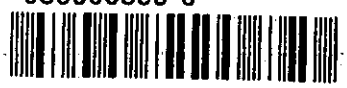
Diels–Alder reactions of heterocyclic fused [alpha]-pyrones



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To my parents,
with love

Diels-Alder reactions of heterocyclic fused α-pyrones

by

Mark Jackson

A Doctoral Thesis

Submitted in partial fulfilment of the requirements
for the award of

Doctor of Philosophy
of the
Loughborough University of Technology

September 1991

Abstract

The chemistry of heterocyclic analogues of orthoquinodimethane is reviewed.

Benzothieno[2,3-*c*]pyran-3-ones and the isomeric [3,2-*c*]pyranones are stable analogues of benzothiophene-2,3-quinodimethane. When heated with alkynes they undergo Diels-Alder reaction to give, after loss of carbon dioxide, dibenzothiophenes.

Likewise, thieno[2,3-*c*]pyran-3-ones and the isomeric [3,2-*c*]pyranones are stable derivatives of thiophene-2,3-quinodimethane. When heated with alkynes they undergo Diels-Alder reaction to give benzothiophenes. Intramolecular Diels-Alder reactions give cycloalka[*g*]- and cycloalka[*e*]benzothiophenes.

Pyrano[3,4-*b*]pyrrol-5(1*H*)-ones and the isomeric [4,3-*b*]pyrrolones are stable analogues of pyrrole-2,3-quinodimethane and undergo Diels-Alder reaction with alkynes to give indoles. This constitutes a novel route from pyrroles to indoles. Reaction with benzyne gives benz[*f*]indoles. Reaction with the acetylene equivalent phenyl vinyl sulphoxide gives 5,6- unsubstituted indoles. Intramolecular Diels-Alder reactions give cycloalka[*g*]- and cycloalka[*e*]indoles.

A short synthesis of the naturally occurring free radical scavenger carazostatin starting from indol-3-ylacetic acid is described, the key step being the regiospecific Diels-Alder reaction of 1-heptylpyrano[3,4-*b*]indol-3-one with ethyl 3-trimethylsilylpropynoate.

Preliminary studies towards the construction of the A and B rings of the tremorgenic indole, Lolitrem B are described.

Acknowledgements

I would like to thank Professor C. J. Moody for his help and encouragement throughout the course of this work.

I am grateful to all the support staff at Imperial College and Loughborough University of Technology, and especially to Mr. P. Sulsh, Mr. A. Daley, and Mr. P. Hartopp for their skilled technical assistance; Mr. R. N. Sheppard for NOE data; Mr. J. C. Kershaw for ^{1}H and ^{13}C NMR; Mr. J. Bilton and Mr. A. J. Greenfield for mass spectroscopy; and Mr. K. I. Jones for microanalytical data.

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My thanks for help in the preparation of this thesis are due to Mrs. J. Stirling and Mrs. B. E. Cattell for the typing of parts of the experimental section.

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Finally, I would like to thank my parents for their constant support throughout my education.

Contents **Page**

Abbreviations

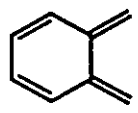
BHT	Butylated hydroxytoluene
bpy	2,2' bipyridyl
Cp	Cyclopentadienyl
DBA	Dibenzoylacetylene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMAD	Dimethyl acetylenedicarboxylate
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
FVP	Flash vacuum pyrolysis
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
IMDA	Intramolecular Diels-Alder
i_p	Peak current
LDA	Lithium diisopropylamide
LICA	Lithium isopropylcyclohexylamide
LUMO	Lowest unoccupied molecular orbital
MCPBA	*m*-Chloroperbenzoic acid
NBS	*N*-Bromosuccinimide
NOE	Nuclear Overhauser effect
PPA	Polyphosphoric acid
s.s.c.e.	Sodium chloride saturated calomel electrode
TBDMS	t-Butyldimethylsilyl
Tf	Trifluoromethanesulphonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulphonyl

CHAPTER 1

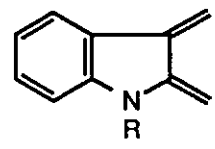
Heterocyclic analogues of orthoquinodimethane

1.1 Introduction

Orthoquinodimethane (**1**) has been used extensively as a reactive intermediate in organic synthesis. Its generation and reactivity have been the subject of a recent review.[1] Indole-2,3-quinodimethanes (**2**) and stable cyclic analogues have also been recently reviewed.[2] Therefore, this review will concentrate on other heterocyclic quinodimethanes.



(**1**)

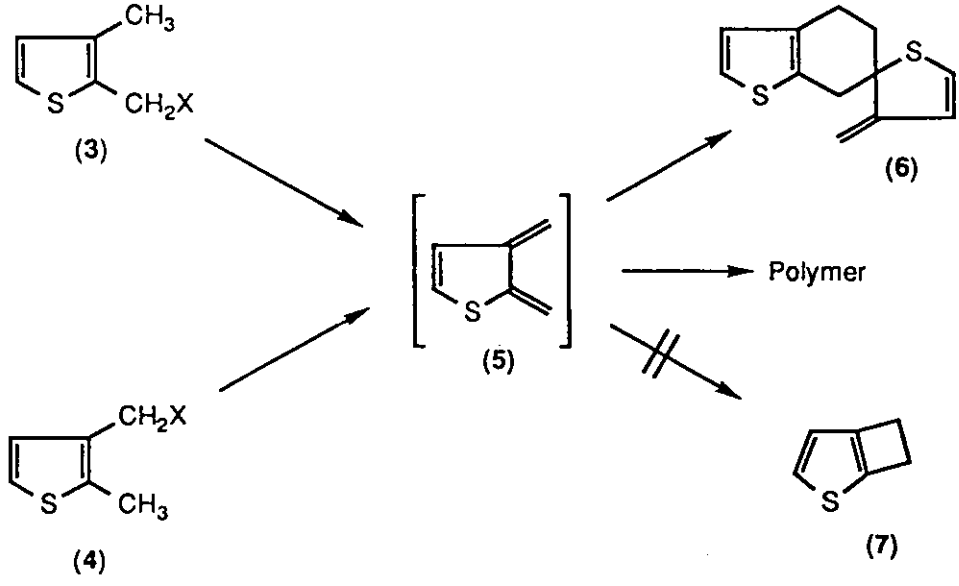


(**2**)

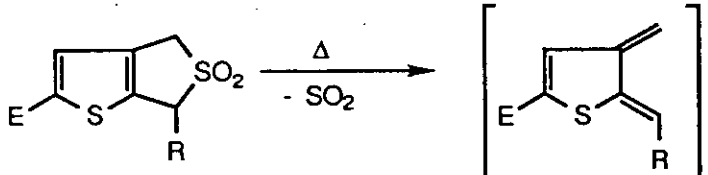
1.2 Thiophene-2,3-quinodimethane

1.2.1 Flash Pyrolysis

Flash vacuum pyrolysis of the isomeric chlorides (**3**; X=Cl) and (**4**; X=Cl) yielded thiophene-2,3-quinodimethane (**5**) which readily dimerised to give a [4+2] spiro dimer of type (**6**) or polymerised.[3]

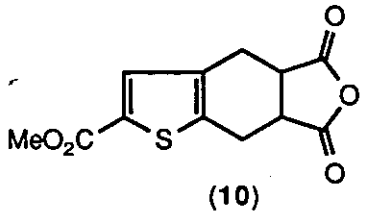
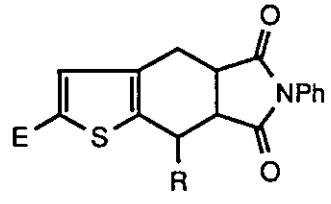
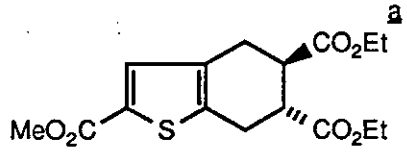
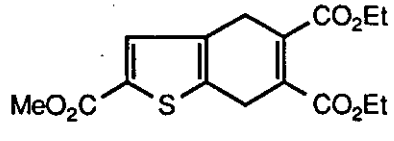


There was no evidence for the formation of the isomeric cyclobuta[*b*]thiophene (**7**) in the gas phase. However, interconversion of (**5**) and (**7**) was possible in an argon matrix by irradiating with light of the appropriate wavelength.[4] Attempts to trap the quinodimethane (**5**) in Diels-Alder reactions were unsuccessful. However, compound (**5**) could be trapped efficiently by sulphur dioxide to give a cyclic sulphone (**8**; R=E=H).[5] The cyclic sulphone (**8**; R=H, E=CO_2Me) was readily synthesised by bis-chloromethylation of methyl thiophene-2-carboxylate, followed by treatment with sodium sulphide, and oxidation to the dioxide. Methylation of the sulphone (**8**; R=H, E=CO_2Me) using LDA and methyl iodide gave a monomethyl derivative (**8**; R=Me, E=CO_2Me). Heating these sulphones in sulpholane at 200°C generated the quinodimethane (**9**) which could be trapped by a range of dienophiles (Table 1).



(**8**) (**9**)

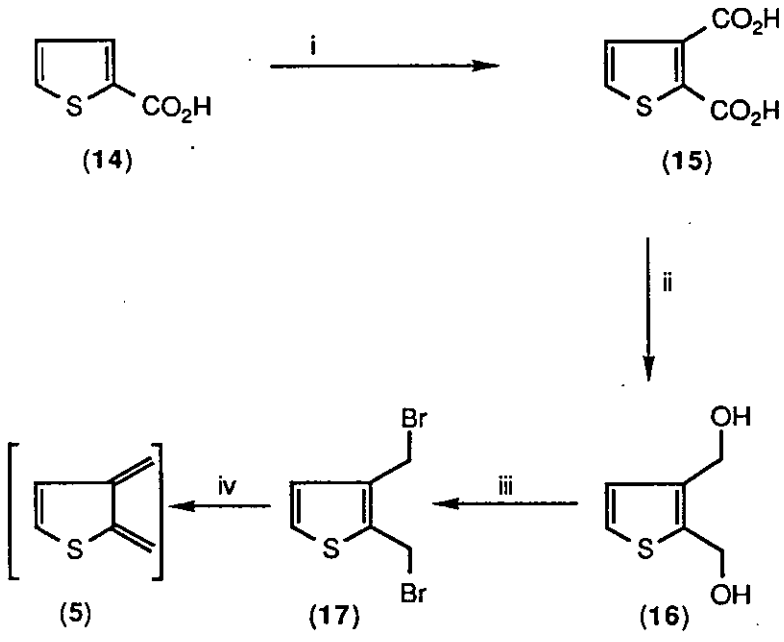
Table 1. Reaction of Quinodimethane (9) with Dienophiles.

Quinodimethane (9)	Dienophile	Adduct	Yield (%)
E = CO_2Me, R = H	Maleic Anhydride	 (10)	80
E = CO_2Me, R = H E = CO_2Me, R = Me E = H, R = H	*N* -Phenylmaleimide	 (11)	78 92 70
E = CO_2Me, R = H	Diethyl Fumarate	 (12)	85
E = CO_2Me, R = H	Diethyl Acetylene-dicarboxylate	 (13)	85

[a] racemate

1.2.2 Iodide ion induced elimination

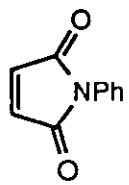
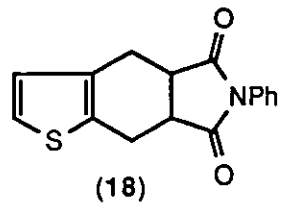
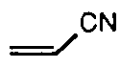
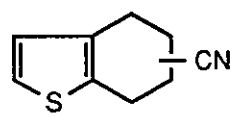
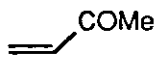
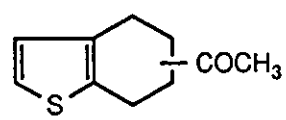
2,3-Di(bromomethyl)thiophene (**17**) was synthesised from thiophene-2-carboxylic acid (**14**) in three steps (Scheme 1).[6] *Ortho*-lithiation of thiophene-2-carboxylic acid (**14**), followed by quenching with carbon dioxide gave the dicarboxylic acid (**15**). Reduction using lithium aluminium hydride gave the diol (**16**) which was converted to the bis-bromide (**17**) by treatment with phosphorus tribromide.



Scheme 1. *Reagents* i) ^{n}BuLi, THF, -78°C, 0.5 h, then CO_2, then HCl (aq.), 95%; ii) $LiAlH_4$, THF, reflux, 24 h, then H_2O, 88%; iii) PBr_3, C_6H_6, 20°C, 4 h, 68%; iv) NaI, DMF.

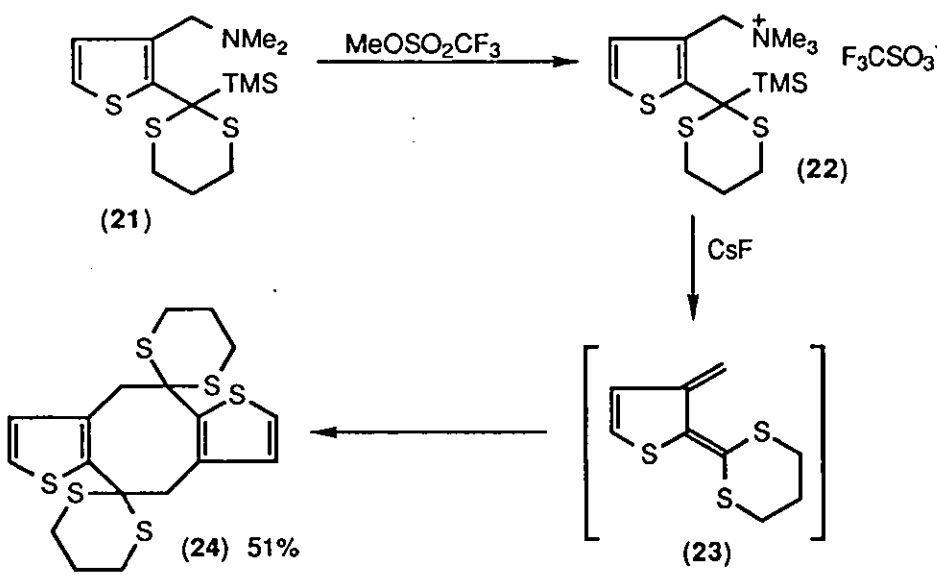
Treatment of the bis-bromide (**17**) with sodium iodide in DMF at 80°C in the presence of a dienophile led to the generation of thiophene-2,3-quinodimethane (**5**) which was trapped as its Diels-Alder adduct (Table 2). The adducts (**19**) and (**20**), obtained by trapping of the quinodimethane (**5**) with the unsymmetrical dienophiles, acrylonitrile and methyl acrylate respectively, were obtained as mixtures of regioisomers but no ratio was given.

Table 2. Reaction of thiophene-2,3-quinodimethane (**5**) with alkenes.

Dienophile	Product	Yield (%)
	 (**18**)	60
	 (**19**)	60
	 (**20**)	50

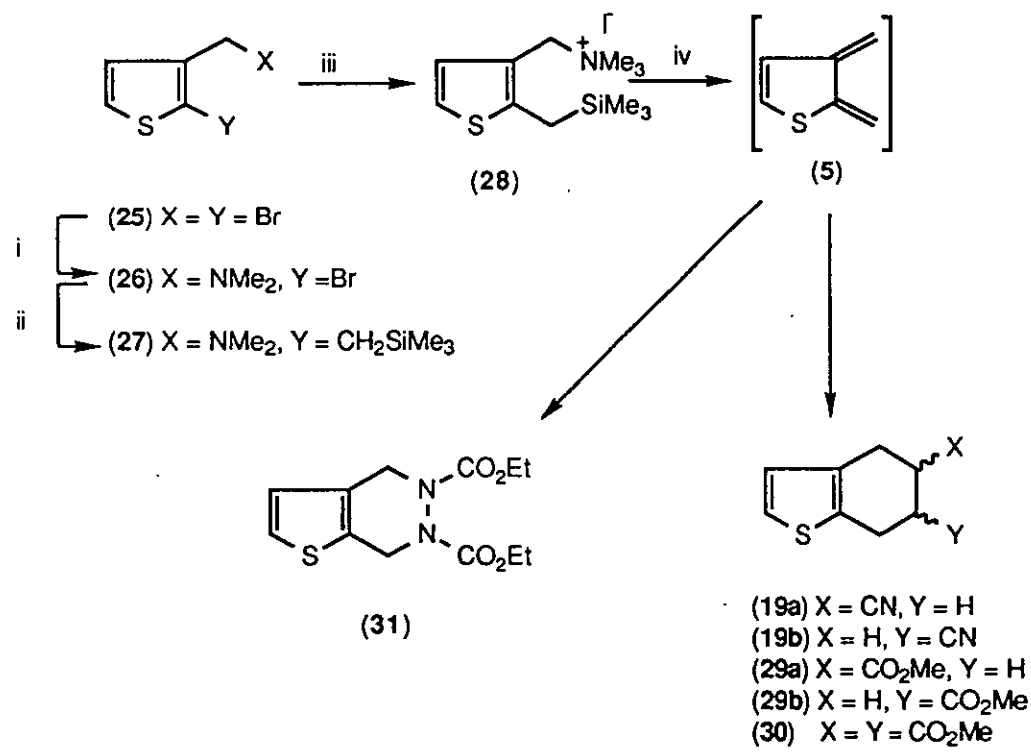
1.2.3 Fluoride ion induced elimination

An early example involved elimination of the triflate salt (**22**), using caesium fluoride, to generate the quinodimethane (**23**) which dimerised to give the eight-membered ring compound (**24**) in 51% yield.[7]



The triflate salt (**22**) was prepared by treatment of 2-[3-(*N*,*N*-dimethylamino)-2-thienyl]-2-trimethylsilyl-1,3-dithiane (**21**) with methyl triflate.

A fluoride ion induced 1,4-elimination of the trimethylsilyl group and trimethylamine from 3-(trimethylammoniummethyl)-2-(trimethylsilyl-methyl)thiophene iodide (**28**) generated thiophene-2,3-quinodimethane (**5**) which was trapped in [4+2] cycloaddition reactions (Scheme 2 and Table 3).[8] Compound (**28**) was synthesised from 2-bromo-3-(bromomethyl)thiophene (**25**) by treatment with dimethylamine, then trimethylsilylmethyl magnesium chloride catalysed by bis-(triphenylphosphine)nickel dichloride, and quaternisation using methyl iodide in acetonitrile.



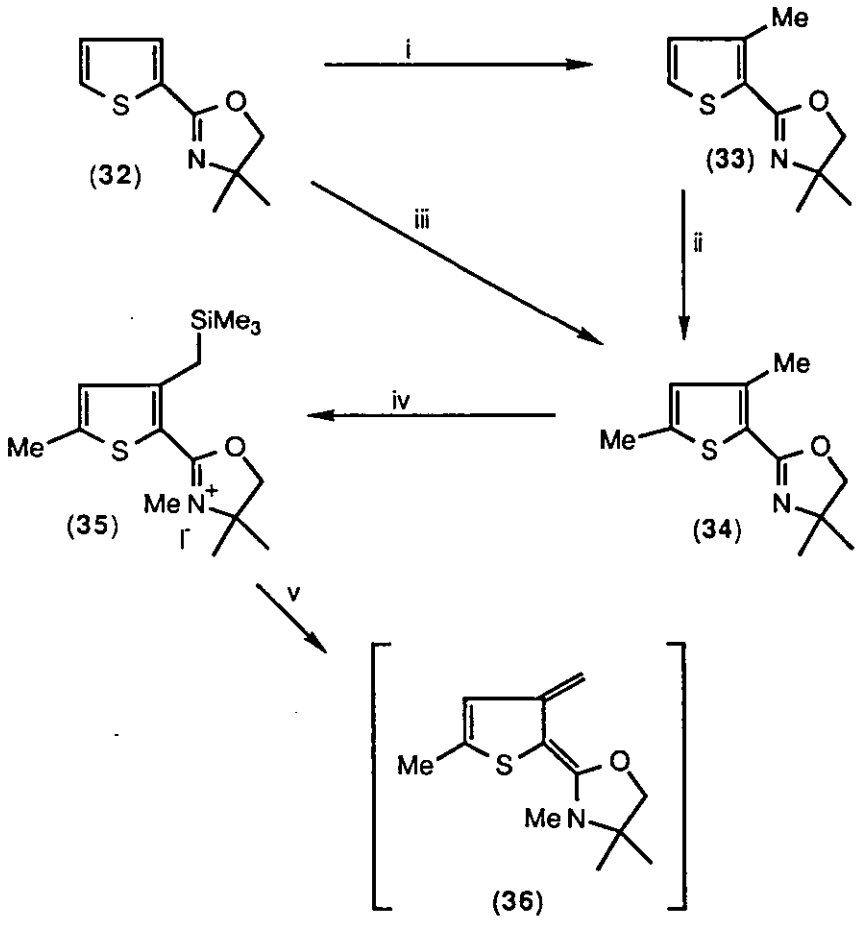
Scheme 2. *Reagents* i) Me_2NH (40%), 15 min, 20°C, 65%; ii) Me_3SiCH_2MgCl, $Ni(PPh_3)_2Cl_2$ (3 mol %), Et_2O, reflux, 20 h, 78%; iii) MeI, MeCN, reflux, 1 h, 98%; iv) F^-.

Table 3. Reaction of thiophene-2,3-quinodimethane (**5**) with dienophiles.

Dienophile	Product (Ratio)	Yield (%)
Acrylonitrile	**19a+b** (1:2.4)	92
Methyl Acrylate	**29a+b** (1:1.8)	90
Dimethyl Maleate	**30**	92
Diethyl Azodicarboxylate	**31**	85

Reaction of (**5**) with acrylonitrile and methyl acrylate showed, in each case, a slight preference for the formation of the 6-substituted tetrahydrobenzothiophenes (**19b**) and (**29b**).

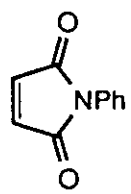
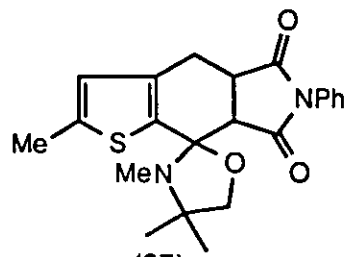
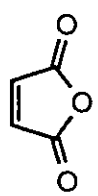
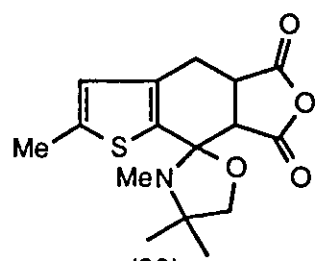
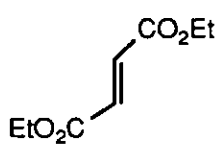
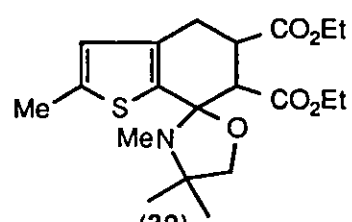
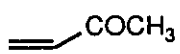
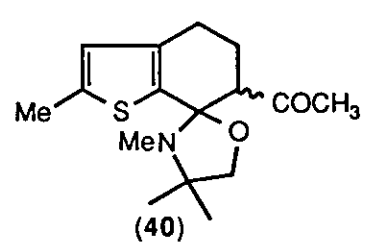
Another example of fluoride ion induced elimination involves treatment of the thiophene (**35**) with caesium fluoride to generate the quinodimethane (**36**) (Scheme 3).[6] 4,4-Dimethyl-2-(2-thienyl)oxazoline (**32**) was *ortho*-lithiated and quenched with methyl iodide to give compound (**33**), which was 5-methylated to give the 3,5-dimethylthiophene (**34**). Compound (**34**) was selectively deprotonated, at the 3-methyl position, and quenched with trimethylsilyl chloride, followed by quaternisation with methyl iodide to give compound (**35**).



Scheme 3. *Reagents* i) ^{n}BuLi, Et_2O, -78°C, 0.25 h, then 0°C, 0.5 h, then MeI, 93%; ii) ^{n}BuLi, THF, -78°C, 0.5 h, then MeI, 100%; iii) ^{s}BuLi (3 eq.), THF, -20°C, 0.5 h, then MeI, 96%; iv) ^{s}BuLi, THF, -78°C, 0.5 h, then warm to 20°C, then TMSCl, then MeI, 83%; v) CsF, MeCN.

The quinodimethane (**36**) could be trapped with a range of dienophiles (Table 4). Electron donating substituents on the 2-methylene group are responsible for a dramatic increase in selectivity relative to quinodimethane (**5**). Adduct (**40**) was obtained as a single regioisomer, but a 1:1 mixture of diastereomers.

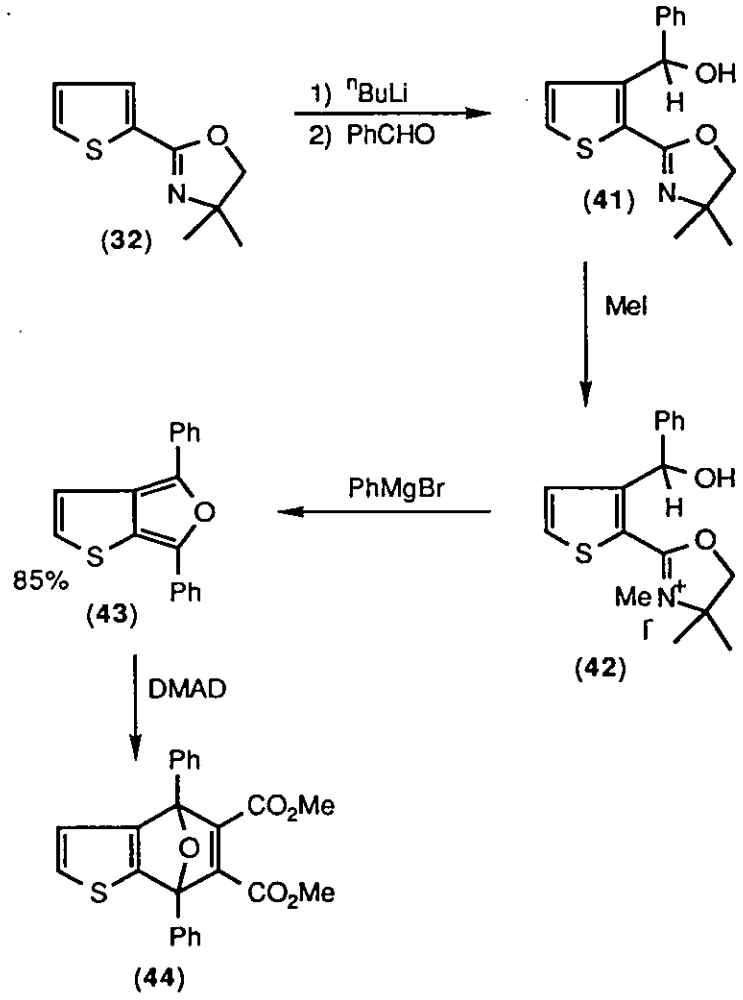
Table 4. Reaction of quinodimethane (**36**) with alkenes.

