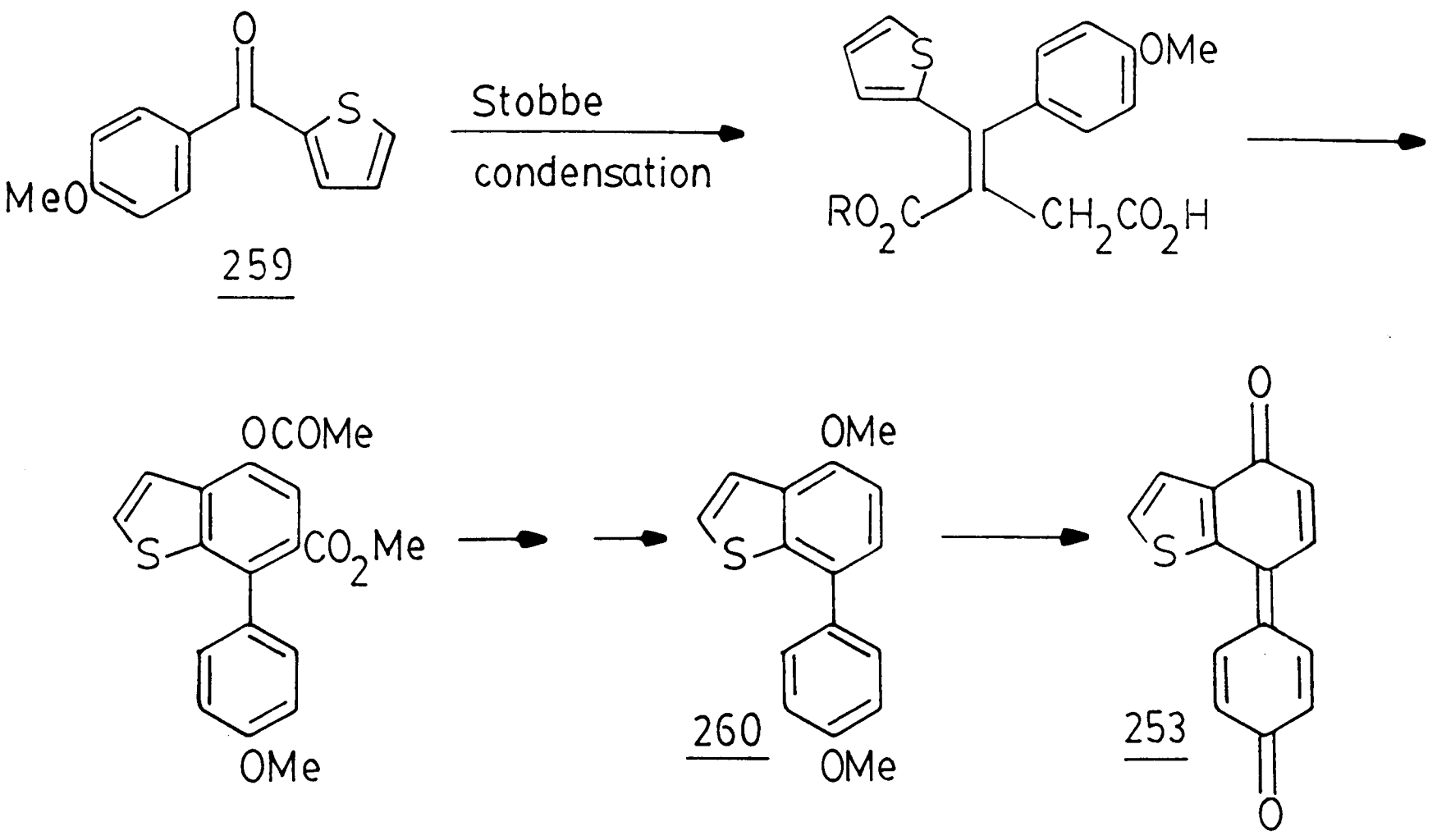
O-Methylation of (258) using sodium hydride and methyl iodide gave the desired 4-methoxybenzo{b}thiophene (256) in 85% yield.



256

It is well known that benzo{b}thiophene undergoes electrophilic substitution mainly at C_7.[190] However, treatment of (256) with 2 moles of n-butyl lithium, followed by diphenyliodonium chloride did not result in the formation of 7-phenyl-4-methoxybenzo{b}thiophene (255), suggesting that formation of dianion at C_2 and C_7 of (256) was not feasible.

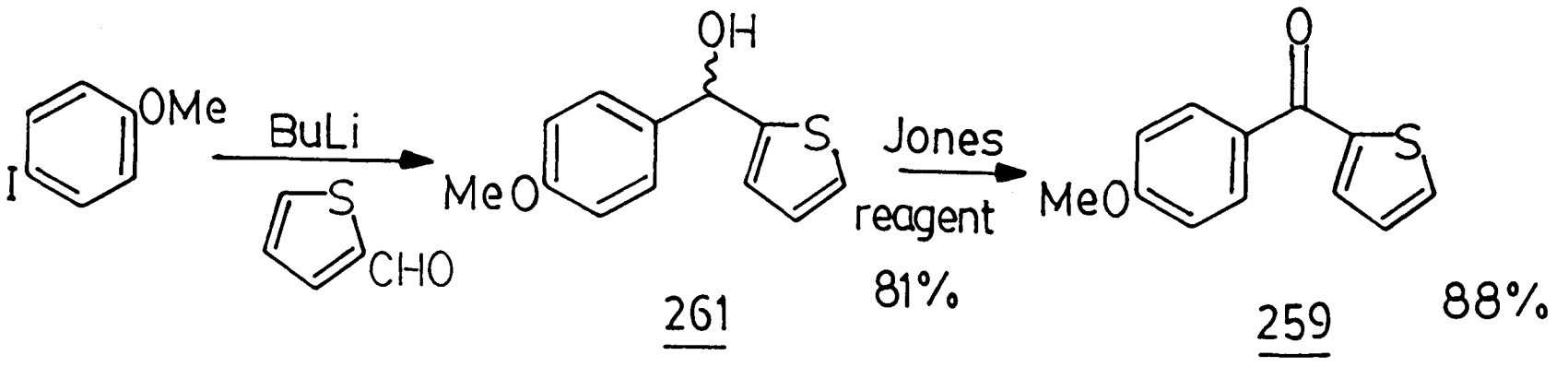
Though other methods are possible for introducing a phenyl group into C_7 of (256), however, it seems more practical to have the phenyl group in place at an early stage of the synthesis. A recent report by Moussa et al[191] on the synthesis of 7-phenyl-benzo{b}thiophene by the Stobbe condensation prompted us to plan along a similar line. Thus, starting from 4-methoxyphenyl 2-thienyl ketone (259) and through the appropriate transformations, one should end up in (4 -methoxyphenyl)-4-methoxybenzo{b}thiophene (260), viz.



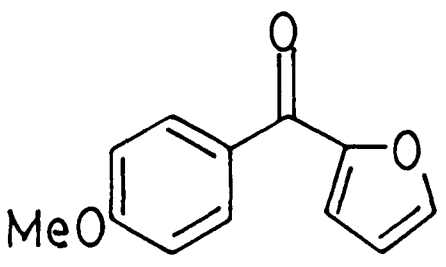
259 260 253

It is thought that by introducing an extra methoxy group at C_4' in (260), it would assist the conversion to (253) via oxidative demethylation at C_4 and C_4'.

Metallation of 4-iodoanisole with n-butyl lithium at -30°C followed by trapping with 2-thiophenecarboxyaldehyde gave 4-methoxyphenyl-2-thienylmethanol (261). Subsequent Jones oxidation gave 4-methoxyphenyl-2-thienyl ketone (259) in 71% yield overall.



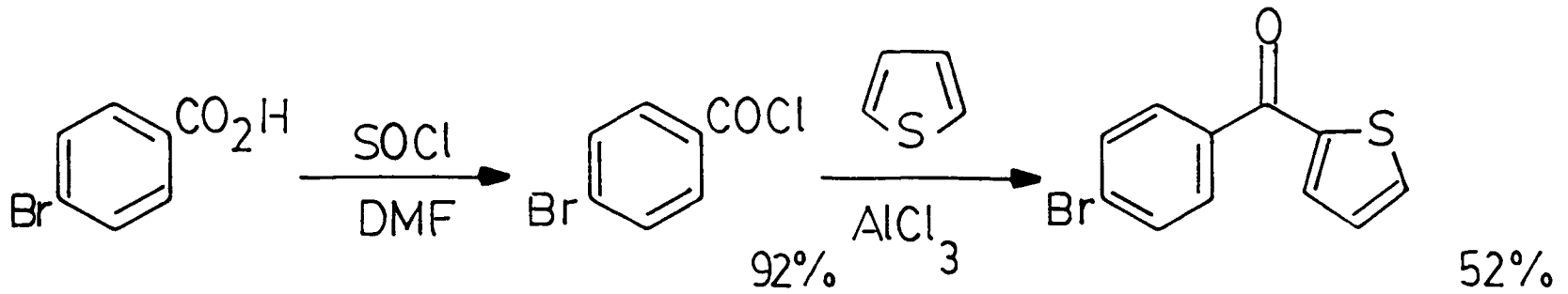
Stobbe condensation of (259) with dimethyl or diethyl succinate under various conditions failed to give any sign of product. Bases like potassium tert-butoxide, sodium hydride, sodium ethoxide at temperature ranging from RT to 100°C for 1 h to 2 days were all ineffective. Apparently the methoxy group in (259) which hopefully serves as a handle later for oxidative demethylation, deactivates the carbonyl group to such an extent that prevents the Stobbe condensation from occurring! Paradoxically the corresponding 4-methoxyphenyl-2-furyl ketone (262) was reported to condense successfully with diethyl succinate.[192]



262

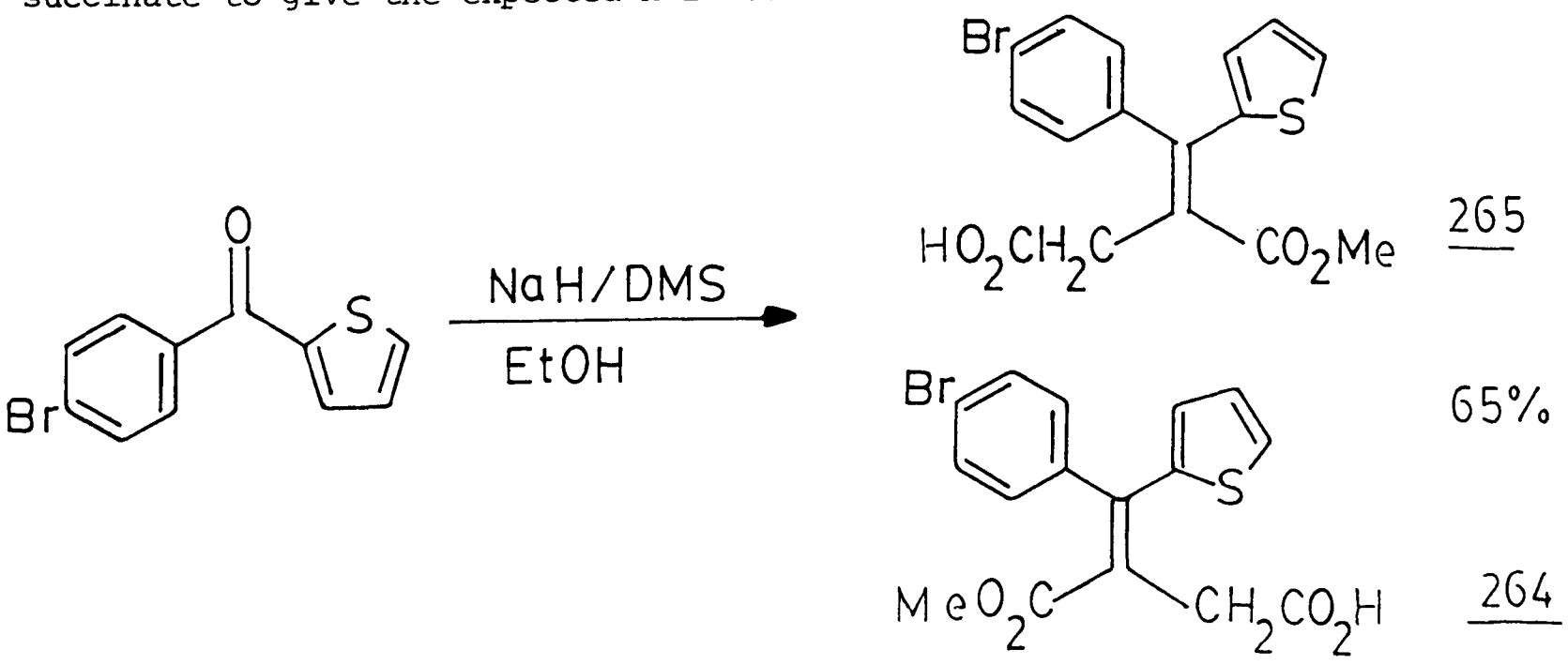
One obvious way to overcome the problem is to replace the methoxy group by an equivalent but easily convertible functional group, having activating property instead. Only two choices are possible, namely, the p-toluenesulphonyl group (p-Me-C_6H_4-SO_2) or a halogen (Br a I). Considering the ease of displacement of a halogen by an alkoxide, in the presence of copper(I)iodide,[193] the bromo group was selected as the alternative for the methoxy group in (259).

Starting from 4-bromobenzoyl chloride, prepared from 4-bromobenzoic acid, excess thionyl chloride and a few drops of DMF, Friedel-Crafts acylation with thiophene gave 4-bromophenyl 2-thienyl ketone (263).

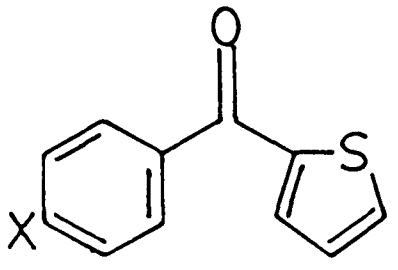


263

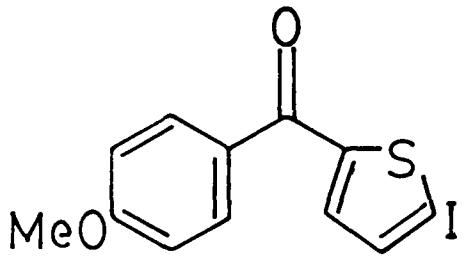
Stobbe condensation of (263) with dimethyl succinate under conditions reported by Moussa et al[191d] gave no reaction. Changing the base to sodium hydride led to no improvement. However, in the presence of a few drops of ethanol,[194] (263) condensed smoothly with dimethyl succinate to give the expected half ester.



Though no isomeric products were reported from the corresponding Stobbe condensation using p-tolyl 2-thienyl ketone (266)[191d], 2-iodo-4-thienyl p-tolyl ketone (267)[191c] and 2-thienyl phenyl ketone (268),[192] ^1H NMR of the above reaction product showed a mixture of half esters (264) and (265) in a ratio of 55:45. In fact, such a mixture of isomers is the usual product of a Stobbe condensation for an unsymmetrical ketone having no α-hydrogens.[195]

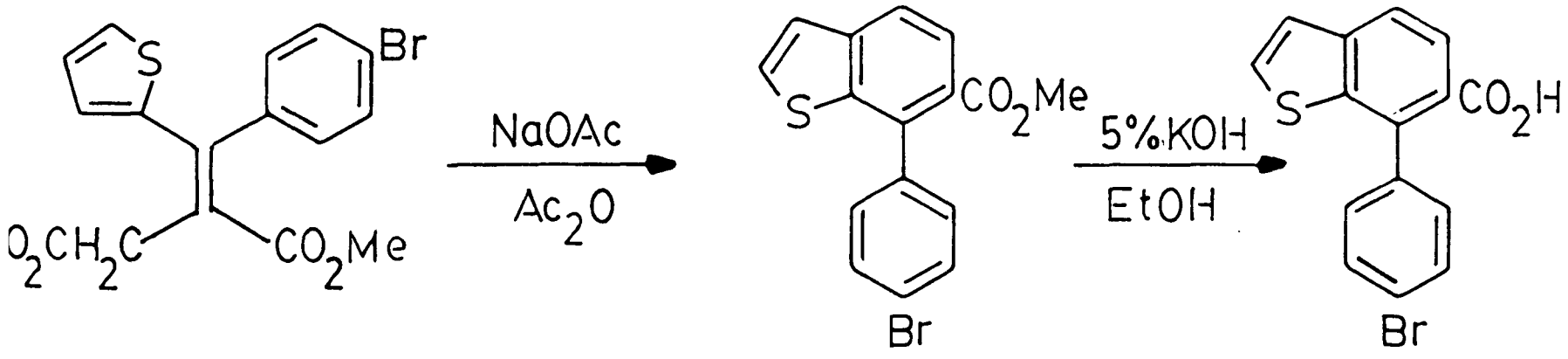


266 X=Me
268 X=H

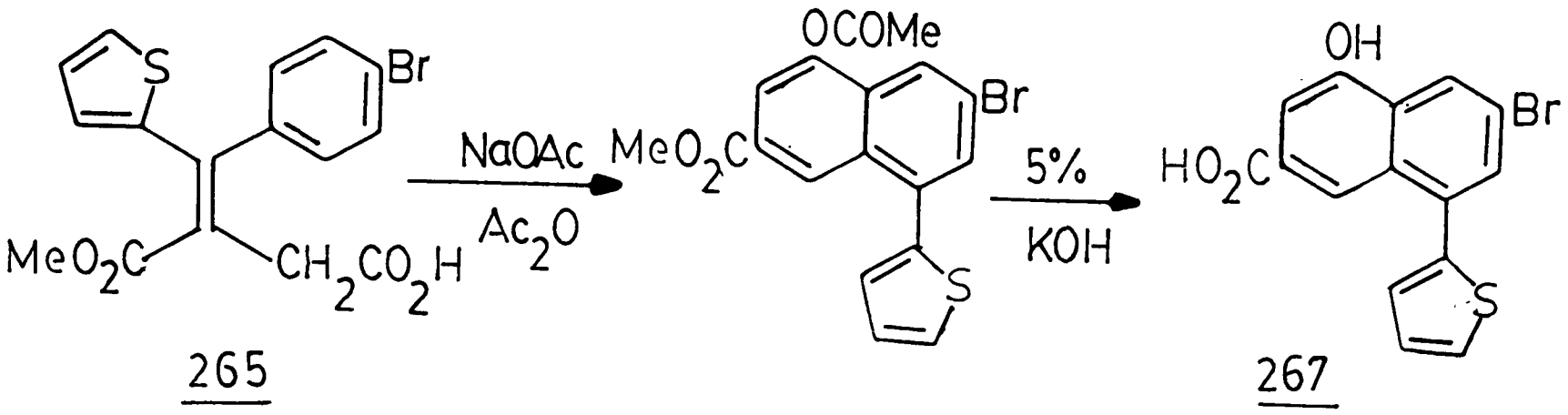


267

Subsequent experiments revealed that separation of the above isomers (264) and (265) was difficult and undesirable. Thus, with the mixture of isomers electrophilic cyclization, using sodium acetate and acetic anhydride,[191d] and subsequent hydrolysis led to 7-(4 -bromophenyl)-4-hydroxybenzo{b}thiophene-6-carboxylic acid (266) and 7-bromo-4-(2-thienyl)-1-naphthol-3-carboxylic acid (267) in 52% overall yield.

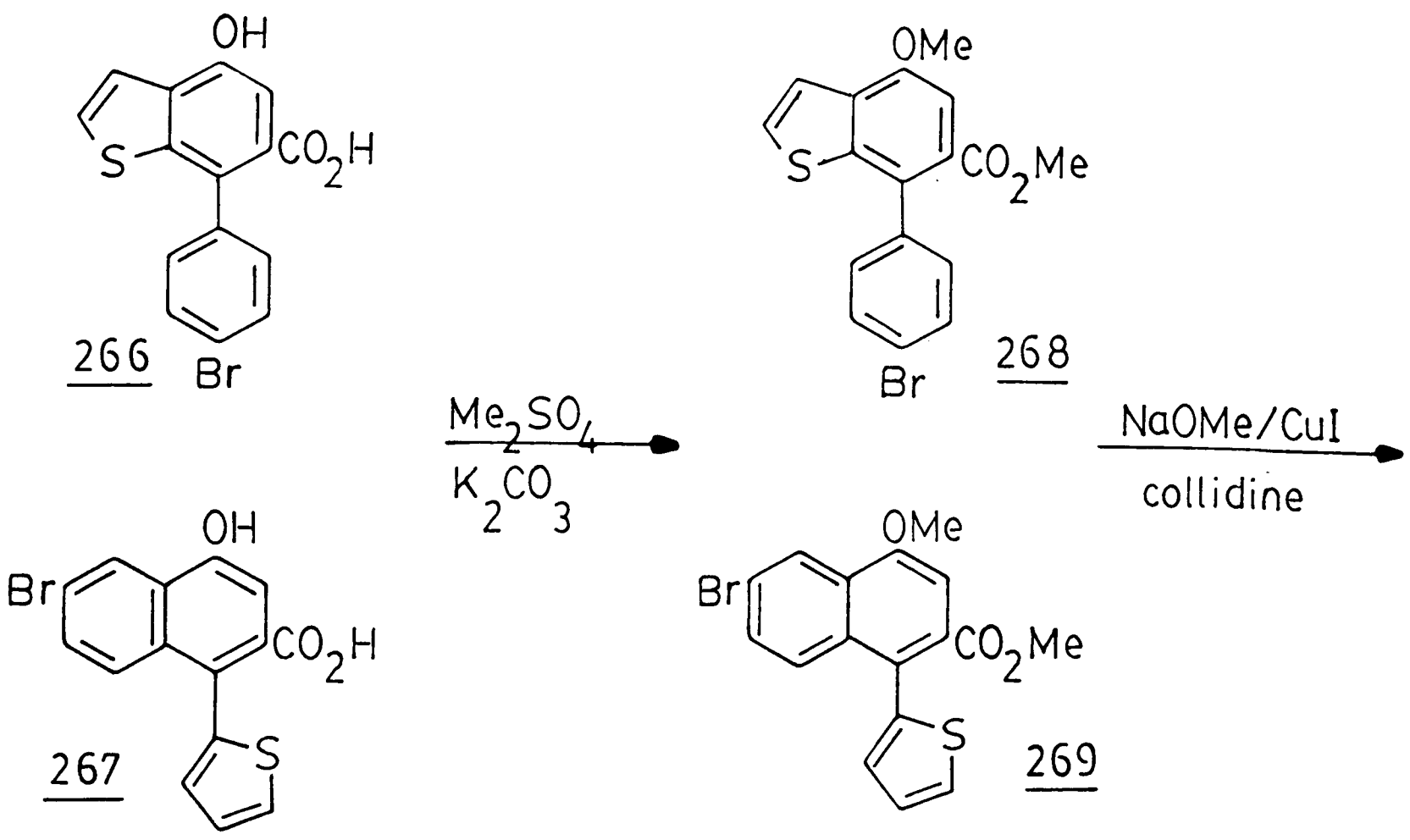


264 266

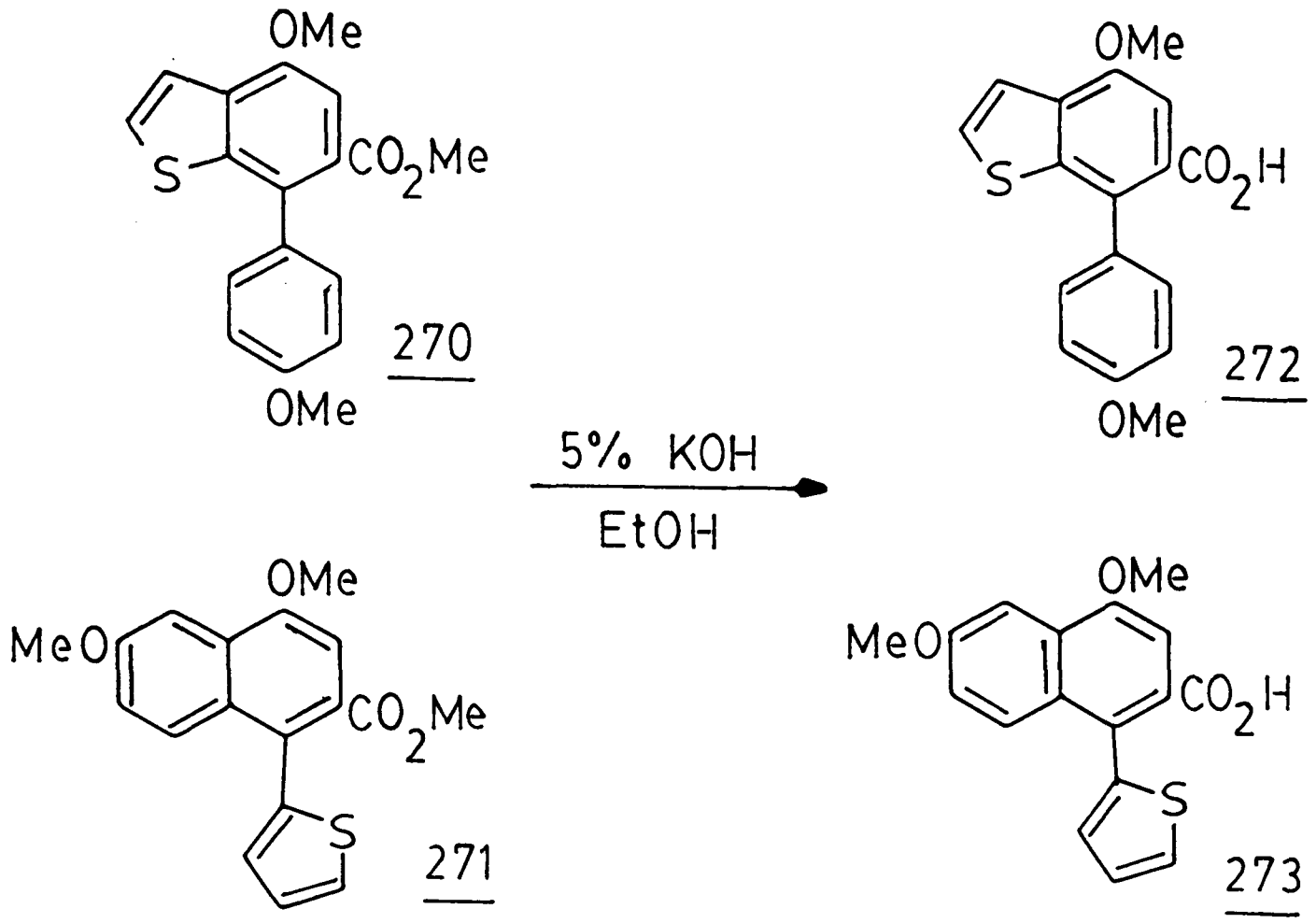


265 267

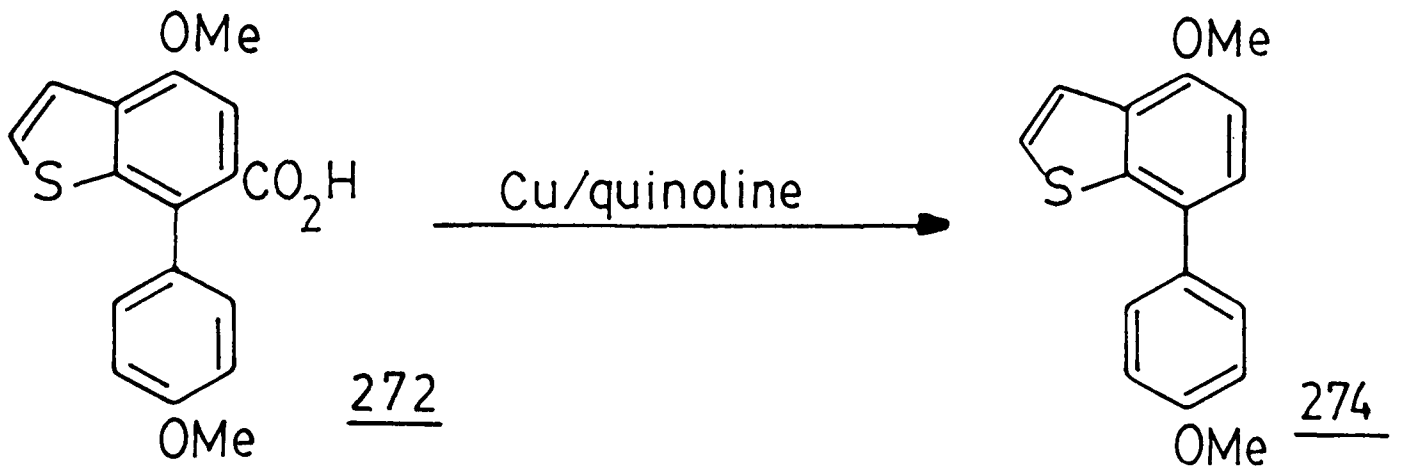
Methylation of the mixture (266) and (267) with dimethyl sulphate gave the corresponding methoxy esters (268) and (269), which on refluxing with excess sodium methoxide, copper(I)iodide in collidine for 6 h[193] gave the expected methyl 7-(4 -methoxyphenyl)-4-methoxybenzo{b}thiophene-6-carboxylate (270) and methyl 1,7-dimethoxy-4-(2-thienyl)-naphtholene-3-carboxylate (271), followed by saponification with 5% KOH/EtOH afforded the mixed acids (272) and (273) in 49% overall yield.

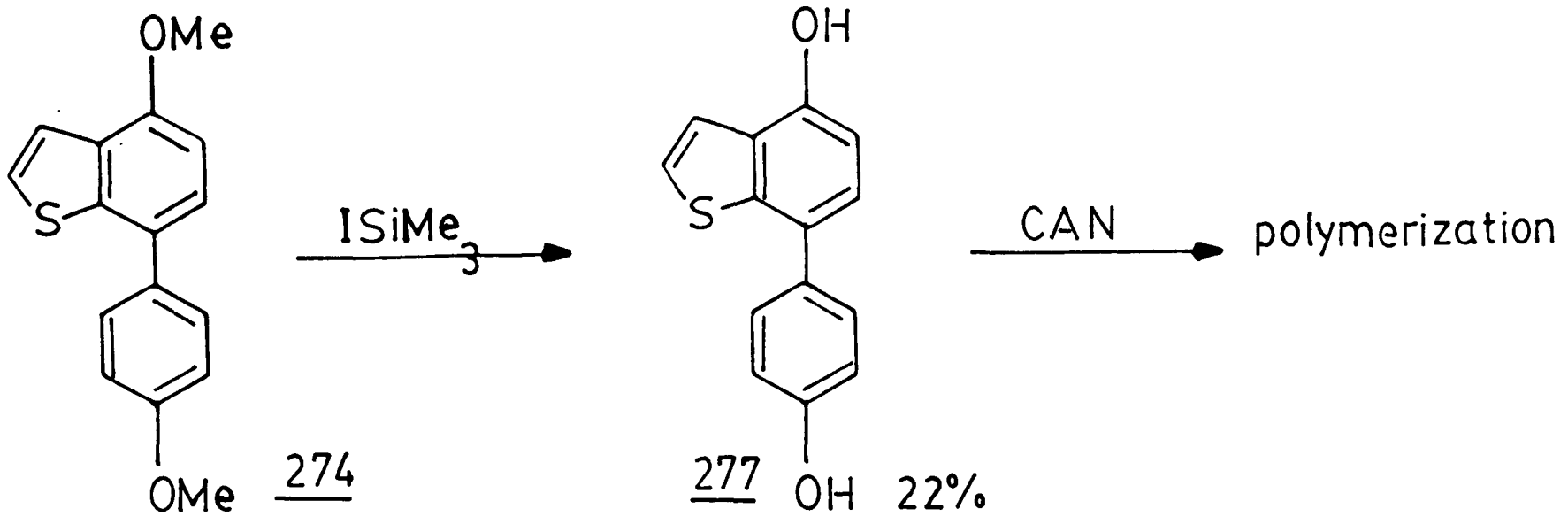


266 268 267 269



Decarboxylation of (272) and (273) using copper in freshly distilled quinoline at 130°C, the procedure of Moussa et al,[191d] gave no reaction, but at the boiling point decarboxylation was complete after 1 hour. Careful flash chromatography on SiO_2 and recrystallization gave the desired (4 -methoxyphenyl)-4-methoxybenzo {b}thiophene (274) in 46.3% yield, characterized fully by spectroscopic and combustion analysis data, and the other possible product, 1,2-dimethoxy-4-(2-thienyl)naphthalene (275), possibly present in the mother liquor, was not sought.





Again, treatment of (274) with silver(II)oxide in acid condition as reported[198] did not result in (253). ^{1}H NMR spectrum suggested that the thiophene ring and the lower methoxyphenyl ring were still present and intact, however an unambiguous structure assignment was not possible from the available data.

Experimental

General Procedures

Melting points were taken on a Kofler hot stage and are uncorrected. Microanalyses were performed by Dr. F.B. Strauss of the Dyson Perrin Laboratory, Oxford.

Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer and were calibrated against a polystyrene film.

Nuclear magnetic resonance spectra at 60 MHz were recorded on a Perkin Elmer R12 spectrometer; 90 MHz spectra were taken on a Hitachi Perkin-Elmer R32 spectrometer. A Bruker WH-300 spectrometer was employed for ^{1}H spectra at 300 MHz and ^{13}C spectra at 75.5 MHz. Chemical shifts were reported in parts per million (δ) relative to internal tetramethylsilane in organic solvents. The multiplicity, the coupling constant (J, if applicable) and the number of protons were given in parenthesis. The following notations were used to denote the multiplicity of the signals: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), dd (double doublet), and m (multiplet). The symbol br refers to broad signals.

Low resolution mass spectra were determined at 70 eV on a VG Micromass ZAB-16F spectrometer. Field ionization and chemical ionization mass spectra were recorded on a VG Micromass ZAB-1F spectrometer. The m/e values were quoted with the assignment (if applicable) and the percentage abundance in parenthesis.

Ultraviolet absorption spectra were recorded on a Perkin-Elmer Lambda 3 UV/VIS spectrophotometer. The molar extinction coefficient (ε) was quoted in parenthesis after the absorption maxima.

Flash column chromatography[199] was performed with Merck Kieselgel 60 No. 9385 or Merck Aluminium oxide 90 aktiv neutral

(70-230 mesh) grade I or III having 1 or 4.7% water respectively. Analytical thin-layer chromatography (TLC) was performed on pre-coated plates (CamLab 'Polygram' SIL G/UV_{254} 0.25 mm silica gel or 'Polygram' ALOXN/UV_{254} 0.2 mm aluminium oxide). Preparative thin-layer chromatography was carried out on Merck silica gel 60 GF 254 No. 7730 on 200x200x1.25 mm layers.

Unless otherwise stated, anhydrous magnesium sulphate was used for drying while evaporation refers to removal of solvent on a Büchi evaporator. Solvents and reagents were purified by standard procedures.[200] n- and tert-butyl lithium were standardized by the method of Watson and Eastham.[201]

The following abbreviations were used:

Ac	acetyl
CS_2	carbon disulphide
CCl_4	carbon tetrachloride
$CHCl_3$	chloroform
DBN	1,5-diazabicyclo{4.3.0}non-5-ene
DBU	1,8-diazabicyclo{5.4.0}undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
CH_2Cl_2	dichloromethane
Et_2O	diethyl ether
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMS	dimethyl succinate
DMSO	dimethyl sulphoxide
EtOAc	ethyl acetate
HMPA	hexamethylphosphoramide
LDA	lithium diisopropylamide
CH_3OH	methanol
NBS	N-bromosuccinimide
$Ni(dppp)Cl_2$	dichloro{1,3-bis(diphenylphosphino)propane}nickel(II)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
PE	petroleum ether (40°-60°C)
Py	pyridine
RT	room temperature (Ca. 18-20°C)
SiO_2	silica
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylenediamine
TFAA	trifluoroacetic anhydride

Methyl 2-acetylbenzoate (75)

The procedure developed by Ono et al[72] was followed. DBU (18.5 g, 0.12 mol), followed by iodomethane (17.3 g, 0.12 mol) was added to a solution of 2-acetylbenzoic acid (20.0 g, 0.12 mol) in benzene (200 ml). After refluxing for 10 h, the mixture was poured into water (200 ml). Washing of the organic layer (10% HCl, 50 ml; H_2O, 2x50 ml), drying, evaporation and fractionation of the residue under vacuum gave methyl 2-acetylbenzoate as a colourless oil (16.7 g, 78%), b.p. 169-170°C/11 torr (lit., b.p. 137-9°C/14 torr)[71]; νmax (neat) 1730 (νC=O), 1620, 1595, 1500, 1460, 1450, 1385, 1300, 1150, 1120, 1080, 980, 760 and 710 cm^{-1}; δ ($CDCl_3$) 2.49 (3H, s), 3.82 (3H, s), 7.45 (3H, m) and 7.78 (1H, m).

1,4-bis(2-methoxycarbonylphenyl)butadiyne (79)

Method A

The procedure developed by Eglinton[73] was followed. A mixture of methyl 2-ethynylbenzoate[70] (4.0 g, 25 mmol) and anhydrous copper(II) acetate[74] (12.0 g, 66 mmol) in $Et_2O/CH_3OH/Py$ (600 ml; 4:1:1) was refluxed for 6 h. The solvent was removed and the residue treated with aqueous HCl (1:1, V/V). Extraction with ether, washing (H_2O), drying and evaporation gave a dark coloured residue, which in chloroform was filtered through a column of Al_2O_3 (active, neutral). Evaporation and recrystallisation of the residue from $CHCl_3$-PE afforded 1,4-bis(2-methoxycarbonylphenyl)butadiyne as off-white prisms (2.2 g, 55%), m.p. 55°C (Found: C, 75.3; H, 4.3. $C_{20}H_{14}O_4$ requires C, 75.5; H, 4.4%); TLC{Al_2O_3, $CHCl_3$} Rf 0.71; m/z 318 (M^+, 100),

303 {$(M-Me)^+$, 77}, 273 (43) and 258 (63); νmax (nujol) 1730 (νC=O), 1600, 1450, 1300, 1120 and 740 cm^{-1}; δ($CDCl_3$) 4.00 (6H, s), 7.50 (6H, m) and 8.10 (2H, m).

Alternatively, Hünig's procedure[75] was also used and the yield was 54.7%.

Method B - via methyl 2-(trimethylsilyl)ethynylbenzoate (80)

The procedure reported by Lau et al[76] was followed. A deaerated solution of methyl 2-iodobenzoate (20 g, 76.5 mmol), triphenylphosphine (150 mg) and palladium(II)acetate (150 mg) in anhydrous triethylamine (100 ml) was treated with ethynyltrimethylsilane (153 mmol, as a THF-hexane solution) under nitrogen. After 23 h reflux, the mixture was worked up as usual[76] and distillation afforded a mixture of methyl 2-(trimethylsilyl)ethynylbenzoate (80) and methyl 2-iodobenzoate (18.9 g), b.p. 90-115°C/0.15 torr.

The above mixture was treated with potassium carbonate (1 g) in methanol (40 ml) under N_2 at 30°C for 3 h. Working up as reported[76] gave a mixture of methyl 2-ethynylbenzoate and methyl 2-iodobenzoate (15.4 g), in a ratio of 45:55 (^1H NMR).

Oxidative coupling of the above mixture (15.4 g) was affected by copper(I)chloride (0.59 g, 6 mmol), TMEDA (1.05 g, 9 mmol) in DME[75] (40 ml) at 35°C for 6 h, working up as reported[75] and flash chromatography on SiO_2. Eluting with 10% Et_2O-PE gave only methyl 2-iodobenzoate, was discarded, while eluting with $CHCl_3$ gave the desired diacetylene. Recrystallisation from $CHCl_3$-PE gave 1,4-bis(2-methoxycarbonylphenyl)butadiyne (79) (2.63 g, 10.8% overall) identical to that obtained via method A.

2,5-bis(2-ethoxycarbonylphenyl)thiophene (81)

The procedure developed by Schulte et al[22] was followed. Sodium (1.25 g, 54.3 mmol) was dissolved in absolute ethanol (30 ml), the solution saturated with hydrogen sulphide, 1,4-bis(2-methoxycarbonylphenyl)butadiyne (79) (1.80 g, 5.45 mmol) added and the hydrogen sulphide stream continued (slowly) while the mixture was refluxed for 1½ h. After pouring into water (250 ml) extraction with $CHCl_3$ and evaporation of the washed (H_2O) and dried extracts gave a viscous brown oil, which was chromatographed on silica. Fractions eluted with 30% ether-PE afforded the thiophene (81) as a deep yellow oil (1.13 g, 54.7%) (Found: C, 69.7; H, 5.4. $C_{22}H_{20}O_4S$ requires C, 69.5; H, 5.3%); m/z 382 {$(M+2)^+$, 8}, 380 (M^+, 100), 351 {$(M-Et)^+$, 2}, 334 {$(M-EtOH)^+$, 20}, 307 {$(M-CO_2Et)^+$, 3}, 289 {$(M-C_4H_{10}O)^+$, 38} and 149 {$(PhCO_2Et)^+$, 23}; νmax (neat) 3080, 1730 ν(C=O), 1650, 1600, 1575, 1480, 1365, 1270, 1130, 1080, 750 and 700 cm^{-1}; δ($CDCl_3$) 1.15 (6H, t), 4.20 (4H, q), 6.95 (2H, s) and 7.47 (8H, m). No reaction occurred when sodium methoxide in methanol was used instead of the ethoxide and (79) was recovered.

4,4-Dimethyl-2-(2-iodophenyl)oxazoline (74)

The procedure adopted was precisely as that reported by Meyer et al.[77] The physical and spectroscopic data of the intermediates are as follows:

2-Iodobenzoyl chloride, b.p. 136°C/35 mm (lit. 159°C/27 mm);[202] N-2-(1-hydroxy-2-methylpropyl)-2-iodobenzamide, m.p. 137-137.5°C (95% EtOH) (Found: C, 41.4; H, 4.8; N, 4.6. $C_{11}H_{14}INO_2$ requires

C, 41.4; H, 4.4; N, 4.4%); 4,4-dimethyl-2-(2-iodophenyl)oxazolinium chloride, m.p. 132-3°C; 4,4-dimethyl-2-(2-iodophenyl)oxazoline (74); m.p. 50°C (PE), b.p. 210°C/55 mm (Found C, 44.0; H, 4.1; N, 4.8. $C_{11}H_{12}INO_2$ requires C, 43.9; H, 4.0; N, 4.7%); m/z 301 (M+, 100), 286 {$(M-CH_3)^+$, 98}, 271 {$(M-C_2H_6)^+$, 42}, 258 {$(M-C_3H_7)^+$, 27}, 230 {$(M-C_4H_7O)^+$, 45} and 103 {$(M-I)^+$, 30}; νmax (neat) 2950, 1670, 1600, 1480, 1450, 1370, 1360, 1050 and 750 cm^{-1}; δ($CDCl_3$) 1.40 (6H, s), 4.10 (2H, s) and 7.41 (4H, m).

Coupling reaction between 2,5-dibromothiophene and 4,4-dimethyl-2-(2-lithiophenyl)oxazoline in the presence of excess copper(I)iodide

n-Butyl lithium (20 mmol) in hexane was added to a solution of 4,4-dimethyl-2-(2-iodophenyl)oxazoline (74) (6.22 g, 20 mmol) in ether (125 ml), under N_2, at -70°C. After 20 min at the same temperature, copper(I)iodide (7.87 g, 41.3 mmol, vacuum dried at 120°C for 6 h) was added. Stirring continued at room temperature for 1 h, and 2,5-dibromothiophene (1 g, 4.13 mmol) was added. After 2 days at RT, the mixture was poured into H_2O. Extraction ($CHCl_3$), washing of the extracts (H_2O), drying and evaporation afforded an oil, which was flash chromatographed on a column of Al_2O_3 (active, neutral). Earlier fraction (10% $CHCl_3$-PE and 30% $CHCl_3$-PE) recovered starting materials, while (Et_2O-$CHCl_3$ 1:9) gave 2,2'-bis(4,4-dimethyl-2-phenyloxazolinium)-biphenyl hydroiodide (83) (0.23 g, 4.4%); m.p. 226-8°C ($CHCl_3$-PE) (Found C, 50.2; H, 4.8; N, 5.2. $C_{22}H_{24}O_2N_2$ 1.4HI requires C, 50.1; H, 4.8 and N, 5.3%); m/z 348 {$(M-HI)^+$, 3%}, 333 {$(M-CH_3)^+$, 1} and 250 {$(M-C_5H_8NO)^+$, 100}; νmax (nujol) 2720, 1655, 1600, 1590, 1320, 1092, 1080, 1040, 950, 770 and 758 cm^{-1}; δ($CDCl_3$) 0.85 (6H, s), 1.63 (6H, s),

4.00 (2H, d,J 8.7 Hz), 4.19 (2H, d,J 8.7 Hz) and 7.10-7.70 (8H, m).

In the absence of copper(I)iodide and after 4h RT stirring, no reaction occurred.

Coupling between 2,5-diiodothiophene and methyl 2-iodobenzoate using the Ullmann reaction

A mixture of 2,5-diiodothiophene (1 g, 2.98 mmol), methyl 2-iodobenzoate (1.72 g, 6.5 mmol) and copper bronze (1.09 g, 15 mmol) in DMF (10 ml) was refluxed for 16 h. After cooling and diluting with CH_2Cl_2, the mixture was filtered through celite; diluted with ether and filtered again. Evaporation of the washed (H_2O) and dried afforded a solid, which was chromatographed on Al_2O_3 (active, neutral). Fractions eluted with $CHCl_3$-Et_2O (9:1) on evaporation afforded a white solid. Recrystallisation from 95% ethanol gave 2,2'-di(methoxycarbonyl)biphenyl (84) (456 mg, 52%), m.p. 72-72.5°C (Found C, 70.7; H, 5.2. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%); m/z 270 (M^+, 12), 211 {$(M-CO_2Me)^+$, 100}, 196 {$(M-C_3H_6O)^+$, 11} and 180 {$(M-C_3H_6O_2)^+$, 11}; νmax (neat) 3100, 3060, 1700, 1620, 1590, 1500, 1450, 1300, 1270, 1200, 1150, 1100, 750 and 710 cm^{-1}; δ($CDCl_3$) 3.55 (6H, s), 7.05-7.65 (6H, m) and 8.00 (2H, m).

2,5-Diiodothiophene

2,5-Dibromothiophene (10 g, 0.04 mol) was dissolved in THF (25 ml) and n-butyl lithium in hexane (0.08 mol) was added dropwise, with stirring, under nitrogen at -78°C. After 20 min at -78°C, a solution of iodine (20.32 g, 0.08 mol) in THF (25 ml) was added dropwise and the whole was allowed to warm to RT (2 h). Working up as

described[203] gave a brown solid, which on recrystallisation from PE afforded 2,5-diiodothiophene as shiny prisms (12.3 g, 92%), m.p. 39-40°C (lit., 40.5°C)[204]; TLC {Al_2O_3, $CHCl_3$} Rf 0.9; m/z 336 (M^+, 100), 209 {$(M-I)^+$, 6} and 82 {$(M-2I)^+$, 39}; δ($CDCl_3$) 6.90 (2H, s).

Attempted intramolecular cyclization of 2,5-bis(2-ethoxycarbonylphenyl)-thiophene (81) using the acyloin reaction

Into a 3-necked creased flask, equipped with a reflux condenser, a N_2 inlet and a Hershberg addition funnel, sodium dried toluene (150 ml) was placed. After blanketing under an oxygen free, nitrogen atmosphere, sodium (113 mg, 4.92 mmol) was added. The stirrer was operated at full speed while the toluene was brought to gentle reflux. When the sodium was finely dispersed, 2,5-bis(2-ethoxycarbonylphenyl)-thiophene (81) (0.47 g, 1.23 mmol) and chlorotrimethylsilane (534 mg, 4.92 mmol) in toluene (50 ml) was added dropwise through the funnel. After 6 h refluxing, the mixture was cooled and filtered (filter stick), under N_2. ^1H NMR showed that only starting materials were present in the filtrate. Using an excess of sodium or sodium-potassium (1:1) alloy[79] and a longer reaction time (20 h) led to no improvement.

2-Bromo-1-ethynylbenzene (93)

A mixture of 2-bromoacetophenone[88] (81.0 g, 0.41 mol) and phosphorous pentachloride (89.9 g, 0.43 mol) was warmed at Ca. 90°C for 15 min. After the vigorous reaction subsided, the mixture was fractionated under vacuum to give 1-(2-bromophenyl)-1-chloroethene (91) (37.2 g, 42%), b.p. 110-2°C/20 torr and 2-bromo-1,1-dichloroethylbenzene (92) (42.5 g, 41%), b.p. 128-130°C/20 torr.

Rf 0.86; m/z 394 (M^+, 100), 360 {$(M-H_2S)^+$, 21} and 234 {$(M-2Br)^+$, 35}; νmax (nujol) 1590, 1550, 1530, 1260, 1210, 1050, 1020, 940, 805, 760, 750, 720, and 700 cm^{-1}; δ($CDCl_3$) 7.40 (10H, m).

2,5-Bis(2-formylphenyl)thiophene (89)

n-Butyl lithium (12.9 mmol) in hexane was added dropwise, with stirring, under nitrogen to a solution of 2,5-bis(2-bromophenyl)-thiophene (97) (1.27 g, 3.22 mmol) in THF (10 ml) at -78°C. The mixture was stirred at -78°C for 15 min then dry DMF (2.0 ml, 25.8 mmol) was added. After stirring overnight while the cooling bath warmed to RT the mixture was poured into water (100 ml). Evaporation of the washed (2N HCl, $NaHCO_3$) dried extracts gave a light brown oil, which was chromatographed on a column of alumina (active, neutral). Fractions eluted with 60% $CHCl_3$-PE on evaporation afforded the desired dialdehyde (89) as pale yellow prisms (0.41 g, 44%), m.p. 98-9°C (PE-$CHCl_3$) (Found: C, 73.6; H, 4.1. $C_{18}H_{12}O_2S$ requires C, 73.9; H, 4.1%); TLC {Al_2O_3, PE/$CHCl_3$ (1:1)} Rf 0.52; m/z 292 (M^+, 10), 291 {$(M-H)^+$, 27}, 263 {$(M-CO)^+$, 22}, 258 {$(M-H_2S)^+$, 15} and 234 {$(M-2CHO)^+$, 21}; νmax (nujol) 2740, 2760, 1685, 1650, 1590, 1280, 1260, 1190, 945, 850, 770 and 765 cm^{-1}; δ($CDCl_3$) 7.00 (2H, s), 7.30 (6H, m), 7.95 (2H, m) and 10.20 (2H, s).

1,4-Bis(2-formylphenyl)butadiyne (98)

To a magnetically well-stirred suspension of copper(I)chloride (1.36 g, 13.5 mmol) in DME (35 ml) was added TMEDA (2.39 g, 20.5 mmol). After 10 min at RT, 2-ethynylbenzaldehyde (8.9 g, 68.5 mmol) was added,

and the mixture was kept at Ca. 40°C for 1¾ h, while air was bubbled through the solution. The mixture was then poured into water (200 ml) and extracted with CH_2Cl_2. Washing of the extracts (H_2O), drying and evaporation gave a brown residue, which was chromatographed on a column of SiO_2. Elution with 40% Et_2O-PE afforded 1,4-bis(2-formylphenyl)-butadiyne (98). Recrystallization from CH_2Cl_2-PE gave yellow prisms (1.14 g, 12.9%), m.p. 138-9°C (Found: C, 82.1; H, 3.9. $C_{18}H_{10}O_2$. $0.3H_2O$† requires C, 82.0; H, 4.0%); m/z 258 (M^+, 62), 230 {$(M-CO)^+$, 23}, 202 {$(M-2CO)^+$, 100} and 200 {$(M-2CHO)^+$, 48}; νmax (nujol) 2200, 1710, 1585, 825 and 760 cm^{-1}; δ($CDCl_3$) 7.20-8.15 (8H, m) and 10.55 (2H, s).

1,4-Bis(2-hydroxymethylphenyl)butadiyne (99)

To 1,4-bis(2-hydroxymethylphenyl)butadiyne (98) (200 mg, 0.78 mmol) in methanol (20 ml) was added powdered sodium borohydride (58 mg, 1.55 mmol). The reduction was completed after 25 min. Most of the solvent was removed and water (30 ml) was added. Extraction (CH_2Cl_2), drying and evaporation gave a yellow solid. Recrystallization from acetone-PE gave 1,4-bis(2-hydroxymethylphenyl)butadiyne (99) as colourless needles (102 mg, 50.2%), m.p. 165-6°C (Found: C, 82.0; H, 5.4. $C_{18}H_{14}O_2$ requires C, 82.4, H, 5.3%); m/z 262 (M^+, 66), 244 {$(M-H_2O)^+$, 38}, 215 {$(M-CH_3O_2)^+$, 100}, 132 ($M^+/2$, 30); νmax (nujol) 3250 (νO-H), 2205, 2140, 1570, 1100, 1050 and 755 cm^{-1}; δ(d_6-acetone) 4.30 (2H, t, J 5.3 Hz, exchanged with D_2O), 4.82 (4H, d, J 5.3 Hz) and 7.10-7.80 (8H, m); UV (EtOH) 204 nm (ε 100000), 227 nm (28968), 247 nm (25992), 258.5 nm (24802), 293 nm (17460), 312 nm (24206) and 332.5 nm (21825).

(† νOH observed in the i.r. spectrum at 3400 cm^{-1})

Reaction between 1,4-bis(2-hydroxymethylphenyl)butadiyne (99) and sodium sulphide

A mixture of 1,4-bis(2-hydroxymethylphenyl)butadiyne (99) (43.9 mg, 0.168 mmol), sodium sulphide nonahydrate (161 mg, 0.67 mmol) and methanol (25 ml) were refluxed for 20 h. After pouring into water (100 ml), extraction with EtOAc and evaporation of the washed (H_2O) and dried afforded a yellow oil, which was chromatographed on a column of SiO_2. Ethyl acetate eluted a yellow solid, very pale yellow prisms (30 mg) from $CHCl_3$-PE, m.p. 108-9°C (Found C, 80.5; H, 5.3. $C_{18}H_{14}O_2.0.3H_2O$ requires C, 80.8; H, 5.5%); m/z 262 (M^+, 100), 244 {$(M-OH)^+$, 7}, 233 {$(M-CHO)^+$, 30}, 215 (25), 132 (61), 118 (51), 115 (36), 103 (33) and 90 (72); νmax ($CHCl_3$) 3550, 2242, 2180, 1635, 1590, 1465, 1372, 1310, 1010 and 750 cm^{-1}; δ($CDCl_3$) 4.63 (1H, s, exchanged with D_2O), 4.82 (2H, s), 5.28 (1H, s), 5.42 (2H, s) and 7.00-7.60 (8H, m). 2-(3-ethynyl-2H-benzopyranyl)benzyl alcohol (101) was tentatively assigned as the product.

2-(2-iodophenyl)-1,3-dioxolan (102)

A mixture of 2-iodobenzaldehyde (14.69 g, 60 mmol), ethylene glycol (7.86 g, 127 mmol) in benzene (50 ml) were refluxed for 2 h while the water formed was removed by a Dean-Stark apparatus. Pouring into water, extraction with CH_2Cl_2, and distillation of the dried extract gave 2-(2-iodophenyl)-1,3-dioxolan (102), as a colourless oil (14.96 g, 89%), b.p. 110-2°C/0.1 torr (Found: C, 38.9; H, 3.2. $C_9H_9O_2I$ requires C, 39.1; H, 3.3%); TLC {SiO_2, PE/Et_2O (9:1)} Rf 0.26; m/z 276 (M^+, 52), 275 {$(M-H)^+$, 100}, 231 {$(M-C_2H_5O)^+$, 25}, 204 {$(C_6H_4I)^+$, 6} and 149 {$(M-I)^+$, 24}; νmax (neat)

3060, 2970, 2940, 2880, 1585, 1565, 1465, 1430, 1375, 1210, 1120, 1090, 1010, 940 and 750 cm^{-1}; $\delta(CDCl_3)$ 4.05 (4H, m), 5.87 (1H, s), 6.80-7.90 (4H, m).