Dienophile	Product	Yield (%)
	 (37)	74
	 (38)	77
	 (39)	85
	 (40)	87

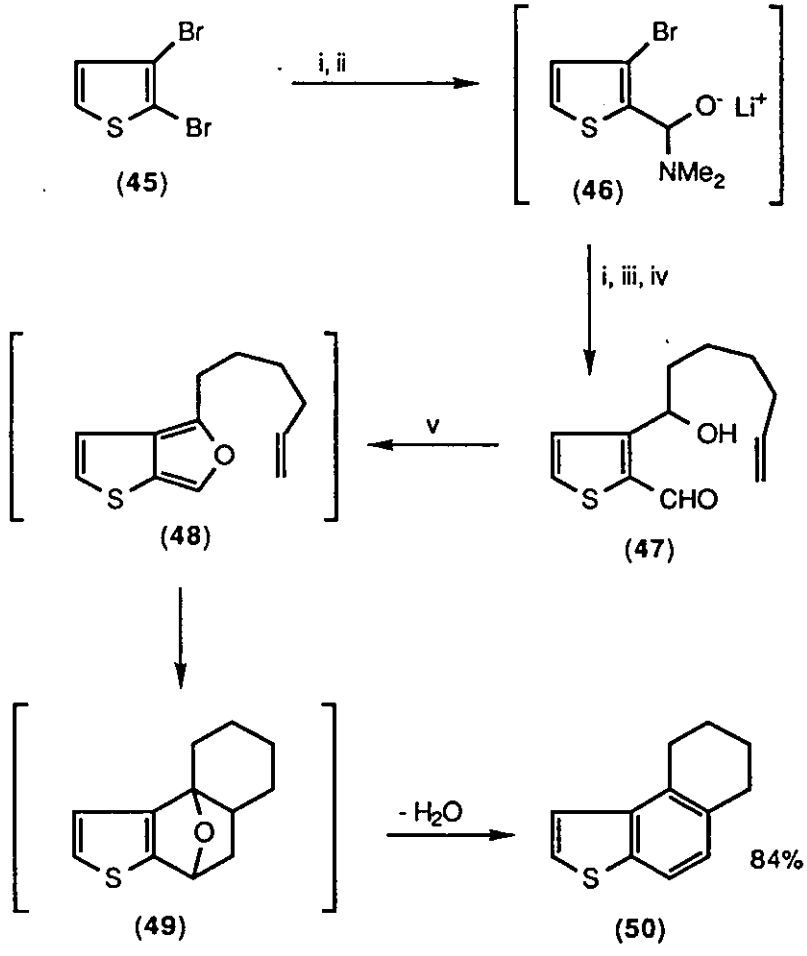
1.3 Cyclic analogues of thiophene-2,3-quinodimethane

1.3.1 Thieno[2,3-*c*]furans

1,3-Diphenylthieno[2,3-*c*]furan (**43**) was synthesised in three steps from 4,4-dimethyl-2-(2-thienyl)oxazoline (**32**).[9] *Ortho*-lithiation of the thienyloxazoline (**32**) followed by quenching with benzaldehyde gave the alcohol (**41**). Quaternisation with methyl iodide followed by treatment with phenylmagnesium bromide gave the thieno[2,3-*c*]furan (**43**), which underwent Diels-Alder reaction with DMAD to give the adduct (**44**).

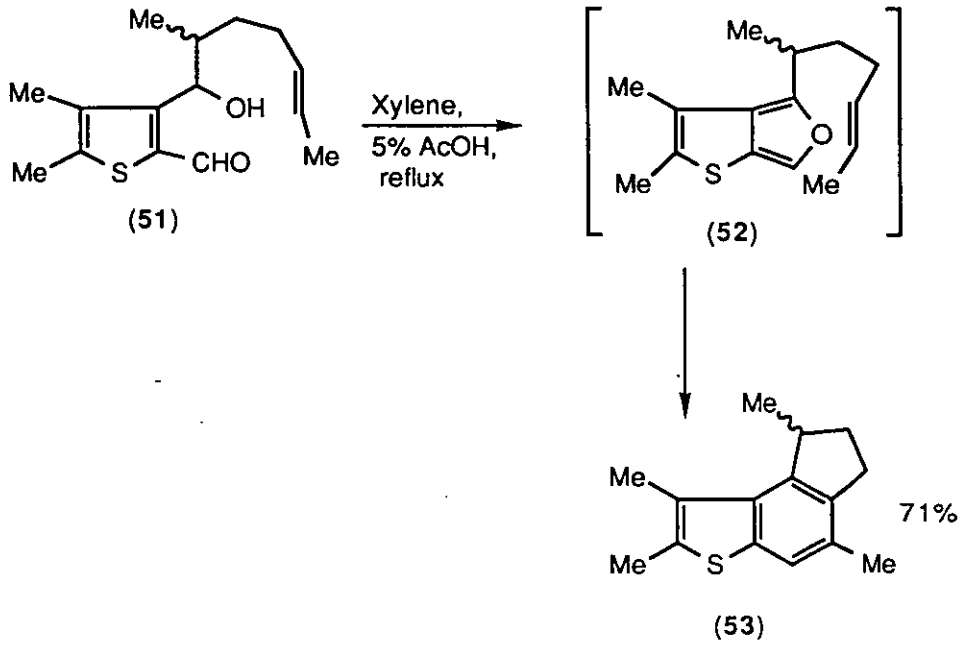


Thieno[2,3-*c*]furans have also been shown to undergo intramolecular Diels-Alder reaction. Tetrahydronaphtho[2,1-*b*]thiophene (**50**) was synthesised utilising an intramolecular Diels-Alder reaction of the 1-alkenylthieno[2,3-*c*]furan (**48**) (Scheme 4).[10] Selective halogen-metal exchange at the 2-position of 2,3-dibromothiophene (**45**), followed by quenching with DMF, gave the intermediate (**46**). Further halogen-metal exchange at the 3-position, followed by condensation with heptenal, gave the thieno[2,3-*c*]furan precursor (**47**) which was converted into the benzothiophene (**50**) upon heating in toluene containing acetic acid.



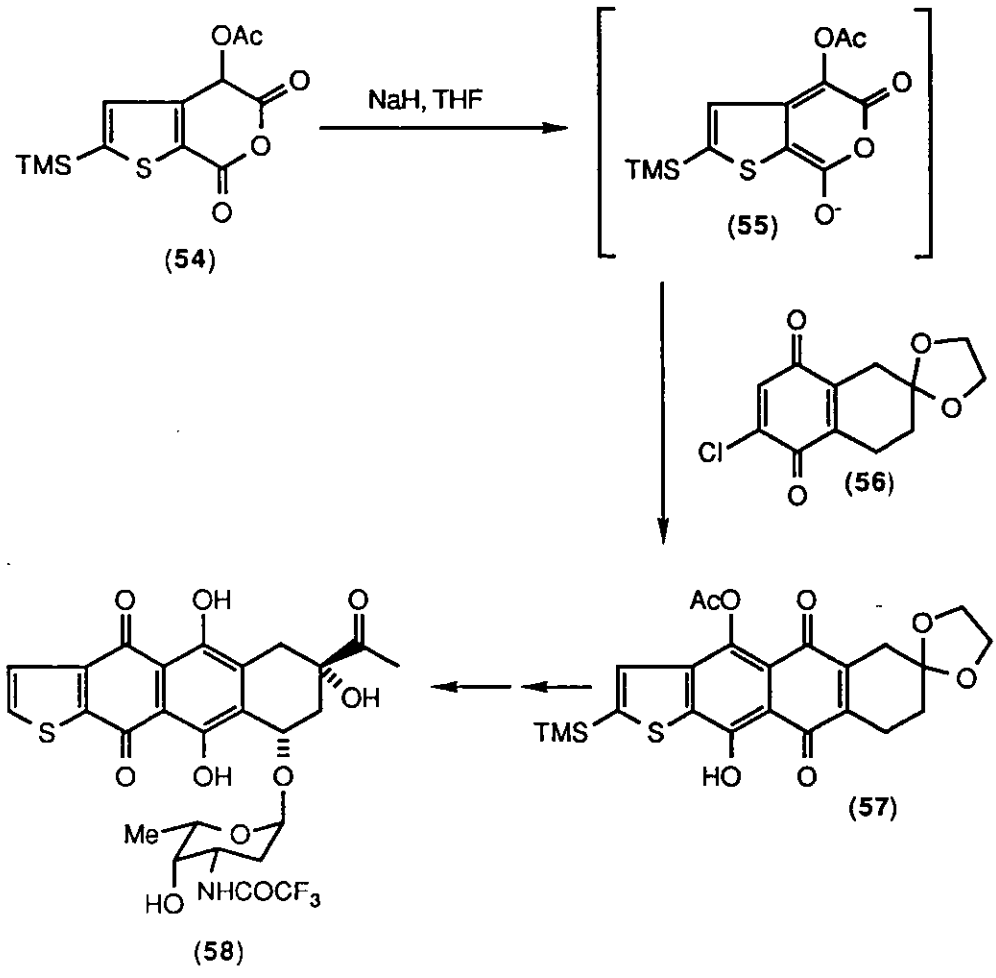
Scheme 4. *Reagents* i) ^{n}BuLi, Et_2O, -78°C; ii) DMF; iii) Heptenal; iv) 2M HCl; v) PhMe, 2% AcOH, reflux.

rac-Thiamarmelerin (**53**) was prepared by intramolecular Diels-Alder reaction of the thieno[2,3-*c*]furan (**52**), which was generated by heating the thiophene (**51**) in xylene containing acetic acid.[11]

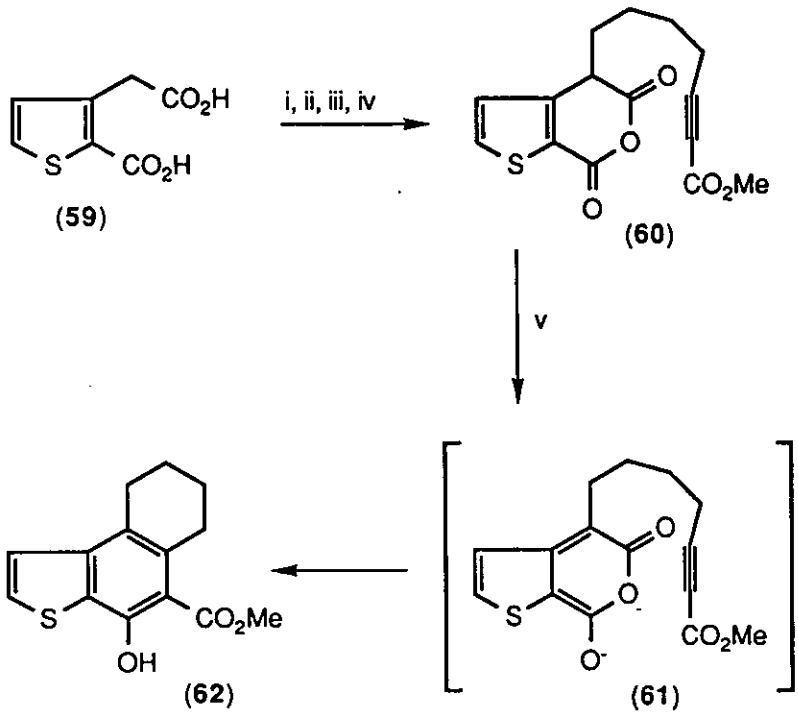


1.3.2 Homophthalic anhydrides

The strong base-induced cycloaddition reaction of the thiophene analogue (**54**) of homophthalic anhydride was used in the synthesis of D-ring thiophene analogues, *e.g.* (**58**), of the anthracycline antibiotic daunomycin.[12] The key step involved deprotonation of the anhydride (**54**) to give the anionic diene (**55**) which underwent regiospecific cycloaddition reaction with the quinone (**56**), followed by elimination of CO_2 and HCl to give the adduct (**57**).



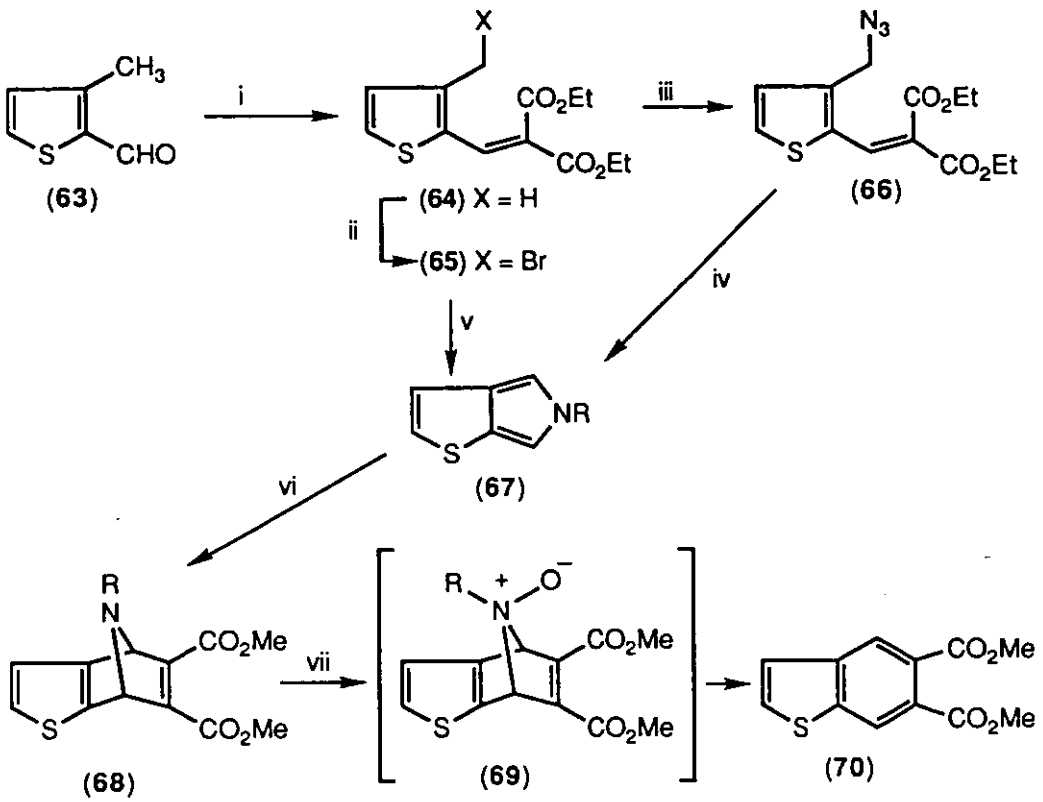
Intramolecular cycloaddition of these anhydrides has also been reported (Scheme 5).[13,14] 2-Carboxythiophene-3-acetic acid (**59**) was esterified using diphenyl diazomethane and alkylated with $I(CH_2)_4$-C≡C-CO_2Me. Selective deprotection of the diphenylmethyl esters, without demethylation of the acetylenic ester, was accomplished using boron trifluoride diethyl ether and acetic acid. Dehydration using (trimethylsilyl)ethoxyacetylene gave the anhydride (**60**). Strong base treatment of (**60**) generated the anionic diene (**61**) which underwent smooth intramolecular cycloaddition reaction, followed by extrusion of carbon dioxide, to give the tetrahydronaphthothiophene (**62**).



Scheme 5. *Reagents* i) Ph_2CN_2, DCM, rt, 2.5 h, 100%; ii) LDA, THF, -78°C, then $I(CH_2)_4$-C≡C-CO_2Me, 1% HMPA-THF, -78°C→*rt*, 2 h, 33%; iii) $BF_3.Et_2O$, AcOH, 0°C→ rt, 1 h, 94%; iv) TMS-C≡C-OEt , DCM, rt, 3-5 h, 100%; v) NaH, THF, rt, 1-2 h, 67%.

1.3.3 Thieno[2,3-*c*]pyrroles

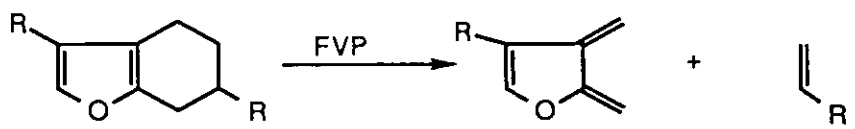
Thieno[2,3-*c*]pyrroles (**67**) are readily prepared from 3-methyl-2-thiophenecarboxaldehyde (**63**) (Scheme 6).[15] Knoevenagel condensation of (**63**) with diethyl malonate gave compound (**64**). Bromination of (**64**), with *N*-bromosuccinimide and dibenzoyl peroxide, gave the bromide (**65**) which was converted to the azide (**66**) upon treatment with sodium azide in ethanol. Treatment of (**66**) with triphenylphosphine followed by water gave the parent compound 5*H*-thieno[2,3-*c*]pyrrole (**67**, R=H). Alternatively, treatment of the bromide (**65**) with ammonia also yielded compound (**67**, R=H). Furthermore, treatment of the bromide (**65**) with primary amines gave a variety of *N*-substituted thieno[2,3-*c*]pyrroles (**67**). Compound (**67**) reacted readily with DMAD to give the adduct (**68**). Oxidation of (**68**) with MCPBA followed by thermolysis gave the benzothiophene (**70**).



Scheme 6. *Reagents* i) $CH_2(CO_2Et)_2$, 92%; ii) NBS, 85%; iii) NaN_3, 98%; iv) PPh_3, H_2O, 78%; v) RNH_2; vi) DMAD, 81-98%; vii) MCPBA, 82% (R=Me).

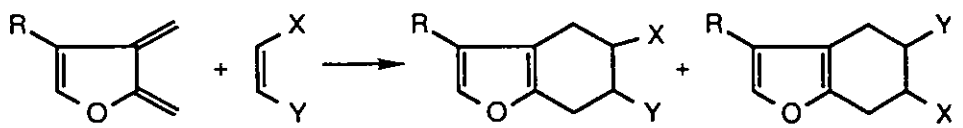
1.4 Furan-2,3-quinodimethane

Furan-2,3-quinodimethane (**72a**) has been prepared by retro Diels-Alder reaction of 4,5,6,7-tetrahydrobenzofuran (**71a**). The quinodimethanes (**72a,b**) were trapped with various dienophiles in 20-50% yield.[16]



(**71a**) R = H
(**71b**) R = Me

(**72a**) R = H
(**72b**) R = Me

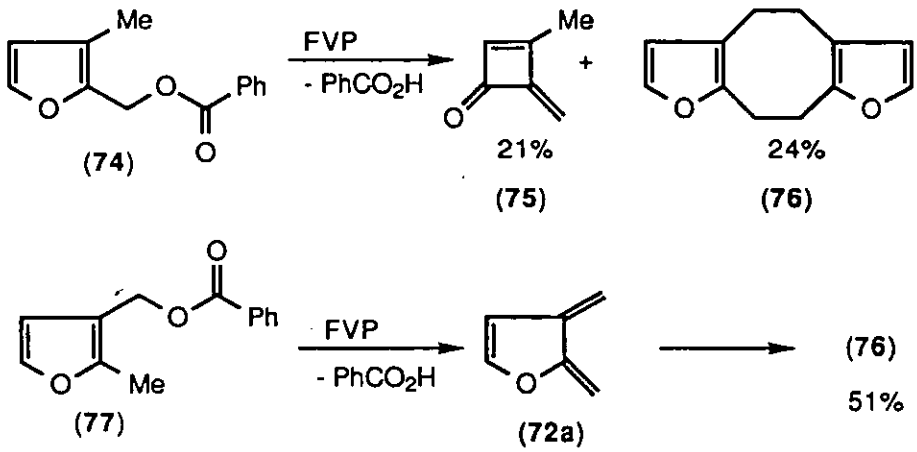


(**72a**) R = H
(**72b**) R = Me

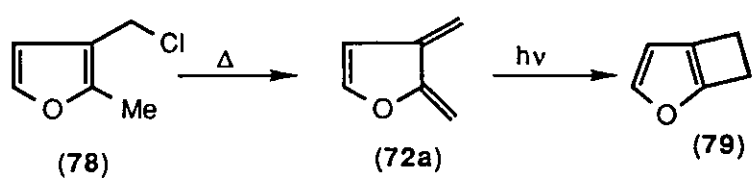
(**73a**) R = X = H, Y = COMe
(**73b**) R = X = H, Y = CO_2Me
(**73c**) R = Me, X = H, Y = COMe
(**73d**) R = Me, X = H, Y = CO_2Me
(**73e**) R = Me, X = Y = CO_2Me

Adduct (**73a**) was obtained as a 1:5 mixture of isomers and adduct (**73b**) as a 1:2 mixture of isomers, but it was not possible to assign the structure of the major isomer.

Flash pyrolysis of the benzoate ester (**74**) gave a mixture of compounds (**75**) and (**76**) upon warming of the cold pyrolysis product to room temperature.[17] Pyrolysis of the ester (**77**) under the same conditions gave the dimer (**76**) in 51% yield.[17,18] If methyl acrylate was added to a solution of the cold pyrolysis products of (**77**) prior to warming, the adduct (**73b**) was obtained, as an unspecified mixture of regioisomers. However, when the quinodimethane (**72b**) was generated by the same route, a 3:1 mixture of the adducts (**73d**) was obtained in 64-75% yield, with the tetrahydrobenzofuran-6-ester predominating.



Furan-2,3-quinodimethane (**72a**) could also be generated from 3-chloromethyl-2-methylthiophene (**78**). It was found that irradiating the quinodimethane (**72a**), in an argon matrix, generated the cyclobuta[*b*]furan (**79**).[19]

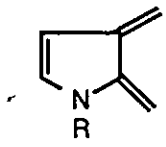


This provides a good illustration of how a thermodynamically unfavourable, and thus thermally inaccessible compound, can be generated photochemically from its thermodynamically more favourable isomeric form.

Furan-2,3-quinodimethane (**72a**) is much more stable than thiophene-2,3-quinodimethane (**5**), and could be isolated at low temperature (-78°C) and its spectral characteristics recorded. Warming above -40°C led to its dimerisation.[17]

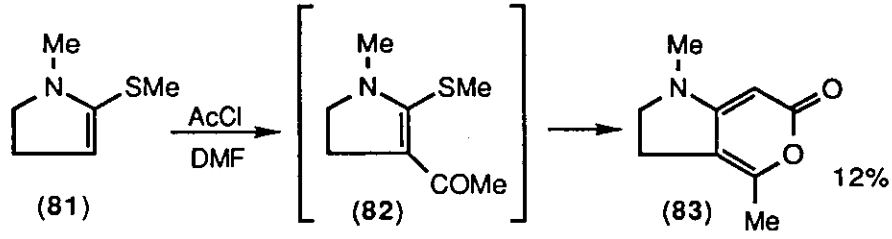
1.5 Pyrrole-2,3-quinodimethane

Nothing has been reported in the literature on the generation of the free quinodimethane (**80**).



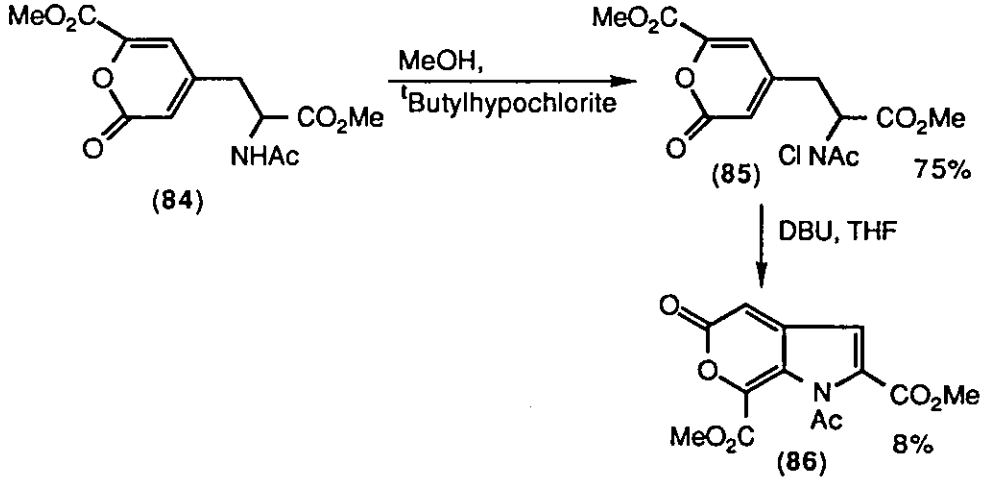
(**80**)

However a couple of cyclic analogues are known. 2,3-Dihydro-1,4-dimethylpyrano[4,3-*b*]pyrrol-6(1*H*)-one (**83**) was prepared from the dihydropyrrole (**81**) by treatment with acetyl chloride in DMF.[20]



(**81**) (**82**) (**83**)

The highly substituted pyrano[3,4-*b*]pyrrol-5(1*H*)-one (**86**) has been obtained from dimethyl *N*-acetylstizolobate (**84**) via the *N*-chloro compound (**85**).[21]

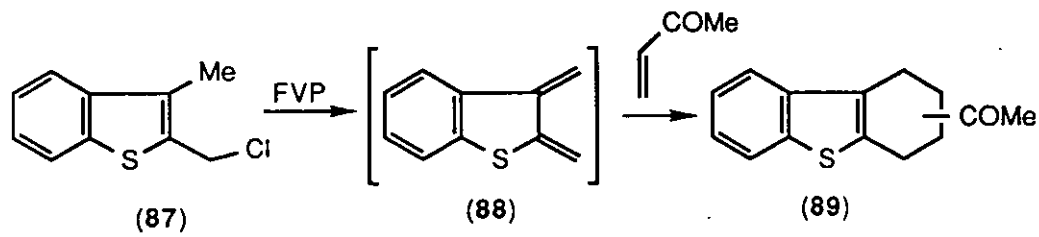


(**84**) (**85**) (**86**)

However, no attempt was made to perform any cycloaddition reactions on these compounds.

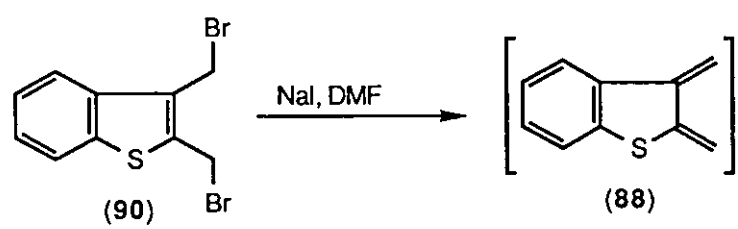
1.6 Benzothiophene-2,3-quinodimethane

Benzothiophene-2,3-quinodimethane (**88**) has been generated by flash pyrolysis of 2-chloromethyl-3-methylbenzothiophene (**87**) and gave a mixture of the isomeric Diels-Alder adducts (**89**) in 45% yield upon co-condensation with methyl vinyl ketone.[3]

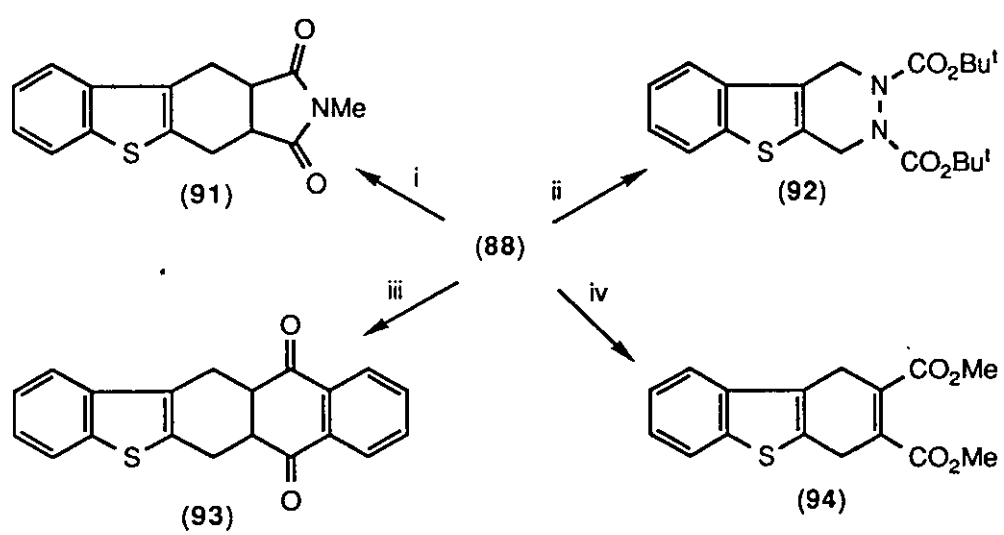


(**87**) (**88**) (**89**)

Benzothiophene-2,3-quinodimethane (**88**) has also been generated by treatment of 2,3-bis(bromomethyl)benzothiophene (**90**) with sodium iodide and was trapped with various dienophiles (Scheme 7).[22]

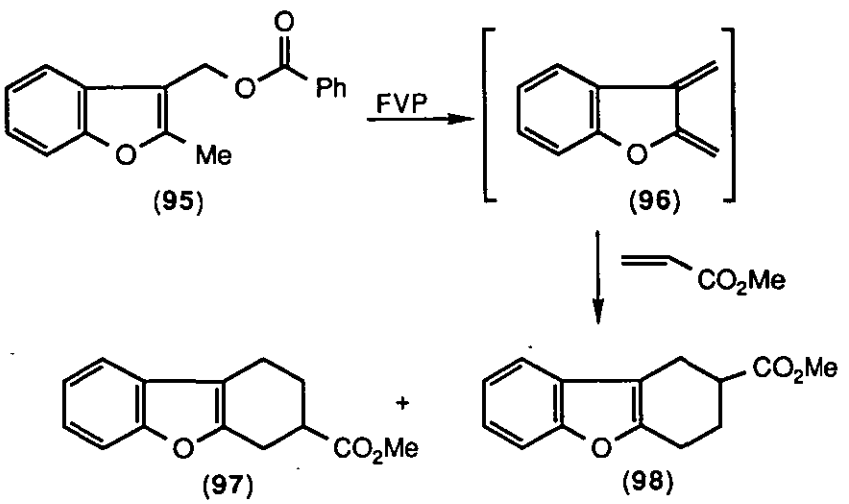


(**90**) (**88**)



Scheme 7. *Reagents* i) *N*-Methylmaleimide, 96%; ii) $Bu^tO_2C\text{-}N{=}N\text{-}CO_2Bu^t$, 50%; iii) Naphthoquinone, 79%; iv) DMAD, 36%.