Attempted coupling of 2,5-dilithiothiophene with 2-(2-iodophenyl)-1,3-dioxolan (102)

The procedure of Murahashi et al[92] was adopted. To a deaerated solution of 2-(2-iodophenyl)-1,3-dioxolan (102) (3.83 g, 13.8 mmol) in THF (30 ml) was added $Ph(PPh_3)_4$ (0.1 g) and the resultant green mixture was stirred under N_2 at RT for 30 min. In the meantime, 2,5-dilithiothiophene, from 2,5-dibromothiophene (1.5 g, 6.2 mmol) and tert-butyl lithium (24.8 mmol, in pentane) in THF (10 ml) was prepared, firstly at -78°C (10 min), then at 0°C (10 min) and finally at RT (10 min). The green mixture was then transferred to the dilithiothiophene under N_2 at RT. A deep brown colour developed gradually. Stirring was continued for 2 days at RT, and poured into water. Working up gave a mixture of starting materials, no sign of cross-coupled products being detected by ^1H NMR.

Attempted intramolecular coupling of 25-bis(2-formylphenyl) thiophene (89)

The procedure developed by McMurry et al[86] was followed. Into a 3-necked round-bottomed flask, equipped with a reflux condenser, a N_2 inlet and a self-sealing rubber septum, DME (freshly distilled over $LiAlH_4$, 30 ml), titanium(III)chloride (1.55 g, 10 mmol) and copper-zinc couple[86] (freshly prepared, 1.5 g, 23 mmol) were placed. After blanketed under nitrogen, the mixture was refluxed for 1 h. The

colour changed from dark purple to dark green. 2,5-Bis(2-formylphenyl)-thiophene (89) (0.131 g, 0.9 mmol) in DME (30 ml) was added, through the rubber septum, to the refluxing mixture by a syringe pump during 9 h. Refluxing was continued for a further 16 h. Another batch of 2,5-bis(2-formylphenyl)thiophene (0.131 g, 90 mmol) in DME (30 ml) was then added and refluxing continued as above. After cooling, the mixture was filtered through a Forisil pad. The solvent was removed under reduced pressure and the residue chromatographed through a column of alumina (active, neutral). Fractions eluted with 50% $CHCl_3$-PE on evaporation afforded pale yellow prisms (0.2 g), m.p. 124-5°C (PE-$CHCl_3$) (Found C, 81.7; H, 6.7%); TLC (Al_2O_3, $CHCl_3$) 0.94; m/z 264 (62.4), 2.50 (44.7), 236 (100) and 91 (9.2); δ($CDCl_3$) 2.50 (6H, s) and 7.30 (10H, m), suggesting that the product was 2,5-bis(2-methylphenyl)thiophene (103).

1,2-Bis(2-formylphenyl)ethane (106)

2,2'-dibromobibenzyl[93] (104) (29.02 g, 85 mmol) was dissolved in dry THF (150 ml) and n-butyl lithium in hexane (0.17 mol) was added dropwise, with stirring, under nitrogen at -78°C. After stirring at -78°C for 15 min dry DMF (26.3 ml, 0.34 mol) was added. Stirring continued overnight while the cooling bath warmed slowly to RT and the mixture poured into water (200 ml), extracted (Et_2O), the extracts washed (H_2O), dried and evaporated. The residual solid on recrystallization from $CHCl_3$-PE afforded 1,2-bis(2-formylphenyl)ethane (106) as pale yellow prisms (7.63 g, 37.7%), m.p. 100-1°C (Found: C, 80.4; H, 5.9. $C_{16}H_{14}O_2$ requires C, 80.7; H, 5.9%); TLC {SiO_2,

PE-Et_2O(9:1) Rf 0.15; m/z 238 (M^+, 4), 220 {$(M-H_2O)^+$, 90}, 219 {$(M-2OH)^+$, 29}, 208 {$(M-CH_2O)^+$, 10}, 119 {$(C_8H_7O)^+$, 32}, 105 {$(C_7H_5O)^+$, 13} and 91 {$(C_7H_7)^+$, 100}; νmax (nujol) 2830, 2740, 1690 ν(C=O), 1600, 1570, 1450 and 750 cm^{-1}; δ($CDCl_3$); 3.28 (4H, s), 7.00-8.00 (8H, m) and 10.20 (2H, s).

1,2-Bis{2-(2,2-dibromoethenyl)phenyl}ethane (107)

The method adopted was similar to that reported.[120] Carbon tetrabromide (30.1 g, 91 mmol) was added to triphenylphosphine (48.1 g, 0.184 mol) in CH_2Cl_2 (250 ml) at 0°C. After 10 min, 1,2-bis(2-formylphenyl)ethane (106) (6.5 g, 27 mmol in CH_2Cl_2 (25 ml) was added dropwise, stirring continued at 0°C for 20 min and at RT for 1 h. Water (50 ml) was now added, the organic layer filtered and the solvent removed under reduced pressure. The residue was chromatographed on a column of SiO_2 (6x4 cm). Elution with 20% $CHCl_3$-PE yielded 1,2-bis{2-(2,2-dibromoethenyl)phenyl}ethane (107) as colourless shiny plates (from PE) (6.07 g, 41%), m.p. 122-3°C (Found: C, 39.5; H, 2.1. $C_{18}H_{14}Br_2$ requires C, 39.3; H, 2.5%); TLC {(SiO_2, PE-Et_2O(9:1)} Rf 0.70; m/z 550 (M^+, 2), 390 {$(M-2Br)^+$, 2}, 309 {$(M-HBr)^+$, 8}, 228 {$(M-H_2Br_4)^+$, 34} and 115 {$(C_9H_7)^+$, 100}; νmax (nujol) 1605, 1590, 1440 (νC=C), 820 and 750 cm^{-1}; δ($CDCl_3$) 2.80 (4H, s) and 7.05-7.90 (10H, m).

1,2-Bis(2-ethynylphenyl)ethane (108)

The procedure adopted was similar to that reported.[120b] n-Butyl lithium in hexane (48.4 mmol) was added, with stirring,

under nitrogen at -78°C to 1,2-bis{2-(2,2-dibromoethenyl)phenyl}ethane (107) (5.8 g, 11 mmol) in dry Et_2O-THF (1:1, 200 ml). The mixture was stirred at -78°C for 1 h, RT for 1 h, poured into water, extracted with ether, and the dried ($MgSO_4$) extract evaporated and chromatographed over SiO_2 (4x5 cm). Elution with 10% Et_2O-PE afforded 1,2-bis(2-ethynylphenyl)ethane (108). Recrystallization from PE (CO_2-acetone cold bath) gave colourless prisms (1.14 g, 45.1%), m.p. 38-9°C (Found: C, 93.8; H, 6.0. $C_{18}H_{14}$ requires C, 93.8; H, 6.1%); TLC {(SiO_2, Et_2O-PE (1:9)} Rf 0.62; m/z 230 (M^+, 54), 229 {$(M-H)^+$, 91}, 228 {$(M-2H)^+$, 13}, 215 {$(M-Me)^+$, 35} and 115 {$(C_9H_7)^+$, 100}; νmax (nujol) 3300 (ν≡C-H), 2100 (νC≡C), 1595, 1480, 1450 and 750 cm^{-1}; δ($CDCl_3$), 3.10 (4H, s), 3.20 (2H, s) and 7.00-7.60 (8H, m).

Intramolecular oxidative coupling of 1,2-bis(2-ethynylphenyl)ethane (108)

A literature procedure[96] was adopted. A solution of 1,2-bis-(2-ethynylphenyl)ethane (108) (0.5 g, 2.2 mmol) in pyridine (freshly distilled from calcium hydride) and dry ether (3:1, 100 ml) was added dropwise during 6 h to a stirred suspension of anhydrous copper(II) acetate[74] (2.73 g, 15 mmol) in the same solvent system (220 ml) at 52-55°C. The solution was stirred at 52°C for a further 1½ h and cooled. The residue after solvent removal was chromatographed on a column of SiO_2. Elution with 10% Et_2O/PE and evaporation afforded a yellow oil (100 mg) (Found: C, 81.9; H, 5.9. $C_{20}H_{16}O_2 \cdot 0.3H_2O$ requires C, 81.8; H, 5.7%); m/z 289 (5), 288 (8), 246 (100), 245 (34), 229 (26) and 215 (26); νmax (neat) 3400, 3060, 3020, 2960, 2930, 2870, 1710, 1610, 1595, 1480, 1450, 1370, 1210, 1060, 905, 775, 760 and 740 cm^{-1}; δ($CDCl_3$) 2.10 (3H, s), 2.20 (1H, br), 3.25 (2H, m), 5.70 (1H, m) and 7.15 (9H, m), considered to be (113) and (114).

2,5-Thiophenedicarboxylic acid

2,5-Dilithiothiophene (40 mmol) in THF was prepared as usual (p. 137). Carbon dioxide (excess) was passed into the solution at -78°C. After 2 h at RT working up gave 2,5-thiophenedicarboxylic acid as pale colour prisms (ethanol-H_2O) (4.9 g, 72%), m.p. 357-8°C (sealed tube) (lit., 358.5-359.5°C)[205]; νmax (nujol) 3200-2500 (νO-H), 1690, 1550, 1470, 1290, 930, 860 and 760 cm^{-1}; δ(DMSO-d_6) 8.20 (2H, s).

An alternative synthesis involving direct metallation of thiophene using n-butyl lithium, TMEDA[206] and subsequent treatment with CO_2 was unsuccessful.

2,5-Bis(α-hydroxybenzyl)thiophene (119)

2,5-Dibromothiophene (10 g, 40 mmol) was dissolved in THF (100 ml) and n-butyl lithium in hexane (82.7 mmol) was added dropwise, with stirring, under nitrogen at -78°C. After 20 min at -78°C, benzaldehyde (8.48 g, 80 mmol) was added. Stirring was continued for 4 h at RT and the whole poured into aqueous HCl (4M, 200 ml). Extraction (EtOAc), washing of the extracts (H_2O), drying and evaporation gave a light brown mass, which on recrystallization from acetone-PE afforded 2,5-bis(α-hydroxybenzyl)thiophene (119) as colourless prisms (10.4 g, 88%), m.p. 96-7°C (Found: C, 72.9; H, 5.3. $C_{18}H_{16}O_2S$ requires C, 73.0; H, 5.4%); m/z 296 (M^+, 1), 278 {$(M-H_2O)^+$, 1}, 190 {$(M-C_7H_7O)^+$, 16} and 105 {$(C_7H_5O)^+$, 56}; νmax (nujol) 3400, 1600, 1490, 1360, 1220, 1130, 1035, 1015, 820, 785, 750, 720 and 700 cm^{-1}; δ($CDCl_3$) 2.90 (2H, b, exchanged with D_2O), 5.90 (2H, s), 6.60 (2H, s) and 7.30 (10H, m).

2,5-Di(benzoyl)thiophene (120)

(1) 2,5-Bis(α-hydroxybenzyl)thiophene (119) (10.6 g, 36 mmol) was dissolved in acetone (150 ml) and Jones reagent (72 mmol, prepared from 7.37 g of chromium trioxide, 6.42 ml conc. H_2SO_4 and 52.6 ml H_2O) was added dropwise, with stirring at 0°C. After 1 h at RT, enough aqueous $NaHSO_3$ was added to discharge the brown colour. Extraction ($CHCl_3$), evaporation of the washed (H_2O) dried extracts, and recrystallization of the residue from $CHCl_3$-PE afforded 2,5-di(benzoyl)thiophene (120) as colourless prisms (8.4 g, 80%), m.p. 115°C (lit., for another synthesis, 114.5-115°C)[207]; TLC (Al_2O_3, $CHCl_3$) Rf 0.77; m/z 293 {$(M+1)^+$, 3}, 292 (M^+, 8), 215 {$(M-Ph)^+$, 11.4}, 188 {$(M-PhCO)^+$, 64}, 111 {$(C_5H_3SO)^+$, 100} and 105 {$(PhCO)^+$, 71}; νmax (nujol) 1680, 1658, 1620, 1600, 1535, 1470, 1400, 1338, 890, 730, 705 and 690 cm^{-1}; δ($CDCl_3$) 7.50 (8H, m) and 7.90 (4H, m).

(2) A mixture of 2,5-thiophenedicarboxylic acid (4.5 g, 26 mmol), phosphorous pentoxide (8.12 g, 57 mmol) and dry benzene (200 ml) after 40 h refluxing as described,[208] gave only 76.4 mg (10%) of 2,5-di(benzoyl)thiophene, identical to that obtained above.

Diethyl 2,5-thiophene-Bis (3-hydroxy-3-phenylpropionate) (121)

2,5-Di(benzoyl)thiophene (120) (5 g, 17.2 mmol), zinc (4 g, 62 mmol, activated before used), ethyl bromoacetate (7.19 g, 43 mmol; freshly distilled), a few crystals of iodine and benzene (50 ml, dried) were refluxed for 8 h and poured into ice/H_2SO_4 (3M, 100 ml). Extraction with $CHCl_3$, washing (H_2O), drying and evaporation gave a solid, which on recrystallization from $CHCl_3$-PE afforded diethyl 2,5-thiophene-bis(3-hydroxy-3-phenylpropionate) (121)

as pale colour needles (4.21 g, 52%), m.p. 138-9°C (Found: C, 66.3; H, 5.9. $C_{26}H_{28}O_6S$ requires C, 66.6; H, 6.0%); TLC (Al_2O_3, $CHCl_3$) Rf 0.14; m/z 468 (M^+, 7); 381 {$(M-CH_2CO_2Et)^+$, 39}, 363 {$(M-C_4H_9O_3)^+$, 51}, 292 {$(M-C_8H_{14}O_4)^+$, 83} and 215 {$(M-C_{14}H_{19}O_4)^+$, 58}; νmax (nujol) 3470 (νO-H), 1720, 1500, 1200 1170, 1050 and 690 cm^{-1}; δ($CDCl_3$) 1.05 (6H, t), 3.12 (2H, s), 4.00 (4H, q), 4.90 (2H, b, exchanged with D_2O), 6.53 (2H, s) and 7.30 (10H, m).

Reaction between sodium hydride/iodomethane and diethyl 2,5-thiophene-bis (3-hydroxy-3-phenylpropionate) (121)

Sodium hydride (113 mg, 4.7 mmol) was added to a solution of 2,5-thiophene-bis(3-hydroxy-3-phenylpropionate) (121) (1 g, 2.13 mmol) in ether-THF (60 ml, 1:1). After 15 min at RT, iodomethane (760 mg, 5.34 mmol) was added and stirring continued for a further 3 h at the same temperature. Working up gave a solid, which was recrystallized from $CHCl_3$-PE to give very pale brown crystals (0.4 g), having identical physical and spectroscopic data to authentic 2,5-di(benzoyl)-thiophene (120).

Diethyl 2,5-thiophene-bis(3-O-trimethylsilyl-3-phenylpropionate) (122)

Diethyl 2,5-thiophene-bis(3-hydroxy-3-phenylpropionate)(121) (500 mg, 1.56 mmol) was dissolved in CH_2Cl_2 (10 ml). DBU (649 mg, 4.23 mmol) was added, with stirring, under nitrogen at RT. After 15 min, chlorotrimethylsilane (463.5 mg, 4.23 mmol) was added. After stirring at RT for 5 h, the mixture was poured into water. Extraction (CH_2Cl_2), washing of the extracts (H_2O), drying ($MgSO_4$) and evaporation

afforded a residue, which was chromatographed on a column of alumina (active, neutral). Chloroform eluted the bis(O-trimethylsilyl) derivative (122) as a very viscous light brown oil (687 mg, 72%); m/z 525 {$(M-OSiMe_3)^+$, 61.7}, 435 {$(M-2OSiMe_3)^+$, 100} and 362 {$(M-C_5H_{11}\ Si_2O_4)^+$, 6.7}; δ($CDCl_3$) 0.10 (18H, broad s), 0.90 (6H, t), 3.24 (4H, s), 3.80 (4H, q), 6.70 (2H, s) and 7.20 (10H, m).

Attempts to distill the product at 0.25 torr (b.p. 218-220°C) led to decomposition, as shown by the microanalytical data (Found: C, 71.1; H, 7.3. $C_{32}H_{44}O_6Si_2S$ requires C, 62.7; H, 7.2).

Attempted intramolecular cyclization of diethyl 2,5-thiophene-bis-(3-O-trimethylsilyl-3-phenylpropionate (122) using the acyloin reaction

The procedure used was exactly the same as that for the attempted cyclization of 2,5-bis(2-ethoxycarbonylphenyl)thiophene (81) as described earlier, but using diethyl 2,5-thiophene-bis(3-O-trimethylsilyl-3-phenylpropionate) (122) (1.27 g, 2.08 mmol), sodium (238 mg, 10 mmol), chlorotrimethylsilane (1.12 g, 10 mmol) and toluene (75 ml). After 2½ h refluxing, the very dark reaction mixture was worked up and chromatographed over alumina (grade III) using $CHCl_3$. ^1H NMR showed no sign of the expected product, but something comparable to that obtained from the dehydration of diethyl 2,5-thiophene-bis(β-hydroxy-3-phenylpropionate)(121) using aqueous oxalic acid: δ($CDCl_3$) 1.10 (3 sets of t), 3.95 (3 sets of q), 6.10 (s), 6.20 (s), 6.30 (s), 6.60 (s) and 7.20 (m), suggesting a mixture of Z, E-diethyl 2,5-thiophene-bis(3-phenyl-prop-2-ene-1-carboxylate) (124).

Reaction between 2,5-bis(2-formylphenyl)thiophene (87), DBU, and acetone-1,3-bis(triphenyphosphonium) chloride

A mixture of acetone-1,3-bis(triphenylphosphonium) chloride[98a] (540 mg, 0.8 mmol), DBU (250 mg, 1.64 mmol) and THF (30 ml, freshly distilled from CaH_2) were refluxed under N_2 for 1 h. 2,5-Bis(2-formylphenyl)thiophene (89) (240 mg, 0.8 mmol) in THF (10 ml) was added and refluxing continued for a further 20 h. The mixture was poured into water and acidified with HCl (2N). Extraction (Et_2O) and evaporation of the washed and dried extracts afforded yellow crystals. Flash chromatography on a column of SiO_2 (30% Et_2O-PE) yielded 2,5-bis(2-formylphenyl)thiophene (89) (Rf 0.33) (86.4 mg, 36%) and 2-(2-formylphenyl)-5-{2-(3-keto-but-1-enyl)}phenyl thiophene (134) (Rf 0.14) (65 mg, 24.5%); m/z 332 (M^+, 10), 317{$(M-CH_3)^+$, 2}, 289 {$(M-CO-CH_3)^+$, 56} and 271 (100); νmax (neat) 3060, 3020, 2850, 2750, 1690, 1660, 1600, 1260, 970, 940, 820 and 760 cm^{-1}; δ($CDCl_3$) 2.32 (3H, s), 6.66 (2'-H, d, J 15.3 Hz), 7.03 (2H, s), 6.90-7.70 (8H, m), 7.90 (1'-H, d, J 15.3 Hz) and 10.31 (1H, s). Longer reaction time (30 h) and higher temperature (90°C, DMSO as solvent) led to no improvement.

Coupling reaction between 2-styrylphenylmagnesium iodide and 2,5-dibromothiophene

The reported procedure[78,108a,108d] was followed. 2-Styryl-phenylmagnesium iodide (43 mmol, prepared from 10 g 2-iodostyrene and 1.04 g magnesium turnings) in ether was added dropwise, with stirring, under nitrogen, to 2,5-dibromothiophene (4.16 g, 17.2 mmol)

and {Ni(dppp)Cl_2} (30 mg) in ether (40 ml) at 0°C. A light tan solution was obtained, refluxed for 9 h and poured into HCl (2M, 100 ml). Extraction (CH_2Cl_2), washing of the extracts (H_2O), drying and evaporation gave a light brown oil, which was purified on preparative TLC (Merck SiO_2 60 GF 254 No. 7730) using 10% Et_2O-PE. Three major bands (Rf 0.63, 0.50 and 0.38, appearing as purple, green and yellow respectively under UV λ 254) were isolated. The first band (Rf 0.63) afforded yellow prisms (300 mg, 9.3%), m.p. 47-9°C; m/z 288 (100), 273 (39), 141 (61), 128 (51) and 115 (64); νmax (neat) 1625, 1595, 1475, 1465, 1440, 1410, 990, 935, 910, 810, 750 and 740 cm^{-1}; δ($CDCl_3$) 5.20 (1H, dd, J 11.3 Hz and 1.3 Hz), 5.63 (1H, dd, J 17.3 Hz), 6.95 (2H, s) and 7.25 (10H, m). All the physical and spectroscopic data were identical to that of an authentic sample of 2,5-bis (2-ethenylphenyl)thiophene (135) prepared by an alternative route. The second band (Rf 0.50) gave a yellow oil (310 mg, 8.7%), which was identified as 2,2'-styrylbiphenyl from its spectroscopic properties: m/z 206 (M^+, 21), 178 {$(M-C_2H_4)^+$, 100}, 152 {$(C_{12}H_{10})^+$, 39} and 103{$(\frac{m}{2})^+$, 77}; δ($CDCl_3$) 5.24 (2H, dd, J 10.7 Hz and 1.33 Hz), 5.65 (2H, dd, J 18 Hz and 1.33 Hz) and 6.90-7.60 (10H, m). The third band (Rf 0.38) after recrystallization from $CHCl_3$-PE (CO_2-acetone bath) gave yellow prisms (280 mg, 4.3%), which was tentatively identified as 2,2'-di (5,5'-2-styrylphenylthienyl), m.p. 105-6°C (Found: C, 74.2; H, 4.5. $C_{24}H_{18}S_2$.0.17 $CHCl_3$† requires C, 74.3; H, 4.7%); m/z 370 (M^+, 92), 185 {$(\frac{m}{2})^+$, 46} and 152 {$(\frac{m}{2}-SH)^+$, 39}; δ($CDCl_3$) 5.26 (2H, dd, J 10.7 Hz and 1.33 Hz), 5.68 (2H, dd, J 17 Hz and 1.33 Hz), 6.80-7.70 (14H, m). A prolonged reaction time (21 h) and refluxing THF led to no improvement.

† $CHCl_3$ resonance present in ^1H NMR.

Coupling between 2,5-dilithiothiophene and 2-bromostyrene, using $Pd(PPh_3)_4$ as catalyst

A reported procedure[92] was adopted. n-Butyl lithium (20 mmol) in hexane was added to 2,5-dibromothiophene (2.5 g, 10 mmol) in THF (10 ml), under N_2, at -78°C, followed by warming to RT. In the meantime, a mixture of 2-bromostyrene (4.16 g, 22.5 mmol), $Pd(PPh_3)_4$ (200 mg) and THF (50 ml) was stirred at RT for ½ h. The 2,5-dilithiothiophene was transferred under N_2 to the second solution and stirring continued at RT for 20 h. Pouring into water (100), followed by extraction (ether), washing of the extracts (H_2O), drying and evaporation afforded an oil, which was subjected to flash chromatography using PE. 2,5-Dibutylthiophene (Rf 0.83) (882 mg, 45%); m/z 196 (M^+, 15), 153 {$(M-C_3H_7)^+$, 100}, 111 {$(M-C_6H_{13})^+$, 21} and 97 (22); ($CDCl_3$) 0.80-1.70 (14H, m), 2.72 (4H, t, J 6.7 Hz), and 6.50 (2H, s) eluted first, followed by 2-bromostyrene (3.0 g, 72% recovery). No trace of coupled product was isolated.

When n- was replaced by tert-butyl lithium (2 moles excess) instead, neither 2-bromostyrene nor 2-iodotoluene showed any sign of reaction.

2,5-Bis(2-ethenylphenyl)thiophene (135)

Methyltriphenylphosphonium bromide (1.83 g, 5.14 mmol) was suspended in THF (20 ml) and n-butyl lithium in hexane (5.14 mmol) was added dropwise, with stirring, under nitrogen at 0°C. After 35 min at 0°C, 2,5-bis(2-formylphenyl)thiophene (89) (0.5 g, 1.71 mmol) in THF (5 ml) was added. Stirring continued at RT for 1½ h and the

mixture was partitioned between methanol-water (1:1) and ether (50 ml each). Washing of the organic phase (brine), drying and evaporation afforded a brown oil, which was chromatographed on a column of SiO_2. Fractions eluted with 10% ether-PE gave 2,5-bis(2-ethenylphenyl)-thiophene (135) after recrystallization from PE (CO_2-acetone cold bath), as very pale yellow prisms (0.36 g, 74%), m.p. 48-9°C (Found: C, 82.2; H, 5.6. $C_{20}H_{16}S \cdot 0.25\ H_2O$† requires C, 82.1; H, 5.6%); m/z 288 (M^+, 100), 273 {$(M-CH_3)^+$, 39}, 141 {$(C_{11}H_9)^+$, 61}, 128 {$(C_{10}H_8)^+$, 51} and 115 {$(C_9H_7)^+$, 64}; νmax (neat) 1625, 1595, 1475, 1465, 1440, 1410, 990, 935, 910, 810, 750 and 740 cm^{-1}; δ($CDCl_3$) 5.20 (1H, dd, J 11.3 Hz and 1.3 Hz), 5.63 (1H, dd, J 17.3 Hz and 1.3 Hz), 6.95 (2H, s) and 7.25 (10H, m).

Hydroboration of 2,5-bis(2-styrylphenyl)thiophene (135) using thexylborane

A 1M solution of thexene in THF (5 ml, 0.5 mmol) was added dropwise to a 1M solution of borane-tetrahydrofuran complex (5 ml, 0.5 mmol), under N_2, at 0°C followed by stirring at the same temperature for 2 h. In the meantime, THF (50 ml) was placed into a 3-necked flask, equipped with a N_2 inlet and two identical dropping funnels, containing the thexylborane, prepared above and diluted with THF (50 ml), and 2,5-bis(2-styrylphenyl)thiophene (135) (144 mg, 0.5 mmol) in THF (50 ml) separately. The two solutions were added simultaneously over 6½ h, followed by stirring at RT for another 12 h. Sodium cyanide (23 mg, 0.54 mmol; dried under vacuum at 100°C for 6 h) was added and stirring continued at RT for 2 h and at 40°C for 1 h. After

† residual water was evident in the i.r. spectrum:
3380 cm^{-1} (νO-H, weak)

cooling to -78°C, trifluoroacetic anhydride (0.085 ml, 0.6 mmol) was added. The cooling bath was removed and after 1 h at RT, aqueous sodium hydroxide (5M, 2 ml), followed by hydrogen peroxide (30%, 2 ml) was added. Oxidation was allowed to proceed at RT overnight. Working up as usual gave a yellow solid (140 mg), shown to be only (135) by ^{1}H NMR.

Ethynyltrimethylsilane - a solution in THF/hexane

n-Butyl lithium (0.3 mol) in hexane was added dropwise, with stirring, under N_2 at -78°C to a saturated solution of acetylene (purified by passing through a trap cooled to -78°C, then through conc. H_2SO_4 and finally through soda-lime) in THF (500 ml). The flow of acetylene was maintained at a minimum throughout the addition of butyl lithium. 20 min after the addition of butyl lithium, the flow of acetylene was stopped and chlorotrimethylsilane (0.306 mol) was added. After stirring overnight (10 h), while the cooling bath warmed slowly to RT, the mother liquor, which was a solution of ethynyltrimethylsilane in THF/hexane, was decanted carefully and was ready for use.

2-(Trimethylsilyl)ethynylbenzaldehyde (137) and 2-ethynylbenzaldehyde (138)

The following procedure was modified from that of Lau et al.[76] A deaerated solution of 2-bromobenzaldehyde (18.5 g, 100 mmol), triphenylphosphine (400 mg), and palladium(II)acetate (200 mg) in anhydrous triethylamine (300 ml) was treated with ethynyltrimethylsilane† (150 mmol, as a THF/hexane solution, prepared as described previously)

† neat ethynyltrimethylsilane[117] can be used instead.

under nitrogen. The mixture was rapidly heated to 80-90°C and maintained at that temperature for 5 h. After cooling, the mixture was filtered. The filtrate was concentrated, mixed with water (100 ml), and extracted with CH_2Cl_2 (3x50 ml). The combined organic phases were dried, concentrated and distilled to give 2-(trimethylsilyl)ethynyl-benzaldehyde (137) as a yellow oil (18.4 g, 91%), b.p. 98°C/0.2 torr (lit., 108°C/2 torr); $\delta(CDCl_3)$ 0.09 (9H, s), 7.27 (3H, m), 7.67 (1H, m) and 10.32 (1H, s).