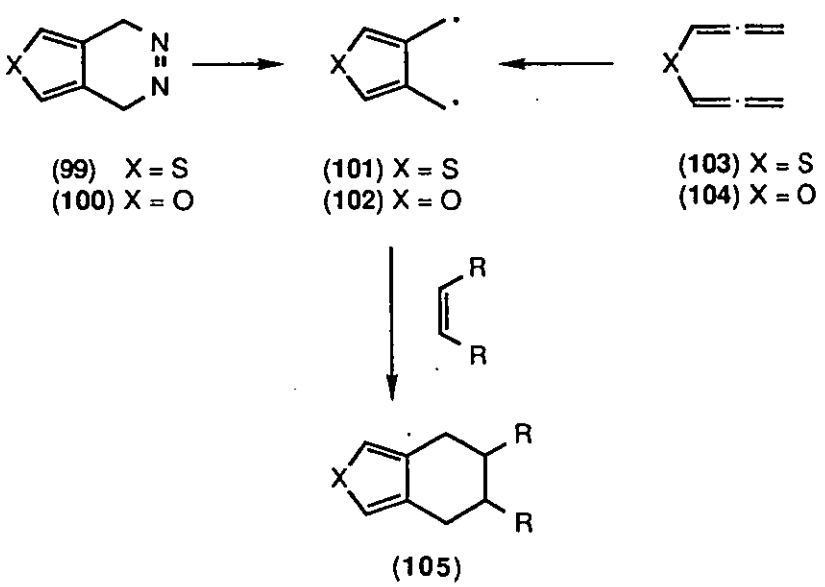
Similarly, pyrolysis of the benzoate ester (**95**) led to the generation of benzofuran-2,3-quinodimethane (**96**), which was trapped with methyl acrylate to give a 3:1 mixture of the tetrahydrodibenzofuran-2-ester (**97**) and -3-ester (**98**) respectively in 35% yield.[23]



(**95**) (**96**) (**97**) (**98**)

1.7 Thiophene-3,4-quinodimethane

Thiophene-3,4-quinodimethane (**101**) and furan-3,4-quinodimethane (**102**) have been generated in solution by flash photolysis of the diazenes (**99, 100**) or bis-allenes (**103, 104**), and captured with alkenes (e.g. maleic anhydride, fumaronitrile, and dimethyl fumarate) to give the adducts (**105**).[24]



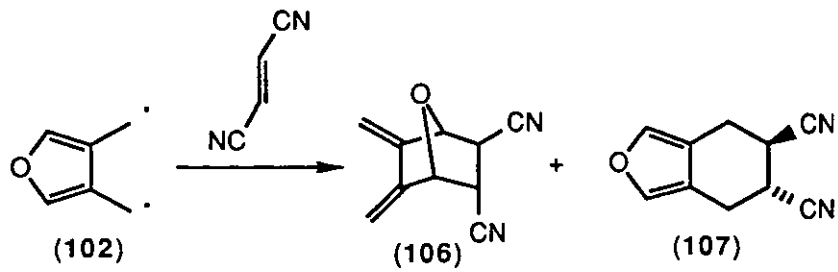
(**99**) X = S
(**100**) X = O

(**101**) X = S
(**102**) X = O

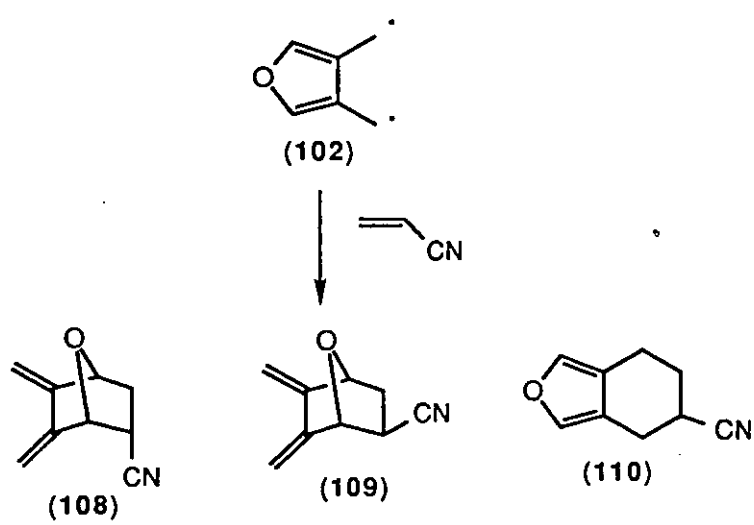
(**103**) X = S
(**104**) X = O

(**105**)

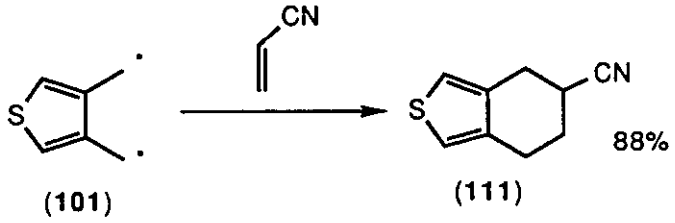
More recently, it has been reported that trapping of furan-3,4-quinodimethane (**102**) with fumaronitrile resulted in formation of the oxygen bridged adduct (**106**) and the tetrahydroisobenzofuran (**107**) in a 95 to 5 ratio.[25] Similarly, acrylonitrile (88:12), maleonitrile (96:4), and dimethyl fumarate (78:22) all favoured formation of the oxygen bridged adduct.



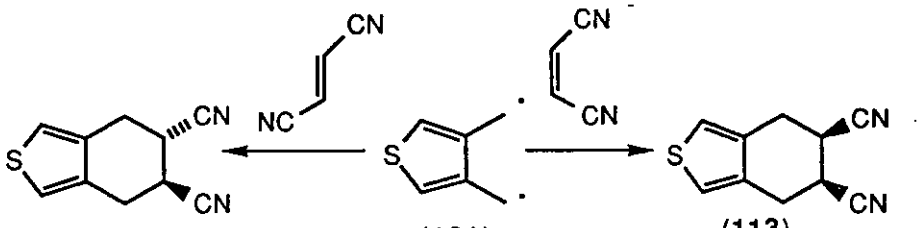
Trapping of the quinodimethane (**102**) with acrylonitrile gave a mixture of endo adduct (**108**), exo adduct (**109**), and isobenzofuran (**110**) in the ratio 64 to 24 to 12 independent of whether the quinodimethane was generated from the diazene (**100**) photochemically (350 nm, -20°C) or thermally (25-60°C). However, it was possible to shift the product composition towards the isobenzofuran (**110**), when working at a high concentration of trapping agent, by raising the temperature (to 167°C).



Generation of thiophene-3,4-quinodimethane (**101**) from the diazene (**99**), either photochemically or thermally, and trapping with acrylonitrile led only to the formation of the isobenzothiophene (**111**). Similarly, trapping of the quinodimethane (**101**) with fumaronitrile gave the trans adduct (**112**) and trapping with maleonitrile gave the cis adduct (**113**).[25]

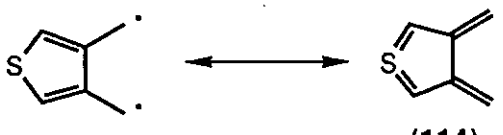


(**101**) (**111**)



(**112**) (**101**) (**113**)

These reactive intermediates are of interest from a theoretical point of view. The thiophene could exist as the biradical (**101**) or the diene (**114**) in which the sulphur atom is tetravalent. This is not possible for the furan. However, ^{13}C nuclear magnetic resonance experiments on ^{13}C labelled diazenes led to the conclusion that the spectra obtained from precursor (**99**) are indeed due to the biradical (**101**), and not any other plausible species e.g. (**115**) or (**116**).[26]

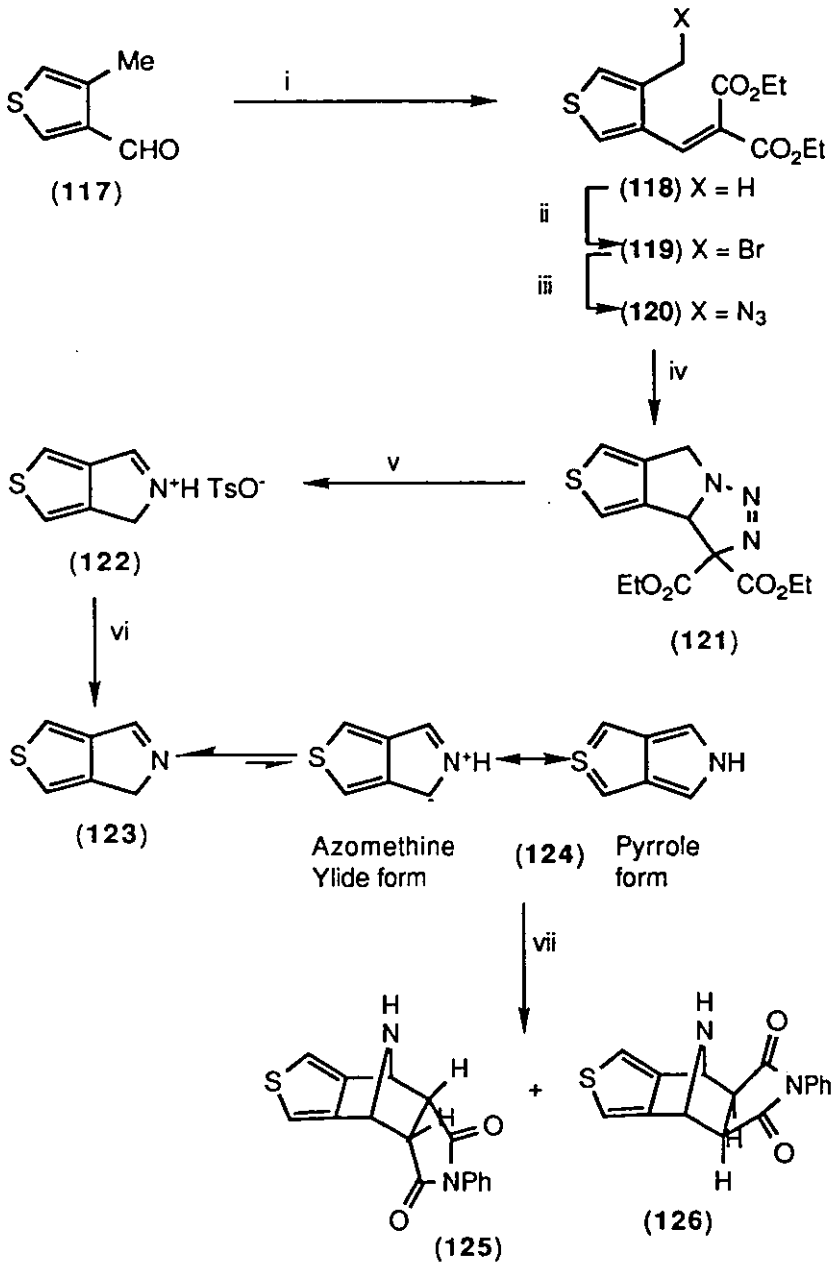


(**101**) (**114**)

(**115**) (**116**)

1.8 Cyclic analogues of thiophene-3,4-quinodimethane

1.8.1 4*H*-Thieno[3,4-*c*]pyrrole

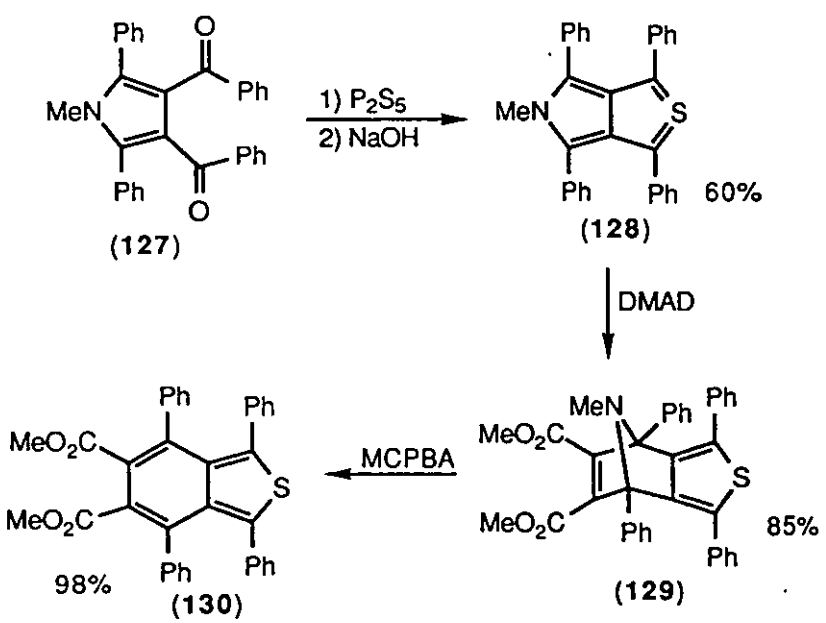


Scheme 8. *Reagents* i) Diethyl malonate, 80%; ii) NBS, dibenzoyl peroxide, 78%; iii) Sodium azide, ethanol, 98%; iv) rt, 4 days, 80%; v) TsOH, Et_2O, 96%; vi) Sodium carbonate, 93%; vii) *N*-Phenylmaleimide, 50%.

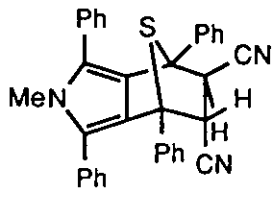
4*H*-Thieno[3,4-*c*]pyrrole (**123**) was synthesised from the azide (**120**) by intramolecular 1,3-dipolar cycloaddition followed by acid catalysed 1,3-dipolar cycloreversion of the dihydrotriazole intermediate (**121**) (Scheme 8).[27] Azide (**120**) was prepared by Knoevenagel condensation of 4-methylthiophene-3-carboxaldehyde (**117**) with diethyl malonate, followed by bromination with *N*-bromosuccinimide and treatment with sodium azide. Compound (**123**) underwent facile cycloaddition with *N*-phenylmaleimide, via the tautomer (**124**), to give a mixture of the endo-adduct (**125**) (12%) and exo-adduct (**126**) (38%).

1.8.2 5-Methyl-1,3,4,6-tetraphenylthieno[3,4-*c*]pyrrole

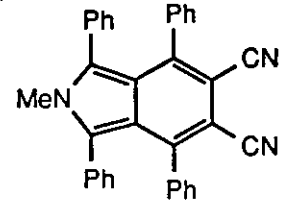
Reaction of tetrabenzoylethane with methylamine and acetic acid gave the pyrrole (**127**) in 90% yield. Treatment of (**127**) with phosphorus pentasulphide, followed by sodium hydroxide, gave the thieno[3,4-*c*]pyrrole (**128**).[28] Reaction of (**128**) with DMAD in chloroform gave the adduct (**129**). Oxidation of (**129**) with MCPBA gave the isobenzothiophene (**130**).



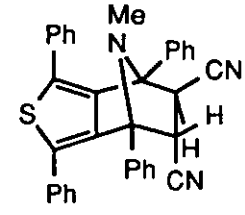
Olefinic dipolarophiles showed a temperature dependent mode of addition to compound (**128**).[29] In refluxing toluene, addition of fumaronitrile occurred across the thiocarbonyl ylide system to give the adduct (**131**), in 67% yield, along with a small amount of isoindole (**132**) (5%) via elimination of the elements of H_2S from (**131**). In refluxing xylene, isoindole (**132**) (53%) was the major product. However, in refluxing benzene addition occurred across the azomethine ylide portion to give the adduct (**133**).



(**131**)



(**132**)

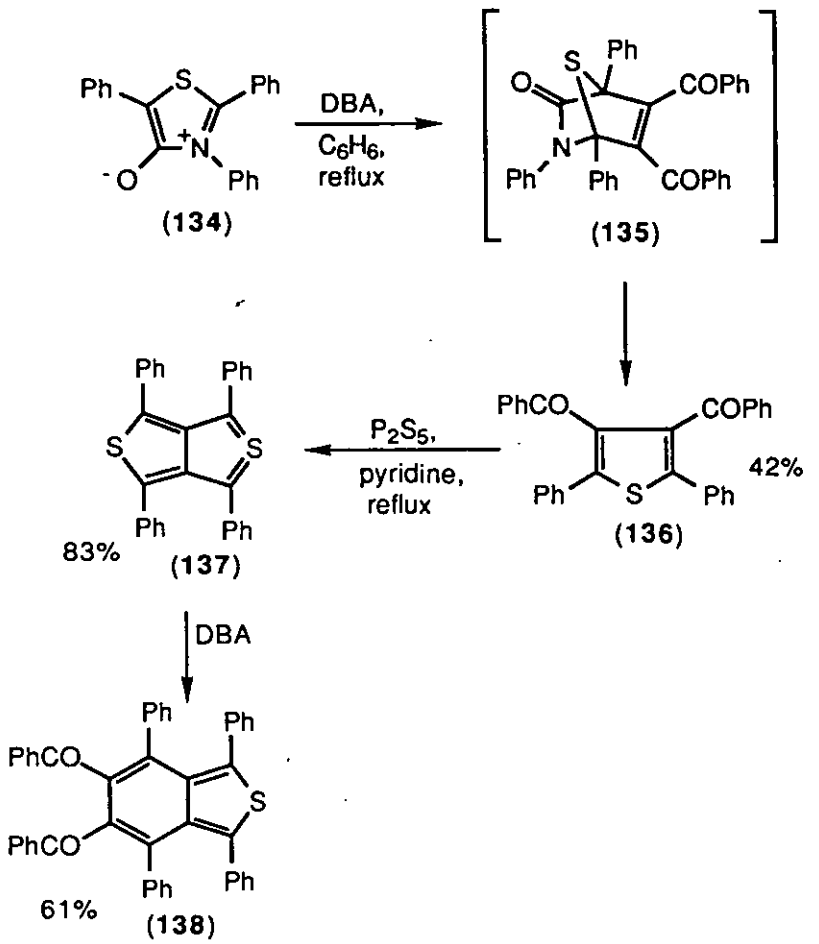


(**133**)

Compound (**133**) was found to undergo ready retro Diels-Alder reaction at higher temperatures and was converted into compound (**132**) (60%) upon refluxing in xylene. This indicates the greater reactivity of the azomethine ylide over the thiocarbonyl ylide dipole and the greater thermodynamic stability of the cycloadducts from the latter.

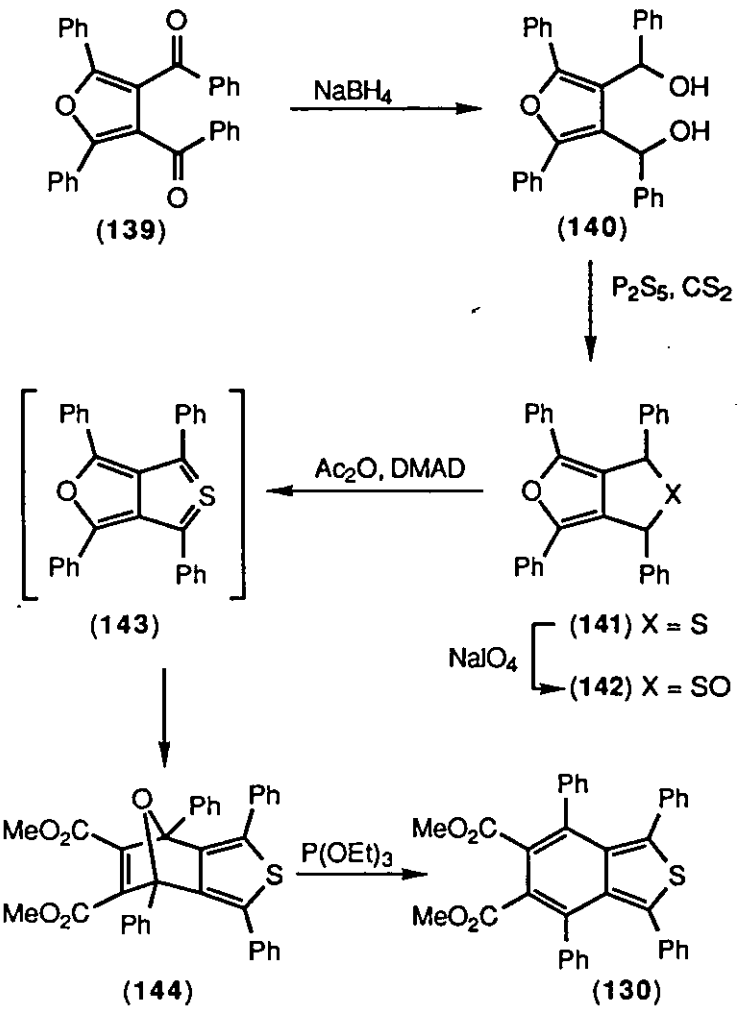
1.8.3 1,3,4,6-Tetraphenylthieno[3,4-*c*]thiophene

Reaction of the mesoionic compound (**134**) with dibenzoylacetylene in refluxing benzene gave the thiophene (**136**).[30] Treatment of (**136**) with phosphorus pentasulphide in refluxing pyridine gave the tetraphenylthieno[3,4-*c*]thiophene (**137**). Cycloaddition reaction of (**137**) with dibenzoylacetylene, followed by extrusion of sulphur, gave the isobenzothiophene (**138**).



1.8.4 1,3,4,6-Tetraphenylthieno[3,4-*c*]furan

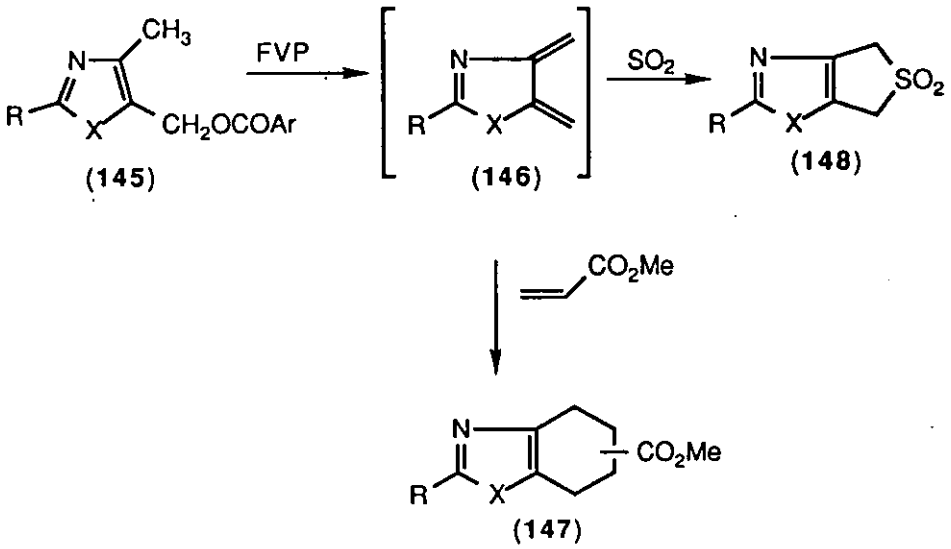
Treatment of tetrabenzoylethane with hydrogen chloride in acetic acid gave the furan (**139**).[31] Treatment of (**139**) with phosphorus pentasulphide did not afford the thieno[2,3-*c*]furan (**143**). Borohydride reduction of (**139**) gave an epimeric mixture of diols (**140**). Treatment of (**140**) with phosphorus pentasulphide in carbon disulphide gave the cyclic sulphide (**141**). Periodate oxidation of (**141**) gave the sulphoxide (**142**), which on refluxing in acetic anhydride in the presence of DMAD gave the adduct (**144**). Deoxygenation of (**144**) with hot triethyl phosphite gave the isobenzothiophene (**130**).


Ph
O
Ph
O
Ph
Ph
O
(139)
NaBH4
Ph
Ph
OH
O
OH
Ph
Ph
(140)
P2S5, CS2
Ph
Ph
O
X
Ph
Ph
(141) X = S
NaIO4
(142) X = SO
Ac2O, DMAD
Ph
Ph
O
S
Ph
Ph
(143)
O
Ph
Ph
MeO2C
S
MeO2C
Ph
Ph
(144)
P(OEt)3
Ph
Ph
MeO2C
S
MeO2C
Ph
Ph
(130)

1.9 Quinodimethanes containing more than one heteroatom

1.9.1 Oxazole, thiazole, and imidazole analogues of orthoquinodimethane

Oxazole-4,5-quinodimethane (**146**; R=H, X=O) was generated by flash pyrolysis of the *p*-chlorobenzoate ester (**145**; R=H, X=O).[32] Co-condensation with methyl acrylate gave a Diels-Alder adduct (**147**; R=H, X=O) which was shown to be a mixture of regioisomers by GC/MS but was not resolvable by ^{1}H NMR spectroscopy.



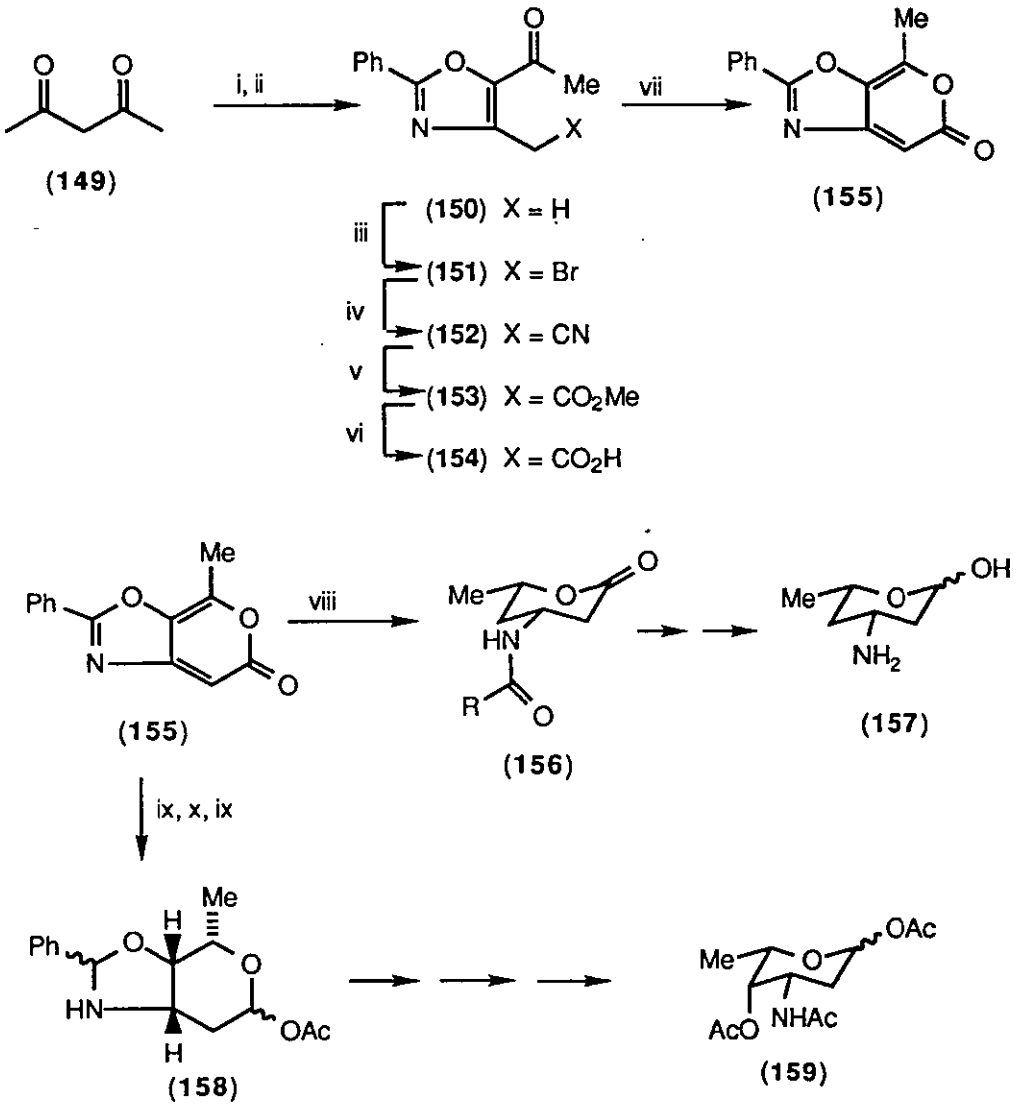
(**145**) (**146**) (**148**) (**147**)

Attempts to trap the thiazole quinodimethanes (**146**; R=H or Ph, X=S) and the imidazole quinodimethane (**146**; R=H, X=NMe) with dienophiles failed. However, both the thiazole quinodimethane (**146**; R=Ph, X=S) and the imidazole quinodimethane (**146**; R=H, X=NMe) were trapped with sulphur dioxide to give the cyclic sulphones (**148**). This is significant since it may be possible to regenerate the quinodimethanes in solution under conditions where they undergo Diels-Alder reaction.