The above product was treated with potassium fluoride dihydrate† (19 g, 202 mmol) in DMF (60 ml) under nitrogen at RT overnight and poured into water. Extraction (CH_2Cl_2), washing of the extracts (H_2O), drying and evaporation gave a brown mass. Recrystallization from PE (CO_2-acetone cold bath) gave 2-ethynylbenzaldehyde (138) (11.7 g, 99%), m.p. 60-1°C (lit.,[116] 60-60.5°C); m/z 130 (M^+, 28), 129 {$(M-H)^+$, 6}, 105 {$(M-C_2H)^+$, 7} and 102 {$(M-CO)^+$, 100}; νmax (nujol) 3230 (νC≡H), 2840, 2740, 2090 (νC≡C), 1680, 1660, 1590, 1270, 1200 and 750 cm^{-1}; $\delta(CDCl_3)$ 3.45 (1H, s), 7.45 (3H, m), 7.80 (1H, m) and 10.43 (1H, s).

4-(2-Ethynyl)phenyl-but-3-ene-2-one (140)

A mixture of aqueous sodium hydroxide (0.65 M, 6.8 ml) and ethanol (6.8 ml) was added over 10 min to an ice-cooled stirred solution of 2-ethynylbenzaldehyde (138) (3.25 g, 25 mmol) in acetone (13.5 ml, 184 mmol). The solution was stirred for a further 4 h at 0°C and aqueous H_2SO_4 (2M, 2.65 ml) was then added. The solution was diluted with water (150 ml) and extracted with ether, and the extracts were washed with saturated aqueous sodium bicarbonate. The residue

† in the original reference, K_2CO_3/MeOH was used. However, great care must be exercised in removing the methanol, or else polymerization of the product occurred.

after solvent removal was chromatographed on a column of grade III alumina (5x4 cm). Fractions eluted with 20% ether-PE on evaporation afforded the ketone (140) as a yellow oil (2.43 g, 57%), which failed to crystallize (lit.,[209] m.p. 64.5°C); m/z 170 (M^+, 32), 169 {$(M-H)^+$, 11}, 155 {$(M-CH_3)^+$, 61} and 127 {$(M-CH_3CO)^+$, 85}; νmax (neat) 3300 (νC≡H), 2100 (νC≡C), 1670 (νC=O), 1620, 1610, 1590, 1475, 1360, 1260, 975 and 755 cm^{-1}; δ($CDCl_3$) 2.34 (3H, s), 3.40 (1H, s), 6.67 (1H, d, J 16.7 Hz), 7.35 (4H, m) and 8.00 (1H, d, J 16.7 Hz).

1,5-bis(2-ethynylphenyl)penta-1,4-dien-3-one (139)

1) from 4-(2-ethynyl)phenyl-but-3-ene-2-one (140) and 2-ethynylbenzaldehyde (138):

Methanolic potassium hydroxide (3.6M, 1.89 ml) was added to a stirred solution of 4-(2-ethynyl)phenyl-but-3-ene-2-one (140) (2.42 g, 14.2 mmol) and 2-ethynylbenzaldehyde (138) (1.85 g, 14.2 mmol) in ether (60 ml, previously passed through basic alumina and flushed with nitrogen). After 4 h at RT, acetic acid (2.8 ml) was added, followed by stirring for 15 min and dilution with water (100 ml). The aqueous layer was extracted with ether and the combined ethereal extracts were washed with saturated aqueous sodium bicarbonate. The residue after solvent removal was chromatographed on a column of grade III alumina (5x4 cm). Elution with 30% ether-PE gave the desired ketone (139) as yellow crystals (0.85 g, 21%), m.p. 101-102°C (lit.,[115] m.p. 101.3-101.7°C); TLC{SiO_2, $CHCl_3$} Rf 0.38; m/z 155 {$(M-C_{10}H_7)^+$, 75}, 127 {$(M-C_{11}H_7O)^+$, 100} and 102 {$(C_8H_6)^+$, 30}; max (CH_2Cl_2) 3300 (νC≡H), 2250 (νC≡C), 1650 (νC=O), 1620, 1600, 1590, 1470, 1090 and 975 cm^{-1}; δ($CDCl_3$) 3.41 (2H, s), 7.09 (2H, d, J 16.0 Hz), 7.30 (8H, m) and 8.29 (2H, d, J 16.0 Hz).

2) from 2-ethynylbenzaldehyde (138):

The following procedure was modified from that given by Sondheimer et al.[96] 2-Ethynylbenzaldehyde (6.82 g, 52 mmol) in ether (20 ml, purified as mentioned above) was added during 25 min, under N_2, to a solution of acetone (1.92 ml, 26 mmol) and methanolic KOH (1.41M, 4.68 ml) in ether (30 ml) at RT. After stirring for 4 h at RT, the mixture was worked up as in (1). The 30% Et_2O/PE eluent, after being evaporated down, was recrystallized from EtOH to give 1,5-bis(2-ethynylphenyl)penta-1,4-dien-3-one (139) (1.95 g, 26.6%) as yellow prisms, having similar physical and spectroscopic properties as that prepared above.

1,5-Bis(2-bromophenyl)penta-1,4-dien-3-one (141)

A solution of 2-bromobenzaldehyde (41.4 g, 223 mmol) in ethanol (20 ml) was added during 3 h, with stirring, to a solution of sodium hydroxide (1.2 g, 30 mmol) in acetone (10.67 ml, 0.145 mol), ethanol (340 ml) and water (340 ml) at RT. Yellow crystals soon started to deposit. After the addition, the mixture was left in the fridge overnight whereby a heavy bright yellow oil separated out. The mother liquor was decanted and the oil, dissolved in $CHCl_3$ (150 ml), was washed (H_2O), dried and evaporated. Trituration with acetone gave a yellow solid which on recrystallization from acetone afforded 1,5-bis(2-bromophenyl)penta-1,4-dien-3-one (141) as yellow prisms (14.7 g, 34%), m.p. 126-7°C (Found: C, 52.3; H, 3.1. $C_{17}H_{12}Br_2O$ requires C, 52.1; H, 3.1%); m/z 394 (M^+, 12), 392 (M^+, 14); 313 {$(M-Br)^+$, 74}, 311 {$(M-Br)^+$, 67} and 211 {$(C_9H_7BrO)^+$, 32}; νmax (nujol) 1650 (νC=O), 1590, 1580, 1190, 975 and 750 cm^{-1}; δ($CDCl_3$) 6.78 (2H, d, J 16.7 Hz), 7.09 (4H, m), 7.55 (4H, m) and 7.96 (2H, d, J 16.7 Hz).

Reaction between ethynyltrimethylsilane and 1,5-bis(2-bromophenyl)-penta-1,4-dien-3-one (141)

The procedure adopted was similar to that reported.[76] A deaerated solution of 1,5-bis(2-bromophenyl)penta-1,4-dien-3-one (141) (5 g, 13 mmol), triphenylphosphine (80 mg) and palladium acetate (40 mg) in anhydrous triethylamine (120 ml) was treated with ethynyltrimethylsilane (3.8 g, 39 mmol) under nitrogen. The mixture was rapidly heated to 80-90°C and maintained at that temperature for 16 h. Working up as reported[76] gave only starting materials. Addition of xylene (50 ml) as cosolvent and conducting the reaction at 100°C for 23 h led to no improvement. When dioxane (50 ml) was used as the cosolvent and after 13 h refluxing, a 5% yield (based on the integral) of 1,5-bis(2-trimethylsilylethynylphenyl)penta-1,4-dien-3-one (142) was observed in the ^{1}H NMR.

4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127)

The procedure adopted was similar to that reported.[96] A solution of 1,5-bis(2-ethynylphenyl)1,4-pentadiene-3-one (139) (4.7 g, 17 mmol) in pyridine and dry ether (3:1, 300 ml) was added dropwise during 5 h to a stirred solution of anhydrous copper acetate[74] (21.4 g) in pyridine and dry ether (3:1, 700 ml) at 60°C (bath). The solution was stirred at 60°C for a further 1½ h and was then cooled. The residue after solvent removal was taken up in dil HCl (0.1M) and extracted with CH_2Cl_2 (3x150 ml). The combined CH_2Cl_2 extracts were washed with saturated aqueous sodium bicarbonate. The residue after solvent removal was recrystallized from $CHCl_3$-PE to give the desired

annulenone (127) as yellow prisms (2.96 g, 62%), m.p. 196°C (decomp.), (lit.,[115] m.p. 194°C (decomp.)); m/z 280 (M^+, 7), 252 {$(M-CO)^+$, 15}, 154 {$(M-C_{10}H_6)^+$, 7} and 126 {$(M-C_{11}H_6O)^+$, 7}; νmax (CH_2Cl_2) 2180 (νC≡C), 1660 (νC=O), 1640, 1620, 1590, 1090, 1010 and 975 cm^{-1}; δ($CDCl_3$) 6.78 (2H, d, J 16.6 Hz), 7.40 (8H, m) and 8.48 (2H, d, J 16.6 Hz).†

Reduction of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127) with sodium borohydride

Sodium borohydride (108 mg, 2.87 mmol) in ethanol (30 ml) was added to a suspension of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (200 mg) in ether (5 ml) at RT. After 2 h at room temperature, most of the solvent was removed and water was added. Extraction (EtOAc), drying and evaporation afforded a brown oil, which was flash chromatographed on a column of SiO_2 using EtOAc-PE (3:7). TLC (SiO_2) showed the eluent contained at least 6 components (Rf=0.60, 0.50, 0.38, 0.30, 0.23 and 0.15). ^1H NMR (300 MHz) showed a very complex spectrum; however, part of the resonance due to the expected alcohol was observed, ($CDCl_3$) 5.08 (1H, t, J 5.5 Hz), 5.88 (2H, dd, J 5.5 Hz + 15 Hz). Similar results were obtained using THF or methanol as solvent and a longer reaction time (16 h).

† The elemental analysis of (127) always afford low values of carbon (Found: C, 84.7; H, 4.6. $C_{21}H_{12}O$ requires C, 90.0; H, 4.3%), in consistent to that reported by Ojima et al.[115]

1,5-Bis(2-ethynylphenyl)-1,4-pentadien-3-ol (145)

To 1,5-bis(2-ethynylphenyl)-1,4-pentadien-3-one (139) (0.5 g, 1.8 mmol) in methanol (25 ml) was added powdered sodium borohydride (0.27 g, 7 mmol). The mixture was stirred at RT for 3 h and poured into water. Extraction (CH_2Cl_2), drying and evaporation gave a residue, which was chromatographed on a column of Al_2O_3 (grade III). Fractions eluted with 30% Et_2O-PE gave 1,5-bis(2-ethynylphenyl)-1,4-pentadien-3-ol (145) as a yellow oil (0.36 g, 72%); m/z 267 {$(M-OH)^+$, 2}, 157 {$(M-C_{10}H_7)^+$, 18}, 128 {$(M-C_{11}H_8O)^+$, 100} and 127 {$(M-C_{11}H_9O)^+$, 40}; νmax (neat) 3400 (νO-H), 3300, 2100 (νC≡C), 1645, 1595, 1560, 1075, 1040, 1020, 965, 905 and 750 cm^{-1}; δ($CDCl_3$) 2.6 (1H, b, exchanged by D_2O), 3.30 (2H, s), 5.00 (1H, t, J 5.9 Hz), 6.33 (2H, dd, J 16 Hz, 5.9 Hz) and 7.20 (10H, m). The above spectroscopic data was similar to that reported.[123]

Attempted preparation of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-ol from 1,5-bis(2-ethynylphenyl)-1,4-pentadien-3-ol (145)

The procedure adopted was similar to that described.[96] A solution of 1,5-bis(2-ethynylphenyl)-1,4-pentadien-3-ol (145) (1 g, 3.52 mmol) in pyridine and dry ether (3:1, 80 ml) was added dropwise during 2½ h to a stirred solution of anhydrous copper acetate[74] (4.43 g) in pyridine and dry ether (3:1, 165 ml) at 60°C (bath). The solution was stirred at 60°C for a further 1½ h and then worked up as usual.[96] The crude product was recrystallized ($CHCl_3$-PE) to give yellow prisms (450 mg, 45.7%), which had physical and spectroscopic properties identical to those of an authentic sample of 4,5,10,11-dibenzo-2,12-cyclotridecadien-6,8-diyn-1-one (127).

4-(2-Iodophenyl)-2-butanone (149)

A literature procedure[138] was followed. A mixture of 2,4-pentandione (33.7 g, 0.33 mol), anhydrous potassium carbonate (47.4 g, 0.34 mol), 2-iodobenzyl bromide (91 g, 0.31 mol) and absolute ethanol (190 ml) was refluxed on an oil bath for 16 h. Working up as reported[138] gave a yellow oil, which was distilled to give 4-(2-iodophenyl)-2-butanone (149) (56.9 g, 67%) as a very pale hygroscopic yellow liquid, b.p. 110-111°C/0.75 torr (Found: C, 42.8; H, 3.9. $C_{10}H_{11}IO \cdot 0.4H_2O$ requires C, 42.7; H, 4.2); m/z 274 (M^+, 3), 217 {$(M-C_3H_5O)^+$, 9}, 147 {$(M-I)^+$, 100} and 104 {$(M-C_2H_3IO)^+$, 14}; νmax (neat) 3400 (w), 1710, 1560, 1465, 1350, 1400, 1360, 1350, 1160, 1010 and 750 cm^{-1}; δ($CDCl_3$) 2.10 (3H, s), 2.85 (4H, m), 6.70-7.50 (3H, m) and 7.75 (1H, d, J 8 Hz).

N-{1-Methyl-2-(2-iodophenyl)propylidine}cyclohexylamine (150)

A reported procedure[136] was modified. A solution of 4-(2-iodophenyl)-2-butanone (10 g, 36.4 mmol), cyclohexylamine (3.6 g, 36.4 mmol) and toluenesulphonic acid (50 mg) in benzene (20 ml, dry) was refluxed in a Dean-Stark separator for 16 h. The benzene was removed and the residue was purified on a Al_2O_3 † (grade I) column. Elution with 30% $CHCl_3$-PE afforded N-{1-methyl-2-(2-iodophenyl)propylidine}-cyclohexylamine (150) (10.3 g, 80%) as a viscous deep yellow oil, m/z 355 (M^+, 1) and 217 {$(C_7H_6I)^+$, 10}; νmax (neat) 2920, 2850, 1660 (νC=N), 1560, 1465, 1450, 1435, 1010, 885 and 750 cm^{-1}; δ($CDCl_3$) 1.0-3.0 (15H, m), 1.80 (3H, s), 6.60-7.50 (3H, m) and 7.75 (1H, d, J 8 Hz). Attempts to purify the product by distillation led to extensive decomposition.

† SiO_2 column decomposed the ketimine back to starting materials.

2-Iodobenzaldehyde (153)

1) via 2-iodobenzyl alcohol (155)

A literature procedure[150] was followed. A solution of 2-iodobenzoyl chloride (82.6 g, 0.31 mol) in dioxane was added over 25 min to a well-stirred suspension of sodium borohydride (23.4 g, 0.62 mol) in dioxane (200 ml) cooled in an ice bath. The mixture was heated on a steam bath for 1 h. Cooled in an ice bath while water (50 ml) was added cautiously to the mixture. Extraction (CH_2Cl_2), washing of the extracts (H_2O), drying ($MgSO_4$) and evaporation afforded the alcohol (155) as white needles (71.1 g, 98%), which was used in the next stage without further purification. Reduction using $LiAlH_4$ and a procedure similar to that reported[210] gave only benzyl alcohol.

2-Iodobenzyl alcohol (71.1 g, 0.30 mol) in CH_2Cl_2 (200 ml) was added to a well-stirred suspension of pyridinium dichromate[151] (174.9 g, 0.47 mol) in CH_2Cl_2 (500 ml). After 3 h at RT, the mixture was diluted with ether (200 ml) and filtered through celite. The filtrate, after being evaporated down, was distilled to give 2-iodobenzaldehyde as a pale yellow oil (53.2 g, 76.4%), b.p. 98-100°C/2.0 torr (lit., 129°C/14 torr)[143]; $\delta(CDCl_3)$ 7.35 (3H, m), 7.85 (1H, m) and 10.04 (1H, s).

2) direct reduction of 2-iodobenzoyl chloride using bis(triphenylphosphine)copper(I) tetrahydroborate

2-Iodobenzoyl chloride (39.98 g, 0.15 mol) in acetone (75 ml) was added dropwise over 10 min to a stirred slurry of bis(triphenylphosphine)-copper(I) tetrahydroborate[148b] (90.47 g, 0.15 mol) and triphenylphosphine (78.7 g, 0.3 mol) in acetone (250 ml). The reaction mixture became warm.

After 1 h, the precipitate of tris(triphenylphosphine)copper(I) chloride was removed by filtration and washed with acetone (250 ml). To the combined filtrate and washings, water (500 ml) and methanol (500 ml) were added; the resulting precipitate of triphenylphosphine-borane was removed by filtration and discarded. The filtrate was concentrated to approximately 1.5 l and the aqueous phase was extracted with ether. The combined ether extracts were washed with saturated brine (200 ml) and dried ($MgSO_4$). Fractionated under vacuum gave 2-iodobenzaldehyde (55-68%), identical to that prepared above.

2-Iodostyrene (157)

Harrison's[156] reported procedure was modified as follows. Methyl-triphenylphosphonium bromide (128.5 g, 0.359 mol) was suspended in THF (300 ml) and n-butyl lithium in hexane (0.359 mol) was added dropwise, with stirring, under nitrogen at 0°C. After 30 min at 0°C a solution of 2-iodobenzaldehyde (79.32 g, 0.342 mol) in THF (100 ml) was added. Stirring was continued at RT for 1 h and the mixture partitioned between methanol-water (1:1) and PE (200 ml each). Extraction (PE), washing of the extracts (H_2O), drying and evaporation afforded a light orange oil, which on fractionation under vacuum, in the presence of hydroquinone (500 mg), gave 2-iodostyrene (157) (56.4 g, 71.7%) as a yellow oil, b.p. 69-70°C/0.3 torr (lit. 88-90°C/3 torr)[154]; $\delta(CDCl_3)$ 5.16 (1H, dd, J 10.6 Hz, 0.65 Hz), 5.46 (1H, dd, J 17.3 Hz, 0.65 Hz), 6.83 (1H, dd, J 17.3 Hz, 10.6 Hz) and 7.00-7.80 (4H, m). The yield dropped to 57% when the scale was doubled and was only 44% when methyltriphenylphosphonium iodide[211] was used. When sodium methyl sulfinyl carbanion[212] was used instead of n-butyl lithium, no reaction occurred.

1,5-Di(2-iodophenyl)pentan-3-one (148)

1) via 2-iodostyrene

The procedure developed by Pelter[105a] was followed. Diborane-THF (85 mmol, as a 1M solution) was added dropwise to 2,3-dimethyl-but-2-ene (7.15 g, 85 mmol) in a flame-dried nitrogen filled round-bottomed flask sealed with a rubber septum and cooled in an ice bath. After 1 h stirring, the cooling bath was removed and stirring continued for a further 1 h. 2-Iodostyrene (38.9 g, 169 mmol) was added dropwise over 30 min and stirring continued for 10 h (or overnight). The solution was transferred, under N_2, to a flame-dried flask equipped with a magnetic stirrer and sodium cyanide (4.46 g, 91 mmol; oven-dried at 100°C/20 torr for 6 h prior to use). After stirring overnight, whereby most of the sodium cyanide went into solution, the cyanoborate solution was cooled to -78°C (dry ice/acetone bath) and trifluoroacetic anhydride (13.0 ml, 92 mmol) was added dropwise over 20 min. When addition was complete, the cooling bath was removed (the reaction mixture was solid at this stage) and allowed to warm to RT, on which it became syrupy and a yellow colour. After being left for 2 h, the septum cap was removed and methanol (47 ml) added followed by 5M NaOH (77.5 ml), with stirring. Finally 30% H_2O_2 (77.5 ml) was slowly added (CARE: much effervescence and heat evolution) and oxidation allowed to proceed for 3 h. Extraction (CH_2Cl_2, 3x200 ml), washing of the extracts {(3M NaOH (400 ml) followed by 3M HCl (400 ml) and H_2O (500 ml)}, drying and evaporation gave the crude product as a viscous light yellow oil, which was chromatographed on a column of SiO_2. Fractions eluted with PE recovered unreacted 2-iodostyrene (4.17 g, 10.7%); with 20% ether-PE afforded the desired

1,5-Di(2-iodophenyl)pentan-3-one (148) (20.7 g, 56.0%) and with CH_2Cl_2 gave 2-(2-iodophenyl)ethanol (160) (6.4 g, 15.3%).

1,5- bis(2-iodophenyl)pentan-3-one (148), a light yellow viscous oil, failed to crystallize, m/z 491 {$(M+1)^+$, 25}, 363 {$(M-I)^+$, 39}, 231 {$(C_8H_8I)^+$, 33}, 217 {$(C_6H_6I)^+$, 100}, 104 {$(C_8H_8)^+$, 46} and 91 {$(C_7H_7)^+$, 33}; νmax (neat) 1710 (νC=O), 1620, 1585, 1560, 1465, 1432, 1010, 750, 720 and 640 cm^{-1}; δ($CDCl_3$) 2.50-3.20 (8H, m), 6.70-7.30 (6H, m) and 7.78 (2H, d, J 8.0 Hz); 2,4-dinitrophenylhydrazone: orange prism (ethanol), m.p. 128-9°C (Found: C, 41.7; H, 3.0; N, 8.4. $C_{23}H_{20}N_4O_4I_2$ requires C, 41.2; H, 3.0; N, 8.4%). 2-(2-Iodophenyl)ethanol (160), a yellow viscous oil, b.p. 138-140°C/2.2 torr (lit. 100°C/0.5 torr)[213]; m/z 248 (M^+, 38), 231 {$(M-OH)^+$, 10}, 217 {$(M-CH_2OH)^+$, 53}, 121 {$(M-I)^+$, 86} and 91 {$(C_7H_7)^+$, 100}; νmax (neat) 3350 (νO-H), 1630, 1585, 1560, 1465, 1430, 1050, 1010, 900, 750, 720 and 640 cm^{-1}; δ($CDCl_3$) 2.40 (1H, br, exchanged by D_2O), 2.90 (2H, t, J 7.9 Hz), 3.75 (2H, t, J 7.9 Hz), 6.65-7.40 (3H, m) and 7.79 (1H, d, J 7.7 Hz).

2) via Ethyl 5-(2-iodophenyl)-3-keto-pentanoate and 2-iodobenzyl bromide

(a) Ethyl 5-(2-iodophenyl)-3-ketopentanoate (151)

The procedure adopted was similar to that reported.[139] n-Butyl lithium in hexane (70 mmol) was added, with stirring, under nitrogen at 0°C to diisopropylamine (6.81 g, 68 mmol; freshly distilled from CaH_2) in THF (200 ml). After 20 min, methyl acetoacetate (3.91 g, 34 mmol) was added slowly. A bright orange colour developed. After another 20 min at 0°C a solution of 2-iodobenzyl bromide (10 g, 34 mmol) in THF (50 ml) was added dropwise. The orange colour was faded gradually.

After stirring at RT overnight (10 h), the mixture was poured into HCl (2N, 100 ml). Extraction (Et_2O), washing of the extracts (saturated $NaHCO_3$; H_2O), drying and evaporation gave a viscous oil, which was chromatographed on a column of SiO_2. Fractions eluted with 30% Et_2O-PE afforded ethyl 5-(2-iodophenyl)-3-ketopentanoate (151) as a light yellow oil (8.46 g, 75%); TLC {(SiO_2; Et_2O-PE (3:7)} Rf 0.37; m/z 332 (M^+; 1), 301 {$(M-OMe)^+$, 1}, 259 {$(M-CH_2CO_2Me)^+$, 6}, 231 {$(M-COCH_2CO_2Me)^+$, 20}, 217 {$(M-CH_2COCH_2Me)^+$, 43}, 205 {$(M-I)^+$, 100}, 173 {$(M-I-CH_3OH)^+$, 23}, 163 (49), 145 {$(M-C_2H_4IO)^+$, 86}, 131 {$(C_9H_7O)^+$, 31} and 103 {$(C_8H_7)^+$, 33}; νmax (nujol) 3400 (w), 1745, 1710, 1650, 1630, 1560, 1465, 1435, 1405, 1320, 1010 and 750 cm^{-1}; δ($CDCl_3$) 2.90 (4H, s), 3.40 (2H, s), 3.67 (3H, s), 4.97 (1H, s; vinyl proton of the enol form, Ca. 8% from integral), 6.70-7.20 (4H, m) and 7.80 (1H, d, J 8 Hz). Attempts to purify the product by distillation led to extensive decomposition.

(b) 1,5-bis(2-iodophenyl)pentan-3-one (148)

A literature procedure[141] was modified as noted. 2-Iodobenzyl bromide (7.15 g, 24 mmol) in acetone (100 ml) was added to a well-stirred refluxing mixture of ethyl 5-(2-iodophenyl)-3-ketopentanoate (8.0 g, 24 mmol; prepared from above), anhydrous potassium carbonate (3.65 g, 26.5 mmol) and acetone (100 ml). After 11 h refluxing, the mixture was poured into H_2O (200 ml). Extraction (CH_2Cl_2), washing of the extracts (H_2O) and evaporation gave a viscous oil, which was refluxed with a mixture of 20% H_2SO_4 and acetic acid (150 ml each) for 10 h. After cooling, the organic phase was separated, diluted with an equal volume of CH_2Cl_2, washed (H_2O), dried and evaporated. The residue was taken up in a minimum volume of $CHCl_3$ and PE was added to precipitate

out the dialkylated product, 2-(2-iodobenzyl)-1,5-bis(2-iodophenyl)-pentan-3-one (152) (2.26 g, 13.3%) as colourless prisms, m.p. 159-160°C. (Found: C, 41.0; H, 2.8. $C_{24}H_{21}OI_3$ requires C, 40.8; H, 3.0%); νmax 1690, 1435, 1380, 1270, 1240, 1012, 765 and 750 cm^{-1}; δ($CDCl_3$) 2.80-3.20 (9H, m), 6.50-7.30 (9H, m) and 7.75 (3H, d, J 7.3 Hz). On cooling the mother liquor a solid was separated out, which on recrystallization from CH_2Cl_2-PE yielded the desired 1,5-bis(2-iodophenyl)pentan-3-one (148) (2.9 g, 33.6%) as colourless prisms, m.p. 71-2°C. (Found: C, 41.3; H, 3.1. $C_{17}H_{16}I_2O$ requires C, 41.6; H, 3.3%), having identical spectroscopic data as that prepared from 2-iodostyrene; UV (EtOH) 203.5 nm (ε 39771), 224 nm (16262) and 252 nm (354).

1,5-Bis(2-bromophenyl)pentan-3-one (163) from 1,5-bis(2-bromophenyl)penta-1,4-dien-3-one (141)

The method reported by Guibe was followed.[126] Tributyltin hydride (0.7 ml, 2.5 mmol) was added dropwise over a period of a few minutes and at RT to a stirred deaerated solution of 1,5-bis(2-bromophenyl)-pentan-3-one (141) (0.5 g, 1.27 mmol; prepared as described on p. 158), acetic acid (0.15 ml, 2.7 mmol) and $Pd(PPh_3)_4$ (30 mg, 0.025 mmol) in benzene (3 ml). After 40 min, the reaction mixture was purified on a column of SiO_2. Fractions eluted with 10% ether-PE (Rf=0.18) on evaporation afforded 1,5-bis(2-bromophenyl)pentan-3-one (163) as colourless needles (0.32 g, 63.8%), m.p. 79-79.5°C. (Found: C, 51.4; H, 4.2. $C_{17}H_{16}Br_2O$ requires C, 51.5; H, 4.0%); m/z 397 {$(M+1)^+$, 36}, 396 (M^+, 5), 395 {$(M-1)^+$, 21}, 316 {$(M-Br)^+$, 87}, 315 {$(M-HBr)^+$, 100}, 183 {$(C_8H_7Br)^+$, 25}, 169 {$(C_7H_5Br)^+$, 56} and 91 {$(C_7H_7)^+$, 33}; νmax (nujol) 3060, 1710 (νC=O), 1565, 1290, 1120, 1090, 1020 and 750 cm^{-1};

$\delta(CDCl_3)$ 2.50-3.20 (8H, m), 6.90-7.30 (6H, m) and 7.50 (2H, d, J 6.65 Hz). If the reaction mixture was worked up after 10 min, 1,5-bis(2-bromophenyl)-1-penten-3-one (162) was detected; TLC {SiO_2, PE/Et_2O (9:1)}Rf 0.1; $\delta(CDCl_3)$ 3.05 (4H, m), 6.55 (1H, d, J 16.7 Hz), 6.90-7.60 (8H, m) and 7.90 (1H, d, J 16.7 Hz).