These FVP experiments show the oxazole and furan quinodimethanes to be similar in stability as indicated by their survival to undergo Diels-Alder reactions rather than polymerisation. The thiazole, imidazole, and thiophene quinodimethanes are more reactive and polymerise even in the presence of dienophiles. Thus, the stability of the quinodimethanes appears to parallel the

degree of aromaticity of the parent heterocycle. The greater the aromatic character of the heterocycle, the higher the reactivity of the derived quinodimethane.

A stable cyclic analogue of oxazole-4,5-quinodimethane has been reported. The oxazolo-α-pyrone (**155**) was prepared from pentane-2,4-dione (Scheme 9).[33]

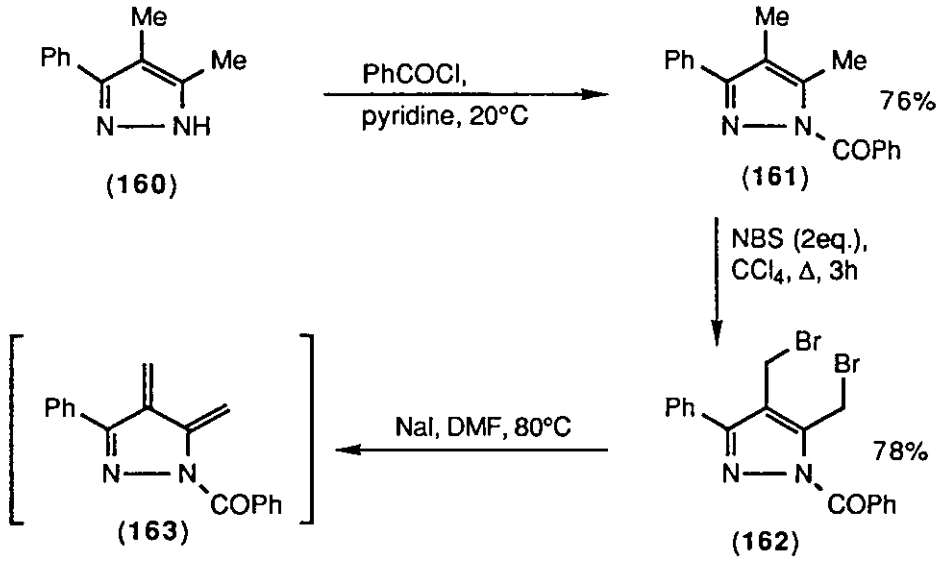


Scheme 9. *Reagents* i) Morpholine, C_6H_6, Dean-Stark, then benzoyl peroxide; ii) NH_4OAc, AcOH; iii) NBS, CCl_4, 72%; iv) HCN, 73%; v) MeOH, HCl (anhydrous), 96%; vi) HCl, AcOH, 81%; vii) $SOCl_2$, $CHCl_3$, 82%; viii) H_2, Adams catalyst; ix) H_2, 5% Rh/Al_2O_3; x) $NaAlH(OCH_2CH_2OMe)_2$, then Ac_2O, pyridine.

However pyrone (**155**) was not used in any cycloaddition reactions. Compound (**155**) was prepared for the purpose of aminosugar synthesis. Hydrogenation of (**155**) using Adams catalyst gave the lactone (**156**) which was subsequently converted to 4-deoxy-*dl*-daunosamine (**157**).[33] Hydrogenation of (**155**) using 5% Rh/Al_2O_3 as catalyst led to the saturated bicyclic compound (**158**) which was subsequently converted to *dl*-triacetyldaunosamine (**159**).[34]

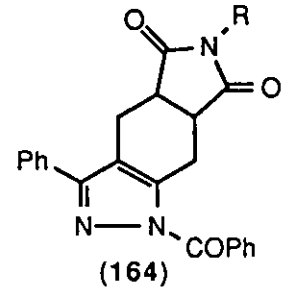
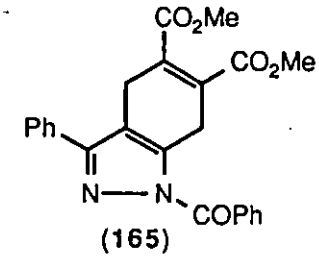
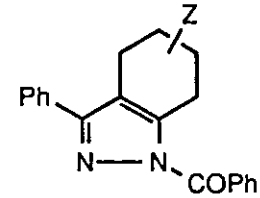
1.9.2 Pyrazole analogue of orthoquinodimethane

1-Benzoyl-3-phenyl-1*H*-pyrazole-4,5-quinodimethane (**163**) was generated by treatment of the bis-bromide (**162**) with sodium iodide in DMF. The bis-bromide (**162**) was prepared by benzoylation of 4,5-dimethyl-3-phenyl-1*H*-pyrazole (**160**), followed by bromination using *N*-bromosuccinimide. The pyrazole quinodimethane (**163**) was trapped as its Diels-Alder adducts (Table 5).



When quinodimethane (**163**) was trapped with the unsymmetrical dienophiles, acrylonitrile, methyl vinyl ketone or methyl acrylate, mixtures of the two regioisomers were obtained in the ratios shown (Table 5). However, the identity of the major regioisomer is not known.

Table 5. Diels-Alder reactions of pyrazole-4,5-quinodimethane (**163**) with dienophiles.

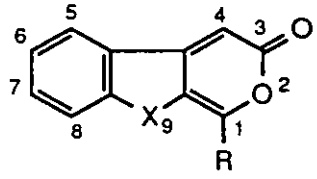
Dienophile	Cycloadduct	Yield % (Ratio)
N -Phenylmaleimide R = Ph	 (164)	52
N -Methylmaleimide R = Me		51
DMAD	 (165)	29
Acrylonitrile Z = CN	 (166)	39 (1:2.6)
Methyl vinyl ketone Z = COMe		31 (1:1.5)
Methyl acrylate Z = CO_2Me		38 (1:1.4)

CHAPTER 2

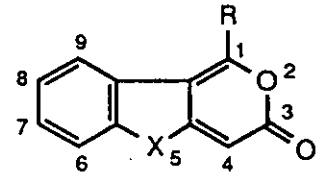
Benzothienopyranones

2.1 Introduction

In view of the recent interest in benzothiophene-2,3-quinodimethane (**88**), a reactive intermediate generated by flash vacuum pyrolysis of 2-chloromethyl-3-methylbenzothiophene,[3] or by reaction of 2,3-bis(bromomethyl)-benzothiophene with sodium iodide,[22] and in order to extend work done on the pyranoindolones (**167**)[36-40] and (**168**)[41] to other heterocyclic systems, we decided to investigate the preparation and Diels-Alder reactions of the benzothieno[2,3-*c*]pyran-3-ones (**169**) and the benzothieno[3,2-*c*]pyran-3-ones (**170**).

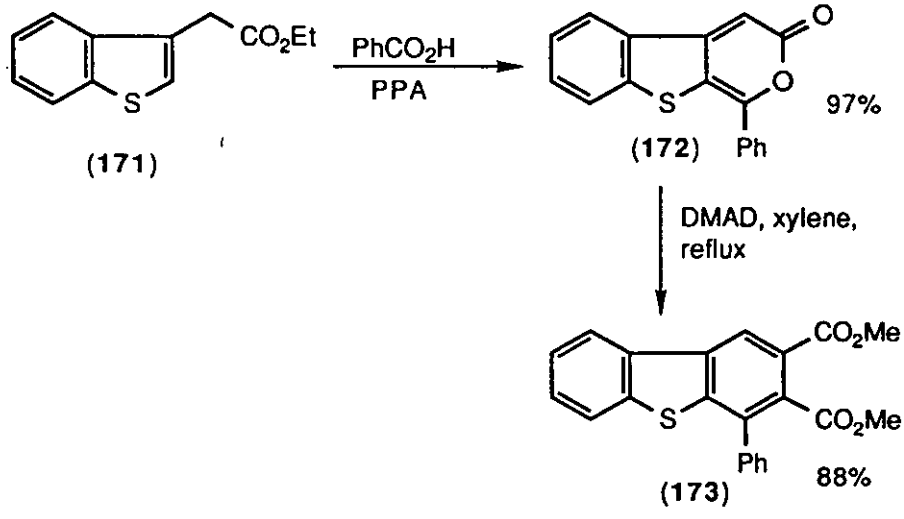


(**167**) X = NH
(**169**) X = S



(**168**) X = NH
(**170**) X = S

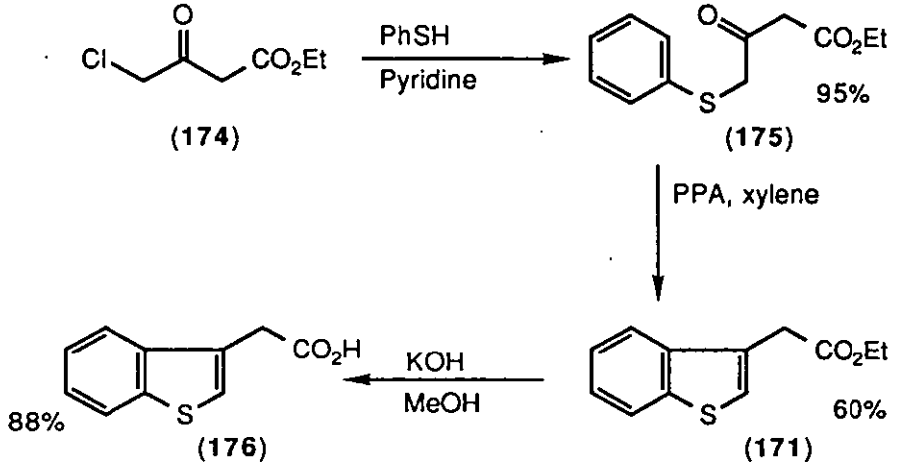
Interestingly, 1-phenylbenzothieno[2,3-*c*]pyran-3-one (**172**) has been prepared before, by reaction of ethyl benzothiophen-3-ylacetate (**171**) with benzoic acid in polyphosphoric acid,[42] and it underwent Diels-Alder reaction with DMAD upon refluxing in xylene to give the dibenzothiophene (**173**).[43]



2.2 Benzothieno[2,3-*c*]pyran-3-ones

2.2.1 Preparation of Benzothiophen-3-ylacetic acid

Ethyl benzothiophen-3-ylacetate (**171**) was prepared by the literature route.[44] Reaction of ethyl 4-chloroacetoacetate with thiophenol gave the sulphide (**175**) which was cyclised by heating in polyphosphoric acid to give the benzothiophene (**171**). Alkaline hydrolysis gave the known benzothiophen-3-ylacetic acid (**176**).[45]

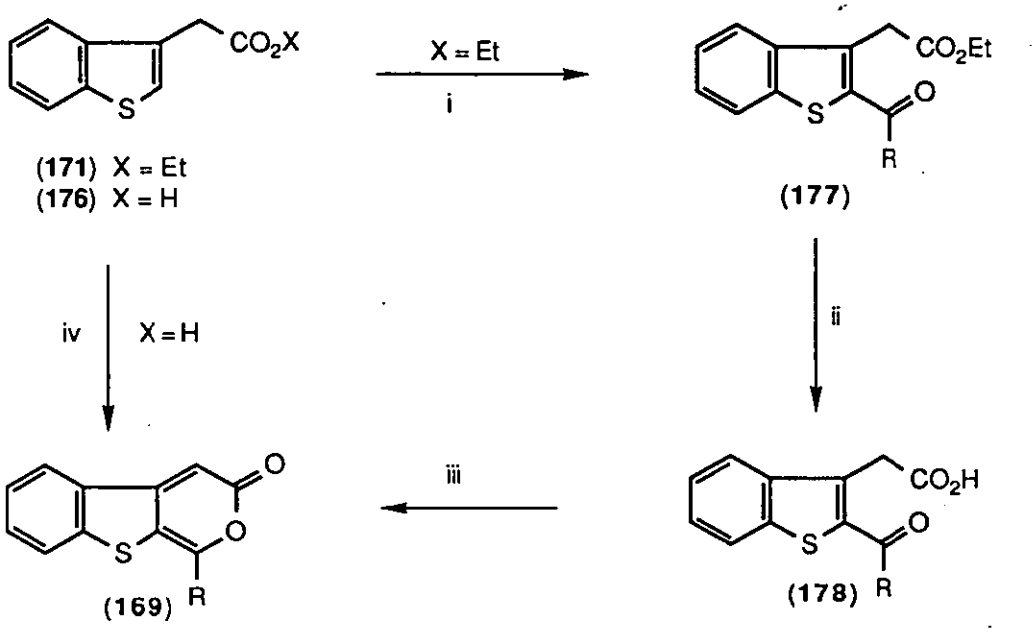


(**174**) (**175**) (**176**) (**171**)

2.2.2 Preparation of Benzothieno[2,3-*c*]pyran-3-ones

The benzothieno[2,3-*c*]pyran-3-one ring system (**169**) was prepared by two methods, either starting from ethyl benzothiophen-3-ylacetate (**171**) or the corresponding acid (**176**) (Scheme 10). The first method, which was needed to prepare the unsubstituted pyranone (**169a**), involved acylation of the ester (**171**) with dichloromethyl methyl ether or acetyl chloride in the presence of tin (IV) chloride to give the 2-formyl compound (**177a**), in 35% yield, or 2-acetyl compound (**177b**), in 43% yield, respectively. Hydrolysis of the esters (**177**) gave the corresponding acids (**178a**), in 91% yield, and (**178b**), in 81% yield. The acids (**178**) cyclised on heating in acetic anhydride to give the pyranones (**169a**), in 54% yield, and (**169b**), in 65% yield. The pyranone

(**169b**) and the pentyl substituted compound (**169c**) could also be prepared from benzothiophen-3-ylacetic acid (**176**) by reaction with acetic anhydride or hexanoic anhydride respectively, in the presence of boron trifluoride diethyl ether, exactly as for the corresponding indoles.[36-40] Pyranone (**169b**) was obtained in 66% yield and pyranone (**169c**) in 36% yield.

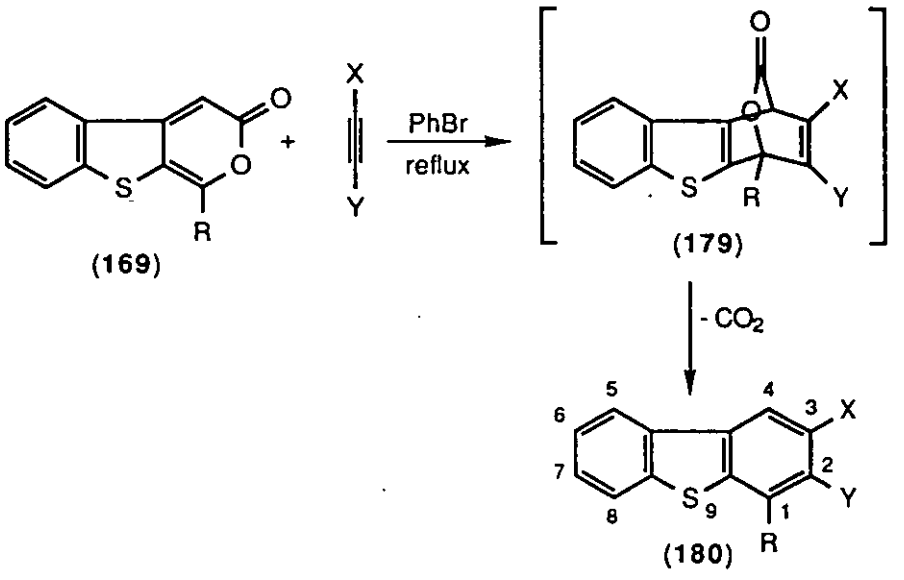


Scheme 10. (**a**, R=H; **b**, R=Me; **c**, R=C_5H_{11}) *Reagents* i) Cl_2CHOMe (or AcCl), $SnCl_4$, CH_2Cl_2; ii) KOH, H_2O, THF, MeOH; iii) Ac_2O, reflux; iv) $(RCO)_2O$, $BF_3.Et_2O$.

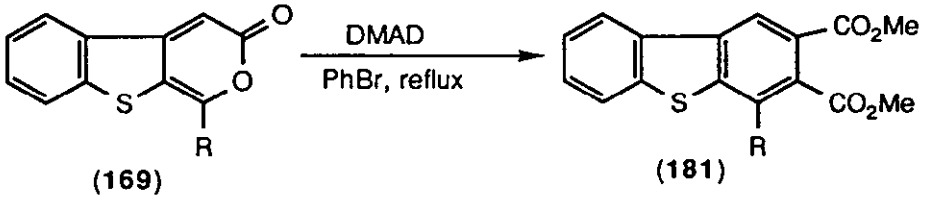
The benzothieno[2,3-*c*]pyran-3-ones (**169**) are yellow crystalline solids, which exhibit the expected spectroscopic properties. For example, the carbonyl frequencies in the IR spectra occur in the range 1690-1710 cm^{-1}, and the signal for 4-H on the pyranone rings is in the range δ 6.6-6.8 in their ^1H NMR spectra. For comparison, the corresponding indole derived pyranones (**167**) have IR carbonyl frequencies at *ca.* 1690 cm^{-1}, and 4-H resonates at about δ 6.5.[38]

2.2.3 Intermolecular Diels-Alder reactions of Benzothieno[2,3-*c*]pyran-3-ones

On heating with alkynes in boiling bromobenzene, the benzothieno[2,3-*c*]pyran-3-ones (**169**) undergo Diels-Alder reaction to give, after loss of carbon dioxide, dibenzothiophenes. The initial carbon dioxide bridged adducts (**179**) were never isolated.

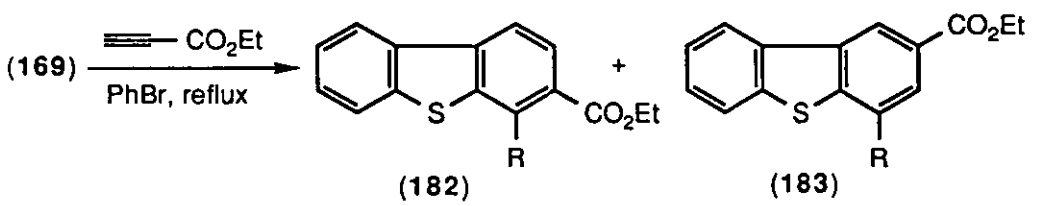


The reactions with the electron deficient alkyne, dimethyl acetylenedicarboxylate (DMAD), proceeded quickest and gave the dibenzothiophene-2,3-diesters (**181a, b, c**) in good to excellent yields. The reactions of the corresponding indole dienes (**167**) with DMAD also gave good yields of products, although they were over in a shorter time.[38]



Compd. (**169**)	R	Time (h)	Compd. (**181**)	Yield (%)
a	H	5	**a**	79
b	Me	8	**b**	93
c	Pentyl	14	**c**	68

The Diels-Alder reactions of the benzothienopyranones (**169**) with other alkynes exhibit varying degrees of regioselectivity. Ethyl propiolate gave essentially equal amounts of the dibenzothiophene 2-(**182**) and 3-esters (**183**), with, in one case, a slight preference for the formation of the 2-ester (**182b**).



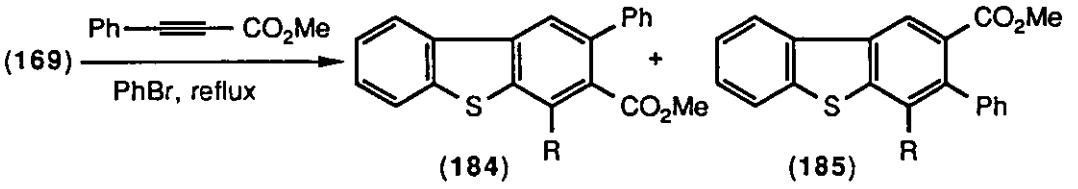
(**182**) (**183**)

Compd. (**169**)	R	Time (h)	Compd. (**182**)/(**183**)	Combined Yield (%)	Ratio (**182**):(**183**)
a	H	36	**a**	65	1:1
b	Me	24	**b**	79	1.5:1
c	Pentyl	36	**c**	54	1:1

The 2-ester (**182b**) could be readily distinguished from the 3-ester (**183b**) due to the resonance of the 1-methyl group, which in the case of the 2-ester resonates downfield, at δ 2.85, relative to that of the 3-ester, at δ 2.60. Also, the 4-H of the 3-ester (**183b**) resonates considerably downfield, at δ 8.66, from any other proton. These results are similar to those obtained with the indole pyranones (**167**), which in the absence of steric factors, also exhibit little regioselectivity in their reactions with ethyl propiolate,[38] and confirm the view that propiolic esters, in contrast to other alkynes, are essentially unselective in their Diels-Alder reactions with 2-pyrones.[46]

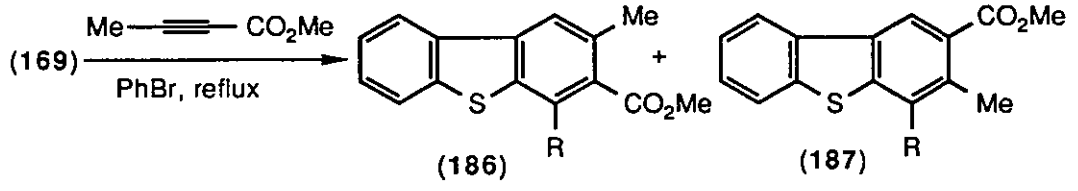
Similarly methyl phenylpropiolate[47,48] exhibited only a small amount of regioselectivity. In each case there was a slight preference for the formation of the 2-ester (**184**). The structure of the dibenzothiophene (**184a**) was confirmed by nuclear Overhauser effect (NOE) difference spectroscopy, in which pre-irradiation of the singlet at δ 3.62 (CO_2Me) caused enhancement of the multiplet at δ 7.38-7.51 (containing phenyl protons) and of the singlet at δ 2.64 (1-Me). Likewise, pre-irradiation of the 1-Me signal caused enhancement of the ester signal but not of the phenyl multiplet. Pre-irradiation of the singlet

at δ 8.01 (4-H) caused enhancement of the doublet at δ 8.15 (5-H) and of the phenyl multiplet.



Compd. (169)	R	Time (h)	Compd. (184)/(185)	Combined Yield (%)	Ratio (184):(185)
b	Me	144	**a**	70	1.2:1
c	Pentyl	264	**b**	70	1.6:1

Methyl tetrolate was somewhat more selective in its Diels-Alder reaction, the ester functionality being found predominately in the 2-position in the product.

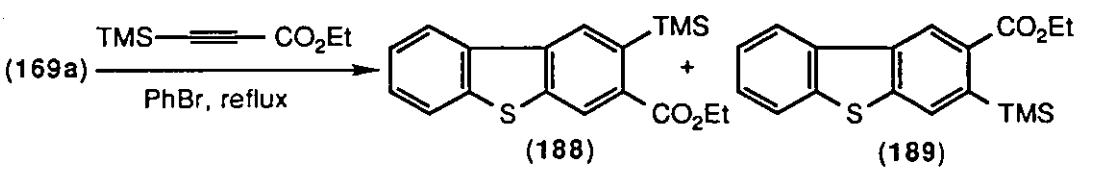


Compd. (169)	R	Time (h)	Compd. (186)/(187)	Combined Yield (%)	Ratio (186):(187)
b	Me	168	**a**	59	5:1
c	Pentyl	264	**b**	34	6:1

The isomers were distinguished by the position of the 4-H resonance which is shifted downfield when the ester is *ortho* to it. The minor products (**187a, b**) showed singlets at δ 8.49 and δ 8.48 respectively, whereas the major products (**186a, b**) showed a singlet at δ 7.85 in each case. This assignment was confirmed by an NOE difference experiment on the mixture of isomers (**186a, 187a**). Pre-irradiation of the major aromatic singlet at δ 7.85 (4-H, **186a**) caused enhancement of the multiplet at δ 8.12 (containing 5-H) and of the singlet at δ 2.50 (3-Me). Pre-irradiation of the minor aromatic singlet at δ 8.49 (4-H, **187a**) gave no enhancement of either methyl peak. Pre-irradiation of the minor methyl signal at δ 2.64 caused enhancement of the other minor methyl signal at δ 2.57 showing them to be *ortho*. Pre-irradiation of the major methyl

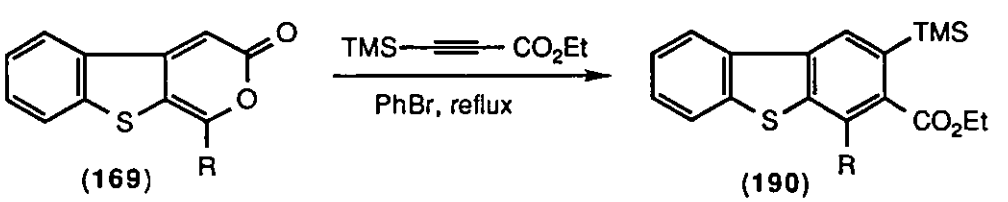
signal at δ 2.50 (3-Me) caused enhancement of the 4-H peak and of the singlet at δ 3.98 (CO_2Me). Pre-irradiation of the other major methyl signal at δ 2.55 (1-Me) also caused enhancement of the ester signal, confirming that the ester is situated between the two methyls in the major product.

However, ethyl 3-trimethylsilylpropynoate, in which the acetylenic hydrogen is replaced by the bulky trimethylsilyl group, was highly regioselective in its Diels-Alder reactions with the benzothienopyranones (**169**) and gave predominately the 3-trimethylsilyldibenzothiophene-2-esters (**188**) and (**190a, b**) in good yield. In the case of the unsubstituted pyranone (**169a**) a small amount of the 2-trimethylsilyldibenzothiophene-3-ester (**189**) was present by ^1H NMR, however pyranones (**169b**) and (**169c**) gave a single regioisomer (**190**) by 270 MHz ^1H NMR.



Ratio (**188**):(**189**), 6:1

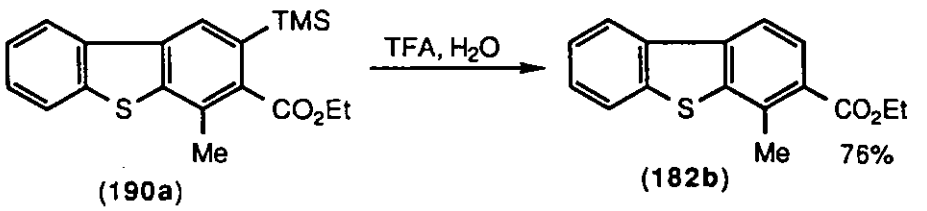
Combined yield 69%



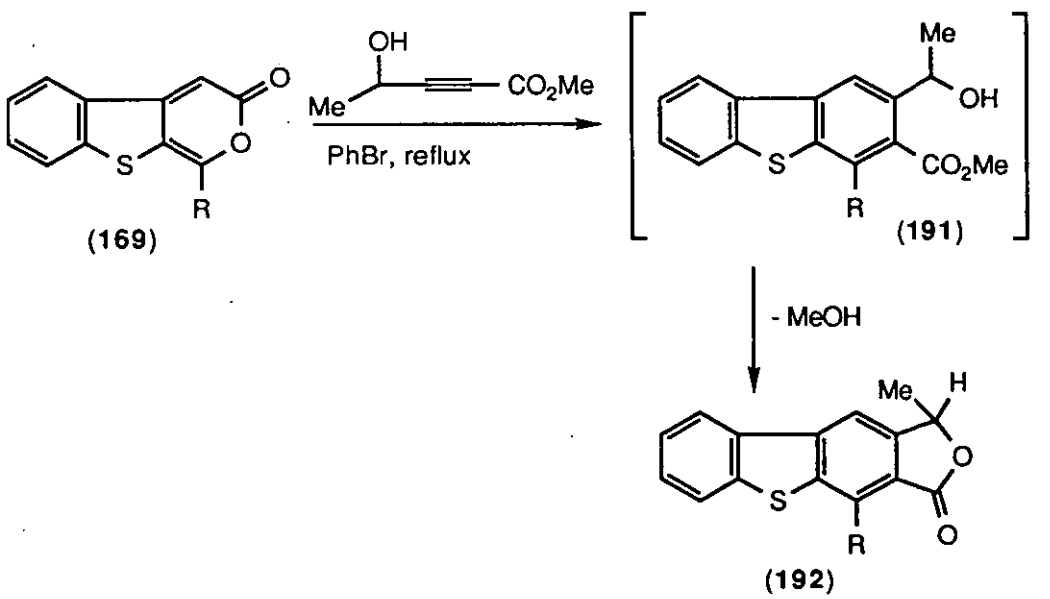
Compd. (**169**)	R	Time (h)	Compd. (**190**)	Yield (%)
b	Me	70	**a**	67
c	Pentyl	168	**b**	60

The structure of the dibenzothiophene (**190a**) was confirmed by NOE difference spectroscopy, in which pre-irradiation of the singlet at δ 0.38 ($SiMe_3$) caused enhancement of the singlet at δ 8.23 (H-4), and *vice versa*. Also, pre-irradiation of the quartet at δ 4.45 (ester CH_2) caused enhancement of both the singlet at δ 2.62 (1-Me) and the singlet at δ 0.38 ($SiMe_3$). Protodesilylation of

(**190a**) with aqueous trifluoroacetic acid gave ethyl 1-methyldibenzothiophene-2-carboxylate (**182b**) in 76% yield, identical to the major product obtained from the reaction of the benzothienopyranone (**169b**) with ethyl propiolate.



The Diels-Alder reactions of the benzothienopyranones (**169b, c**) with methyl 4-hydroxypent-2-ynoate[47,48] were also highly regioselective, although the initial product, the dibenzothiophenes (**191**) could not be isolated, cyclising to the lactones (**192**) under the reaction conditions.

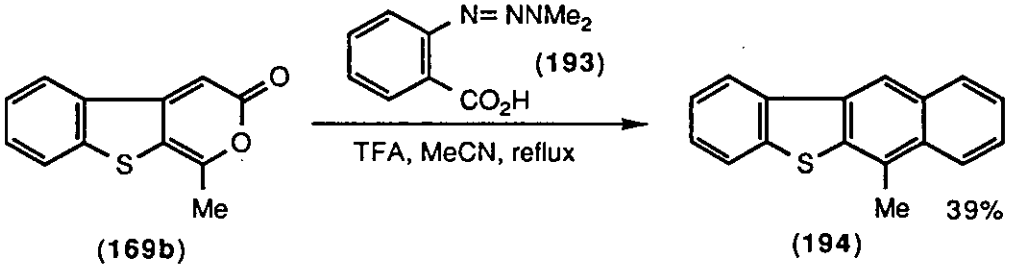


Compd. (169)	R	Time (h)	Compd. (192)	Yield (%)
b	Me	80	**a**	46
c	Pentyl	192	**b**	55

The structure of the lactone (**192a**) was confirmed by NOE difference spectroscopy, in which pre-irradiation of the singlet at δ 7.98 due to 10-H caused enhancements of the signals at 5.63 (quartet, 1-H), and 1.67 (doublet,

1-Me), and 8.22 (doublet, 9-H). No effects were observed on pre-irradiation of the singlet due to the 4-Me group at δ 2.96.

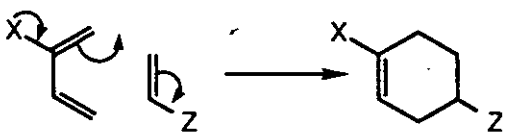
The benzothienopyranone (**169b**) also reacted with benzyne. Thus heating the pyranone with the benzyne precursor, 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**)[49], in boiling bromobenzene for 12 h gave the benzo-fused derivative (**194**) in 39% yield. Compound (**193**) was preferred to the diazonium salt, produced by diazotisation of anthranilic acid, as the source of benzyne due to its ease of handling.



(**169b**) (**194**)

Thus the benzothieno[2,3-*c*]pyran-3-ones (**169**) undergo intermolecular Diels-Alder reactions with alkynes to give dibenzothiophenes in good yield. With the exception of ethyl propiolate, the regiochemistry of the cycloaddition is the same as that observed with the corresponding indole derived dienes (**167**).
Since the benzothieno[2,3-*c*]pyran-3-ones react best with the most electron deficient dienophiles, the Diels-Alder reaction can be said to be operating under conditions of 'normal' electron demand. The reaction is said to be HOMO (diene) - LUMO (dienophile) controlled. In general, when a diene with an electron donating substituent situated terminally (1-substituted) reacts with an electron poor dienophile, the '*ortho*' product (**195**) is obtained. However, when the electron donating substituent is situated internally (2-substituted), the '*para*' product (**196**) is obtained. This can be explained in terms of 'simple' arrow pushing (as indicated on the diagrams) or, more correctly, in terms of the coefficients of the frontier orbitals.[50]

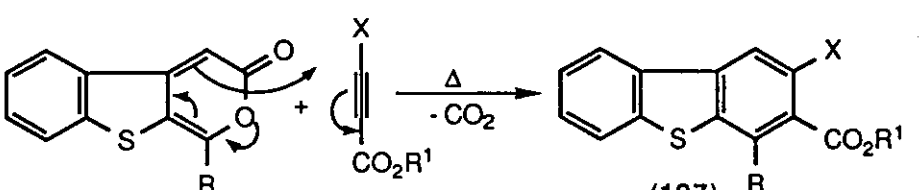
(195)



(196)

X = electron donating group
Z = electron withdrawing group

The benzothieno[2,3-*c*]pyran-3-ones (**169**) react with unsymmetrical dienophiles such that the electron withdrawing ester substituent tends to finish in the 2-position in the dibenzothiophene products. This can be explained by the oxygen in the pyrone ring (1-substituent) having a stronger effect than the sulphur (2-substituent). In simple arrow pushing terms, the direction of addition can be said to be controlled by the ring oxygen atom rather than the sulphur atom. One possible explanation for this is that the sulphur 'lone pair' is delocalised into the benzene ring.



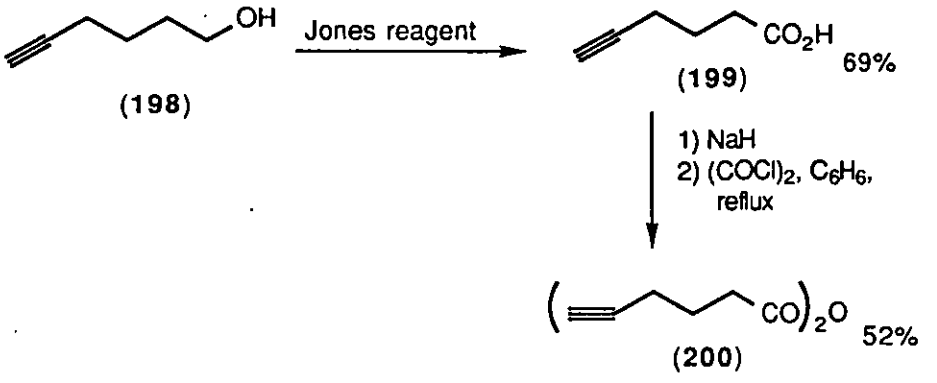
(**169**) X=Me, TMS; R^1=Me, Et

(**197**) Major isomer

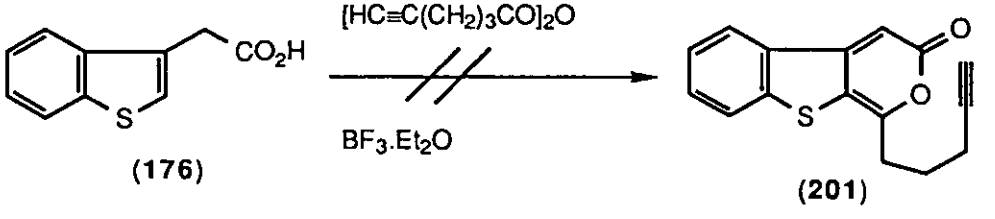
In the Diels-Alder reaction with ethyl 3-trimethylsilylpropynoate, steric effects also appear to have an influence. Pyranones (**169b**) and (**169c**) give only one regioisomer with this alkyne, whereas pyranone (**169a**) gives some of the minor isomer (**189**).

2.2.4 Attempted intramolecular Diels-Alder reaction of benzothieno[2,3-*c*]pyran-3-ones.

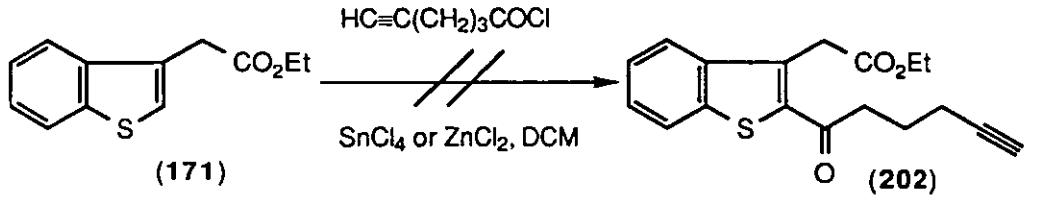
Oxidation of the commercially available hex-5-yn-1-ol (**198**) using Jones reagent gave hex-5-ynoic acid (**199**) which was converted into its anhydride (**200**) by deprotonation with sodium hydride, followed by treatment with 0.5 equivalents of oxalyl chloride, and refluxing in benzene.[48]



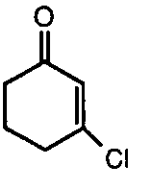
However, this anhydride did not react with benzothiophen-3-ylacetic acid (**176**) to give the pyranone (**201**) suitable for intramolecular Diels-Alder reaction.



The second route involved acylation of ethyl benzothiophen-3-ylacetate (**171**) with hex-5-ynoyl chloride, catalysed by either tin (IV) chloride or zinc (II) chloride. However, no acylated product (**202**) was obtained. The only products isolated were starting material and the cyclohexanone (**203**) which arose from cyclisation of the acid chloride, and was identified by its IR (1 680, 1 610 cm^{-1}) and NMR spectra.



(171) (202)

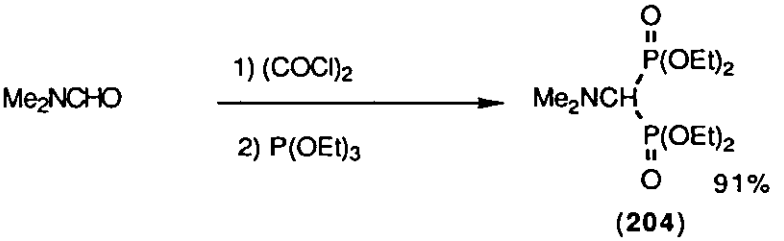


(203)

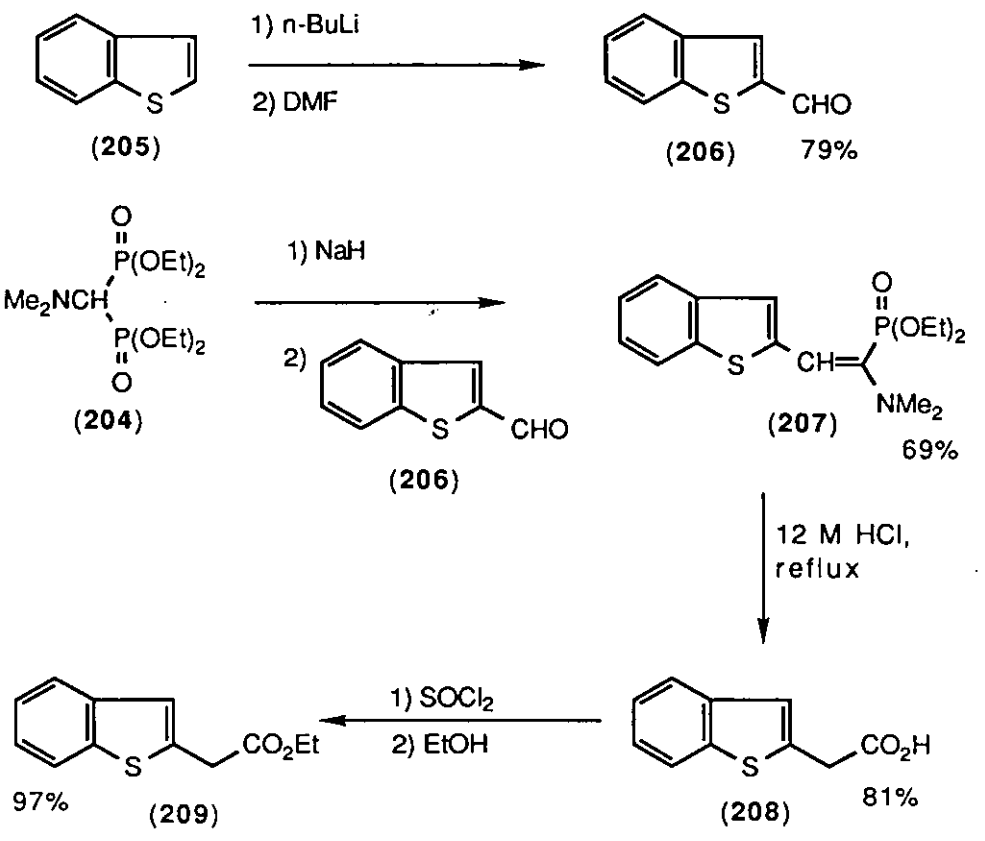
2.3 Benzothieno[3,2-*c*]pyran-3-ones

2.3.1 Preparation of benzothiophen-2-ylacetic acid

Benzothiophen-2-ylacetic acid (**208**) was prepared by the literature route.[51] 2-Formylbenzothiophene (**206**) was prepared by lithiation of benzothiophene and quenching with DMF. Tetraethyl dimethylaminomethylenediphosphonate (**204**) was prepared by reaction of DMF with oxalyl chloride followed by two equivalents of triethyl phosphite. Deprotonation of tetraethyl dimethylaminomethylenediphosphonate (**204**) with sodium hydride followed by reaction with 2-formylbenzothiophene (**206**) gave the enamine phosphonate (**207**), which was hydrolysed in concentrated hydrochloric acid to give benzothiophen-2-ylacetic acid (**208**). Treatment of the acid with thionyl chloride followed by ethanol gave the known ethyl benzothiophen-2-ylacetate (**209**).[52]

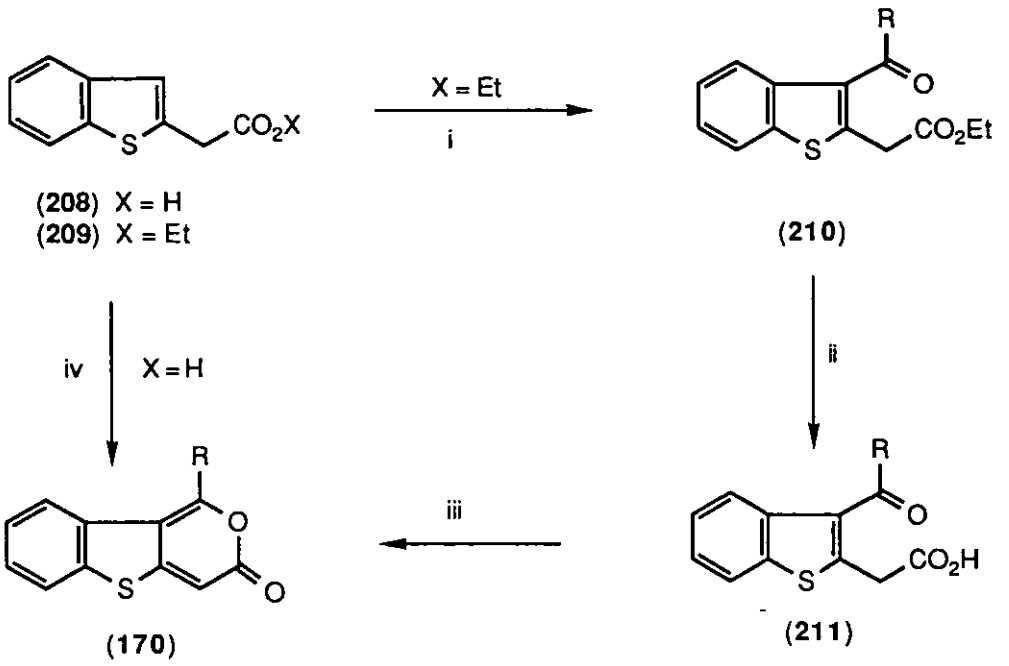


(204)



2.3.2 Preparation of Benzothieno[3,2-*c*]pyran-3-ones.

The isomeric benzothieno[3,2-*c*]pyran-3-ones (**170**) were prepared from ethyl benzothiophen-2-ylacetate (**209**) or the corresponding acid (**208**). The ester (**209**) could be formylated or acetylated at the 3-position using dichloromethyl methyl ether or acetyl chloride in the presence of tin (IV) chloride to give the corresponding 3-acyl compounds (**210a, b**) in 76 and 46% yield respectively (Scheme 11). Hydrolysis of the ester (**210**) proved difficult, and the corresponding acids (**211**) could never be obtained pure. Nevertheless the impure formyl acid (**211a**) could be cyclised to the parent benzothienopyranone (**170a**) [42% from ester (**210a**)], by refluxing in acetic anhydride. The 1-methylbenzothienopyranone (**170b**) could be prepared more efficiently from the acid (**208**) in 58% yield by reaction with acetic anhydride in the presence of boron trifluoride diethyl ether (Scheme 11).

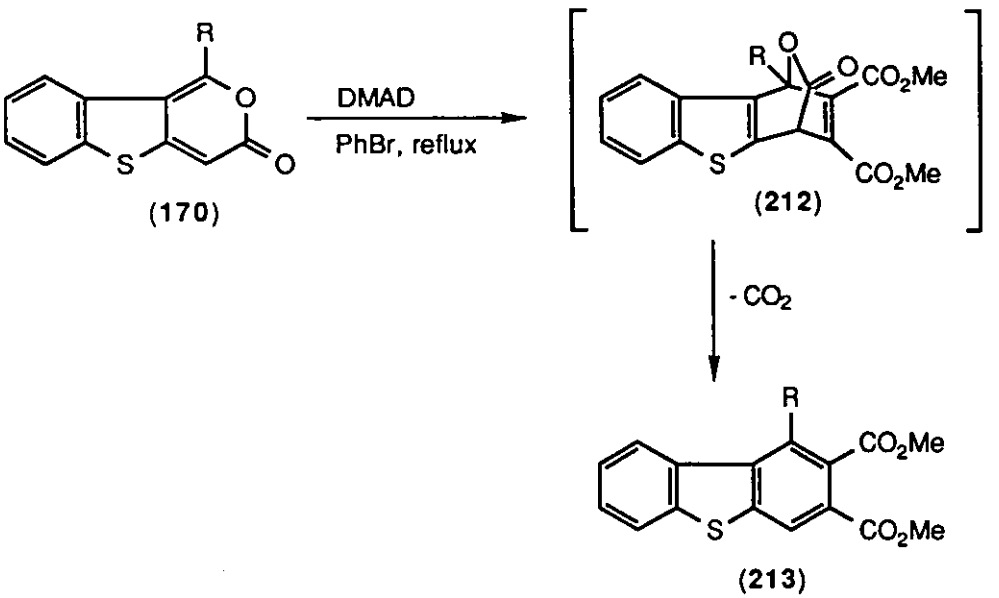


Scheme 11. (**a**, R=H; **b**, R=Me) *Reagents* i) Cl_2CHOMe (or AcCl), $SnCl_4$, CH_2Cl_2; ii) KOH, H_2O, THF, MeOH; iii) Ac_2O, reflux; iv) Ac_2O, $BF_3.Et_2O$.

The benzothieno[3,2-*c*]pyran-3-ones (**170**) are yellow/orange solids with the expected spectroscopic characteristics (carbonyl absorptions at *ca.* 1705 cm^{-1} in their IR spectra, and peaks at *ca.* δ 6.5 for 4-H in their NMR spectra).

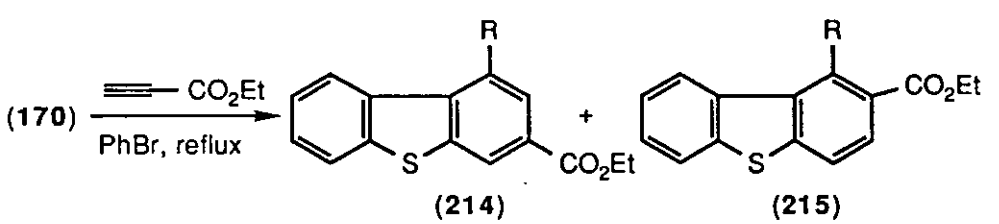
2.3.3 Diels-Alder reactions of Benzothieno[3,2-*c*]pyran-3-ones

The benzothieno[3,2-*c*]pyran-3-ones (**170**) exhibit similar Diels-Alder reactivity to the [2,3-*c*]-isomers (**169**). Thus heating with DMAD in boiling bromobenzene gave the dibenzothiophene diesters (**213**) in good yield. Again, isolation of the carbon dioxide bridged adducts (**212**) was not possible.

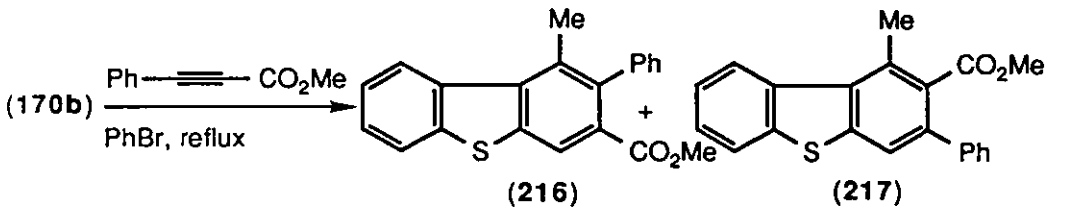


Compd. (170)	R	Time (h)	Compd. (213)	Yield (%)
a	H	7	a	73
b	Me	9	b	73

The reactions with ethyl propiolate and methyl phenylpropiolate[47,48] exhibit very little regioselectivity, although there is a slight preference for the formation of the 3-esters (**215**) and (**217**).



Compd. (170)	R	Time (h)	Compd. (214)/(215)	Combined Yield (%)	Ratio (214):(215)
a	H	24	a	74	1:1.6
b	Me	40	b	76	1:1.9



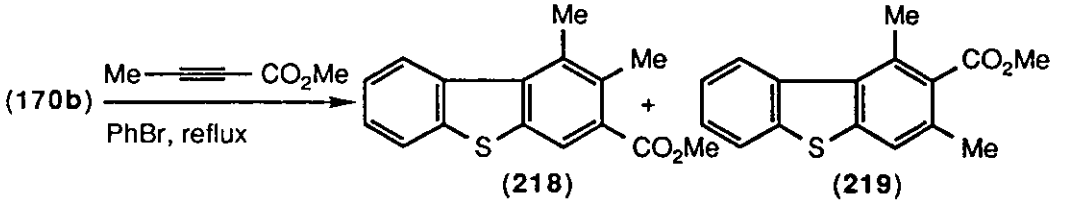
(216) (217)

Ratio (216):(217), 1:3

Combined yield 66%

The structure of the major component (**217**) of the mixture resulting from Diels-Alder reaction of the pyranone (**170b**) with methyl phenylpropiolate was confirmed by NOE difference spectroscopy. Pre-irradiation of the singlet at δ 2.94 (4-Me) caused enhancement of the multiplet at δ 8.45 (containing 5-H) and of the singlet at δ 3.63 (CO_2Me).

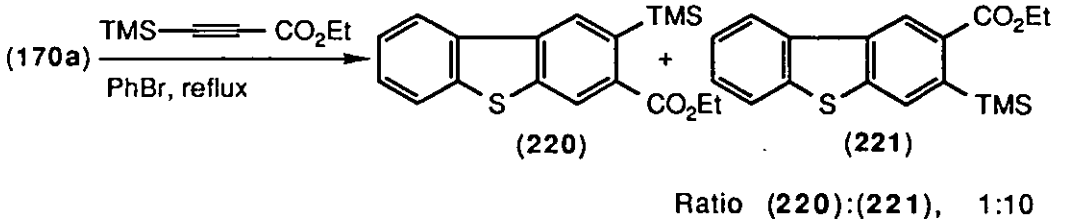
As before the corresponding reactions of methyl tetrolate and ethyl 3-trimethylsilylpropynoate were more selective, with the silylated alkyne being highly regioselective.



(218) (219)

Ratio (218):(219), 1:10

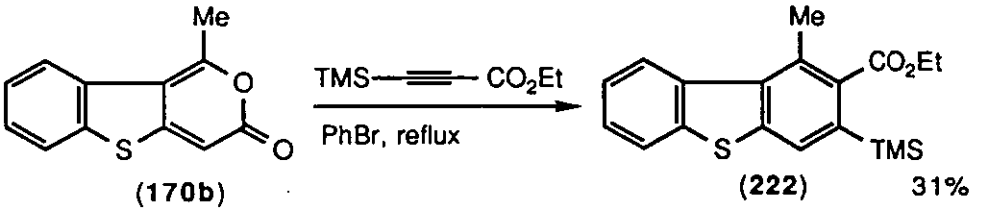
Combined yield 35%



(220) (221)

Ratio (220):(221), 1:10

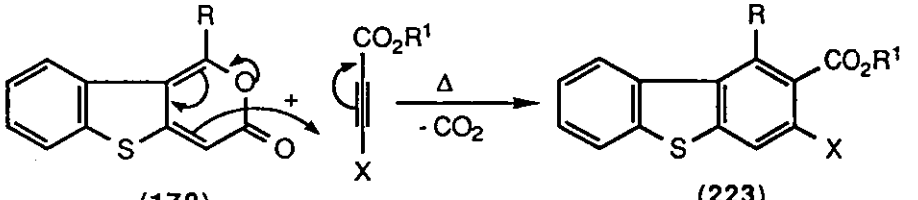
Combined yield 78%



(170b) (222) 31%

The structure of compound (**222**) was confirmed by NOE difference spectroscopy. Pre-irradiation of the singlet at δ 0.36 ($SiMe_3$) resulted in enhancement of the singlet at δ 7.94 (1-H). Pre-irradiation of the singlet at δ 2.89 (4-Me) caused enhancement of the multiplet at δ 8.39-8.42 (5-H) and the ester signals but not the $SiMe_3$ signal. Structure of compound (**221**) was also confirmed in this manner. Pre-irradiation of the singlet at δ 8.82 (4-H) caused enhancement of the multiplet at δ 8.23 (5-H) but not of the $SiMe_3$ signal. Pre-irradiation of the singlet at δ 0.44 ($SiMe_3$) caused strong enhancement of the singlet at δ 8.17 (1-H) and weak enhancement of the ethyl ester signals.

The direction of addition, however, is, perhaps not surprisingly, opposite to that of the isomeric dienes (**169**), a feature which parallels the chemistry of the related indole dienes (**167**) and (**168**).[38,41] As stated above, the direction of addition can be said to be controlled by the ring oxygen.



(**170**) (**223**)

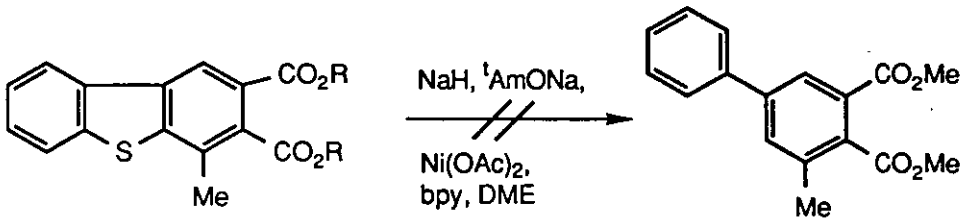
X=Me, TMS
R^1=Me, Et

Major isomer

2.4 Desulphurisation

Desulphurisation of the dibenzothiophenes presented above would provide a useful route to polysubstituted biphenyls. Our first studies used the method of Caubere.[53] Desulphurisation of the dibenzothiophene (**181b**) was attempted using the nickel containing complex reducing agent,

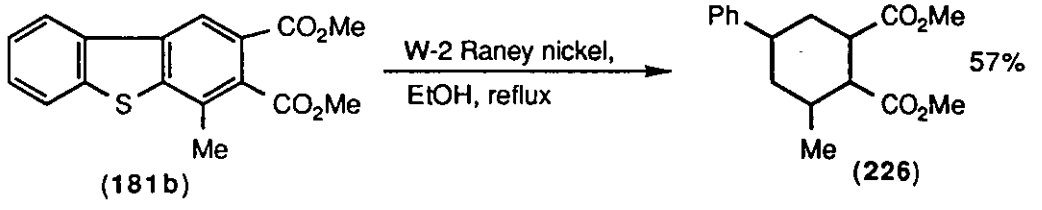
NaH/^{t}AmONa/Ni(OAc)$_2$/2,2'-bipyridyl. No biphenyl (**225**) was detected. The only compound isolated was the dibenzothiophene di-acid (**224**) in 85% yield. The di-acid was characterised by its NMR spectrum and its mass spectrum which showed a weak molecular ion at *m/z* 286 and a strong peak at 268 corresponding to loss of water.