1,5-Bis(2-iodophenyl)-penta-1,4-dien-3-one (161)

This was obtained in a way similar to that reported for dibenzalacetone[158] but using 2-iodobenzaldehyde. After 2 h stirring at 20°C, the yellow solid was filtered and recrystallized from ethyl acetate to give 1,5-bis(2-iodophenyl)penta-1,4-dien-3-one (161) (75%) as yellow prisms, m.p. 131-2°C (Found: C, 42.1; H, 2.6. $C_{17}H_{12}I_2O$ requires C, 42.0; H, 2.5%); m/z 359 {$(M-I)^+$, 7}, 257 {$(C_9H_6IO)^+$, 1} and 232 {$(M-21)^+$, 100}; νmax (nujol) 1700, 1645, 1685, 1190, 1010, 975, 960, 760, 750 and 730 cm^{-1}; $\delta(CDCl_3)$ 6.95-8.05 (8H, m), 7.20 (2H, d, J 16.7 Hz) and 7.85 (2H, d, J 16.7 Hz); UV (EtOH) 195 nm (ε 16327), 235 nm (5442) and 313 nm (11338).

Attempted synthesis of 1,5-bis(2-iodophenyl)pentan-3-one (148) from 1,5-bis(2-iodophenyl)penta-1,4-dien-3-one (161)

The method reported by Guibe was followed.[126] Tributyltin hydride (0.66 ml, 2.4 mmol) was added dropwise over a period of a few minutes and at RT to a stirred deaerated solution of 1,5-bis(2-iodophenyl)-penta-1,4-dien-3-one (0.5 g, 1 mmol), acetic acid (0.12 ml, 2.1 mmol) and $Pd(PPh_3)_4$ (10 mg, 0.02 mmol) in benzene (3 ml). After 20 min, the reaction mixture was purified on a column of SiO_2. Fractions

eluted with 10% Et_2O-PE on evaporation afforded a viscous yellow oil (0.21 g) with the following physical properties: TLC {SiO_2, PE/Et_2O (9:1)}Rf 0.32; m/z 364 (2), 363 (8), 237 (28), 133 (31), 105 (67) and 91 (100); νmax (neat) 3060, 3020, 2950, 2920, 2880, 2840, 1710 (νC=O), 1600, 1580, 1560, 1490, 1460, 1450, 1010, 750 and 700 cm^{-1}; δ($CDCl_3$) 2.50-3.10 (8H, m), 6.70-7.40 (8H, m) and 7.75 (1H, d, J 7.9 Hz). All the data suggested that the product isolated was 1-(2-iodophenyl)-5-phenylpentan-3-one (164). By using an equimolar amount of tributyltin hydride and 1,5-bis(2-iodophenyl)penta-1,4-dien-3-one, a roughly 1:1 mixture (from ^1H NMR) of 1,5-bis(2-iodophenyl)pentan-3-one (148) and 1,5-bis(2-iodophenyl)-1-penten-3-one (165) was obtained.

1,5-Bis{(2-trimethylsilyl)ethynylphenyl}penta-1,4-dien-3-one (142) 1) via 1,5-Bis(2-iodophenyl)penta-1,4-dien-3-one (161)

Into a 3-necked flask, equipped with a N_2 inlet, a dry-cold condenser and a stopper, a mixture of 1,5-bis(2-iodophenyl)penta-1,4-dien-3-one (161) (30 g, 62 mmol), $Pd(PPh_3)_4$ (0.5 g), copper(I) iodide (36 mg), triethylamine (250 ml) and xylene (200 ml, sodium dried) was placed. After deaerating for 5 min, ethynyltrimethylsilane (186 mmol, as a THF/hexane solution, prepared as described previously) was added. The mixture was warmed to Ca. 85°C slowly on an oil bath and maintained at that temperature for 11 h. After cooling, the mixture was filtered. The filtrate was concentrated, mixed with ether (200 ml), and washed successively with 5% HCl, saturated $NaHCO_3$ and H_2O (200 ml each). The ethereal phase was dried ($MgSO_4$), concentrated and filtered through a SiO_2 column (5x8 cm) using 30%

Et_2O/PE. The filtrate, after evaporation, was diluted with an equal volume of PE (40-60°C) and cooled at -78°C to precipitate 16.1 g of a crystalline solid. Recrystallization from PE gave 1,5-bis{2-(trimethylsilyl)ethynylphenyl}penta-1,4-dien-3-one (142) (16.7 g, 63.0%) as bright yellow prisms, m.p. 102-3°C (Found: C, 76.0; H, 7.1. $C_{27}H_{30}Si_2O$ requires C, 76.1; H, 7.0%); TLC {(SiO_2, Et_2O-PE (3:7)} Rf 0.5; m/z 426 (M^+, 4), 411 {$(M-CH_3)^+$, 3}, 227 {$(C_{14}H_{15}SiO)^+$, 7} and 73 {$(Me_3Si)^+$, 100}; νmax (nujol) 2160, 2070, 1660, 1620, 1600, 1590, 1275, 1250, 1185, 1090, 982, 980, 970, 780 and 750 cm^{-1}; δ($CDCl_3$) 0.30 (18H, s), 7.15 (2H, d, J 16.7 Hz), 7.45 (8H, m) and 8.27 (2H, d, J 16.7 Hz); UV (EtOH) 225 nm (ε 31030), 251 nm (29638) and 324.5 nm (19593).

2) via 1,5-Bis(2-ethynylphenyl)penta-1,4-dien-3-one (139)

A recently reported procedure[162] was adopted. 1,5-Bis(2-ethynylphenyl)penta-1,4-dien-3-one (139) (0.5 g, 1.7 mmol) and DBU (0.65 g, 4.26 mmol) were successively added to a stirred suspension of silver nitrate (30 mg, 0.177 mmol) in CH_2Cl_2 (2 ml). The mixture was heated at 40°C and chlorotrimethylsilane (0.46 g, 4.26 mmol) was added to this. After stirring for 30 h at the same temperature, the mixture was cooled and Ca. 2g SiO_2 was added. After evaporation to dryness, the residue was purified on a SiO_2 column. Elution with 30% Et_2O/PE afforded 1,5-bis{2-(trimethylsilyl)ethynylphenyl}penta-1,4-dien-3-one (142) (297 mg, 39.3%), having similar physical and spectroscopic data as that prepared above.

Reaction between 2-(trimethylsilyl)ethynylbenzaldehyde (137), acetone-1,3-bis(triphenylphosphonium) chloride and DBU

A mixture of acetone 1,3-bis(triphenylphosphonium) chloride[98a] (1.62 g, 2.49 mmol), DBU (790 mg, 4.95 mmol) in DMSO (25 ml, freshly distilled from CaH_2) was stirred, under N_2, at RT for 1 h. A solution of 2-(trimethylsilyl)ethynylbenzaldehyde (137) (1 g, 4.95 mmol) in DMSO (2 ml) was added and stirring continued at Ca. 40°C for 12 h. Pouring into water, extraction (CH_2Cl_2), washing of the extracts, drying and evaporation afforded a yellow oil shown by ^1H NMR to be a mixture of 1,5-bis{2-(trimethylsilyl)ethynylphenyl}penta-1,4-dien-3-one (142), 4-{2-(trimethylsilyl)ethynylphenyl}-but-3-ene-2-one, and their corresponding desilyated analogues. Reaction at 20°C or 85°C and using THF for 6 h to 2 days led to similar results.

1,5-Bis{2-(trimethylsilyl)ethynylphenyl}penta-3-one (166) and 1,5-bis(2-ethynylphenyl)pentan-3-one (167)

1) via 1,5-bis(2-iodophenyl)pentan-3-one (148)

A deaerated solution of 1,5-bis(2-iodophenyl)pentan-3-one (19.6 g, 40 mmol), copper(I)iodide (36 mg), and $Pd(PPh_3)_4$ (0.5 g) in anhydrous triethylamine (300 ml) was treated with ethynyltrimethylsilane (11.76 g, 0.12 mol) under nitrogen. The mixture was rapidly heated to Ca. 90°C and maintained at that temperature for 16 h. After cooling, the mixture was filtered. The dark brown filtrate was concentrated, washed successively with 10% HCl, saturated $NaHCO_3$, H_2O (200 ml each) and dried. The residue after solvent removal was chromatographed on a column of SiO_2. Fractions eluted with 10% Et_2O/PE on evaporation afforded 1,5-bis{2-(trimethylsilyl)ethynylphenyl}pentan-3-one (166)

(9.97 g, 58%), which was used without further purification. TLC {SiO_2, PE/Et_2O (9:1} Rf 0.34; m/z 430(M^+, 2), 357 {$(M-SiMe_3)^+$, 3}, 284 {$(M-2SiMe_3)^+$, 7}, 128 {$(C_{10}H_8)^+$, 2} and 73 {$(SiMe_3)^+$, 100}; νmax (neat) 3060, 2960, 2900, 2860, 2150, 2110 (νC≡C), 1720 (νC=O), 1600, 1480, 1450, 1410, 1250, 1070, 1040, 850, 750 and 700 cm^{-1}; δ($CDCl_3$) 0.23 (18H, s), 2.50-3.20 (8H, m), 7.00-7.50 (8H, m).

The above product was treated with potassium fluoride dihydrate (5.8 g, 62 mmol) in DMF (60 ml) under nitrogen at RT for 1 h and poured into water (100 ml). Extraction (CH_2Cl_2), washing of the extracts (H_2O), drying and evaporation afforded a viscous oil which was purified on a column of SiO_2. Fractions eluted with 20% Et_2O/PE on evaporation afforded the desired 1,5-bis(2-ethynylphenyl)pentan-3-one (167) as a light brown oil (88-92%), TLC {SiO_2, PE/Et_2O (7:3)} Rf 0.52; m/z 294 (M^+, 1), 269 {$M-C_2H)^+$, 7}, 129 {$(C_{10}H_9)^+$, 70} and 115 {$(C_9H_7)^+$, 100}; νmax (neat) 3300 (νC≡H), 3060, 2100 (νC≡C), 1710 (νC=O), 1600, 1485, 1450, 1370, 1080 and 760 cm^{-1}; δ($CDCl_3$) 2.50-3.15 (8H, m), 3.15 (2H, s) and 6.95-7.50 (8H, m). 2,4-dinitrophenylhydrazone: orange prisms, m.p. 114-5°C (acetone) (Found: C, 57.3; H, 4.3; N, 10.1. $C_{27}H_{22}N_4O_4.H_2SO_4$ requires C, 57.4; H, 4.3; N, 9.9%).

2) via 1,5-Bis{2-(trimethylsilyl)ethynylphenyl}penta-1,4-dien-3-one (142)

A literature report[126] was modified as noted. Tributyltin hydride (19.7 ml, 73.2 mmol) was added dropwise over a period of 10 min and at RT to a stirred deaerated solution of 1,5-bis{2-(trimethylsilyl)ethynylphenyl}-penta-1,4-dien-3-one (142) (13 g, 30.5 mmol), acetic acid (3.67 ml, 64 mmol) and $Pd(PPh_3)_4$ (0.7 g, 0.6 mmol) in benzene (120 ml). After 20 min, the solvent was removed and the residue purified on a column

of Al_2O_3 (grade I). Fractions eluted with 40% Et_2O/PE on evaporation afforded 1,5-bis{2-(trimethylsilyl)ethynylphenyl}pentan-3-one (166) which, when desilylated with potassium fluoride in a manner described earlier, gave 1,5-bis(2-ethynylphenyl)pentan-3-one (167) (6.1 g, 70%).

When the reduction was carried out with equi-molar amounts of tributyltin hydride and 1,5-bis{2-(trimethylsilyl)ethynylphenyl}penta-1,4-dien-3-one (142), 1,5-bis{2-(trimethylsilyl)ethynylphenyl}-1-penten-3-one (170) (85%) was obtained as colourless prisms; m.p. 72-3°C (PE) (Found: C, 75.7; H, 7.4. $C_{27}H_{32}OSi_2$ requires C, 75.7; H, 7.5%); TLC {SiO_2, PE/Et_2O (95:5)} Rf 0.15; m/z 428 (M^+, 1), 413 {$(M-CH_3)^+$, 7}, 355 {$(M-SiMe_3)^+$, 15}, 227 {$(C_{14}H_{15}SiO)^+$, 5} and 73 {$(SiMe_3)^+$, 100}; νmax (nujol) 2160, 1665, 1620, 1590, 1300, 1250, 1172, 975, 870, 840, 760 and 750 cm^{-1}; δ($CDCl_3$) 0.2 (18H, s), 3.10 (4H, m), 6.72 (1H, d, J 16.7 Hz), 7.05-7.70 (8H, m) and 8.10 (1H, d, J 16.7 Hz); UV (EtOH) 203 nm (ε 8667), 242.5 nm (5465), 249 nm (13936) and 292 nm (5438).

Further reduction of 1,5-bis{2-(trimethylsilyl)ethynylphenyl}-1-penten-3-one (170) with butyltin hydride (1.2 equivalent), in a manner described earlier, gave 1,5-bis{2-(trimethylsilyl)ethynylphenyl}pentan-3-one (166) in 80% yield.

4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-one (171)

A literature procedure[96] was modified as noted. A solution of 1,5-bis(2-ethynylphenyl)pentan-3-one (167) (1 g, 3.49 mmol) in pyridine (freshly distilled from calcium hydride) and dry ether (3:1; 70 ml) was added dropwise during 3 h to a stirred suspension of anhydrous copper acetate[74] (4.4 g, 24 mmol) in pyridine and dry ether (3:1; 170 ml) at 50°C (oil bath). The solution was stirred at 50°C for

a further ½ h and cooled. The residue after solvent removal was chromatographed on a column of SiO_2 (mesh 60 to 120). Elution with 40% Et_2O-PE on evaporation gave a yellow mass. Recrystallization from ether gave 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-one (171) (761 mg, 76.8%) as yellow rods, m.p. 175-6°C (decomp.) (Found: C, 89.0; H, 5.2. $C_{21}H_{16}O$ requires C, 88.7; H, 5.6%); TLC {SiO_2, Et_2O/PE (2:8)} Rf 0.22; m/z 284 (M^+, 100), 255 {$(M-CHO)^+$, 30} and 128 {$(C_{10}H_8)^+$, 24}; νmax (nujol) 2200 (νC≡C), 1695 (νC=O), 1160, 1100, 1035, 950, 760 and 750 cm^{-1}; δ(300 MHz, $CDCl_3$) 2.92 (4H, m), 3.08 (4H, m) and 7.17-7.38 (8H, m); ^{13}C NMR (75.5 MHz), δ 32.3 (t), 42.3 (t), 80.8 (s), 88.9 (s), 122.3 (s), 126.7 (d), 129.7, 129.8 ($3sp^2$-H), 145.9 (s) and 211.8 (s); UV (EtOH) 200 nm (ε 22458), 219.5 nm (15701), 277 nm (4041), 288 nm (6426), 295.5 nm (8281), 309.5 nm (9871), 317 nm (11593), 332 nm (9076), 339 nm (9208); addition of 1 drop of $HClO_4$ caused the whole spectrum to shift by 2 nm.

Longer reaction time and wet solvents caused a dramatic decrease in yield.

Reaction between 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-one (171) and sodium sulphide

A mixture of 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-one (171) (200 mg, 0.7 mmol), sodium sulphide nonahydrate (680 mg, 2.8 mmol) in methanol (10 ml) was refluxed for 5½ h. Most of the solvent was evaporated and water (20 ml) was added. Extraction (EtOAc), washing of the extracts (H_2O), drying and evaporation afforded an oil, which was carefully chromatographed on a column of SiO_2 using CH_2Cl_2. The yellow spot (Rf=0.23) was collected and after recrystallization from

CH_2Cl_2-PE (CO_2-acetone bath) afforded 2,3,6,7-dibenzo-1,4,5,8-tetrahydrofluoren-9-one (173) (25 mg, 12.6%) as off-white needles, m.p. 215-6°C (decomp.) (Found: C, 88.5; H, 5.8. $C_{21}H_{16}O$ requires C, 88.7; H, 5.6%); m/z 284 (M^+, 72), 256 {$(M-CO)^+$, 16}, 156 {$(M-C_{10}H_8)^+$, 100} and {$(C_{10}H_8)^+$, 100}; νmax (nujol) 1602, 1585, 1570, 770 and 750 cm^{-1}; δ($CDCl_3$) 3.11 (4H, b.s), 3.83 (4H, b.s) and 7.00-7.70 (8H, m); UV (EtOH) 195 nm (ε 25806), 233 nm (9319), 315 nm (7373) and 370 nm (17204).

4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-ol (179)

To 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-one (178) (343 mg, 1.2 mmol) in ethanol (25 ml) was added powdered sodium borohydride (0.182 g, 2.4 mmol). The reduction was complete after 10 min as shown by TLC (SiO_2; PE-ether 9:1). Most of the solvent was removed and water (30 ml) was added. Extraction (CH_2Cl_2, 3x10 ml), drying and evaporation gave a white solid. Recrystallization from PE-$CHCl_3$ (dry ice cold bath) gave 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-ol (179) as colourless needles (0.321 g, 93.6%), m.p. 146-7°C (Found: C, 88.0; H, 6.6. $C_{21}H_{18}O$ requires C, 88.1; H, 6.3%); m/z 287 $(M+1)^+$, 36 , 286 (M^+, 100), 285 {$(M-1)^+$, 21}, 269 {$(M-OH)^+$, 77}, 141 {$(C_{11}H_9)^+$, 50}, 128 {$(C_{10}H_8)^+$, 50} and 115 {$(C_9H_7)^+$, 31}; νmax (nujol) 3360 (νO-H), 3060, 2200 (νC≡C), 1375, 1180, 1050, 950 and 750 cm^{-1}; δ ($CDCl_3$, 300 MHz); 1.58 (1H, d, exchanged with D_2O), 1.83 ($2H_1$, m), 217 ($2H_2$, m), 2.87 ($4H_3$, m), 4.07 (H_2, m) and 7.13-7.38 (8H, m).

1,2,8,9-dibenzo-5-hydroxy{9}(2,5)thiophenophane (180)

The procedure reported by Schulte et al[22] was followed. A mixture of 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-ol (179) (1 g, 3.5 mmol), sodium sulphide nonahydrate (3.36 g, 13.9 mmol) and methanol (60 ml) was refluxed for 17 h. Most of the solvent was removed and the residue taken up in H_2O. Extraction (EtOAc), washing (H_2O), drying and evaporation gave a brown viscous oil, which was chromatographed on a column of SiO_2. Fractions eluted with 30% EtOAc-PE on evaporation gave a yellow foam solid. Recrystallization from Et_2O-PE (CO_2-acetone bath) gave 1,2,8,9-dibenzo-5-hydroxy{9}(2,5)thiophenophane (180) (333 mg, 29.8%) as yellow prisms, m.p. 92-3°C (Found: C, 78.3; H, 5.9; S, 10.2. $C_{21}H_{20}OS$ requires C, 78.7; H, 6.2; S, 10.0%); m/z 321 {$(M+1)^+$, 85}, 320 (M^+, 100), 303 {$(M-OH)^+$, 57}, 269 {$(M-OH-H_2S)^+$, 25} and 115 {$(C_9H_7)^+$, 28}; νmax (nujol) 3340, 3080, 1620, 1595, 1370, 1365, 1050, 1035, 756 and 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ1.42 (1H, b, exchanged by D_2O), 1.58 ($H_{4e}+H_{6e}$, m), 1.82 ($H_{4a}+H_{6a}$, m), 2.60 ($H_3+H_3+H_7+H_7$, m), 3.78 (H_5, tt, $\underline{J}\ H_5H_{4a(6a)}$ 9 Hz, $\underline{J}\ H_5H_{4e(6e)}$ 2 Hz), 6.93 ($H_{13}+H_{14}$, s), 7.28 (6H, m) and 7.55 (2H, m), assignment of $H_{4a(6a)}$ and $H_{4e(6e)}$ was made possible by the addition of shift reagent, $Eu(fod)_3$; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.13 (Sp^3-C), 32.95 (Sp^3-C), 71.44 (Sp^3-C), 126.20, 126.90, 128.55, 128.89, 130.37 (Sp^2-C) and 134.17, 142.02, 142.93 (Sp-C); UV (EtOH) 196 nm (ε 25600), 277 nm (10467) and 332 nm (2439), UV (EtOH + $HClO_4$), 190.5 nm (ε 25608), 270 nm (9349) and 327.5 nm (1118).

Reaction between 1,2,8,9-dibenzo-5-hydroxy{9}(2,5)thiophenophane (180) and trifluoromethanesulfonic (triflic) anhydride

A literature procedure[166d] was adopted. To a 2-necked flame-dried flash, equipped with a N_2 inlet and a pressure equalizing funnel, triflic anydride (180 mg, 0.65 mmol) and CH_2Cl_2 (5 ml, distilled over P_2O_5) were placed. After cooling to -40°C, solid sodium carbonate (36 mg, 0.34 mmol; dried under vacuum at 200°C overnight) was added, followed by a solution of 1,2,8,9-dibenzo-5-hydroxy{9}(2,5)thiophenophane (180) (161 mg, 0.5 mmol) in CH_2Cl_2 (10 ml) over 20 min at the same temperature. After 2 h, the cooling bath was removed and after a further hour, the dark brown solution was poured into water. Extraction (CH_2Cl_2), washing of the extracts (H_2O), drying and evaporation afforded an oil, which was carefully chromatographed on a column of silica. Fractions eluted with 10% EtOAc-PE afforded 1,2,8,9-dibenzo-{9}(2,5)thiophenoph-4-ene (186) (60 mg, 48.5%) as an oil;† TLC {SiO_2, EtOAc/PE (4:6)} Rf 0.60; m/z 302 (M^+, 34), 269 {$(M-SH)^+$, 100} and 115 (30); νmax (neat) 3060, 3020, 2930, 2860, 1600, 1480, 1450, 1218, 1105, 975, 965, 955, 810, 760 and 750 cm^{-1}; δ(300 MHz, $CDCl_3$) 1.65 (H_6+$H_{6'}$, m), 2.92 (H_7+$H_{7'}$, m), 3.20 (H_3, d, J 15 Hz), 3.32 ($H_{3'}$, dd, J 15 Hz + 10 Hz); 4.92 (H_4+H_5, m), 6.84 (H_{13}, d, J 4.5 Hz), 6.95 (H_{14}, d, J 4.5 Hz) and 7.16-7.50 (8H, m). Decoupling H_3 and $H_{3'}$ (at δ 3.30), the group at 4.92 collapsed to a doublet (H_4, d, J 15 Hz) and two double doublet (H_5, JH_4H_5 15 Hz, JH_5H_6, 3 Hz and JH_5H_6 10 Hz). Fractions eluted with 40% EtOAc-PE recovered (49) (30 mg, 18.6% recovery).

† attempted distillation under high vacuum led to extensive decomposition.

1,2,8,9-dibenzo-5-iodo{9}(2,5)thiophenophane (191)

A literature procedure[168] was followed. A solution of iodotrimethylsilane (223 mg, 1.12 mmol) in CH_2Cl_2 (1 ml) was added to a solution of 1,2,8,9-dibenzo-5-hydroxy{9}(2,5)thiophenophane (180) in the same solvent (178.8 mg, 0.56 mmol), under N_2, at RT. After 2 h, the mixture was washed with aqueous sodium metabisulphite, water, dried and evaporated down. Careful chromatography on a column of SiO_2 using CH_2Cl_2 afforded 1,2,8,9-dibenzo-5-iodo{9}(2,5)-thiophenophane (191) 163.5 mg, 68%) as very pale yellow prisms, after recrystallization from PE (CO_2-acetone bath), m.p. 78-9°C†; TLC {SiO_2, EtOAc/PE (3:7)} Rf 0.73; m/z 430 (M^+, 11); 302 {$(M-HI)^+$, 100}, 269 {$(M-I-H_2S)^+$, 80}; 146 (46), 128 (56) and 115 (43); νmax (nujol) 3060, 1262, 1180, 1140, 1040, 1030, 895, 800, 760, 745 and 730 cm^{-1}; δ($CDCl_3$, 300 MHz), 2.00 (4H, m), 2.65 (4H, m), 4.44 (1H, m), 6.94 (2H, s) and 7.00-7.62 (8H, m).

Reaction between 1,2,8,9-dibenzo-5-iodo{9}(2,5)thiophenophane (191) and silver tetrafluoroborate

A solution of 1,2,8,9-dibenzo-5-iodo{9}(2,5)thiophenophane (191) (48 mg, 0.11 mmol) in 1,2-dichloroethane (2 ml, distilled over P_2O_5) was added to a suspension of silver tetrafluoroborate (21.7 mg, 0.22 mmol) in the same solvent (2 ml). After 15 min, a yellow solid began to precipitate out. After 75 min, the mixture was filtered through celite and evaporated down under reduced pressure at RT (Ca. 20°C) afforded a brown oil (26.8 mg), which was shown to be just 1,2,8,9-dibenzo-{9}(2,5)thiophenoph-4-ene (186) by ^1H NMR ($CDCl_3$, 300 MHz).

† Last trace of PE could not be removed under high vacuum and microanalysis gave a high carbon and hydrogen ratio. (Found C, 60.1; H, 5.1. $C_{21}H_{19}IS$ requires C, 58.6; H, 4.4%).

1,2,8,9-Dibenzo-5-keto{9}(2,5)thiophenophane (172)

Jones reagent (1.3 mmol; 0.5 ml of a 2.67 M solution, prepared from 2.67 g CrO_3, 2.3 ml conc. H_2SO_4 and 7.7 ml H_2O) was added to a stirred solution of 1,2,8,9-dibenzo-5-hydroxy{9}(2,5)thiophenophane (150 mg, 0.47 mmol) in acetone (6 ml) at RT. After 1 h, saturated sodium metabisulphite solution (5 ml) was added. Extraction (CH_2Cl_2), washing (H_2O), drying and evaporation afforded a yellow oil, which in CH_2Cl_2 was filtered through a small column of SiO_2. After evaporation the residue was recrystallized from CH_2Cl_2-PE (CO_2-acetone bath) to give 1,2,8,9-dibenzo-5-keto{9}(2,5)thiophenophane (172) (186.3 mg, 61.7%) as colourless prisms, m.p. 132-3°C (Found: C, 78.7; H, 5.7; S, 10.3. $C_{21}H_{18}OS$ requires C, 79.2; H, 5.7; S, 10.1%); m/z 318 (M^+, 100), 290 {$(M-CO)^+$, 3}, 285{$(M-SH)^+$, 14} and 228 {$(M-C_3H_6OS)^+$, 9}; νmax (nujol) 3058, 1715, 1415, 1380, 1080, 810, 780, 760, 755 and 745 cm^{-1}; δ($CDCl_3$) 2.48 (4H, m), 2.92 (4H, m), 6.86 (2H, s) and 7.30 (8H, m); UV (EtOH) 206 nm (ε 55247), 215 nm (33933), 293 nm (13601), 299 nm (16266), 313 nm (18509), 320 nm (21314), 334 nm (16546) and 342 nm (16406); UV (EtOH + 1 drop $HClO_4$) 215.5 nm (ε 54406), 224 nm (32812), 292 nm (13181), 298 nm (15985), 311.5 nm (18229), 318.5 nm (21033), 333 nm (15985) and 341 nm (15985).

1,2,8,9-Dibenzo-5-keto{9}(2,5)thiophenophane-4-tosylhydrazone (192)

A mixture of 1,2,8,9-dibenzo-5-keto{9}(2,5)thiophenophane (172) (174 mg, 0.55 mmol), 4-toluenesulphonylhydrazine (102 mg, 0.6 mmol), conc. HCl (4 drops) and 95% ethanol (15 ml) was refluxed for ½ h. Filtration and thorough washing with PE gave 1,2,8,9-dibenzo-5-keto{9}(2,5)thiophenophane-4-tosylhydrazone (192) (228 mg, 82.6%) as shiny,

colourless prisms, m.p. 231-2°C (Found: C, 69.2; H, 5.3; N, 5.9. $C_{28}H_{26}N_2O_2S_2$ requires C, 69.1; H, 5.4; N, 5.8%); m/z 487 $\{(M+1)^+$, 36}, 333{$(M-CH_3C_6H_4SO_2)^+$, 56}, 318 {$(M-CH_3C_6H_4-SO_2NH)^+$, 26} and 303 {$(M-CH_3C_6H_4SO_2NHN)^+$, 100}; νmax (nujol) 3200, 3060, 1598, 1490, 1375, 1340, 1170, 1150, 1085, 1030, 810, 760, 755, 690 and 670 cm^{-1}; δ(DMSO-d_6) 1.90-2.95 (8H, m), 2.35 (3H, s); 3.12 (1H, s), 6.93 (2H, s), 7.35 (10H, m) and 7.78 (2H, d, J 8 Hz).

Reaction between 1,2,8,9-dibenzo-5-keto{9}(2,5)thiophenophane tosylhydrazone (192) and lithium diisopropylamide

A solution of 1,2,8,9-dibenzo-5-keto{9}(2,5)thiophenophane tosylhydrazone (192) (200 mg, 0.41 mmol) in THF (15 ml) was added to LDA (4.1 mmol, prepared as described previously) at -78°C over 5 min. A light yellow colour developed. After 15 min at -78°C, the temperature was allowed to warm up slowly to 0°C and maintained there for 2 h. A dark brown colour developed gradually. The mixture was poured into saturated ammonium chloride (50 ml) and extracted with CH_2Cl_2. Washing of the extracts (H_2O), drying and evaporation gave a brown oil which was flash chromatographed on SiO_2 using EtOAc-PE (3:7). A mixture of alkenes (186), (193) and (194) was obtained {Rf 0.64; SiO_2; Et_2O-PE(1:9)} as a light brown oil (68 mg, 54.8%); m/z 302 (M^+, 55), 269 {$(M-SH)^+$, 100}, 268 {$(M-H_2S)^+$, 21}, 253 (18), 239 (15), 215 (13), 141 (28), 128 (27) and 115 (41); νmax (neat) 3060, 3000, 2960, 2930, 2860, 1470, 1455, 1440, 1380, 1260, 1100, 1040, 975, 805, 760 and 710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) was summarized below:

	(186)	(193)	(194)
H13/H14	6.84, d, $\underline{J}H_{13}H_{14}$ 3.75 Hz	6.89, d, $\underline{J}H_{13}H_{14}$ 3.75 Hz	7.00, d, $\underline{J}H_{13}H_{14}$ 3.75 Hz
H13/H14	6.95, d, $\underline{J}H_{13}H_{14}$ 3.75 Hz	6.99, d, $\underline{J}H_{13}H_{14}$ 3.75 Hz	7.06, d, $\underline{J}H_{13}H_{14}$ 3.75 Hz
H_3'	3.32,dd, $\underline{J}H_3'H_3$ 15 Hz	3.20, m	-
	and $\underline{J}H_3H_4$ 10 Hz		
H3	3.20, d, $\underline{J}H_3H_3'$ 15 Hz	3.20, m	6.35, d, $\underline{J}H_3H_4$ 16.3 Hz
H4	4.92, m	5.22, m	5.22, m
H5	4.92, m	5.35, m	1.82, m
H_6+H_6'	1.65, m	1.50, m	1.50, m
H_7+H_7'	2.92, m	2.75, m	2.75, m
aromatic	← 7.16 - 7.50, m →		

decoupling at 3.20 ($H_3'H_3'$)

H4	d, $\underline{J}H_4H_5$ 15 Hz	d, $\underline{J}H_4H_5$ 10 Hz
H5	dd, $\underline{J}H_4H_5$=$\underline{J}H_5H_6$ 10 Hz	dt, $\underline{J}H_4H_5$ 10 Hz, $\underline{J}H_5H_6$
	and $\underline{J}H_5H_6'$ 3 Hz	=$\underline{J}H_5H_6'$ 7.5 Hz

Attempted dehydrogenation of 1,2,8,9-dibenzo-5-keto{9}(2,5)thiophenophane (172)

1) using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

A mixture of 1,2,8,9-dibenzo-5-keto{9}(2,5)thiophenophane (172) (91.7 mg, 0.29 mmol) and DDQ (327 mg, 1.44 mmol) was refluxed in dioxane (10 m) for 23 h. The solvent was removed and the residue was chromatographed through a column of Al_2O_3 (grade I). Fractions eluted with 50% EtOAc-PE afforded yellow crystals (27.8 mg, 34%), which were shown to be 4,5,10,11-dibenzo-cyclotrideca-6,8-diyn-1-one (171) by ^1H NMR, MS and m.p.

2) using tetrachloro-o-benzoquinone (o-chloranil)

A literature procedure[172] was followed. A mixture of (172) (50 mg, 0.16 mmol) and o-chloranil (120 mg, 0.47 mmol) were refluxed in ether for 3 h and worked up as above afforded (171) (30 mg, 67%) as shown by ^1H NMR, MS and m.p.

3) using benzeneseleninic anhydride

A literature report was followed.[174] A mixture of (172) (55.7 mg, 1.77 mmol) and benzeneseleninic anhydride (130 mg, 0.36 mmol) in chlorobenzene (3 ml, distilled over P_2O_5) was refluxed for 1 h. Working up as reported[174] gave diphenyl diselenide (60 mg), m.p. 61-2°C (lit.,[174] 61-3°C) as the only isolable product.

4) using palladium(II)chloride

Following a literature procedure,[173] a solution of palladium(II) chloride (288 mg, 1.62 mmol) in conc. hydrochloric acid (0.5 ml) was

added to a suspension of (147) (171.7 mg, 0.54 mmol) in tert-butanol (15 ml). After maintaining at Ca. 80°C for 2 h, the reaction mixture was worked up as reported,[173] and only (147) was recovered.

Bromination and dehydrobromination of 1,2,8,9-dibenzo-5-keto{9}(2,5)-thiophenophane (172)

A mixture of 1,2,8,9-dibenzo-5-keto{9}(2,5)-thiophenophane (172) (50 mg, 0.16 mmol), bromine (100 mg, 0.63 mmol) and acetic acid (3 ml) was stirred at RT for 3½ h. The mixture was poured into saturated aqueous sodium bicarbonate and extracted with CH_2Cl_2. Washing of the extracts (H_2O), drying and evaporation gave the crude bromo-derivative as a yellow oil (62.8 mg); m/z 554 (M^+, 12), 475 {$(M-Br)^+$, 16}, 395 {$(M-2Br)^+$, 19}, 315{$(M-3Br)^+$, 28}, 285 (33), 282 {$(M-SH-3Br)^+$, 31}, 271 (25), 251 (100), 239 (36) and 226 (23). The crude bromo-derivative was stirred with DBN (5 equivalents) at RT for 60 h and diluted with CH_2Cl_2. Washing (1M HCl, H_2O), drying and evaporation afforded a black residue which was chromatographed on SiO_2 with Et_2O-PE (1:1). A yellow oil (7 mg) was obtained. m^+/z 438 (3), 436 (2), 363 (16), 362 (72), 360 (100), 359 (31), 358 (33), 281 (52), 280 (23), 252 (59), and 250 (48). ^1H NMR ($CDCl_3$, 300 MHz), 7.00-7.78 (m), 7.96 (d, J 7.5 Hz), 8.05 (t, J 7.5 Hz), 8.32 (d, J 7.5 Hz), 8.36 (s), 8.39 (s), 8.46 (s), 8.51 (s) and 8.80 (s). Unambiguous assignment of the structure was not possible.

β-chlorovinyl phenyl ketone (203)

The procedure of Price and Pappalardo[175] was modified as noted. No cooling was required during the addition of the benzoyl chloride. After the addition, the mixture was refluxed on a water bath for 5 h before working up, and distillation gave β-chlorovinyl phenyl ketone (54) as a pale yellow oil (45%), b.p. 136-8°C/22 torr (lit.,[176] 134-6°C/17 torr); TLC {SiO_2, $CHCl_3$/PE (1:1)} Rf 0.27; νmax (neat) 3080, 1650 (νC=O), 1600, 1580, 1450, 1330, 1260, 1200, 1010, 935, 890, 770, 690 and 600 cm^{-1}; δ($CDCl_3$) 7.25 (5H, m) and 7.90 (2H, m).

1-Chloro-3-phenyl-1-penten-4-yn-3-ol (204)

A solution of β-chlorovinyl phenyl ketone (42.65 g, 0.26 mol) in THF (50 ml) was added dropwise, with stirring, under nitrogen to a solution of lithium acetylide (0.33 mol) in THF[119] at -78°C. Stirring was continued overnight while the cooling bath was allowed to warm slowly to RT. With cooling, a saturated aqueous NH_4Cl (200 ml) was added. Extraction (Et_2O) and working up gave a viscous brown oil, which was distilled (CARE: explosive decomposition occurred towards the end) to give 1-chloro-3-phenyl-1-penten-4-yn-3-ol (55) as a colourless oil (20.0 g, 40%), b.p. 133-6°C/0.8 torr (lit., 118-9°C/0.35 torr)[176]; νmax (neat) 3460 (νO-H), 3300 (νC≡H), 3060, 3020, 2110 (νC≡C), 1670, 1635, 1600, 1500, 1490, 1450, 1030, 940, 820 and 765 cm^{-1}; δ($CDCl_3$) 2.74 (1H, s), 3.48 (1H, s, exchanged with D_2O), 6.07 (1H, d, J 13.3 Hz), 6.57 (1H, d, J 13.3 Hz) and 7.45 (5H, m).

3-Phenyl-2-penten-4-ynal (205)

The compound was prepared as reported[176] and isolated (54%) as yellow prisms (CCl_4/cyclohexane, 2:1), m.p. 59.5-60°C (lit., Ca. 65°C)[176]; νmax (nujol) 3200 (νC≡H), 2840, 2738, 2080 (νC≡C), 1660 (νC=O), 1640, 1590, 1580, 1560, 1450, 1380, 1325, 1230, 1150, 845, 760, 730, 700 and 685 cm^{-1}; δ($CDCl_3$) 3.75 (1H, s), 6.80 (1H, d, J 7.8 Hz), 7.40 (3H, m), 7.75 (2H, m) and 10.28 (1H, d, J 7.8 Hz).

3-Bromo-3-phenyl-propen-1-al (208)

The compound was prepared as reported[178] and isolated in 23% yield (c.f. lit.,[178] 45%) as a yellow oil, b.p. 92°C/0.3 mm (lit.,[178] 106-7°C/0.7 mm); δ($CDCl_3$) 6.70 (1H, d, J 6.5 Hz), 7.40 (3H, m), 7.60 (2H, m) and 10.02 (1H, d, J 6.5 Hz).

3-Phenyl-5-trimethylsilyl-pent-2-ene-4-yn-1-al (209) and 3-phenyl-2-penten-4-ynal (205)

The following procedure was modified from that given by Lau et al[76] and Sonogashira et al.[134] A deaerated solution of 3-bromo-3-phenyl-propen-1-al (18.6 g, 88 mmol), copper(I)iodide (18 mg) and tetrakis (triphenylphosphine)palladium(0) (0.2 g) in anhydrous triethylamine (200 ml) was treated with ethynyltrimethylsilane (132 mmol, in THF/hexane, prepared as described earlier) under nitrogen. The mixture was rapidly heated to Ca. 90°C and maintained at that temperature for 18 h. After working up as usual[76] the brown oil was distilled to give 3-phenyl-5-trimethylsilyl-pent-2-ene-4-yn-1-al (209) as a yellow oil (11.5 g, 57.3%), b.p. 130-4°C/1 torr; m/z 228 (M^+, 1), 213 {$(M-CH_3)^+$, 16},

199{$(M-CH_2O)^+$, 6}, and 73 {$(Me_3Si)^+$, 100}; νmax (neat) 3060, 2960, 2930, 2900, 2830, 2740, 2140 (νC≡C), 1670 (νC=O), 1580, 1560, 1495, 1450, 1325, 1250, 1135, 1000, 990, 850, 760 and 685 cm^{-1}; δ($CDCl_3$) 0.20 (9H, s), 6.55 (1H, d, J 7.8 Hz), 7.25 (3H, m), 7.55 (2H, m) and 10.15 (1H, d, J 7.8 Hz). The compound was very hygroscopic and hydrolysed to the corresponding 3-phenyl-2-penten-4-ynal on exposure to air, as evident from the IR spectrum and the microanalytical data: νmax (neat) 3300 (νC≡H) and 2260 (νC≡C), (Found: C, 74.6; H, 7.4. $C_{14}H_{16}SiO \cdot 1/10\ C_{11}H_8O$ requires C, 74.4; H, 6.9%).

The above product (11.5 g, 50 mmol) and potassium fluoride dihydrate (10.9 g, 116 mmol) in DMF (60 ml) was stirred under N_2 at RT overnight and poured into water. Extraction (CH_2Cl_2), washing, drying and evaporation gave a brown mass. Recrystallization from CCl_4/cyclohexane (2:1) gave 3-phenyl-2-penten-4-ynal (205) as yellow prisms (7.02 g, 90%), having similar physical and spectroscopic properties as described earlier (p. 186).

6-Phenyl-3,5-octadien-7-yn-2-one (206)

The following procedure was modified from that given by Nakagawa et al.[176] A solution of NaOH (0.78 g, 1.95 mmol) in ethanol (4.4 ml) and water (4.4 ml) was added during 20 min to an ice-cooled solution of 3-phenyl-2-penten-4-ynal (3.0 g, 19 mmol) in acetone (31 ml). After being stirred at the same temperature for 2 h, the reaction mixture was neutralized with 1M sulphuric acid and diluted with water (200 ml). The mixture was extracted with ether, and the extracts were washed with saturated $NaHCO_3$. The residue after solvent removal was chromatographed on a column of grade III alumina (5x4 cm). Fractions

eluted with 20% ether-PE on evaporation afforded the desired ketone (206) as yellow crystals (2.50 g, 67%), m.p. 69-72°C (lit.,[176] 70-72°C); TLC {SiO_2, $CHCl_3$} Rf 0.27; m/z 196 (M^+, 59), 195 {$(M-H)^+$, 21}, 181 {$(M-CH_3)^+$, 24}, 153 {$(M-MeCO)^+$, 100} and 127 {$(M-C_4H_5O)^+$, 14}; νmax (nujol) 3240 (νC≡H), 2080, 1700, 1680 (νC=O), 1650, 1585, 1495, 1445, 1360, 1280, 1250, 980, 910, 760, 730 and 690 cm^{-1}; δ($CDCl_3$, 90 MHz), 2.28 (3H, s), 3.65 (1H, s), 6.28 (H_1, d, J 16Hz), 7.01 (H_3, d, J 11 Hz), 7.40 (3H, m), 7.65 (2H, m) and 7.75 (H_2, dd, J 16 Hz, 11 Hz). An alternative procedure, adopted from Sondheimer et al,[96] gave only 35% yield.

3,11-Diphenyl-3,5,8,10-tridecatetraene-1,12-diyn-7-one (207)

The procedure adopted was similar to that reported by Sondheimer et al,[96] and the residue after solvent removal was chromatographed on a column of grade III Al_2O_3 (5x4 cm). Fractions eluted with 50% Et_2O-PE on evaporation yielded the desired ketone (207) (20%) as a yellow solid, m.p. 113-114°C ($CHCl_3$-hexane) (Found: C, 86.3; H, 5.0. $C_{25}H_{18}O \cdot 0.13\ CHCl_3$† requires C, 86.3; H, 5.2%); TLC {SiO_2, $CHCl_3$} 0.25; m/z 334 (M^+, 8), 181 {$(M-C_{12}H_9)^+$, 18} and 153 {$(M-C_{13}H_9O)^+$, 15}; νmax (CH_2Cl_2) 3300 (νC≡H), 2920, 2840, 2090 (νC≡C), 1660, 1640 (νC=O), 1600, 1590, 1580, 1570, 1550, 1345, 1080 and 985 cm^{-1}; δ($CDCl_3$) 3.66 (1H, s), 6.65 (H_1, d, J 15.3 Hz), 7.10 (H_3, d, J 11.3 Hz), 7.40 (3H, m), 7.70 (2H, m) and 7.98 (H_2, dd, J 15.3 Hz, 11.3 Hz); UV (EtOH) 193.5 nm (ε 22326), 246.5 nm (8546), 277 nm (10268), 389 nm (31600) and 396 (31335), UV (EtOH + 1 drop $HClO_4$) 195.5 (ε 22524), 248.5 nm (9142), 280 nm (10600), 403 nm (31491) and 410 nm (31219).

† could not be removed at 100°C under high vacuum.

5,10-Diphenyl-2,4,10,12-cyclotridecatetraene-6,8-diyn-1-one (201)

The procedure adopted was similar to that reported.[96] On evaporation of the ether extracts gave a residue which was recrystallized from $CHCl_3$/hexane to give the desired annulenone (201) (65%) as a deep red solid, m.p. 192-3°C (decomp.). (Found: C, 86.7; H, 4.6. $C_{25}H_{16}O$. 0.15 $CHCl_3$† requires C, 86.8; H, 4.6%); m/z 332 (m^+, 7), 303 {$(M-COH)^+$, 10}, 185 {$(M-C_{12}H_3)^+$, 100} and 157 (22); νmax (CH_2Cl_2) 2900, 2850, 2100, 2160 (νC≡C), 1650 (νC=O), 1620, 1600, 1100, 1000 and 972 cm^{-1}; δ($CDCl_3$) 6.10 (H_1, d, J 16.7 Hz), 6.90 (H_3, d, J 9.75 Hz), 7.35 (10H, m), and 9.84 (H_2, dd, J 16.7 Hz, 9.75 Hz); UV (EtOH) 195.5 nm (ε 22924), 237 nm (11462), 269 nm (9635) and 307 nm (7973); UV (EtOH + 1 drop $HClO_4$) 194.5 nm (ε 23664), 236.5 nm (11733) and 314 nm (7844). Both spectra showed tailing down to 700 nm.

Hydroboration of 2,5-Bis(1-hydroxy-1-phenyl-but-3-enyl)thiophene (212)

The procedure developed by Pelter[105a] was followed.

A solution of 2,5-bis(1-hydroxy-1-phenyl-but-3-enyl)thiophene (1 g, 2.67 mmol) in THF (10 ml) was added during 40 min to 2,3-dimethyl-2-butylborane (3.21 mmol; prepared as described on p.165) cooled to 0°C. After stirring at 0°C for 4 h, the solution was transferred, under nitrogen, to a flame-dried flask equipped with a magnetic stirrer and potassium cyanide (0.21 g, 3.21 mmol; oven-dried at 100°C/20 torr for 6 h before being used). After stirring at RT overnight, the cyanoborate solution was cooled to -78°C and trifluoroacetic anhydride (0.498 ml, 3.5 mmol) was added. The cooling

† could not be removed at 100°C under high vacuum.

bath was removed and after 2 h the mixture was oxidized (30% H_2O_2, 3.21 ml) and worked up as on p.165. The crude product, a yellow viscous oil, was chromatographed on a column of SiO_2. Fractions eluted with 70% $CHCl_3$-PE on evaporation afforded white crystals. Recrystallization from toluene-PE gave white needles (0.35 g), m.p. 162-3°C (Found: C, 76.3; H, 6.4; S, 8.9. $C_{24}H_{24}O_2S$ requires C, 76.7; H, 6.4; S, 8.5%); m/z 376 (16.7), 346 (3.3), 299 (73.3), 257 (6.7), 229 (76.6) and 105 (100); νmax (nujol) 3080, 3070, 3020, 1600, 1490, 1235, 1050, 820, 760 and 700 cm^{-1}; δ($CDCl_3$) 1.70-2.70 (8H, m), 4.0 (4H, m), 6.48 (2H, broad s) and 7.3 (10H, m). From all the data obtained, structure (214) was tentatively assigned. m/z 376 (M^+, 16.7), 346 {$(M-CH_2O)^+$, 3.3}, 299 {$(M-Ph)^+$, 73.3}, 257 {$(M-C_3H_6)^+$, 6.7}, 229 {$(M-C_{10}H_{13}O)^+$, 76.6} and 105 {$(C_7H_5O)^+$, 100}; νmax (nujol) 1600, 1490 (s.s. νC=C), 1050 (s.b. νC-O-C), 760 (s.s. δCH) and 695 (s.s. δCH of thiophene); δ($CDCl_3$) 1.70-2.70 (8H, m; H_1 and H_2); 4.0 (4H, m, H_3), 6.48 (2H, broad s, H_4) and 7.30 (10H, m, H_5).

Attempted synthesis of 2,5-bis{2-(2-hydroxyethyl)phenyl}thiophene

2,5-Bis(2-bromophenyl)thiophene (97) (0.5 g, 1.27 mmol) was dissolved in dry THF (10 ml) and n-butyl lithium in hexane (3.81 mmol) was added dropwise, with stirring, at -78°C. The mixture was stirred at -78°C for 15 min then a solution of ethylene oxide (3 ml, Ca. 60 mmol) in THF (10 ml) was added. Stirring continued for 14 h whereby the mixture was allowed to warm to RT slowly. The mixture was poured into aqueous HCl (Ca. 1M, 50 ml). Extraction ($CHCl_3$), washing (H_2O), drying and evaporation gave a yellow solid which on recrystallization from $CHCl_3$ afforded shiny yellow plates (0.14 g, 46.7%), m.p. 144-5°C

(dec.) (lit. 153-4°C)[214]; m/z 236 (m^+, 100) and 158 {$(M-C_6H_6)^+$, 1}; δ($CDCl_3$) 7.30 (2H, s) and 7.50 (10H, m); UV (ether) λmax 217 nm (ε=9689), 230.5 nm (9317) and 329.5 nm (22733). All the above physical and spectroscopic data are identical with that of an authentic sample of 2,5-diphenylthiophene (223) prepared by an alternative route.

Attempted synthesis of diethyl 2,5-thiophene-bis(2-phenylacetate)

1) 2,5-Thiophene-bis(phenyl-2-carboxylic acid) (224)

A mixture of 2,5-bis(2-ethoxycarbonylphenyl)thiophene (81) (3.43 g, 9 mmol) and sodium hydroxide (2.5 g, 0.147 mol) in ethanol (50 ml) was refluxed for 1 h. After being evaporated down, the residue was acidified with 6N HCl. Extraction (EtOAc), washing (H_2O), drying and evaporation gave a solid. Recrystallization from acetone-PE gave 2,5-thiophene-bis(phenyl-2-carboxylic acid) (224) (2.0 g, 68.6%), (Found C, 67.0; H, 4.2. $C_{18}H_{12}O_4S$ requires C, 66.7; H, 3.7%); m.p. 188-9°C; δ(acetone-d_6) 7.10 (2H, s), 7.30-8.00 (8H, m) and 10.14 (2H, broad, exchanged with D_2O).

2) bis{2-(diazoacetyl)phenyl}-2,5-thiophene (225)

A mixture of 2,5-thiophene-bis(phenyl-2-carboxylic acid) (224) (1.84 g, 5.68 mmol) and excess thionyl chloride was stirred at RT for 2 h, after which the excess thionyl chloride was removed in vacuo.

A solution of the above crude acid chloride in dried ether (25 ml) was added dropwise to a solution of triethylamine (1.6 ml) and diazomethane[215] (excess) in ether (150 ml) at 0°C. After 2 h at the

same temperature, the solvent was removed under reduced pressure at room temperature. Recrystallization of the residue from $CHCl_3$-PE afforded bis{2-(azoacetyl)phenyl}-2,5-thiophene (225) as very pale brown crystals (0.35 g, 16.6%), m.p. 116-7°C (decomp.) (Found C, 64.6; H, 3.3. $C_{20}H_{12}N_4O_2S$ requires C, 64.5; H, 3.2%); m/z 372 (M^+, 2), 316 {$(M-2N_2)^+$, 100}, 302 (36), 288 (41), 258 (39) and 245 (25); νmax (nujol) 2100 (νN=N), 1995 (νN=N), 1610 (νC=O), 1600, 1210, 1040, 870, 818, 810, 770, 760 and 755 cm^{-1}; δ($CDCl_3$) 5.25 (2H, s), 7.03 (2H, s) and 7.20-7.70 (8H, m).

3) diethyl 2,5-thiophene-bis(2-phenylacetate)

A literature procedure[179] was adopted. A freshly prepared solution of silver benzoate (18 mg) in triethylamine (0.3 ml) was added to a refluxing solution of 2,5-thiophene-bis{2-(azoacetyl)phenyl} (225) (350 mg, 0.94 mmol) in ethanol (10 ml) under nitrogen. After 1 h at the same temperature, the mixture was cooled, filtered through celite and evaporated down. CH_2Cl_2 (15 ml) was added, followed by washing successively with 10% sodium carbonate, water and finally dried. ^1H NMR showed that the residue was (225) (300 mg).

2-iodophenylacetylene (232)

(a) 2-iodoacetophenone

A reported procedure[88] was adopted. Starting from 2-iodobenzoyl chloride, prepared from 2-iodobenzoic acid and excess thionyl chloride at 60°C for 1 h in 96.8% yield, b.p. 132°C/15 torr (lit. 135/19 torr),[216] 2-iodoacetophenone was obtained in 50.6% yield, b.p. 158-162°C/20 torr

(lit., 144°C/15 torr)[143].

(b) 1-(2-iodophenyl)-1-chloroethene (230) and 2-iodo-1,1-dichloroethylbenzene (231)

A mixture of 2-iodoacetophenone (46.33 g, 0.188 mol) and phosphorous pentachloride (41.5 g, 0.199 mol) was warmed at 80-90°C for 15 min. After the vigorous reaction subsided, the mixture was fractionally distilled to give 1-(2-iodophenyl)-1-chloroethene (230) (38.15 g, 76.7%), b.p. 140-145°C/25 torr and 2-iodo-1,1-dichloroethylbenzene (231) (5.74 g, 10.1%), b.p. 152-4°C/25 torr.

(c) 2-iodophenylacetylene

The above mixture (230) plus (231) was refluxed with potassium hydroxide (16 g, 0.28 mol) in ethanol (50 ml) for 3 h and poured into ice. Extraction (CH_2Cl_2), washing of the extracts (H_2O), drying and evaporation gave an oil. Fractional distillation gave a pale yellow liquid (23.7 g), b.p. 88-92°C/2 torr; νmax (neat) 3300 and 2100 cm^{-1}; δ($CDCl_3$) 3.21 (1H, s), 5.35 (1H, d), 5.60 (1H, d) and 6.80-7.90 (8H, m), suggesting a mixture of 2-iodophenylacetylene (232) and 1-(2-iodophenyl)-1-chloroethene (230). Integration suggested a ratio of 73:27.

Z-(2-Bromophenyl)ethoxyethene (94) and 2-bromophenylacetaldehyde (95)

A mixture of 1-(2-bromophenyl)-1-chloroethene (62.8 g) and 2-bromo-1,1-dichloroethylbenzene (68.3 g), prepared from 2-bromoacetophenone (123.2 g) and phosphorous pentachloride (136.7 g) as described on p. 138, was refluxed with ethanolic KOH (1.96 mol KOH in 350 ml EtOH) for 21 h and poured into water (600 ml). Extraction (Et_2O), washing (H_2O),

drying, evaporation and fractionation of the residue gave Z-(2-bromophenyl)ethoxyethene (94) (69.5 g, 55%), b.p. 160-1°C/32 torr.† m/z 228 (M^+, 59), 226 (M^+, 61), 200, 198 {$(M-Et)^+$, 30} and 171, 169 {$(M-C_3H_6O)^+$, 23}; νmax (neat) 3040, 2980, 2930, 2880, 1640, 1550, 1470, 1430, 1380, 1300, 1200, 1120, 1100, 1080, 1020, 765 and 750 cm^{-1}; δ($CDCl_3$) 1.25 (3H, t, J 6.5 Hz), 3.85 (2H, q, J 6.5 Hz), 5.55 (1H, d, J 7.3 Hz), 6.20 (1H, d, J 7.3 Hz), 6.75-7.55 (3H, m) and 8.05 (1H, dd, J 6.8 Hz and 1.5 Hz).