(**181b**) R = Me
(**224**) R = H

(**225**)

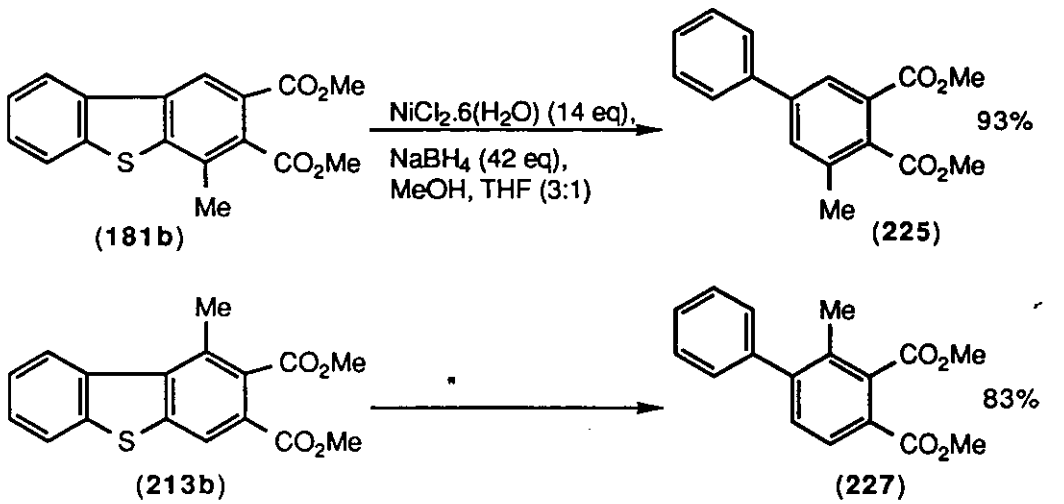
Heating compound (**181b**) with W-2 Raney-nickel[54] in ethanol effected desulphurisation but also resulted in reduction of the substituted aromatic ring to give the substituted cyclohexane (**226**) in 57% yield. The cyclohexane (**226**) was identified by its high resolution mass spectrum (observed molecular ion 290.1511, $C_{17}H_{22}O_4$ requires 290.1518) and NMR spectrum, in particular the presence of a doublet at δ 1.02 (*J* 7 Hz) due to the methyl attached to the cyclohexane ring.



(**181b**)

(**226**)

Recently a method of desulphurising dibenzothiophene derivatives with nickel boride has been published.[55] The nickel boride is generated *in situ* from nickel chloride hexahydrate and sodium borohydride. The desulphurisation of the dibenzothiophenes (**181b**) and (**213b**) was accomplished using this procedure.



Hence, dimethyl 5-methylbiphenyl-3,4-dicarboxylate (**225**) was prepared from the dibenzothiophene (**181b**) in 93% yield and dimethyl 2-methylbiphenyl-3,4-dicarboxylate (**227**) was prepared from the dibenzothiophene (**213b**) in 83% yield. A disadvantage of this procedure is that very large excesses of nickel chloride hexahydrate and sodium borohydride are required, which would be inconvenient when working on a larger scale, and the reactivity of nickel boride decreases rapidly with time. Hence, in order to achieve complete conversion of dibenzothiophene into biphenyl, further portions of the desulphurising reagents had to be added as the reaction progressed. The 1-methyl substituted dibenzothiophene (**181b**) was desulphurised less readily than the 4-methyl substituted compound (**213b**), presumably due to steric effects. Heating was required to effect complete conversion of dibenzothiophene (**181b**) into the biphenyl (**225**).

2.5 Conclusions

The isomeric benzothienopyranones (**169**) and (**170**), easily prepared from benzothiophen-2- or -3-ylacetic acid, are stable benzothiophene-2,3-quinodimethane type dienes, which react with alkynes to give dibenzothiophenes in good yield. This method provides a useful alternative to traditional routes to dibenzothiophenes[56] such as dehydration of α-phenylthio substituted cyclohexanones followed by oxidation,[57] iodide mediated photolysis of diaryl

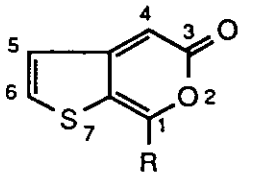
sulphides[58] or treatment of 2-allylbenzothiophenes with dichloromethyl methyl ether.[59] The value of this Diels-Alder route to dibenzothiophenes is enhanced by the fact that the dienes (**169**) and (**170**) exhibit opposite regioselectivity with the commercially available alkyne, ethyl 3-trimethylsilylpropynoate, the resulting trimethylsilyl substituted compounds being potentially versatile intermediates for further transformation into a variety of dibenzothiophenes. Furthermore, desulphurisation of the dibenzothiophenes provides a route to polysubstituted biphenyls.

CHAPTER 3

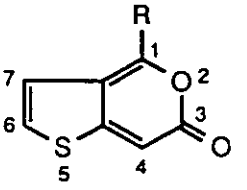
Thienopyranones

3.1 Introduction

Owing to the recent interest shown in thiophene-2,3-quinodimethane (**5**) and stable cyclic analogues thereof (Chapter 1), we decided to turn our attention to the preparation of thieno[2,3-*c*]pyran-3-ones (**228**) and thieno[3,2-*c*]pyran-3-ones (**229**).

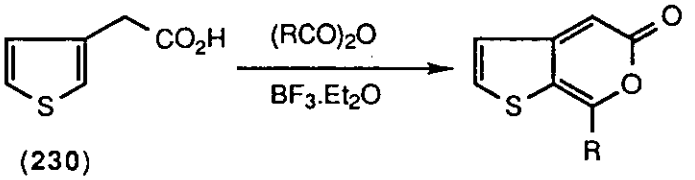


(**228**)



(**229**)

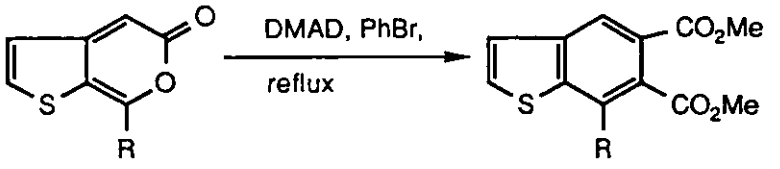
Initial experiments by Dr. P. Shah in our laboratory had shown that the 1-methyl (**228b**) and 1-pentyl (**228e**) substituted thieno[2,3-*c*]pyran-3-ones could be prepared in one step from the commercially available 3-thienylacetic acid (**230**) by treatment with acetic anhydride or hexanoic anhydride respectively, in the presence of boron trifluoride diethyl ether.[48]



(**230**)

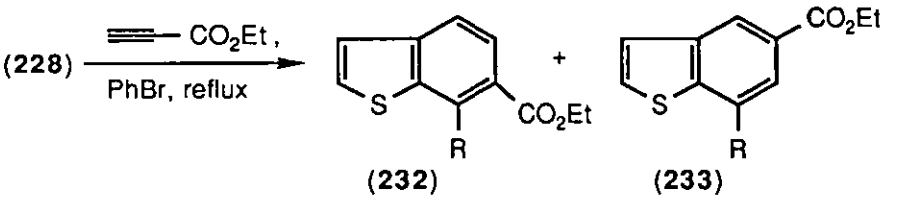
(**228b**) R=Me, 28%
(**228e**) R=Pentyl, 44%

The pyranones (**228b, e**) were shown to undergo Diels-Alder reaction with DMAD and ethyl propiolate to give, after loss of carbon dioxide, benzothiophenes.



(228) (231)

Compd. (228)	R	Time (h)	Compd. (231)	Yield (%)
b	Me	1.5	**b**	59
e	Pentyl	2	**e**	69



(232) (233)

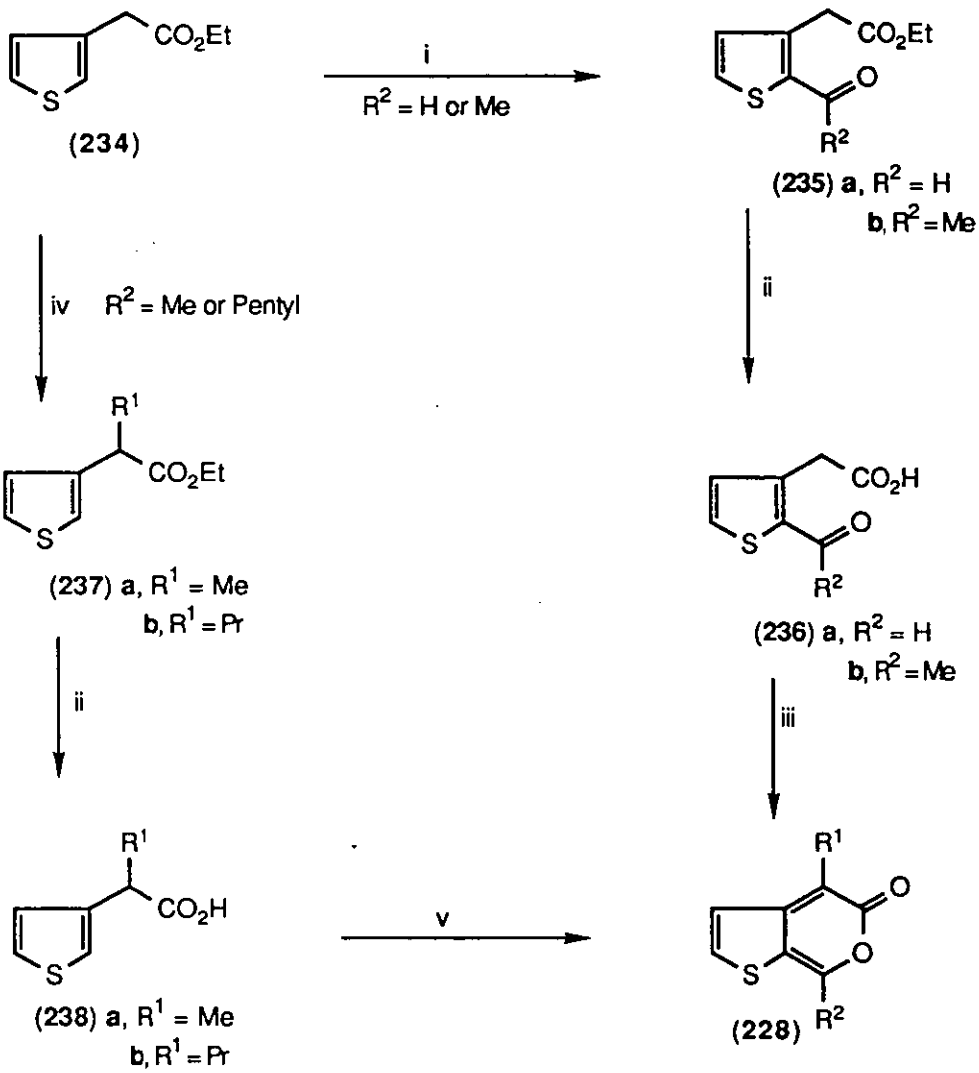
Compd. (228)	R	Time (h)	Compd. (232)/(233)	Combined Yield (%)	Ratio (232):(233)
b	Me	5	**b**	64	2:1
e	Pentyl	12	**e**	62	1.8:1

3.2 Thieno[2,3-*c*]pyran-3-ones

3.2.1 Preparation of thieno[2,3-*c*]pyran-3-ones

The thieno[2,3-*c*]pyran-3-one ring system (**228**) was prepared by two methods, either starting from ethyl 3-thienylacetate (**234**) or the corresponding acid (**230**), both of which are commercially available. The first method (Scheme 12) which was needed to prepare the unsubstituted pyranone (**228a**) involved formylation of the ester (**234**) with dichloromethyl methyl ether in the presence of tin(IV) chloride to give the 2-formyl derivative (**235a**), which was obtained along with its 5-formyl isomer as a 1:1 mixture in 91% combined yield. Similarly, acetylation of the ester (**234**) with acetyl chloride in the presence of tin(IV) chloride gave the 2-acetyl derivative

(**235b**), which was obtained along with its 5-acetyl isomer as a 6:1 mixture in 78% combined yield.



	R^1	R^2
a	H	H
b	H	Me
c	Me	Me
d	Pr	Me
e	H	C_5H_{11}

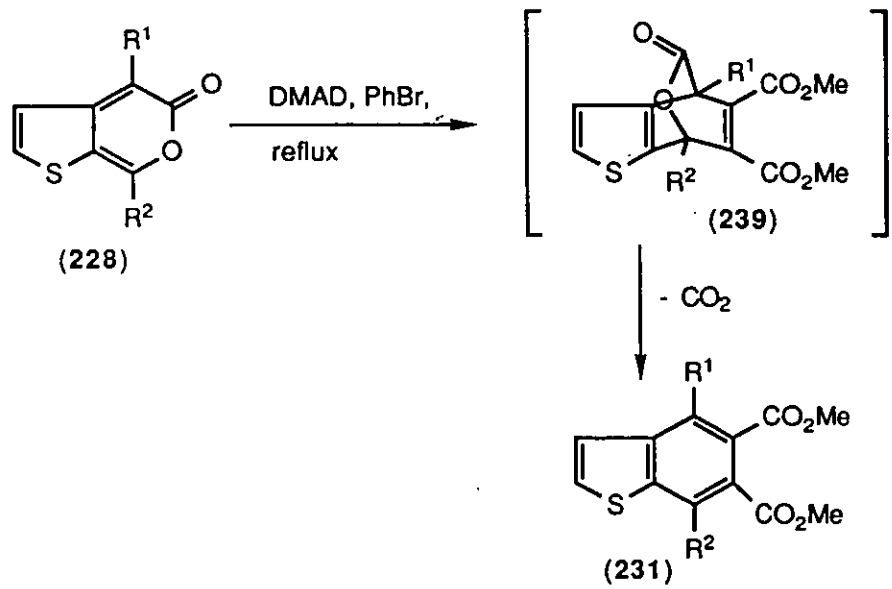
Scheme 12. *Reagents* i) Cl_2CHOMe (or AcCl), $SnCl_4$, CH_2Cl_2; ii) KOH, H_2O, THF; iii) Ac_2O, reflux; or $ClCO_2Bu^i$, Et_3N, THF; iv) LICA, THF, -78°C then R^1I, DMSO; v) $(R^2CO)_2O$, $BF_3.Et_2O$.

Since separation of the isomers was difficult at this stage, the mixtures were progressed to the desired thienopyranones (**228a**) and (**228b**) by hydrolysis to the acids (**236a**), in 91% yield, and (**236b**), in 75% yield, followed by cyclodehydration, and purification. Cyclisation of acid (**236a**) into the unsubstituted pyranone (**228a**) was achieved in 29% yield using isobutyl chloroformate and triethylamine in tetrahydrofuran. The pyranone (**228b**) was obtained in 77% yield from the acid (**236b**) by refluxing in acetic anhydride. The pyranone (**228b**) and the pentyl substituted compound (**228e**) could also be prepared directly from 3-thienylacetic acid (**230**) in modest yield, by reaction with the appropriate carboxylic acid anhydride in the presence of boron trifluoride diethyl ether, as shown in the introduction. This approach could also be used for the preparation of the 1,4-disubstituted thienopyranones (**228c**) and (**228d**). Thus ethyl 3-thienylacetate was deprotonated using lithium isopropylcyclohexylamide (LICA) as base,[60] and the resulting ester enolate alkylated with iodomethane or 1-iodopropane to give the substituted 3-thienylacetates (**237a**) and (**237b**) in 84% and 86% yield respectively. Hydrolysis to the corresponding acids (**238a**) and (**238b**), in yields of 87% and 85% respectively, followed by reaction with acetic anhydride and boron trifluoride diethyl ether gave the desired thienopyranones (**228c**) in 25% yield and (**228d**) in 30% yield (Scheme 12).

3.2.2 Intermolecular Diels-Alder reactions

The thieno[2,3-*c*]pyran-3-ones (**228**) are yellow crystalline solids with the exception of (**228e**) which is a viscous oil, and exhibit the expected spectroscopic properties. For example, the carbonyl frequencies in the IR spectra occur in the range 1680-1710 cm^{-1}, and the signal for 4-H on the pyranone rings is in the range δ 6.2-6.4 in their ^1H NMR spectra. When heated with alkynes in boiling bromobenzene they undergo Diels-Alder reaction to give, after loss of carbon dioxide, benzothiophenes. Compared with the analogous benzothieno[2,3-*c*]pyran-3-ones, the thiophene derivatives (**228**) are more reactive dienes, and react relatively rapidly with a range of electron deficient alkynes. Thus reaction with dimethyl acetylenedicarboxylate (DMAD) gave the

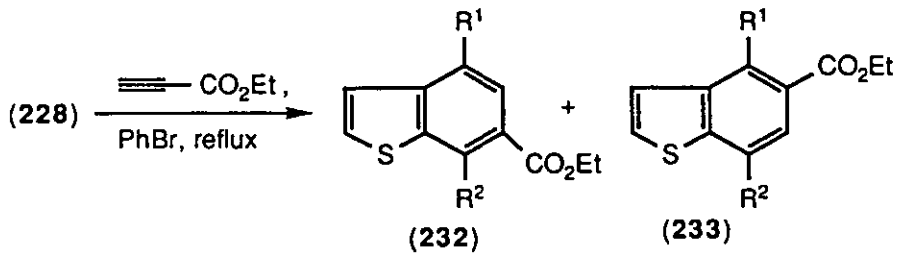
benzothiophene-5,6-diesters (**231a, c, d**) in good to excellent yield. Again, carbon dioxide was lost spontaneously and the carbon dioxide bridged adducts (**239**) were not detected.



(228) (239) (231)

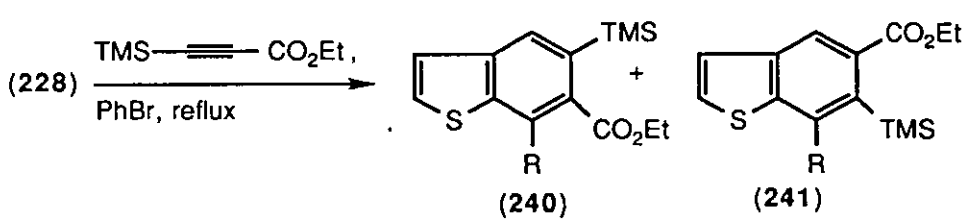
Compd. (228)	R^1	R^2	Time (h)	Compd. (231)	Yield (%)
a	H	H	4	a	77
c	Me	Me	12	c	92
d	Pr	Me	3	d	66

With the unsymmetrical alkyne ethyl propiolate, the Diels-Alder reactions exhibit little regioselectivity and give essentially equal amounts of the benzothiophene-6-esters (**232**) and 5-esters (**233**), with the 6-ester predominating slightly. This lack of regioselectivity with ethyl propiolate as dienophile is in line with earlier results on similar systems.[38,41] The structures of the benzothiophenes (**232**) and (**233**) were assigned on the basis of their ^{1}H NMR spectra. In the case of the 6- and 5-esters (**232a**) and (**233a**), the peaks in the aromatic region associated with the minor isomer (**233a**) were in excellent agreement with the reported values for the known methyl benzothiophene-5-carboxylate.[61] The 6-ester (**232d**) was assigned as the major isomer from reaction of pyranone (**228d**) with ethyl propiolate, due to the position of the 7-methyl resonance which occurs downfield at δ 2.83 when the ester is *ortho* and at δ 2.56 when the ester is *meta*.



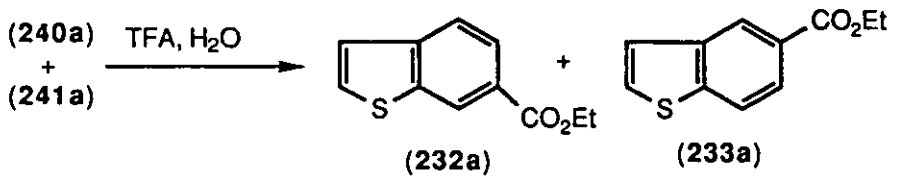
Compd. (228)	R^1	R^2	Time (h)	Compd. (232)/(233)	Combined yield (%)	Ratio (232):(233)
a	H	H	4	a	74	1.3:1
c	Me	Me	12	c	96	1:1
d	Pr	Me	3	d	61	1.2:1

However, ethyl 3-trimethylsilylpropynoate in which the bulky trimethylsilyl group replaces the acetylenic hydrogen, is regioselective in its Diels-Alder reactions with the thienopyranones (**228**), and gives the 5-trimethylsilylbenzothiophene-6-carboxylates (**240a, b, c**) as the major products.



Compd. (228)	R	Time (h)	Compd. (240)/(241)	Combined yield (%)	Ratio (240):(241)
a	H	4	a	58	4:1
b	Me	20	b	72	9:1
e	Pentyl	24	c	23	12:1

The structures of the benzothiophenes (**240a**) and (**241a**) were determined by protodesilylation using aqueous trifluoroacetic acid. The 6-ester was assigned as the major adduct by again comparing the aromatic peaks in the mixture with those of the known methyl benzothiophene-5-carboxylate.[61]

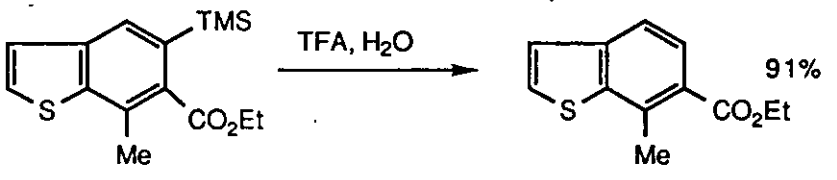


(232a) (233a)

Ratio (232a):(233a), 4:1

Combined yield 79%

In the case of the benzothiophene (**240b**), treatment with aqueous trifluoroacetic acid resulted in protodesilylation and formation of ethyl 7-methylbenzothiophene-6-carboxylate (**232b**), isolated pure after chromatography, thus confirming the structure.

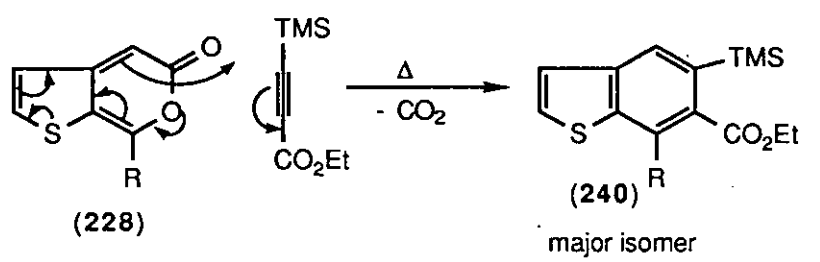


(240b) (232b)

The 7-methyl substituted benzothiophene 6- and 5-esters (**232b**) and (**233b**) were easily distinguishable; in the 6-isomer, 4-H and 5-H occurred as 2 doublets (*J* 8 Hz), whereas in the 5-isomer,[48] 4-H and 6-H were approximate singlets. Also, the 7-methyl group in the 6-ester resonated downfield (at δ 2.88) relative to that in the 5-ester (at δ 2.61).

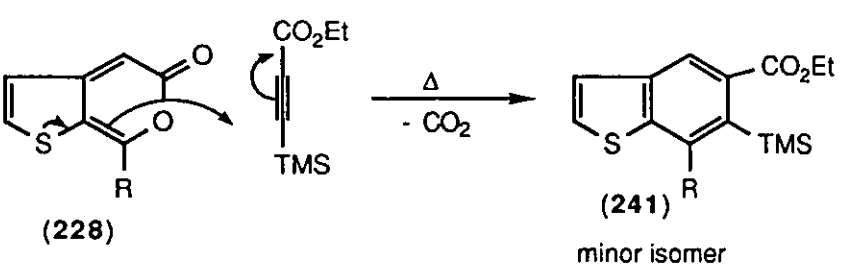
The thieno[2,3-*c*]pyran-3-ones (**228**) are much more reactive than their benzothieno counterparts. If the reactions are again assumed to be controlled by 'normal' electron demand, then the closer in energy HOMO (diene) and LUMO (dienophile), the faster the reaction. Electron donating substituents on the diene raise the energy of the HOMO and hence bring it closer in energy to LUMO (dienophile). Hence, the greater reactivity of the thieno[2,3-*c*]pyran-3-ones can be explained by them being more electron rich dienes than the benzothieno[2,3-*c*]pyran-3-ones (**169**). This can be explained by the sulphur 'lone pair' in the benzothieno[2,3-*c*]pyran-3-ones being delocalised into the benzene ring, whereas in the thieno[2,3-*c*]pyran-3-ones it can be directed into the diene.

Again, the fact that Diels-Alder reaction with ethyl 3-trimethylsilylpropynoate gives the 5-trimethylsilylbenzothiophene-6-ester (**240**) as the major product can be explained if it is assumed that the pyrone ring oxygen controls the direction of cycloaddition. However, some of the 6-trimethylsilylbenzothiophene-5-ester (**241**) is observed, even in the case of the pyranones (**228b**) and (**228e**), where its formation is sterically unfavourable. This can be most simply explained by assuming that the sulphur 'lone pair' does make some contribution. Hence, the sulphur 'lone pair' can act in the same direction as the oxygen 'lone pair', accounting for the major isomer. Or the sulphur 'lone pair' can act against the oxygen 'lone pair', accounting for the minor isomer and explaining why the thieno[2,3-*c*]pyran-3-ones (**228**) are less regioselective than the benzothieno[2,3-*c*]pyran-3-ones (**169**).