A mixture of Z-(2-bromophenyl)ethoxyethene (94) (3 g, 13 mmol) HCl (6M, 10 ml) and ethanol (2 ml) was refluxed for 3 min. Working up and fractionation gave 2-bromophenylacetaldehyde (95) (2.12 g, 82%), b.p. 158°C/30 torr. (Found: C, 48.3; H, 3.4. C_8H_7BrO requires C, 48.2; H, 3.5%); m/z 199 (M^+, 3), 169 {$(M-C_2H_2O)^+$, 62} and 119 {$(M-Br)^+$, 100}; νmax (neat) 3050, 2820, 2720, 1720, 1690, 1640, 1630, 1565, 1470, 1440, 1310, 1020, 930 and 750 cm^{-1}; δ($CDCl_3$) 3.87 (2H, d, J 1.33 Hz), 6.90-7.70 (4H, m) and 9.70 (1H, t, J 1.33 Hz).

Z,E-(2-Iodophenyl)ethoxyethene (229)

To a solution of Z-(2-bromophenyl)ethoxyethene (94) (52.71 g, 0.232 mol) in THF (80 ml), n-butyl lithium in hexane (0.278 mol) was added dropwise, with stirring, under nitrogen at -78°C. A pink precipitate was formed. After 20 min at -78°C, a solution of iodine (70.6 g, 0.278 mol) in THF (100 ml) was added dropwise over 40 min. The cooling bath was removed and stirring continued at RT for 1½ h. Pouring into water (150 ml), extraction (CH_2Cl_2), washing of the

† The compound was unstable in air and hydrolysed to 2-bromophenylacetaldehyde slowly, as shown by the microanalytical and MS data: (Found: C, 46.9; H, 3.7. C_8H_7BrO . 0.3 H_2O requires C, 47.0; H, 3.7%); m/z as that for 2-bromophenylacetaldehyde (95).

extracts (saturated $NaHSO_3$, followed by saturated $NaHCO_3$), drying ($MgSO_4$) and evaporation gave a brown oil (^1H NMR showed only the Z-isomer), which on fractionation isomerized to give Z and E-(2-iodophenyl)ethoxyethene (229) (ratio 46:54) (35.61 g, 56%), b.p. 130-2°C/0.95 torr. (Found C, 43.5; H, 3.6. $C_{10}H_{11}IO$ requires C, 43.8; H, 4.0%); m/z 274 (M^+, 100), 273 {$(M-H)^+$, 85}, 246 {$(M-C_2H_6)^+$, 11}, 226 {$(M-EtOH)^+$, 10}, 147 {$(M-I)^+$, 4} and 118 {$(M-C_2H_5I)^+$, 15}; νmax (neat) 3050, 2980, 2920, 2880, 2890, 1640, 1580, 1550, 1460, 1430, 1390, 1380, 1335, 1330, 1230, 1160, 1100, 1000, 930, 920, 800, 765 and 750 cm^{-1}; δ($CDCl_3$) 1.28 (6H, 2t, J 6.5 Hz), 3.85 (4H, q, J 6.5 Hz), 5.40 (1H, d, J 7.3 Hz), 5.92 (1H, d, J 13.3 Hz), 6.15 (1H, d, J 7.3 Hz), 6.54-6.90 (2H, m), 6.75 (1H, d, J 13.3 Hz), 7.00-7.40 (2H, m), 7.75 (2H, d, J 7.8 Hz) and 8.00 (1H, dd, J 7.8 Hz and 1.5 Hz). Before distillation, only the Z-isomer was present: δ($CDCl_3$) 1.28 (3H, 2t, J 6.5 Hz), 3.85 (2H, q, J 6.5 Hz), 5.40 (1H, d, J 7.3 Hz), 6.15 (1H, d, J 7.3 Hz), 6.75 (1H, dt, J 7.8 Hz and 2.0 Hz), 7.20 (1H, m), 7.75 (1H, dd, J 7.8 Hz and 1.5 Hz) and 8.00 (1H, dd, J 7.8 Hz and 1.5 Hz).

Z,E-{(2-Trimethylsilylethynyl)phenyl}ethoxyethene and Z,E-(2-ethynylphenyl) ethoxyethene (228)

A deaerated solution of Z,E-(2-iodophenyl)ethoxyethene (35.61 g, 0.129 mol), copper(I)iodide (18 mg) and $Pd(PPh_3)_4$ (0.3 g) in anhydrous triethylamine (200 ml) was treated with ethynyltrimethylsilane (19.1 g, 0.195 mol) under nitrogen. The mixture was rapidly heated to Ca. 90°C and maintained at that temperature for 12 h. Working up gave Z,E-{(2-trimethylsilylethynyl)phenyl}ethoxyethene (22.0 g, 70%) as a brown oil;†=

† Attempts to purify the product by distillation led to extensive decomposition.

ǂ The Z,E-isomers were inseparable on TLC.

m/z 244 (m^+, 100), 229 {$(M-CH_3)^+$, 16.3}, 215 {$(M-Et)^+$, 12.4}, 201 {$(M-C_3H_8)^+$, 54.6}, 199 {$(M-OEt)^+$, 11.3} and 185 {$(M-C_3H_7O)^+$, 68.8}; νmax (neat) 3070, 2140, 2060 (νC≡C), 1640 (νC=C), 1590, 1470, 1440, 1300, 1250, 1205, 1165, 1100, 1080, 930, 860, 840, 750 and 730 cm^{-1}; δ($CDCl_3$) 0.21 (18H, s), 1.29 (6H, m), 3.85 (4H, q), 5.75 (1H, d, J 7.3 Hz), 6.18 (1H, d, J 7.3 Hz), 6.21 (1H, d, J 13.3 Hz), 7.25 (8H, m) and 8.10 (1H, bd, J 7.8 Hz) (from the integral Z:E isomer was roughly 4:6).

The above crude product (22.0 g) was treated with anhydrous potassium carbonate (1.78 g, 0.128 mol) in methanol (150 ml) at 60°C for 6 h. The solvent was removed and CH_2Cl_2 (100 ml) was added. The solution was washed with aq. $NaHCO_3$ (50 ml), dried ($MgSO_4$) and evaporated down. Chromatography on a column of SiO_2 with 10% ether-PE gave essentially pure Z,E-(2-ethynylphenyl)ethoxyethene (228) (17.1 g, 75%) as a viscous light orange oil;†‡ m/z 172 (M^+, 16), 159 {$(M-CH)^+$, 26}, 143 {$(M-Et)^+$, 17}, 115 {$(M-OEt)^+$, 57} and 103 {$(M-C_3H_7O)^+$, 100}; νmax (neat) 3280 (νC≡H), 3070, 2090 (νC≡C), 1640 (νC=C), 1590, 1470, 1440, 1245, 1220, 1100, 1080, 920, 830 and 750 cm^{-1}; δ($CDCl_3$) 1.30 (6H, t), 3.23 (2H, s), 3.88 (4H, q), 5.77 (1H, d, J 7.3 Hz), 6.23 (1H, d, J 7.3 Hz), 6.26 (1H, d, J 13.3 Hz), 7.25 (8H, m) and 8.15 (1H, d, J 7.8 Hz). The product was used in the next stage without further purification.

† Attempts to purify the product by distillation led to extensive decomposition.

‡ The Z,E-isomers were inseparable on TLC.

1,4-bis{2-(Z,E-2-ethoxyethenyl)phenyl}butadiyne (227)

The procedure developed by Hünig[75] was followed. To a magnetically well-stirred suspension of copper(I)chloride (1.95 g, 19 mmol) in DME (70 ml) was added TMEDA (3.45 g, 29.6 mmol). After 10 min at RT, Z,E-(2-ethynylphenyl)ethoxyethene (227) (17.0 g, 98 mmol) was added, and the mixture was kept at Ca. 35°C for 11 h while air was bubbled through the solution. Working up as usual gave a black viscous oil, which was filtered through a short column of SiO_2 with 10% ether-PE. Rechromatography on a column of SiO_2 using 10% ether-PE gave an orange oil (12.5 g, 74.6%), from which on storage white prisms (0.67 g) crystallized out. These consisted of pure 1,4-bis{(E-2-ethoxyethenyl) phenyl}butadiyne (227), m.p. 90-90.5°C (ether) (Found: C, 84.2; H, 6.4. $C_{24}H_{22}O_2$ requires C, 84.0; H, 6.4%); TLC {(SiO_2, Et_2O/PE (1:9)} Rf 0.36; m/z 342 (M^+, 21), 313 {$(M-Et)^+$, 66}, 285 {$(M-COEt)^+$, 64}, 284 {$(M-2Et)^+$, 31}, 256 {$(M-C_5H_{10}O)^+$, 26}, 239 (69), 228 {$(M-2EtCO)^+$, 100} and 226 (95); νmax (nujol) 2140, 1630, 1590, 1310, 1230, 1190, 1170, 1155, 1080, 950, 938, 850, 810, 770, 750 and 650 cm^{-1}; δ($CDCl_3$) 1.35 (6H, t, J 7.3 Hz), 3.92 (4H, q, J 7.3 Hz), 6.20 (2H, d, J 13.3 Hz) and 6.90-7.55 (10H, m). The mother liquor contained a mixture of Z,E-isomers: δ($CDCl_3$) 1.3 (t, J 6.7 Hz), 3.90 (q, J 6.7 Hz), 5.75 (d, J 7.3 Hz), 6.21 (d, J 7.3 Hz), 6.22 (d, J 13.3 Hz), 6.90-7.60 (m) and 8.12 (d, J 8 Hz).

bis{2-(Z,E-2-Ethoxy-1-ethenyl)phenyl}-2,5-thiophene (226) and its reaction with hydrochloric acid

A mixture of crude 1,4-bis{2-(Z,E-2-ethoxyethenyl)phenyl}butadiyne (3.26 g, 11 mmol) (226), sodium sulphide nonohydrate (10.57 g, 44 mmol) in methanol (60 ml) was refluxed for 20 h. Working up and careful chromatography on SiO_2 (Et_2O-PE, 1:9) afforded an orange oil (1.38 g). m/z 376 (M^+, 39), 342 {$(M-H_2S)^+$, 20}, 313 {$(M-H_2S-Et)^+$, 67}, 285 {$(M-EtCO-H_2S)^+$, 100}, 284 {$(M-H_2S-2Et)^+$, 39}, 257 (62), 255 (33), 239 (62), 228 {$(M-2EtCO-H_2S)^+$, 85)} and 226 (79); νmax (neat) 3050, 2980, 2920, 2880, 2240, 2200, 2130, 1640, 1590, 1100, 905, 750 and 730 cm^{-1}; δ($CDCl_3$) 1.30 (12H, 2 sets of t), 3.85 (8H, 2 sets of q), 6.15 (2H, d, J 12 Hz), 6.25 (2H, d, J 12 Hz), 6.75-7.60 (20H, m) and 7.05 (2H, s), integration estimated a roughly 1:1 mixture of (226) and (227).

The above mixture was refluxed with aqueous HCl (6N, 20 ml) and THF (20 ml) for 1 h. A pale brown crystalline solid (0.37 g) separated, was filtered off, and the mother liquor was worked up in the usual way. The pale brown crystalline solid was insoluble in water and only slightly in boiling DMSO. Examining of it in DMSO-d_6 by ^1H NMR at 110°C showed no signal. ^1H NMR of the red oil (0.5 g) obtained from the mother liquor after working up, showed a small aldehyde proton at δ9.75 and a broad multiplet between 6.90-8.30.

Reaction between methoxymethinephosphorane and 2,5-bis(2-formylphenyl)thiophene (89)

n-Butyl lithium (9.25 mmol) in hexane was added dropwise with stirring, under nitrogen to a suspension of (methoxymethyl)triphenylphosphonium chloride (3.17 g, 9.25 mmol) in THF (30 ml) at 0°C. After stirring at the same temperature for 35 min, a solution of 2,5-bis(2-formylphenyl)thiophene (89) (0.9 g, 3.08 mmol) in THF (10 ml) was added. After a further 1½ h at RT, the mixture was partitioned between aqueous methanol (1:1) and CH_2Cl_2. The organic layer was separated and washed. The residue, after solvent removal, was refluxed with a mixture of 6N HCl and THF (2:3) for 6 h and worked up. Careful chromatography on a column of SiO_2 with Et_2O-PE (1:9) afforded Z,E-isomers of 2,5-bis{2-(pent-2-enyl)phenyl}thiophene (233) (126 mg, 11%) as a pale yellow oil, m/z 372 (M^+, 10), 328 {$(M-C_3H_6)^+$, 31}, 285 {$(M-2C_3H_6)^+$, 100}, 261 (46) and 236 (36); δ($CDCl_3$), 0.92 (t), 1.10-1.60 (p), 1.95-2.40 (m) and 6.60-8.20 (m); and dinaphtho{2,1-b:1',2'-d}thiophene (234) (43.7 mg, 5%), m.p. 250-1°C (PE) (lit., 253°C);[217] m/z 284 (M^+, 15), 258 {$(M-2CH)^+$, 20}, 236 {$(M-C_4H_4)^+$, 16} and 182 {$(M-C_8H_6)^+$, 30}; νmax (nujol) 3060, 1580, 1425, 1430, 1085, 1020, 750, 745, 740, 695 and 690 cm^{-1}; δ($CDCl_3$) 7.10-8.00 (12H, m).

4,4-Dimethyl-2-(2-halobenzyl)oxazoline (235), (238)

Meyers' general approach to oxazoline synthesis was followed.[77] 2-halophenylacetic acid (0.15 mol) and thionyl chloride (0.30 mol) were mixed and stirred at RT overnight. The excess thionyl chloride was removed by distillation and the residue distilled in vacuo to give the acid chloride as a colourless liquid.

A solution of 2-amino-2-methylpropan-1-ol (0.20 mol) in CH_2Cl_2 (100 ml) was added to a solution of the acid chloride (0.1 mol) in CH_2Cl_2 (40 ml), with the reaction temperature held below 20°C. The mixture was stirred for 2 h, dried ether (150 ml) was added and filtered. To the crude amide (80 mmol) thus collected, thionyl chloride (0.26 mol) was added dropwise with stirring. After 15 min, the liquid was poured slowly into water (100 ml). The solution was basified (1M NaOH) and the product extracted with ether. The combined extracts were washed (H_2O), dried ($MgSO_4$), and the solvent removed to leave the crude product as a pale yellow oil; this was distilled to give 4,4-dimethyl-2-(2-halobenzyl)oxazoline.

2-Bromophenylacetyl chloride (85%), b.p. 142-3°C/11 torr.[218] gave 4,4-dimethyl-2-(2-bromobenzyl)oxazoline (162) (42%, based on 2-bromophenylacetyl chloride), a colourless liquid, b.p. 172°C/5 torr (Found C, 54.0; H, 5.4; N, 5.3. $C_{12}H_{14}BrNO$ requires C, 53.8; H, 5.3; N, 5.2%); m/z 270 {$(M+2)^+$, 100}, 268 (M^+, 100), 254 {$(M-CH_2)^+$, 23}, 226 {$(M-C_3H_6)^+$, 25} and 188 {$(M-Br)^+$, 100}; νmax (neat) 3060, 2960, 2920, 2895, 1660 (νC=N), 1590, 1570, 1470, 1440, 1360, 1280, 1150, 1030, 980 and 750 cm^{-1}; δ($CDCl_3$) 1.21 (6H, s), 3.70 (2H, s), 3.85 (2H, s) and 7.27 (4H, m).

2-Iodophenylacetyl chloride (96%), b.p. 156°C/9 torr (lit., 145°C/15 torr)[219] gave 4,4-dimethyl-2-(2-iodobenzyl)oxazoline (165) (49%, based on 2-iodophenylacetyl chloride), a colourless liquid, b.p. 188-9°C/14 torr (Found C, 45.4; H, 4.4; N, 4.4. $C_{12}H_{14}INO$ requires C, 45.7; H, 4.5; N, 4.4%); m/z 316 {$(M+1)^+$, 17}, 300 {$(M-CH_3)^+$, 7}, 285 {$(M-C_2H_6)^+$, 2}, 272 {$(M-C_3H_7)^+$, 4}, 217 {$(M-C_5H_8NO)^+$, 20} and 188 {$(M-I)^+$, 100}; νmax (neat) 3050, 2960, 2920, 2880, 2860, 1660 (νC=N), 1582, 1560, 1460, 1435, 1420, 1360, 1270, 1145, 1010, 980 and 740 cm^{-1}; δ($CDCl_3$) 1.25 (6H, s), 3.78 (2H, s), 7.00 (3H, m) and 7.80 (1H, d, J 7.8 Hz).

Coupling between 4,4-dimethyl-2-(2-magnesiobenzyl)oxazoline and 2,5-dibromothiophene

Into a 3-necked flame-dried flask equipped with a N_2 inlet, condenser and dropping funnel, magnesium (356 mg, 14.8 mmol), a crystal of iodine and THF (10 ml) were placed. After blanketing under N_2, a solution of 4,4-dimethyl-2-(2-bromobenzyl)oxazoline (235) (4 g, 14.8 mmol) in THF (10 ml) was added dropwise. After the vigorous reaction subsided, the mixture was refluxed for 1 h to complete the reaction. In the meantime, into a 3-necked flame-dried flask, equipped with a N_2 inlet, a condenser and a septum cap, 2,5-dibromothiophene (1.44 g, 2.94 mmol), {$Ni(dppp)Cl_2$} (10 mg) and THF (10 ml) were placed. After blanketing under N_2 and cooling in an ice bath, the Grignard reagent prepared previously was added dropwise, under N_2, to the above mixture. The cooling bath was removed and replaced by an oil bath. After 18 h refluxing the mixture was acidified to pH 7-8. Extraction ($CHCl_3$), washing of the extracts (H_2O), drying and evaporation afforded an oil,

which was subjected to flash chromatography (Al_2O_3). Elution with PE recovered 2,5-dibromothiophene, while with ether, 4,4-dimethyl-2-benzyloxazoline (236) (2.2 g, 80%) was obtained; m/z 190 {$(M+1)^+$, 72}, 189 (M^+, 63), 188 {$(M-1)^+$, 42}, 174 {$(M-CH_3)^+$, 62}, 159 {$(M-2CH_3)^+$, 22} and 91 {$(C_7H_7)^+$, 100}; $\delta(CDCl_3)$ 1.20 (6H, s), 3.48 (4H, s) and 7.28 (5H, s). When HMPA was added as a co-solvent in the reaction, 2,2'-bis-{3-(4,4-dimethyl-oxazoline)methyl}biphenyl (237) was also obtained in 5% yield; m/z 376 (M^+, 100), 189 (34), 188 {$(\frac{m}{2})^+$, 23} and 91 (43); $\delta(CDCl_3)$ 1.22 (12H, s), 3.52 (4H, s), 3.80 (4H, s) and 6.90-7.60 (8H, m).

When 4,4-dimethyl-2-(2-iodobenzyl)oxazoline (238) was used instead, no reaction occurred.

2-Halobenzyl bromide and 2-halobenzyl cyanide

Free radical bromination of 2-bromotoluene using NBS and a few crystals of benzoyl peroxide in CCl_4 for 15 h gave 2-bromobenzyl bromide (89.7%), b.p. 94-6°C/1.2 torr. (lit., 120-30°C/13 torr).[220] Cyanide displacement, in a manner similar to that reported,[182] gave 2-bromobenzyl cyanide (84%), b.p. 152-3°C/30 torr (lit. 131-2°C/8 torr).[182] Similarly, starting from 2-iodotoluene, 2-iodobenzyl bromide (79.2%), b.p. 210°C/113 torr (lit. m.p. 52-3°C)[221] and 2-iodobenzyl cyanide (85%), b.p. 128°C/1 torr (lit. 140°C/4 torr)[219] were obtained.

2-{(Trimethylsilyl)ethynyl}benzyl cyanide (243) and 2-ethynylbenzyl cyanide (240)

The following procedure was modified from that given by Lau et al[76] and Sonogashira et al.[134] A deaerated solution of 2-iodobenzyl cyanide (8.0 g, 33 mmol), copper(I)iodide (19 mg), and $Pd(PPh_3)_4$ (0.2 g) in anhydrous triethylamine (200 ml) was treated with ethynyltrimethylsilane (50 mmol, as a THF/hexane solution) under nitrogen. The mixture was rapidly heated to Ca. 90°C and maintained at that temperature for 16 h. After cooling, the mixture was filtered. The dark brown filtrate was concentrated, mixed with water (100 ml) and extracted with CH_2Cl_2 (3x50 ml). The combined organic phases were dried, concentrated and distilled to give 2-{(trimethylsilyl)ethynyl}benzyl cyanide (243) (4.92 g, 70%), b.p. 122-4°C/1.3 torr; m/z 213 (M^+, 5), 198 {$(M-CH_3)^+$, 100}, 171 {$(M-C_2H_4N)^+$, 10}, 140 {$(M-SiMe_3)^+$, 21}, 128 {$(M-C_4H_9Si)^+$, 46} and 116 {$(M-C_5H_9Si)^+$, 91}; νmax (neat) 2960, 2900, 2240 (νC≡N), 2150, 2060 (νC≡C), 1485, 1450, 1410, 1250, 1230, 910, 860, 755 and 730 cm^{-1}; δ($CDCl_3$) 0.05 (9H, s), 3.57 (2H, s) and 7.00 (4H, m).

The above product was treated with potassium fluoride dihydrate (4.35 g, 46 mmol) in DMF (30 ml) under nitrogen at RT overnight and poured into water (60 ml). Extraction (CH_2Cl_2), washing of the extracts (H_2O), drying and fractionation under reduced pressure to give 2-ethynylbenzyl cyanide (240) (2.60 g, 80%), b.p. 94-5°C/0.7 torr.; m/z 141 (M^+, 100), 140 {$(M-1)^+$, 79}, 116 {$(C_8H_6N)^+$, 31} and 114 {$(M-HCN)^+$, 50}; νmax (neat) 3290 (νC≡H), 3060, 2242 (νC≡N), 2100 (νC≡C), 1600, 1580, 1485, 1090, 1028, 950 and 750 cm^{-1}; δ($CDCl_3$) 3.38 (1H, s), 3.82 (2H, s) and 7.1-7.6 (4H, m).

Coupling reaction between 2-iodobenzyl cyanide and ethynylzinc chloride

A literature procedure was followed.[183] A solution of anhydrous zinc chloride (279 mg, 2 mmol; dried in vacuum oven at 120°C overnight before use) in THF (5 ml) was added to a suspension of lithium acetylide-ethylenediamine complex (189 mg, 2 mmol) in THF (5 ml), under N_2, at 0°C. After stirring at RT for ½ h, a solution of 2-iodobenzyl cyanide (250 mg, 1 mmol) and tetrakis(triphenylphosphine) palladium(0) (11 mg, 0.01 mmol) in THF (3 ml) was added. The mixture was refluxed under nitrogen for 24 h and worked up as reported.[183] ^1H NMR of the crude product showed only starting materials.

1,4-Bis(2-cyanomethylphenyl)butadiyne (241)

The procedure developed by Hünig[75] was followed. To a magnetically well-stirred suspension of copper(I)chloride (1.41 g, 14 mmol) in DME (50 ml) was added TMEDA (2.48 g, 107 mmol). After 10 min at RT, 2-ethynylbenzyl cyanide (168) (10.06 g, 71 mmol) was added, and the mixture was kept at 35-40°C for 4½ h while air was bubbled through the solution. The mixture was then poured into water (200 ml) and extracted with CH_2Cl_2 (4x60 ml). Washing of the extracts (H_2O), drying ($MgSO_4$) and evaporation gave a brown solid which on recrystallization from $CHCl_3$-PE afforded the 1,4-bis(2-cyanomethylphenyl)butadiyne (241) (6.1 g, 61.4%), m.p. 118-9°C (Found: C, 85.9; H, 4.20. $C_{20}H_{12}N_2$ requires C, 85.7; H, 4.30%); m/z 281 {$(M+1)^+$, 21}, 280 ($M^{\cdot+}$, 100), 279 {$(M-1)^+$, 100}, 253 {$(M-HCN)^+$, 61}, 226 {$(M-2HCN)^+$, 15} and 140 {$(C_{10}H_6N)^+$, 20}; νmax (nujol) 2240 (νC≡N), 1400 and 750 cm^{-1}; δ($CDCl_3$) 3.88 (4H, s) and 7.1-7.7 (8H, m).

2,5-Bis(2-cyanomethylphenyl)thiophene (242)

The procedure reported by Schulte et al[22] was followed. A mixture of 1,4-bis(2-cyanomethylphenyl)butadiyne (241) (1.0 g, 3.56 mmol), sodium sulphide nonahydrate (3.48 g, 14 mmol) and methanol (60 ml) was refluxed for 10 h. Most of the solvent was removed and the residue taken up in H_2O. Extraction (CH_2Cl_2), washing (H_2O), drying and evaporation gave a brown viscous oil, which was chromatographed on a column of SiO_2. Fractions eluted with 60% ether-PE gave the desired thiophene as a yellow oil. Recrystallization from $CHCl_3$-PE (CO_2-acetone cold bath) afforded yellow prisms (0.44 g, 39.4%), m.p. 104-104.5°C (Found: C, 76.1; H, 4.6; N, 8.8. $C_{20}H_{14}N_2S$ requires C, 76.4; H, 4.5; N, 8.9%); TLC {SiO_2 PE/ether (4:6)} Rf 0.49; m/z 314 (M^+, 100) and 287 {$(M-HCN)^+$, 7}; νmax (nujol) 2240 (νC≡N), 1480, 1410, 820, 810, 778 and 765 cm^{-1}; δ($CDCl_3$) 3.82 (4H, s), 7.02 (2H, s) and 7.20-7.70 (8H, m). ^{13}C NMR ($CDCl_3$) 22.47 (CH_2, t), 78.91, 79.86, 117.16, 121.06 (Sp-C) and 128.28, 129.71, 130.16, 133.62 (Sp^2-C).

Attempts to scale up the reaction threefold under similar conditions led to extensive polymerization and no sign of the expected thiophene was observed. Using ethanolic sodium hydroxide led to a similar result.

2,5-bis(1-hydroxy-1-phenyl-but-3-ynyl)thiophene (246)

A literature procedure[222] was adopted. A solution of 2,5-dibenzoylthiophene (1 g, 3.45 mmol) in THF (5 ml) was added to a mixture of propargyl bromide (1.04 ml, 13.8 mmol), mercury(II)chloride and iodine (a small crystal each) in THF (10 ml) at -60°C. The mixture

was stirred at 0°C for 1 h, at RT overnight and poured into saturated aqueous NH_4Cl. Extraction ($CHCl_3$), drying and evaporation gave a thick oil, which was chromatographed on SiO_2 with Et_2O-$CHCl_3$ (1:1). 2,5-bis(1-hydroxy-1-phenyl-but-ynyl)thiophene (246) (1.05 g, 82.3%) was obtained as a viscous yellow oil,† m/z 355 {(M^+-OH), 100}, 333 {$(M^+-C_3H_3)^+$, 50} and 294 {$(M-2C_3H_3)^+$, 15}; νmax (neat) 3515, 3290, 3060, 3020, 2920, 2109, 1600, 1490, 1450, 1420, 1350, 1250, 1220, 1050, 1000, 805, 750, 710 and 700 cm^{-1}; δ($CDCl_3$) 1.80 (2H, t, J 2 Hz), 2.93 (1H, d, J 2 Hz), 2.98 (2H, s, exchanged with D_2O), 6.56 (2H, s) and 7.00-7.48 (10H, m).

Oxidative coupling of 2,5-bis(1-hydroxy-1-phenyl-but-3-ynyl)thiophene (246)

A solution of 2,5-bis(1-hydroxy-1-phenyl-but-3-ynyl)thiophene (246) (920 mg, 2.48 mmol) in ether-pyridine (50 ml, 1:3) was added during 4½ h to a suspension of copper acetate (3.13 g, 17.3 mmol) in the same solvent mixture (110 ml) at 50°C. After stirring at the same temperature for a further 1½ h, the solvent was removed and the residue extracted with $CHCl_3$. Filtration, washing (H_2O), drying and evaporation afforded a residue, which was recrystallized from $CHCl_3$-PE to give a very pale brown powder (0.52 g), m.p. 102-3°C (Found C, 72.9; H, 4.6%); m/z 293 (28), 279 (100), 278 (28), 265 (13), 203 (13), 189 (30), 173 (26), 136 (9), 121 (23) and 105 (84); νmax (nujol) 3420, 3290, 1605, 1490, 1460, 1445, 1045, 800, 760 and 700 cm^{-1}; δ($CDCl_3$, 300 MHz), 2.08 (s), 3.08 (b, s), 3.00-3.58 (m), 6.73 (m) and 7.00-8.00 (m). Unambiguous structural assignment is not possible.

† attempts to purify by distillation led to extensive decomposition.