(**228**) (**240**) major isomer

R = H, Me, or Pentyl

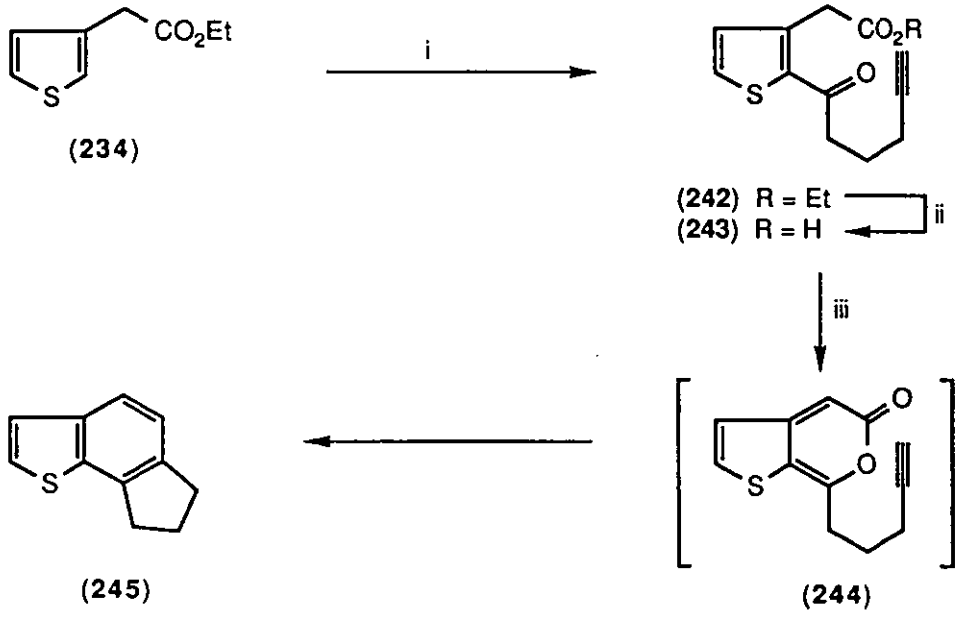


(**228**) (**241**) minor isomer

3.2.3 Intramolecular Diels-Alder reactions

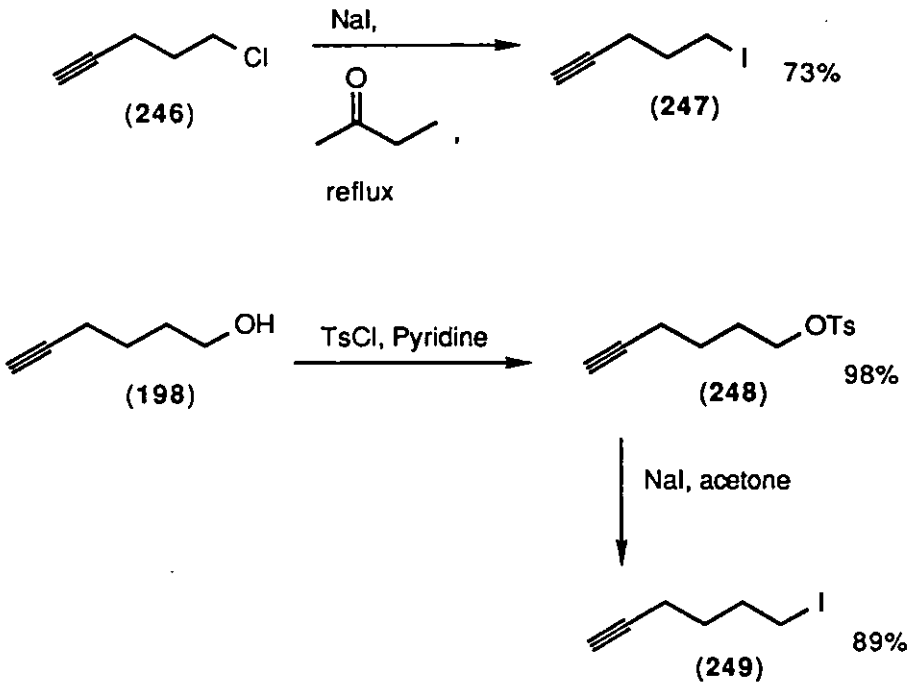
In continuation of the interest, in our laboratory, in the intramolecular Diels-Alder (IMDA) reactions of heterocyclic fused pyrones,[39] we have also studied IMDA reactions of thieno[2,3-*c*]pyran-3-ones as a route to cycloalkabenzothiophenes. The substrates for the IMDA reactions were the thienopyranones (**244**) and (**252**). The 1-substituted derivative (**244**) was

prepared by acylation of ethyl 3-thienylacetate with hex-5-ynoyl chloride in the presence of zinc chloride (Scheme 13). The resulting 2-acyl thiophene (**242**), in common with earlier results, was obtained along with the unwanted 5-acyl isomer as a 5:1 mixture in a combined yield of 43%. The 2-acyl thiophene (**242**) was hydrolysed, and the resulting acid (**243**) was obtained in 66% yield after recrystallisation. Since the pyranone (**244**) proved difficult to isolate, the IMDA reaction was simply effected by heating the acid (**243**) in acetic anhydride for 5 h, and gave 7,8-dihydroindeno[4,5-*b*]thiophene (**245**) directly in 77% yield (Scheme 13).

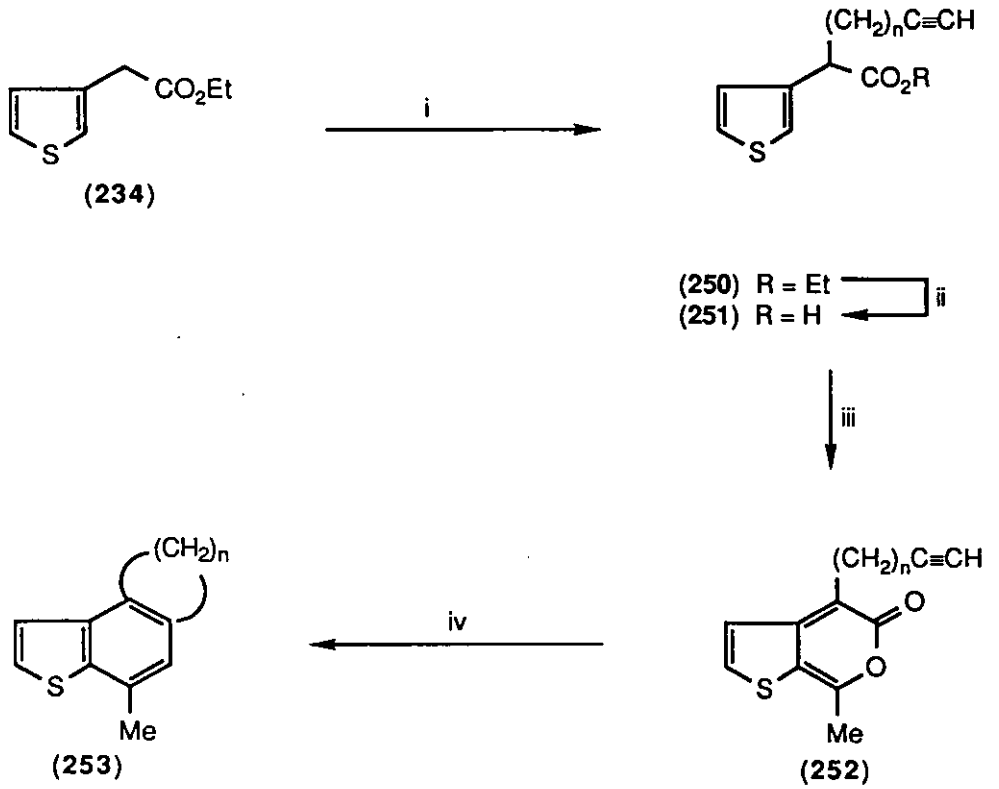


Scheme 13. *Reagents* i) $HC{\equiv}C(CH_2)_3COCl$, $ZnCl_2$, CH_2Cl_2; ii) KOH, H_2O, THF, MeOH; iii) Ac_2O, reflux.

The thienopyranones (**252**) in which the side chain bearing the triple bond is attached at the 4-position, were also prepared from ethyl 3-thienylacetate by alkylation of the ester enolate with 5-iodopentyne (**247**) and 6-iodohexyne (**249**) to give the esters (**250a**), in 76% yield, and (**250b**), in 68% yield, respectively (Scheme 14). 5-Iodopentyne (**247**) was prepared from the commercially available 5-chloropentyne (**246**) by heating with sodium iodide in methyl ethyl ketone. 6-Iodohexyne (**249**) was prepared by treatment of hex-5-yn-1-ol (**198**) with tosyl chloride in pyridine, followed by treatment of the resulting tosylate (**248**) with sodium iodide in acetone.



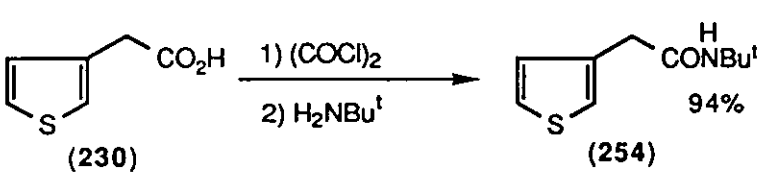
Hydrolysis of the esters (**250a**) and (**250b**) gave the acids (**251a**), in 94% yield, and (**251b**), in 93% yield, respectively. Treatment with acetic anhydride and boron trifluoride diethyl ether gave the required pyranones (**252a**), in 23% yield, and (**252b**) in 10% yield. The α-alkynyl substituted acids react less well than the α-alkyl substituted acids, with acetic anhydride in the presence of boron trifluoride diethyl ether. A possible explanation for this is that interaction of boron trifluoride with the triple bond may lead to unwanted decomposition pathways. On heating in boiling bromobenzene, the pyranones (**252**) underwent facile IMDA reaction to give, after loss of carbon dioxide, the cycloalka[*e*]benzothiophenes (**253a**) (81%) and (**253b**) (71%) (Scheme 14).



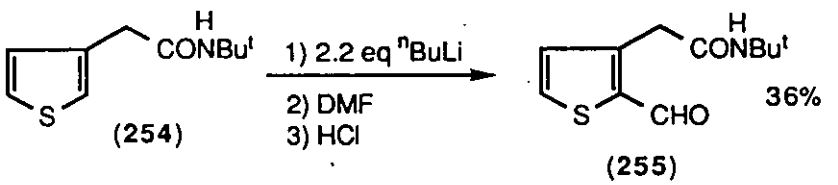
Scheme 14. (**a**, n=3; **b**, n=4) *Reagents* i) LICA, THF, -78°C, then $I(CH_2)_nC{\equiv}CH$; ii) KOH, H_2O, MeOH, THF; iii) Ac_2O, $BF_3.Et_2O$; iv) bromobenzene, reflux.

3.2.4 Investigation of alternative routes to thieno[2,3-*c*]pyran-3-ones

As an alternative to acylation of ethyl 3-thienylacetate (**234**), which did not proceed completely regiospecifically, we decided to investigate lithiation of the t-butyl amide (**254**) which was readily prepared from 3-thienylacetic acid (**230**). 3-Thienylacetic acid was converted into its acid chloride by treatment with oxalyl chloride and then reacted with an excess of t-butylamine to give the amide (**254**).

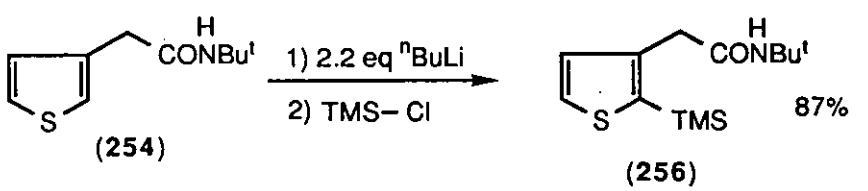


Initial deprotonation of nitrogen was expected to direct the second lithiation *ortho*.[62] Treatment of the amide (**254**) with two equivalents of butyllithium, followed by quenching with DMF gave the 2-formyl compound (**255**) in 36% yield. However, hydrolysis of the amide (**255**) without decomposition did not prove possible.



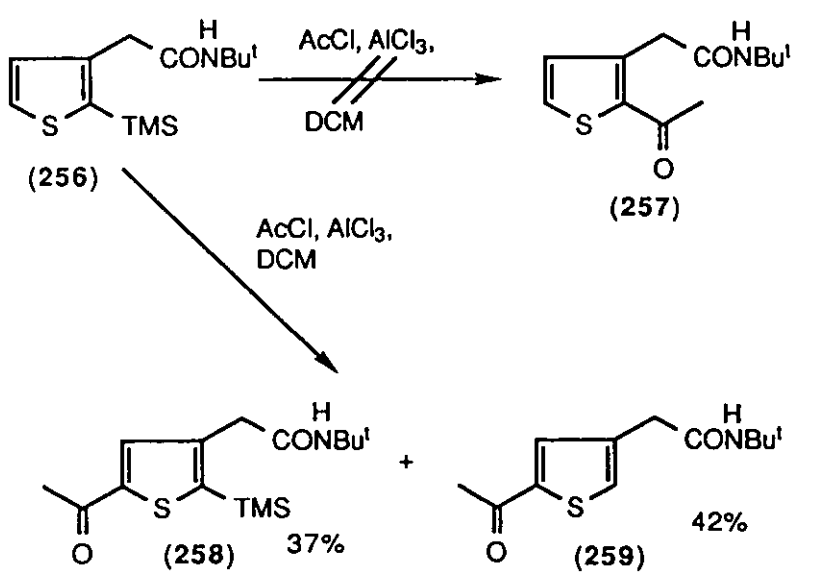
(**254**) (**255**)

The amide (**254**) could also be lithiated and quenched with trimethylsilyl chloride to give the 2-trimethylsilylthiophene (**256**) in 87% yield.



(**254**) (**256**)

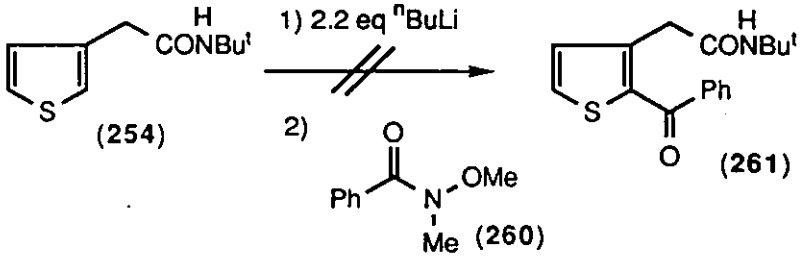
Attempts to perform an *ipso*-substitution on compound (**256**), using acetyl chloride and aluminium chloride in dichloromethane, did not give the desired 2-acetylthiophene (**257**).



(**256**) (**257**) (**258**) (**259**)

Instead, a mixture of compounds (**258**) and (**259**), both resulting from acetylation at C-5, was obtained in 37% and 42% yield respectively. Presumably, (**259**) is formed from (**258**) by desilylation in work-up.

Attempted acylation of the amide (**254**) using the *N*-methoxy-*N*-methylamide (**260**), a useful acylating agent for aryllithium species, developed by Weinreb,[63] was also unsuccessful. Only starting material was recovered from the reaction mixture.

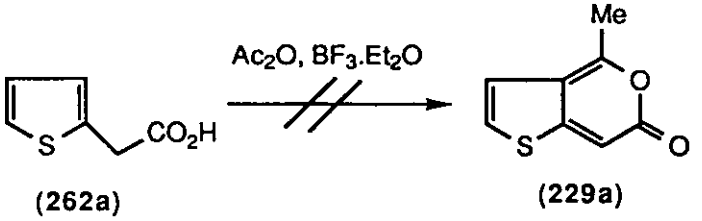


At this point, this methodology was abandoned as a possible route to the thieno[2,3-*c*]pyran-3-one ring system.

3.3 Thieno[3,2-*c*]pyran-3-ones

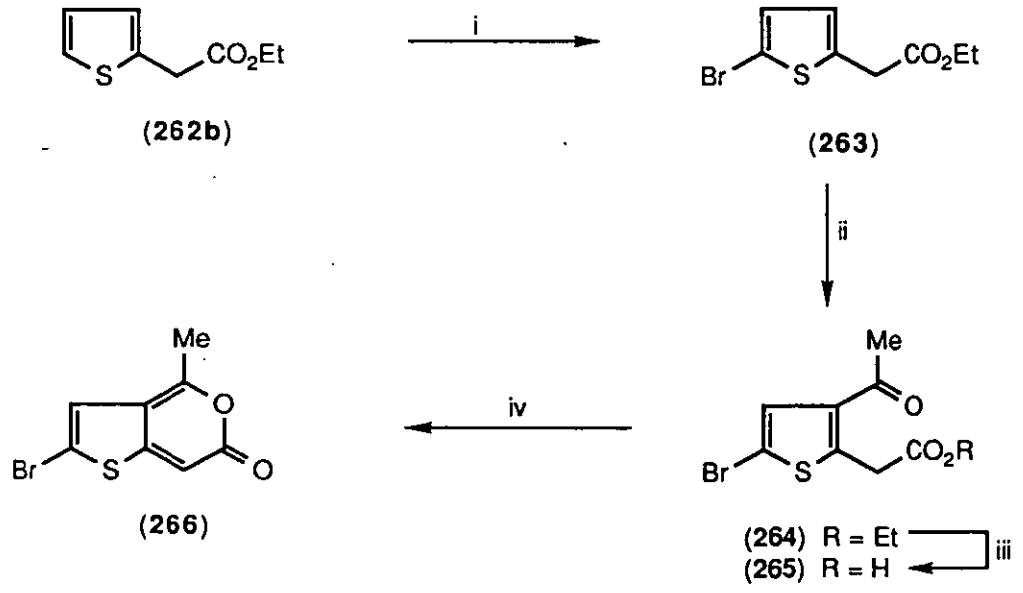
3.3.1 Preparation of thieno[3,2-*c*]pyran-3-ones

Reaction of the commercially available 2-thienylacetic acid (**262a**) with acetic anhydride in the presence of boron trifluoride diethyl ether did not result in the formation of 1-methylthieno[3,2-*c*]pyran-3-one (**229a**). Only black polymeric material was isolated from the reaction mixture.



However, the thieno[3,2-*c*]pyran-3-one ring system (**229**) was prepared from the commercially available ethyl 2-thienylacetate (**262b**), although

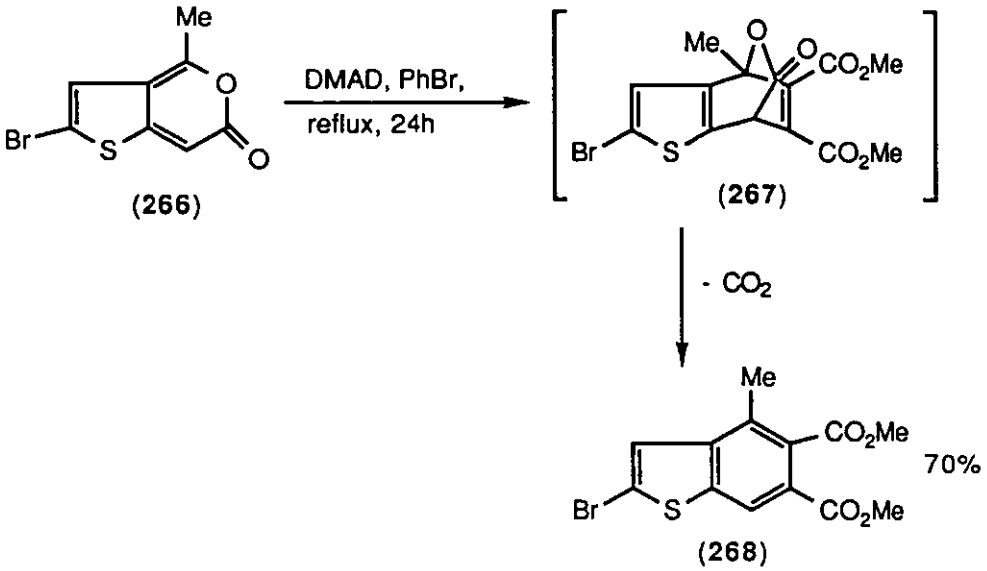
blocking of the 5-position with a bromine atom was necessary (Scheme 15). Thus, although acetylation (AcCl, $SnCl_4$) of ethyl 2-thienylacetate gave the 5-acetyl derivative (49%), acetylation of ethyl 5-bromo-2-thienylacetate (**263**), prepared in 70% yield by bromination of ethyl 2-thienylacetate with *N*-bromosuccinimide (NBS), under similar conditions gave the 3-acetyl compound (**264**) in 38% yield. Hydrolysis gave the corresponding acid (**265**), which without purification, was cyclodehydrated to the required pyranone (**266**) in 61% yield (from the ester).



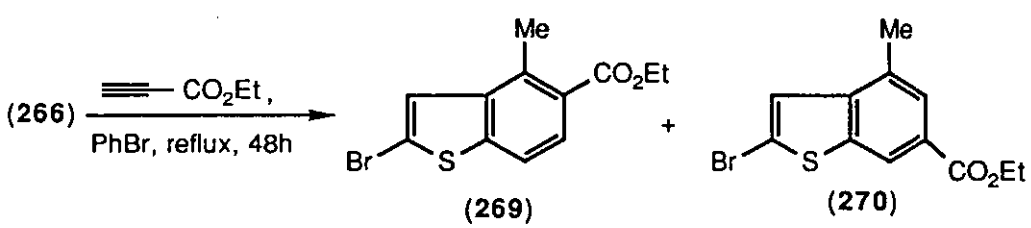
Scheme 15. *Reagents* i) NBS, $CHCl_3$, AcOH; ii) AcCl, $SnCl_4$, $ClCH_2CH_2Cl$; iii) KOH, H_2O, MeOH; iv) Ac_2O, reflux.

3.3.2 Diels-Alder reactions of thieno[3,2-*c*]pyran-3-ones

The thieno[3,2-*c*]pyran-3-one system (**266**) is less reactive in Diels-Alder reactions with alkynes than its [2,3-*c*]-isomer (**228b**). Thus its reaction with DMAD takes 24 h, and gives a 70% yield of the benzothiophene diester (**268**). Again, no carbon dioxide bridged adduct (**267**) could be isolated.



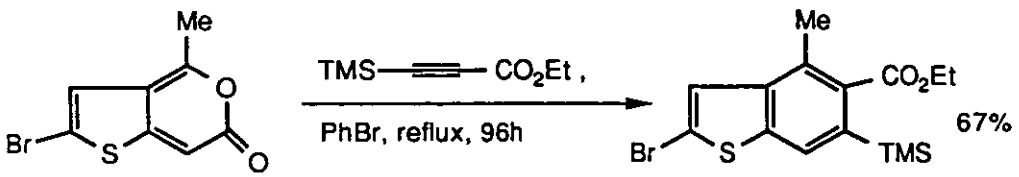
Likewise the reactions of pyranone (**266**) with ethyl propiolate and ethyl 3-trimethylsilylpropynoate were slower than the corresponding reactions of the isomeric pyranone (**228b**), and proceeded to give a 1.4:1 mixture of the benzothiophene-5-ester (**269**) and 6-ester (**270**), easily distinguishable by NMR, and the 6-trimethylsilylbenzothiophene-5-ester (**271**) as the only product, respectively.



Ratio (**269**):(**270**) 1.4:1

Combined yield 66%

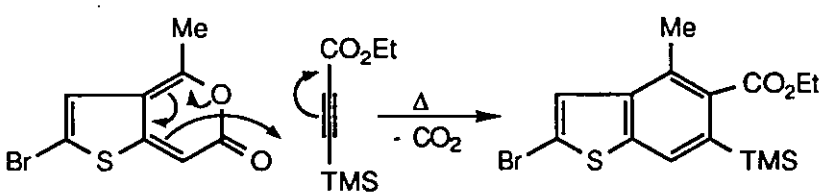
The 5-ester (**269**) was characterised by two doublets (*J* 8.5 Hz) at δ 7.82 and δ 7.57, corresponding to the resonances 6-H and 7-H. Whereas, the 6-ester (**270**) was readily characterised by two singlets, at δ 8.27 and δ 7.79, corresponding to the resonances 5-H and 7-H.



(266) (271)

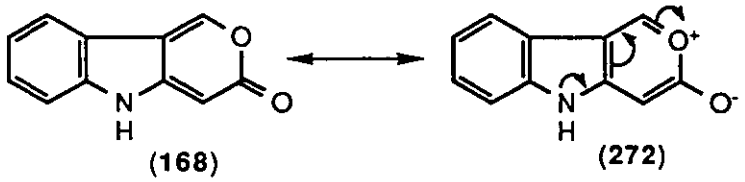
The structure of (**271**) was confirmed by NOE difference spectroscopy in which pre-irradiation of the singlet at δ 0.32 (Me_3Si) resulted in enhancement of the singlet at δ 7.77 (7-H) and *vice versa*. Also pre-irradiation of the singlet at δ 2.53 (4-Me) resulted in enhancement of the singlet at δ 7.42 (3-H), but not of the Me_3Si signal.

Hence the direction of addition of the thieno[3,2-*c*]pyran-3-one (**266**) to unsymmetrical alkynes is, perhaps not surprisingly, opposite to that of the isomeric diene (**228b**), a feature which parallels the chemistry of the closely related indole[38,41] and benzothiophene derived dienes. The regiochemistry can again be explained by assuming the direction of addition to be controlled by the pyrone ring oxygen.



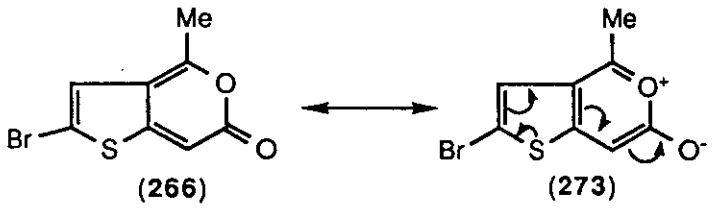
(266) (271)

The thieno[3,2-*c*]pyran-3-one (**266**) is less reactive than its [2,3-*c*]-isomer (**228b**), suggesting that there is less electron donation into the diene from the sulphur atom. It is possible that the electronegative bromine atom lowers the HOMO of the diene by inductive electron withdrawal, hence increasing the separation of HOMO (diene) and LUMO (dienophile) and lowering the reactivity. The low reactivity of the pyrano[4,3-*b*]indol-3-ones (**168**) was explained by contribution of an aromatic tautomer (**272**), stabilised by the nitrogen 'lone pair'.[41]



(168) (272)

However, in the case of the thieno[3,2-*c*]pyran-3-one (**266**), the sulphur 'lone pair' can also act to destabilise the aromatic tautomer (**273**).



(266) (273)

It is also questionable whether sulphur would be as efficient as nitrogen at stabilising such a tautomer, since there was little difference in reactivity between the benzothieno[3,2-*c*]pyran-3-ones (**170**) and the benzothieno[2,3-*c*]pyran-3-ones (**169**). Before being able to comment further on the reactivity of the thieno[3,2-*c*]pyran-3-one system, it would be useful to prepare the compound (**229**, R = Me). However, debromination of compound (**266**) by halogen-metal exchange was not possible, due to the extremely low solubility of the thieno[3,2-*c*]pyran-3-one (**266**), even at room temperature, whereas successful halogen-metal exchange, without decomposition, would probably have to be carried out at low temperature.

3.4 Conclusions

The thieno[2,3-*c*]pyran-3-ones (**228**), readily prepared from commercially available thiophenes, are stable thiophene-2,3-quinodimethane type dienes which react with alkynes to give benzothiophenes. The method allows the ready synthesis of benzothiophenes, polysubstituted in the benzene ring, which are less readily synthesised by classical methods,[56] for example the widely used acid-catalysed cyclisation of α-phenylthio-substituted ketones.[64] The substitution

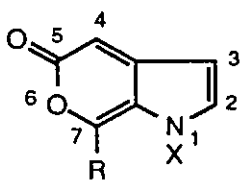
patterns obtainable complement those achieved by a recently published one-pot method for the preparation of highly substituted benzothiophenes, whereby an aryl bromide, an internal alkyne, and sulphur dichloride were transformed into 2,3,4,7-tetrasubstituted benzothiophenes.[65] Given the variation in substitution patterns available, this is a versatile route to benzothiophenes, especially when the reaction is extended by incorporating a trimethylsilyl group from the commercially available alkyne, ethyl 3-trimethylsilylpropynoate. The fact that IMDA reactions can be easily carried out adds to the versatility of the reaction.

CHAPTER 4

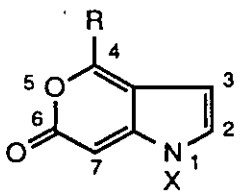
Pyranopyrrolones

4.1 Introduction

In the 120 years since Baeyer's first synthesis of indole,[66] this heteroaromatic compound has attracted much attention, not least because of the wide-ranging and potent biological activity of indoles, both synthetic and naturally occurring. Research in indole chemistry continues unabated with many groups devoting considerable effort to developing new methods for the synthesis of, and functionalisation of, the indole ring system.[67] Hence, a logical extension of the heterocyclic fused α-pyrone chemistry developed so far would be to investigate the preparation of the pyrano[3,4-*b*]pyrrol-5(1*H*)-ones (**274**) and the isomeric pyrano[4,3-*b*]pyrrol-6(1*H*)-ones (**276**) which, upon Diels-Alder reaction with alkynes, would be expected to give indoles, polysubstituted in the benzene ring.



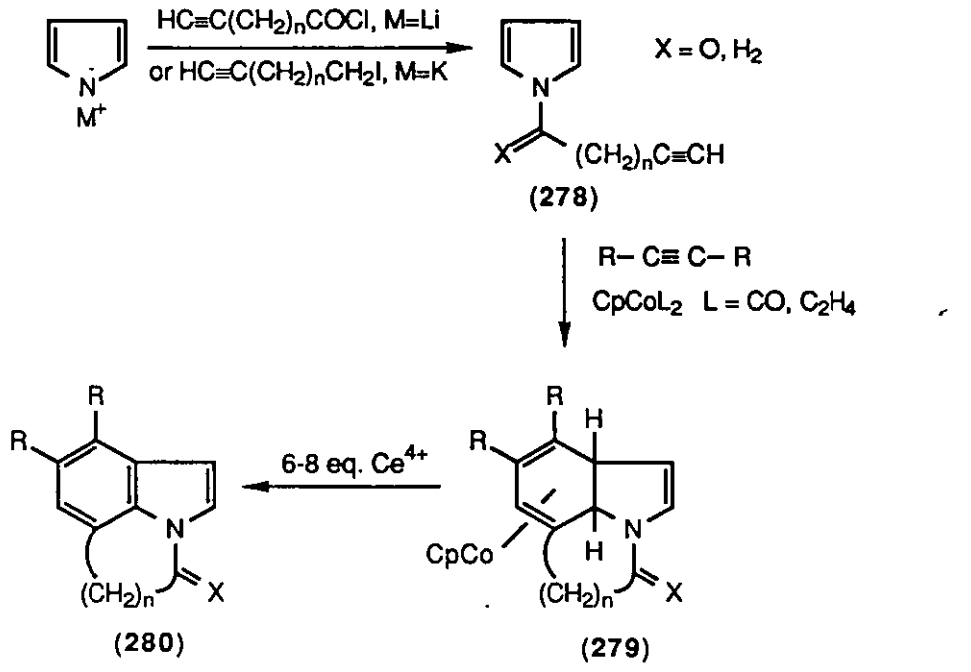
(**274**) X = H
(**275**) X = SO_2Ph



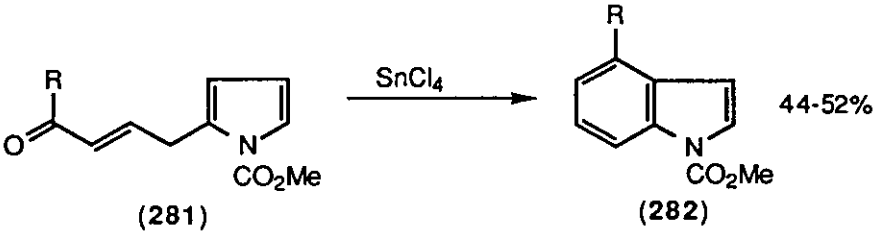
(**276**) X = H
(**277**) X = CO_2Bu^i

As stated in Chapter 1, little is known about pyrrole-2,3-quinodimethane (**80**). Although cyclic analogues are known, no Diels-Alder reactions have been reported. Hence, this would constitute a novel route to indoles from pyrroles.