Mercaptoacetaldehyde diethylacetal (257)

The compound was prepared as reported,[189] by the reduction of 1,1,1',1'-tetraethoxyethyl disulphide[189,223] using sodium in liquid ammonia (74% yield). Reduction using lithium aluminium hydride was easier to effect but gave 45% yield.

Into a 2-necked flask, equipped with a dropping funnel and a carbon dioxide/acetone cold trap, lithium aluminium hydride (3.96 g, 104 mmol) and THF (150 ml) were placed. 1,1,1',1'-tetraethoxyethyl disulphide[189] (34.9 g, 136 mmol) was added dropwise at RT. After 20 min refluxing from a water bath, water was added cautiously at 0°C to decompose the complex. Carbon dioxide was then bubbled into the mixture until a pH of 7-8 was reached. Extraction (Et_2O), washing of the extracts (H_2O), drying and fractionation gave mercaptoacetaldehyde diethylacetal (257) as a stenching colourless liquid (9.18 g, 45%), b.p. 86-9°C/40 torr (lit., 62-4°C/12 torr).[189] ($CDCl_3$) 1.10 (6H, t, J 6.5 Hz), 1.50 (1H, d, J 8.0 Hz), 2.55 (2H, dd, J 8.0 Hz, 5.3 Hz), 3.50 (4H, 2 sets of q) and 4.40 (1H, t, J 5.3 Hz).

4-Hydroxybenzo{b}thiophene (258)

The compound was prepared as reported.[188] The yield and physical data for the intermediates are summarized below.

3-(2,2-Diethoxyethylthio)cyclohexanone (56%), b.p. 139-140°C/0.8 torr (lit. 114°C/0.05 torr)[188]; 4-oxo-2,4,5,6,7,7a-hexahydrobenzo{b}-thiophene (62%), b.p. 92-6°C/0.2 torr (lit. 86°C/0.5 torr)[188]; 4-oxo-4,5,6,7-tetrohydrobenzo{b}thiophene (62%), m.p. 36°C (lit 36°C)[188] and 4-hydroxybenzo{b}thiophene (258) (65%), m.p. 80-1°C (lit., 80-1°C).[188]

Direct synthesis of 4-hydroxybenzo{b}thiophene from 4-oxo-2,4,5,6,7,7a-hexahydrobenzo{b}thiophene gave only 12% yield (lit., 25%).[188]

4-Methoxybenzo{b}thiophene (256)

4-Hydroxybenzo{b}thiophene (1.36 g, 9.15 mmol) was dissolved in THF (10 ml). Sodium hydride (0.24 g, 10 mmol) was added, with stirring, under nitrogen at RT. After 20 min, iodomethane (2.60 g, 18.3 mmol) was added. Stirring was continued at RT overnight. The mixture was then poured into water, worked up as usual to give a residue, which was purified on a column of alumina (active, neutral). Fractions eluted with 30% $CHCl_3$-PE on evaporation afforded 4-methoxybenzo{b} thiophene (256) as a viscous pale colour oil (1.22 g, 82%); m/z 164 (M^+, 100), 149 {$(M-CH_3)^+$, 89.2}, 134 {$(M-OMe)^+$, 33} and 121 {$(M-C_2H_4O)^+$, 69.4}; νmax (neat) 1605, 1595, 1510, 1485, 1375, 1285, 1260, 1065, 770 and 715 cm^{-1}; δ($CDCl_3$) 3.85 (3H, s), 6.68 (2H, d, J 7.3 Hz) and 7.30 (4H, m). Spectroscopic data in consistence to that reported.[224]

Attempted synthesis of 4-methoxy-7-phenylbenzo{b}thiophene (255)

4-Methoxybenzo{b}thiophene (256) (500 mg, 3.1 mmol) was dissolved in dry THF (20 ml) and n-butyl lithium in hexane (62 mmol) was added dropwise, with stirring, under nitrogen at -78°C. After 25 min at -78°C, a solution of diphenyliodonium chloride (1.1 g, 3.4 mmol) in THF (10 ml) was added. Stirring was continued overnight while the cooling bath was allowed to warm to RT slowly. Working up as usual

and chromatography of the crude product on a column of alumina (active, neutral), eluting with PE, gave iodobenzene, and subsequently 30% $CHCl_3$-PE eluted 4-methoxybenzo{b}thiophene (450 mg). No sign of 4-methoxy-7-phenylbenzo{b}-thiophene (255) was observed.

4-Methoxyphenyl-2-thienylmethanol (261)

4-Iodoanisole (10 g, 43 mmol) was dissolved in dry ether (100 ml) and n-butyl lithium (43 mmol) was added, with stirring under nitrogen at -30°C. After 20 min at -30°C, a solution of 2-thiophenecarboxy-aldehyde (4.82 g, 43 mmol) in ether (10 ml) was added. Stirring was continued at RT for 1 h and the whole poured into 2M HCl (100 ml). Extraction ($CHCl_3$), washing of the extracts (H_2O), drying and evaporation gave a solid, which after recrystallization from methanol afforded 4-methoxyphenyl-2-thienylmethanol (261) as very pale yellow prisms (7.7 g, 81%), m.p. 47-8°C (Found: C, 64.8; H, 5.5. $C_{12}H_{12}O_2S.0.1CH_3OH$† requires C, 65.1; H, 5.6%); m/z 220 (M^+, 40), 203 {$(M-OH)^+$, 36}, 187 {$(M-CH_4O_2)^+$, 12}, 135 (100), 113 {$(M-Ph-OMe)^+$, 55}, 109 (39.4) and 85 (41); νmax (nujol) 3350, 1610, 1580, 1510, 1375, 1350, 1250, 1170, 1030, 830, 755 and 700 cm^{-1}; δ($CDCl_3$) 2.6 (1H, b, exchanged with D_2O), 5.90 (1H, b, d), 6.81 (2H, d, J 9.1 Hz), 6.85 (2H, m), 7.22 (1H, m) and 7.31 (2H, d, J 9.1 Hz).

† the last trace could not be removed under high vacuum.

4-Methoxyphenyl-2-thienyl ketone (259)

4-Methoxyphenyl-2-thienylmethanol (7.4 g, 34 mmol) was dissolved in acetone and Jones reagent (68 mmol, prepared from 6.8 g of chromium trioxide, 5.93 ml conc. H_2SO_4 and 48.6 ml H_2O) was added dropwise, with stirring at 0^oC. After 1 h at RT, enough aqueous $NaHSO_3$ was added to discharge the brown colour. Extraction ($CHCl_3$), washing (H_2O), drying and evaporation left a solid. Recrystallization from methanol gave 4-methoxyphenyl 2-thienyl ketone (259) as very pale colour prisms (6.52 g, 88%), m.p. 67-8°C (Found: C, 66.0; H, 4.6. $C_{12}H_{10}O_2S$ requires C, 66.0; H, 4.6%); TLC (Al_2O_3, $CHCl_3$) Rf 0.61; m/z 218 (M^+, 100), 203 {$(M-CH_3)^+$, 10}, 187{$(M-OMe)^+$, 11}, 135 {$(M^+-C_4H_3S)^+$, 100}, 111 {$(PhOMe)^+$, 48}, 107 (10) and 92 (23); νmax (nujol) 1630, 1600, 1570, 1500, 1350, 1250, 1170, 1050, 1020, 880, 830, 780, 760 and 740 cm^{-1}; δ($CDCl_3$) 3.85 (3H, s), 6.98 (2H, d, J 9.1 Hz), 7.15 (1H, m), 7.68 (2H, m) and 7.92 (2H, d, J 9.1 Hz).

4-Bromophenyl 2-thienyl ketone (263)

The following procedure was based on that given by Moussa.[191c] A solution of thiophene (36.7 ml, 0.46 mol) and 4-bromobenzoyl chloride (100.76 g, 0.46 mol) in CS_2 (100 ml) was gradually added with stirring to a cooled (ice bath) suspension of anhydrous powdered aluminium chloride (61.2 g, 0.46 mol). Reaction started within ½ h. After the addition, the ice bath was removed and stirring continued at RT overnight. Pouring onto ice, extraction (ethyl acetate), filtration (through celite), washing (H_2O), drying and evaporation gave a brown solid. Recrystallization from $CHCl_3$-PE afforded 4-bromophenyl 2-thienyl

ketone (263) as pale colour prisms (63.9 g, 52.1%), m.p. 93-4°C (Found: C, 49.6; H, 2.9; S, 12.0. $C_{11}H_7BrSO$ requires C, 49.4; H, 2.6; S, 12.1%); m/z 268 {$(M+1)^+$, 3}, 267 (M^+, 25), 266 {$(M-1)^+$, 25}, 187 {$(M-Br)^+$, 16} and 111 {$(C_5H_3SO)^+$, 100}; νmax (nujol) 1625 (νC=O), 1580, 1565, 1512, 1410, 1350, 1290, 1065, 1050, 1005, 880, 865, 845, 835, 745, 740 and 725 cm^{-1}; δ($CDCl_3$) 7.10 (1H, m) and 7.65 (6H, m). 4-Bromobenzoyl chloride was prepared from 4-bromobenzoic acid (100 g), excess thionyl chloride and a catalytic quantity of DMF in 92% yield; b.p. 132-4°C/19 torr (lit., 181-2°C/125 torr).[225]

Z and E-3-Methoxycarbonyl-4-(4-bromophenyl)-4-(2-thienyl)-but-3-enoic acid (264) (265) and the corresponding diacids

The procedure developed by Daub and Johnson[194] was followed. A mixture of 4-bromophenyl 2-thienyl ketone (40 g, 0.15 mol), dimethyl succinate (65.7 g, 0.45 mol), sodium hydride (7.19 g, 0.30 mol) and ethanol (a few drops) was stirred, under a N_2 atmosphere at RT, in a flame-dried flask for 19 h. After 3 h, benzene (10 ml) was added to facilitate stirring. The mixture was acidified with acetic acid, and ether (20 ml) was added before filtering through a celite bed. Working up as reported[226] gave Z and E-3-methoxycarbonyl-4-(4-bromophenyl)-4-(2-thienyl)-but-3-enoic acid (264) (265) as a light brown viscous oil (36.6 g, 65%); m/z 380 {$(M-1)^+$, 2}, 336 {$(M-CO_2)^+$, 12}, 276 {$(M-C_3H_5O_4)^+$, 57}, 197 {$(C_{13}H_9S)^+$, 100} and 195 {$(C_{13}H_7S)^+$, 26}; δ(DMSO-d_6) 3.40 (2H, b), 3.62 (6H, s), 3.70 (2H, b), 6.80-7.60 (14H, m). Integration showed E:Z isomer was roughly 55:45.

Saponification with 10% aqueous NaOH for 4 h gave a light brown viscous oil, which on trituration with PE gave the corresponding

dibasic acids as a pale colour solid (18.3 g, 65%), m.p. 152-3°C (Et_2O-PE) (Found: C, 50.2; H, 3.2; $C_{14}H_{11}BrO_2S \cdot 0.5\ H_2O$ requires C, 50.6; H, 3.6);† m/z 367 (M^+, 12), 350 {$(M-OH)^+$, 34}, 348 {$(M-H_3O)^+$, 34}, 278 {$(M-C_2HO_4)^+$, 66}, 276 {$(M-C_2H_3O_4)^+$, 67}, 197 {$(M-C_2H_3BrO_4)^+$, 100} and 195 {$(C_{13}H_7S)^+$, 28}; νmax (nujol) 3300-2500 (νO-H), 1715, 1690 (νC=O), 1640, 1600, 1580, 1485, 1270, 1200, 1070, 1010, 860 and 700 cm^{-1}; δ(DMSO-d_6) 3.25 (1H, b, s), 3.60 (1H, b, s), 6.90-76.0 (7H, m) and 7.80 (1H, b, exchanged with D_2O).

When the Stobbe condensation was conducted as reported by Moussa,[191c] no reaction occurred.

Methyl 7-(4-bromophenyl)-4-acetoxybenzo{b}thiophene-6-carboxylate, Methyl 7-bromo-4-(2-thienyl)-1-acetoxynaphthyl-3-carboxylate and the corresponding hydroxy acids (266) (267)

The procedure reported by Moussa[191d] was followed. A mixture of Z and E 3-methoxycarbonyl-4-(4-bromophenyl)-4-(2-thienyl)but-3-enoic acid 45:55 (11.22 g, 63.6 mmol) described in the previous experiment, anhydrous sodium acetate (24.25 g, 136 mmol) and acetic anhydride (70 ml) was refluxed for 16 h and poured into water. Extraction (CH_2Cl_2), washing (H_2O), drying and evaporation afforded the crude product, which was purified on a column of SiO_2. Fractions eluted with 30% Et_2O-PE gave methyl 7-(4-bromophenyl)-4-acetoxybenzo{b}thiophene-6-carboxylate and methyl 7-bromo-4-(2-thienyl)-1-acetoxynaphthyl-3-carboxylate as a light brown oil; m/z 405 (M^+, 2), 362 {$(M-COMe)^+$, 53} and 252 {$(M-C_3H_6BrO_2)^+$, 33}; νmax (neat) 1770, 1720 (νC=O), 1640, 1610, 1590,

† analytical data suggested that decarboxylation of the acid occurred.

1575, 1480, 1250, 1200, 1100, 1070, 1020, 920, 850, 740 and 700 cm^{-1}; δ($CDCl_3$) 2.25 (3H, s), 2.30 (3H, s), 3.50 (6H, s), 6.80-7.80 (13H, m) and 8.00 (1H, m).

The product isolated above was boiled with aqueous alcoholic potassium hydroxide (5%, w/v, 100 ml) for 3 h. After most of the solvent was removed, the residue was acidified (dil. HCl), extracted with CH_2Cl_2, dried and evaporated down. On trituration with PE, a pale brown solid was obtained. Recrystallization from PE-$CHCl_3$ gave a mixture of 7-(4-bromophenyl)-4-hydroxybenzo{b}thiophene-6-carboxylic acid (266) and 7-bromo-4-(2-thienyl)-1-naphthol-3-carboxylic acid (267) as pale colour prisms (11.63 g, 52.4% after 2 steps), m.p. 162-3°C (Found: C, 51.5; H, 2.8; S, 8.7. $C_{15}H_9BrSO_3$ requires C, 51.6; H, 2.6; S, 9.1%); m/z 350 {$(M+1)^+$, 97}, 349 (M^+, 20), 348 {$(M-1)^+$, 100}, 252 {$(M-H_2BrO)^+$, 53} and 224 {$(M-CH_2BrO_2)^+$, 28}; νmax (nujol)· 3500-2500 (νO-H), 1680 (νC=O), 1585, 1570, 1450, 1300, 1215, 1010, 845, 785, 730 and 700 cm^{-1}; δ(DMSO-d_6) 6.90-7.10 (1H, b), 7.25 (1H, d, J 5.2 Hz), 7.28 (2H, d, J 6.5 Hz), 7.62 (2H, d, J 6.5 Hz), 7.65 (1H, d, J 5.2 Hz), 6.95-7.80 (6H, m), 8.35 (1H, m), 10.40 and 10.90 (4H, broad, exchanged by D_2O).

Methyl 7-(4-bromophenyl)-4-methoxybenzo{b}thiophene-6-carboxylate (268), methyl 7-bromo-4-(2-thienyl)-1-methoxy-naphthalene-3-carboxylate (269), and their corresponding acids

A mixture of 7-(4-bromophenyl)-4-hydroxybenzo{b}thiophene-6-carboxylic acid (266), 7-bromo-4-(2-thienyl)-1-naphthol-3-carboxylic acid (267) (1.2:1) (5 g, 14.3 mmol), anhydrous potassium carbonate (16.2 g, 117 mmol), dimethyl sulphate (4.08 ml, 96 mmol) in acetone (150 ml) were refluxed for 18 h and poured into water. Extraction (CH_2Cl_2), washing (H_2O,

followed by 2M HCl), drying and evaporation afforded a brown solid, which on trituration with PE gave methyl 7-(4-bromophenyl)-4-methoxybenzo{b}thiophene-6-carboxylate (268) and methyl 7-bromo-4-(2-thienyl)-1-methoxy-naphthalene-3-carboxylate (269) as a pale colour solid (3.47 g, 64.4%), m.p. 129-130°C (ether) (Found: C, 54.2; H, 3.1. $C_{17}H_{13}BrSO_3$ requires C, 54.1; H, 3.5%); m/z 378 (M^+, 100), 376 (M^+, 93), 363 {$(M-Me)^+$, 20}, 361 {$(M-Me)^+$, 21}, 266 {$(M-CH_3BrO)^+$, 21} and 223 {$(M-C_3H_6BrO_3)^+$, 13}; νmax (nujol) 3100, 1720 (νC=O), 1580, 1485, 1235, 1165, 1120, 1050, 995, 825, 785, 710 and 700 cm^{-1}; δ($CDCl_3$) 3.60 (3H, s), 3.62 (3H, s), 3.96 (3H, s), 3.98 (3H, s), 6.90-7.70 (13H, m) and 8.45 (1H, m).

The methoxy ester (2.5 g, 6.6 mmol) obtained above was refluxed with 5% ethanolic KOH (20 ml) for 3 h. The alkaline solution was filtered and acidified with HCl (6M). Extraction (EtOAc), drying and evaporation gave a residue which on trituration with PE afforded 7-(4-bromophenyl)-4-methoxybenzo{b}thiophene-6-carboxylic acid and 7-bromo-4-(2-thienyl)-1-methoxy-naphthalene-3-carboxylic acid (1.88 g, 78.4%) as a pale colour solid; m.p. 208-9°C (Found: C, 51.9; H, 2.8. $C_{16}H_{11}BrO_3S \cdot \frac{1}{4}H_2O$. requires C, 52.1; H, 3.1%); m/z 364 (M^+, 100), 362 (M^+, 95), 349 {$(M-Me)^+$, 34}, 347 {$(M-CH_3)^+$, 36}, 331 {$(M-MeOH)^+$, 14} and 329 {$(M^+-MeOH)^+$, 13}; νmax (nujol) 2500 (νO-H), 1690 (νC=O), 1580, 1570, 1410, 1270, 1250, 1230, 1050, 850, 820, 770 and 700 cm^{-1}; δ(DMSO-d_6) 3.98 (3H, s), 4.02 (3H, s), 7.00-8.00 (13H, m) and 8.48 (1H, m). (The mixture precipitated out on addition of D_2O.)

Methyl 7-(4-methoxyphenyl)-4-methoxybenzo{b}thiophene-6-carboxylate (270), methyl 1,7-dimethoxy-4-(2-thienyl)-naphthalene-3-carboxylate (271) and their corresponding acids (272) (273)

A literature procedure[193] was followed. Freshly cut sodium (0.83 g, 36 mmol) was added, under nitrogen, to methanol (10 ml) in the reaction flask. When dissolution was complete the warm solution was diluted with 2,4,6-collidine (10 ml, distilled and dried), followed by copper(I)iodide (1.14 g, 6 mmol; vacuum dried at 100°C for 6 h), then methyl 7-(4-bromophenyl)-4-methoxybenzo{b}thiophene-6-carboxylate (268), methyl 7-bromo-4-(2-thienyl)-1-methoxynaphthol-3-carboxylate (269) (4.54 g, 12 mmol) (1.2:1) and more collidine (35 ml). The mixture was stirred under nitrogen while being maintained at refluxing temperature (bath temp. Ca. 140°C) for 6 h. After cooling, an equal volume of 6N HCl was added. Extraction (Et_2O), washing of the extracts (H_2O), filtration through celite, drying and evaporation gave a brown oil, which was chromatographed on a column of SiO_2. Fractions eluted with 60% Et_2O-PE on evaporation gave a yellow solid. Recrystallization from $CHCl_3$/PE (CO_2-acetone bath) gave colourless prisms (3.35 g, 85.0%), shown to be roughly an equal molar mixture of methyl 7-(4-methoxyphenyl)-4-methoxybenzo{b}thiophene (270) and methyl 1,7-dimethoxy-4-(2-thienyl)-naphthalene-3-carboxylate (271) by ^1H NMR, m.p. 157-8°C (Found: C, 63.7; H, 4.3. $C_{18}H_{16}O_4S \cdot 0.1\ CHCl_3$ requires C, 63.9; H, 4.7%); m/z 328 (M^+, 100), 313 {$(M-CH_3)^+$, 44}, 297 {$(M-OCH_3)^+$, 13}, 254 {$(M-CH_3-CO_2CH_3)^+$, 10} and 239 {$(M-2CH_3-CO_2CH_3)^+$, 8}; νmax (nujol) 3110, 1725, 1690, 1670, 1620, 1610, 1595, 1570, 1518, 1500, 1410, 1335, 1285, 1250, 1220, 1190, 1165, 1120, 1110, 1095, 1050, 1035, 990, 895, 850, 835, 785 and 700 cm^{-1}; δ($CDCl_3$) 3.60 (3H, s), 3.62

(3H, s), 3.70 (3H, s), 3.90 (3H, s), 3.97 (3H, s), 4.02 (3H, s), 6.85-7.75 (14H, m); UV (EtOH) 192 nm (ε 20089), 206 nm (22817), 235.5 nm (25050), 270 nm (8309) and 315 nm (6076); separation of the two isomers by chromatography or fractional crystallization was unsuccessful.

The above mixture of isomers was saponified by refluxing with 5% EtOH/KOH for 2½ h. Worked up as usual and after recrystallization from EtOAc/PE gave the corresponding acids (272) and (273) (71%) as colourless prisms, m.p. 175-6°C (Found: C, 65.0; H, 4.4. $C_{17}H_{14}SO_4$ requires C, 65.0; H, 4.5%); m/z 314 (m^+, 100) and 299 {$(M-CH_3)^+$, 46}; νmax (nujol) ~3300-2500, 1700, 1670, 1620, 1610, 1600, 1580, 1570, 1520, 1500, 1430, 1370, 1360, 1335, 1280, 1250, 1230, 1210, 1195, 1175, 1105, 1090, 1050, 1030, 900, 860, 835, 810 and 700 cm^{-1}; δ(DMSO-d_6), 3.75 (3H, s), 3.82 (3H, s), 3.93 (3H, s), 4.00 (3H, s), 6.85-7.66 (14H, m), 7.8-8.6 (2H, broad s., exchanged with D_2O).

7-(4 -methoxyphenyl)-4-methoxybenzo{b}thiophene (274)

A mixture of methyl 7-(4-methoxyphenyl)-4-methoxybenzo{b}thiophene-6-carboxylate (272) and methyl 7-methoxy-4-(2-thienyl)-1-methoxynaphthol-1-carboxylate (273) (1.2:1) (3.82 g, 12 mmol), copper powder (2.5 g, 39.5 mmol) and quinoline (10 ml, freshly distilled from CaH_2) was refluxed for 1 h. After cooling, the mixture was diluted with an equal volume of CH_2Cl_2 and filtered through celite. Washing (6M HCl, H_2O) of the filtrate, drying and evaporation gave a brown oil, which was chromatographed on a column of SiO_2. Fraction eluted with 30% Et_2O-PE on evaporation gave a pale yellow oil solidified on standing. Recrystallization from ether gave 7-(4-methoxyphenyl)-4-methoxybenzo{b}

thiophene (274) (1.5 g, 84.2%) as colourless prisms, m.p. 105-6°C (Found: C, 70.9; H, 5.2; S, 12.2. $C_{16}H_{14}O_2S$ requires C, 71.1; H, 5.2; S, 11.9%); TLC {(SiO_2; Et_2O-PE (3:7)} Rf 0.49; m/z 270 (M^+, 100), 255 {$(M-CH_3)^+$, 92} and 240 {$(M-2CH_3)^+$, 6}; νmax (nujol) 1610, 1590, 1575, 1495, 1380, 1360, 1350, 1290, 1280, 1250, 1245, 1175, 1160, 1105, 1040, 1030, 890, 835, 820, 810, 775, 710 and 700 cm^{-1}; δ($CDCl_3$) 3.75 (3H, s), 3.85 (3H, s), 6.69 (1H, d, J 8 Hz), 6.89 (2H, d, J 7.8 Hz), 7.15 (1H, d, J 8 Hz), 7.20 (1H, d, J 5.2 Hz), 7.58 (1H, d, J 5.2 Hz) and 7.62 (2H, d, J 8.7 Hz); UV (EtOH) 199.5 nm (ε 30916), 216.5 nm (23689), 242 nm (ε 13317), 276 nm (13651) and 310 nm (5086).

Attempted oxidation of 7-(4-methoxyphenyl)-4-methoxybenzo{b}thiophene (274)

1) with cerium(IV)ammonium nitrate (CAN)

Cerium(IV)ammonium nitrate (1.09 g, 1.99 mmol) in water (10 ml) was added to a solution of 7-(4-methoxyphenyl)-4-methoxybenzo{b}thiophene (274) (180 mg, 0.67 mmol) in acetonitrile (10 ml) during 5 min at RT. After 1 h, the mixture was extracted with CH_2Cl_2. Washing of the extracts, drying and evaporation afforded an oil which was chromatographed on SiO_2. Fractions eluted with Et_2O-PE (2:8) afforded a yellow oil (90 mg), m/z 315 (100), 270 (11), 254 (25), 239 (20), 211 (24), 195 (11) and 139 (16); ^1H NMR (300 MHz, $CDCl_3$) 3.74 (3H, s), 6.10 (1H, d, J 10Hz), 6.80 (1H, d, J 9.5 Hz), 6.87 (1H, d, J 10 Hz), 7.21 (1H, d, J 5 Hz), 7.26 (1H, d, J 9.5 Hz) and 7.30 (d, J 5 Hz). Fractions eluted with Et_2O afforded a red solid (8 mg), m.p. 124-5°C (acetone-PE), m/z 276 (52), 272 (36), 256 (100), 241 (52), 213 (16), 184 (14), 169 (15), 135 (97), 106 (16), 84 (33) and 77 (26), ^1H NMR

($CDCl_3$, 300 MHz), 3.88 (s), 4.08 (s), 7.02 (d, J 9.5 Hz), 7.27 (s), 7.33 (d, J 9.5 Hz), 7.38 (s), 7.57 (d, J 5 Hz), 7.60 (s) and 7.87 (d, J 5 Hz).

2) with iodotrimethylsilane

A mixture of 7-(4-methoxyphenyl)-4-methoxybenzo{b}thiophene (274) (500 mg, 1.85 mmol) and iodotrimethylsilane (10 ml) in $CHCl_3$ (20 ml) was refluxed, under N_2, for 4 days and poured into CH_3OH (10 ml). Washing (saturated sodium bisulphite, H_2O), drying and evaporation afforded very pale brown solid (230 mg), which was flash chromatographed on SiO_2 with EtOAc-PE (7:3). 7-(4-Hydroxyphenyl)-4-hydroxybenzo{b}-thiophene (202) was obtained as off-white prisms (100 mg, 22.3%), m.p. 181-2°C (acetone-PE) (Found: C, 69.1; H, 3.9. $C_{14}H_{10}O_2S$ requires C, 69.4; H, 4.1%); m/z 242 (M^+, 100), 241 {$(M-H)^+$, 13} and 213 (23); νmax (nujol) 3250, 1680, 1610, 1570, 1495, 1245, 938, 908, 820 and 805 cm^{-1}; ^1H NMR ($CDCl_3$) 6.70-7.60 (8H, m).

Subsequent oxidation of the above phenol with excess CAN, under similar conditions to that described earlier, led to extensive polymerization.

3) with silver(II)oxide/phosphoric acid

A literature procedure was followed.[198] Phosphoric acid (1 ml, 85%) was added to a mixture of 7-(4-methoxyphenyl)-4-methoxybenzo{b}-thiophene (270) (100 mg, 0.37 mmol), silver(II)oxide (730 mg) in dioxane (10 ml). After 15 min at RT, CH_2Cl_2 (10 ml) and water (15 ml) were added. Filtration (celite), washing, drying and evaporation

afforded a residue which was chromatographed on SiO_2 with EtOAc/PE (1:1) to give a red oil (20 mg); m/z 316 (6), 300 (9), 272 (57), 242 (100), 227 (19), 199 (24), 171 (67), 169 (15) and 139 (21); ^1H NMR ($CDCl_3$, 300 MHz) showed a very complicated spectrum, the essential features of which were: 3.89 (s), 4.42 (s), 6.25 (s), 7.03 (d, J 10 Hz), 7.45 (d, J 5 Hz), 7.62 (d, J 5 Hz), 7.63 (d, J 10 Hz) and 8.09 (s).

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