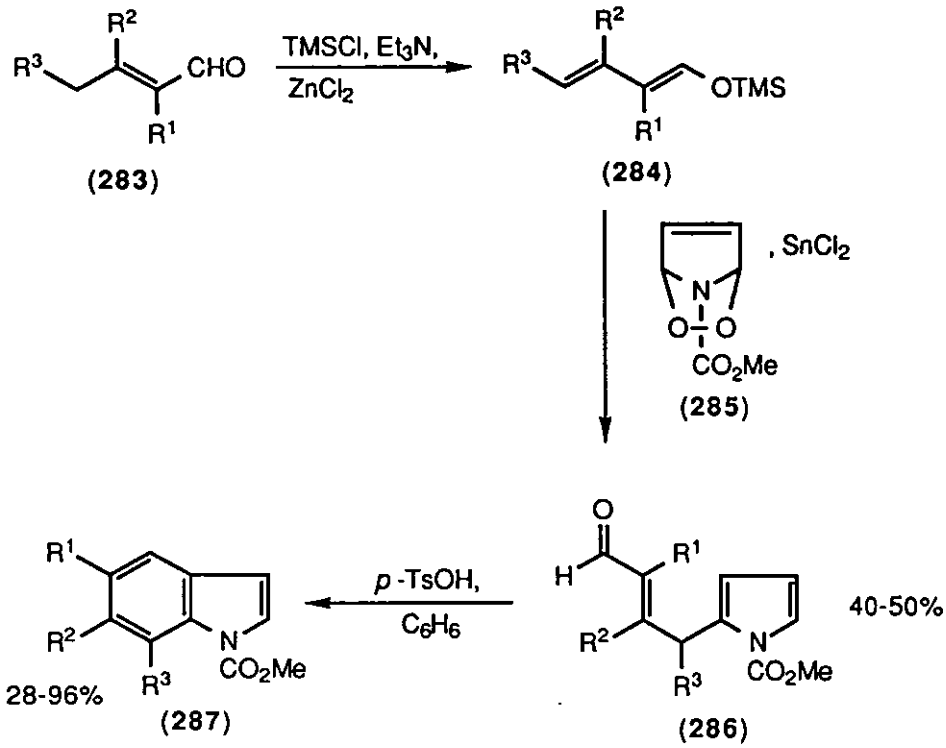
However, indoles have been prepared from pyrroles before by a variety of routes, and a few recent examples are given below. Cobalt mediated [2+2+2] cycloadditions to the pyrrole 2,3-double bond, lead to 3a,7a-dihydroindole cyclopentadienylcobalt complexes (**279**).[68] Removal of the metal and aromatisation to the indoles (**280**) was accomplished by treatment of the complexes (**279**) with an excess of ceric ammonium nitrate.



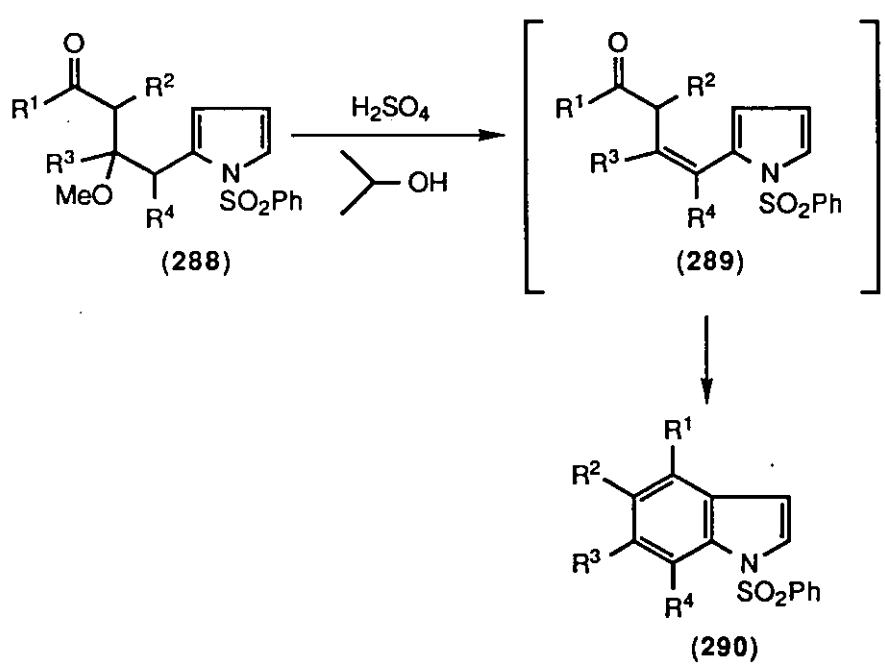
Indoles can also be prepared from pyrroles by intramolecular Friedel-Crafts reaction. For example, tin (IV) chloride catalysed cyclisation of the enone (**281**) led to the indole (**282**).[69] Presumably an isomerisation of the trans enone (**281**) must occur prior to cyclisation.



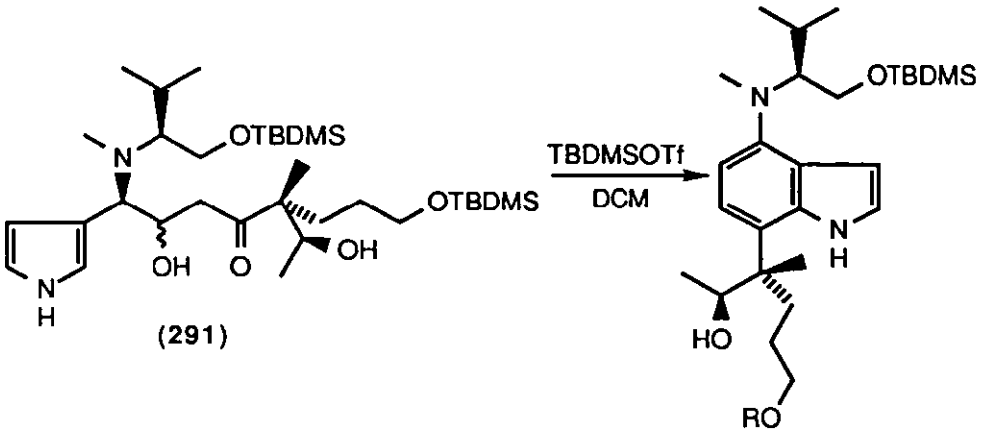
Similarly, the enal (**286**) could be converted into the polysubstituted indole (**287**) upon refluxing in benzene containing a catalytic amount of *p*-toluenesulphonic acid.[70] The enal (**286**) was prepared by condensation of the trimethylsilyloxybutadiene (**284**) with the endo-peroxide (**285**).



The pyrrole (**288**) afforded the indole (**290**) upon refluxing with sulphuric acid in propan-2-ol.[71]



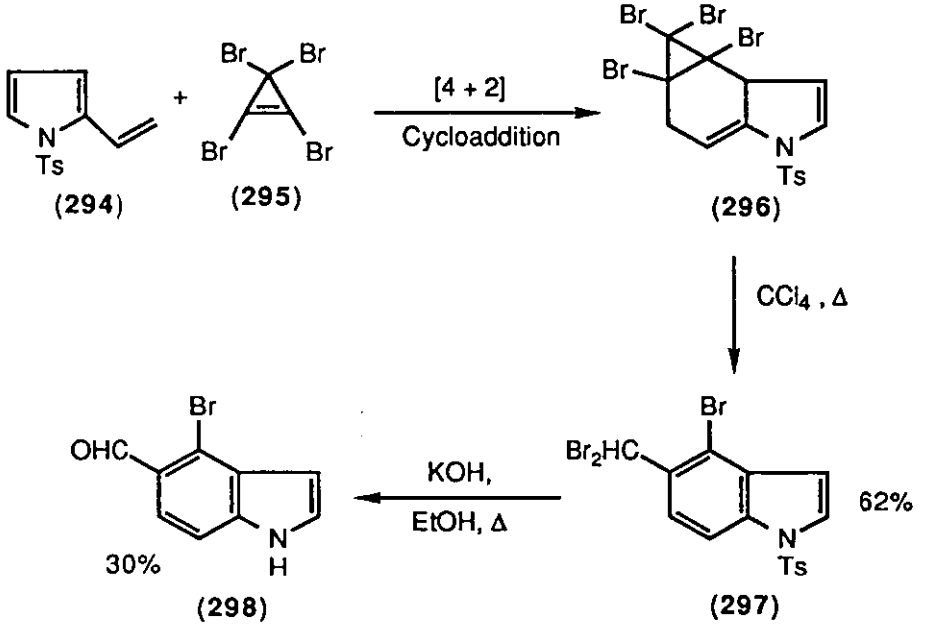
Treatment of the pyrrole (**291**) with t-butyldimethylsilyl triflate led to the mixture of indoles (**292**) and (**293**).[72]



(291)

(292) R = H, 57%
(293) R = TBDMS, 11%

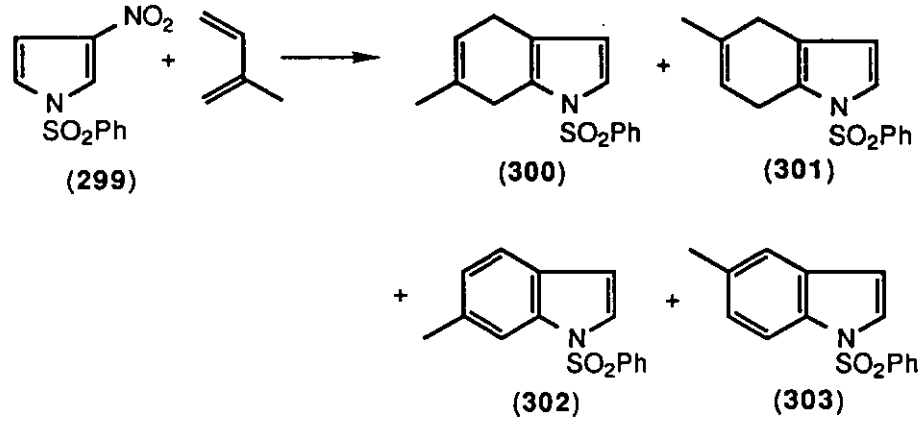
The 4,5-substituted indole (**297**) was prepared by [4+2] cycloaddition of 1-tosyl-2-vinylpyrrole (**294**) with tetrabromocyclopropene (**295**).[73]



(294) (295) (296) (298) (297)

Diels-Alder reaction of 3-nitro-1-phenylsulphonylpyrrole (**299**) with isoprene, gave a mixture of the 4,7-dihydroindoles (**300, 301**) and the indoles (**302, 303**) in the ratio 6:2:3:1 in 49% combined yield. Oxidation of the 4,7-dihydroindoles (**300, 301**), using *p*-quinone, gave a 3:1 mixture of 6-

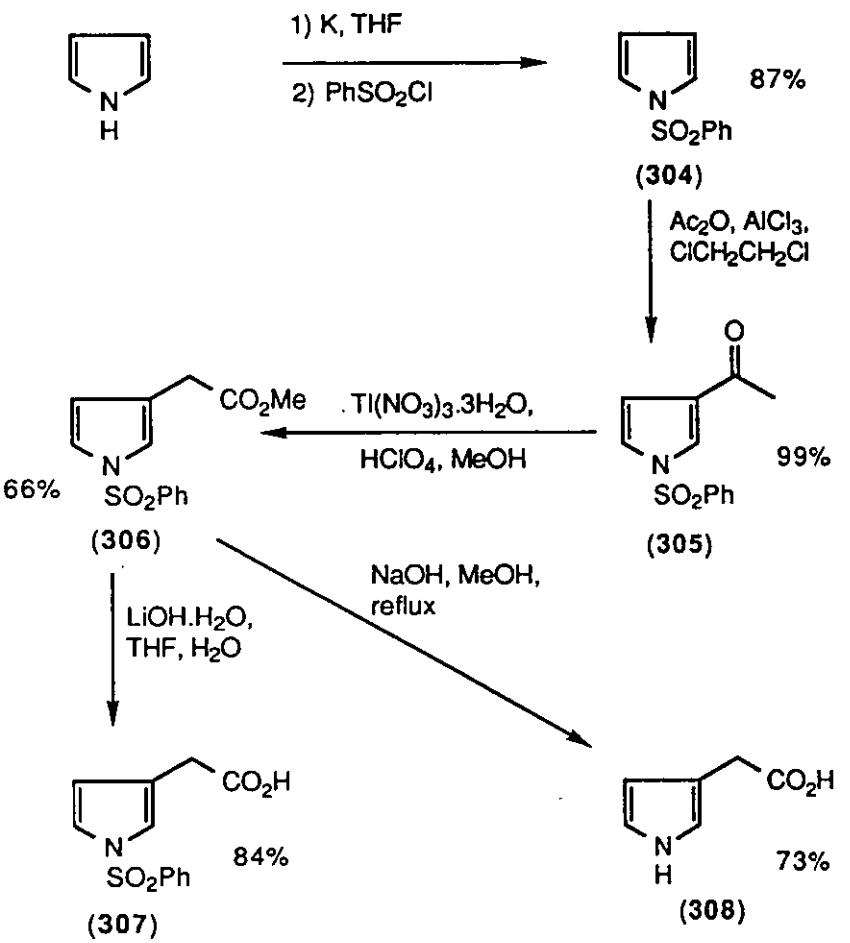
methyl- (**302**) and 5-methyl-1-phenylsulphonylindole (**303**) in 91% combined yield.[74]



4.2 Pyrano[3,4-*b*]pyrrol-5(1*H*)-ones

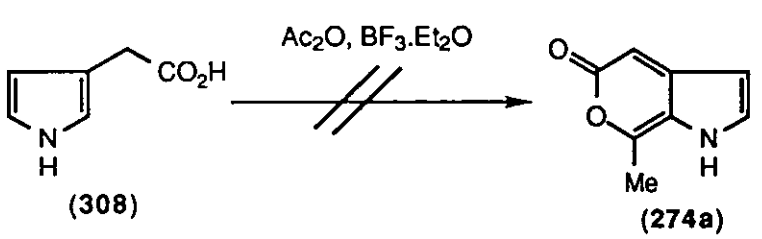
4.2.1 Preparation of pyrrol-3-ylacetic acid

Pyrrol-3-ylacetic acid (**308**) was prepared by the literature route.[75] Deprotonation of pyrrole using potassium in THF, followed by treatment with phenylsulphonyl chloride gave 1-phenylsulphonylpyrrole (**304**).[76] 1-Phenylsulphonylpyrrole was 3-acetylated using a mixture of acetic anhydride and aluminium chloride in 1,2-dichloroethane to give the ketone (**305**). Rearrangement of the ketone (**305**) using a mixture of thallium trinitrate trihydrate and perchloric acid in methanol gave the ester (**306**). The ester (**306**) could be selectively hydrolysed, without affecting the phenylsulphonyl group, using lithium hydroxide hydrate in aqueous THF, to give 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**). Alternatively, both the ester and phenylsulphonyl groups could be hydrolysed, by refluxing with aqueous sodium hydroxide in methanol, to give pyrrol-3-ylacetic acid (**308**).



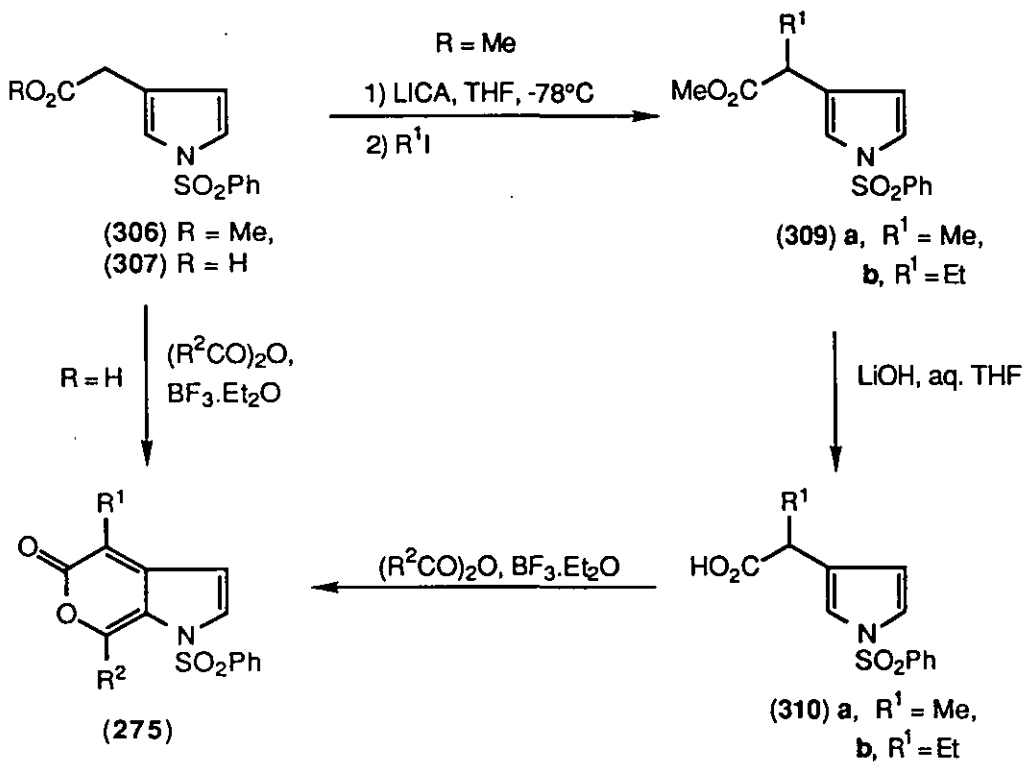
4.2.2 Preparation of pyrano[3,4-*b*]pyrrol-5(1*H*)-ones

Reaction of pyrrol-3-ylacetic acid (**308**) with acetic anhydride in the presence of boron trifluoride diethyl ether led only to the formation of intractable tars. No 7-methylpyrano[3,4-*b*]pyrrol-5(1*H*)-one (**274a**) was isolated.



However, reaction of 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**) with acetic anhydride in the presence of boron trifluoride diethyl ether afforded 7-

methyl-1-phenylsulphonylpyrano[3,4-*b*]pyrrol-5(1*H*)-one (**275b**) in 43% yield. Similarly, treatment of the same acid with propionic anhydride, hexanoic anhydride, or isobutyric anhydride in the presence of boron trifluoride diethyl ether gave the 7-ethyl (**275c**), the 7-pentyl (**275d**), and the 7-isopropyl (**275e**) substituted pyranopyrrolones in 36%, 33%, and 19% yield respectively.

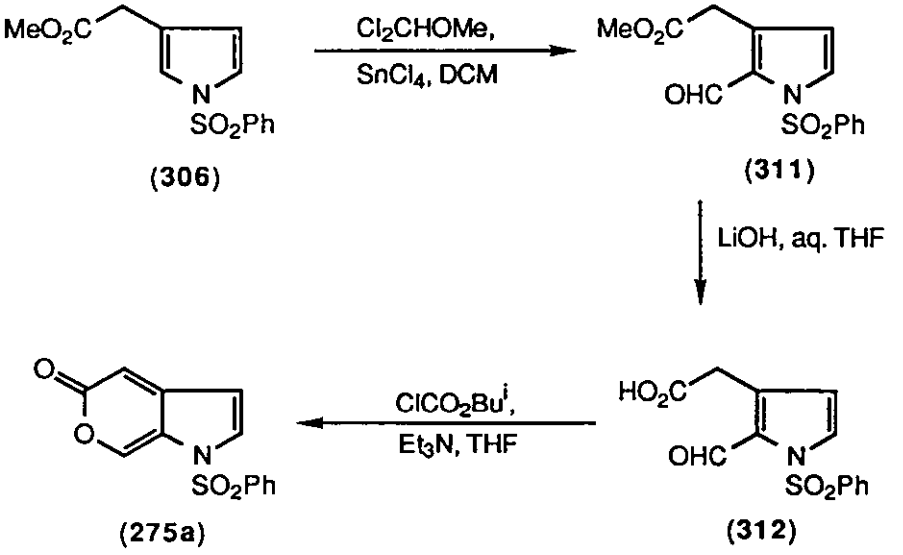


	R^1	R^2
b	H	Me
c	H	Et
d	H	C_5H_{11}
e	H	Pr^i
f	Me	Me
g	Et	Me

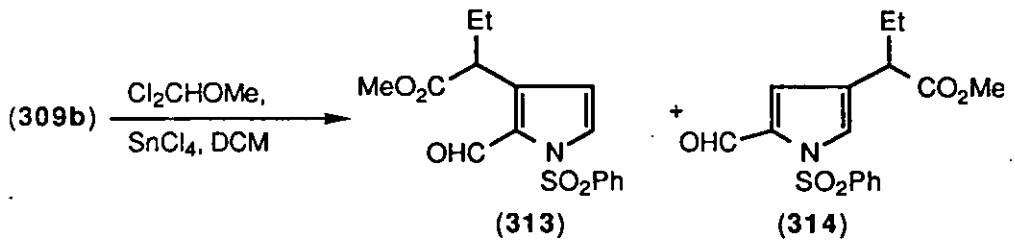
The 4,7-disubstituted pyranopyrrolones (**275f, g**) were prepared in a similar fashion. Alkylation of methyl 1-phenylsulphonylpyrrol-3-ylacetate (**306**) using lithium isopropylcyclohexylamide as base, followed by quenching with methyl iodide or ethyl iodide gave the α-substituted esters (**309a, b**) in 93%

and 83% yield respectively. The esters were hydrolysed, with the 1-phenylsulphonyl group remaining intact, using lithium hydroxide hydrate, to give the α-substituted acids (**310a, b**) in 97% and 82% yield respectively. Treatment of the acids (**310a, b**) with acetic anhydride in the presence of boron trifluoride diethyl ether gave the 4,7-dimethyl substituted pyranopyrrolone (**275f**) in 25% yield and the 4-ethyl-7-methyl substituted pyranopyrrolone (**275g**) in 30% yield respectively.

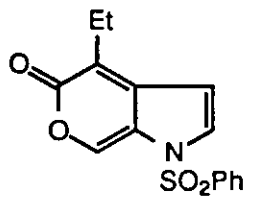
Since formic anhydride is not a readily available compound, the parent pyranopyrrolone (**275a**) had to be prepared by a different route. Formylation of methyl 1-phenylsulphonylpyrrol-3-ylacetate (**306**), using dichloromethyl methyl ether and tin (IV) chloride in dichloromethane, gave the 2-formyl compound (**311**) along with its 5-substituted isomer as a 1:1 mixture in 92% yield. Separation was not possible at this stage. Hydrolysis of the mixture, using lithium hydroxide hydrate in aqueous THF, gave a 1:1 mixture of the 2-formyl acid (**312**) and its 5-formyl isomer in 80% yield. Cyclodehydration, using isobutyl chloroformate and triethylamine in dry THF, followed by purification gave 1-phenylsulphonylpyrano[3,4-*b*]pyrrol-5(1*H*)-one (**275a**) in 21% yield.



However, formylation of the ethyl substituted ester (**309b**), using dichloromethyl methyl ether and tin (IV) chloride, gave the 2-formyl derivative (**313**) along with its 5-formyl isomer (**314**) as a 1:2 mixture of isomers in 78% combined yield. 2-Formylation has become less favourable, relative to 5-formylation, owing to extra steric hindrance at the 2-position which results from the presence of the ethyl substituent. Hence, this was not considered a useful route to the 4-substituted pyranopyrrolone (**275h**).



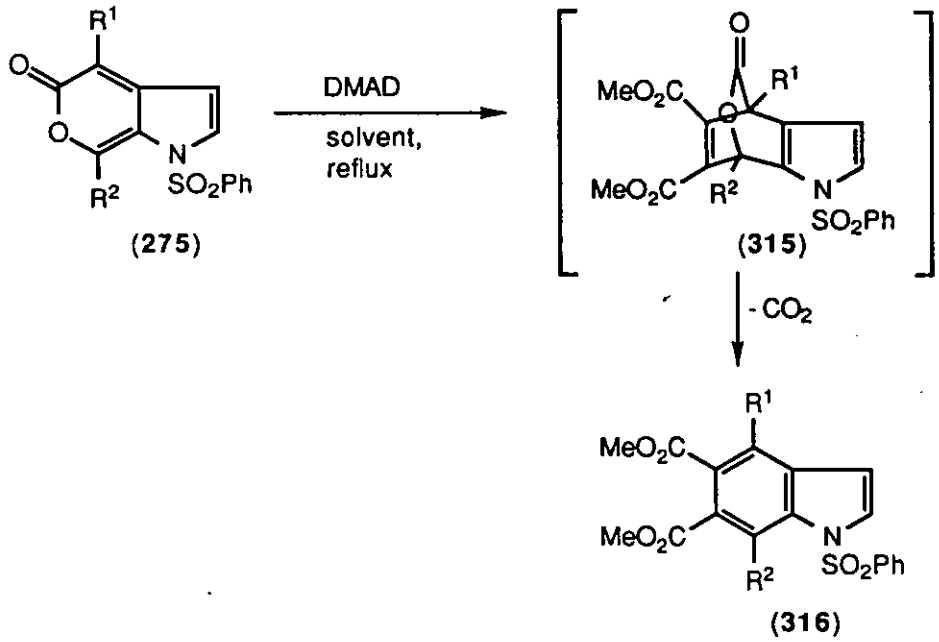
Ratio (**313**):(**314**), 1:2
Combined yield 78%



(**275h**)

4.2.3 Intermolecular Diels-Alder reactions

On heating with the electron-deficient alkyne, dimethyl acetylenedicarboxylate, the pyranopyrrolones (**275**) underwent Diels-Alder reaction to give, after loss of carbon dioxide, the indole-5,6-diesters (**316**). Again, the carbon dioxide bridged adducts (**315**) were not isolated.

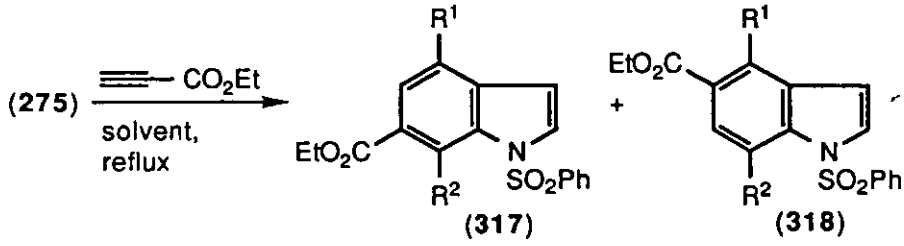


(275) (315) (316)

Compd. (275)	R^1	R^2	Solvent	Time (h)	Compd. (316)	Yield (%)
a	H	H	PhCl	4	a	58
b	H	Me	PhBr	24	b	60
b	H	Me	MeCN	15	b	70
d	H	Pentyl	PhBr	18	c	51
e	H	Pr^i	PhCl	30	d	59
f	Me	Me	PhCl	12	e	71

For the Diels-Alder reactions of the benzothienopyranones (**169, 170**) and the thienopyranones (**228, 266**) bromobenzene had been the solvent of choice, its high boiling point offering fast reaction. However, the pyranopyrrolones (**275**) showed signs of decomposition competing with Diels-Alder reaction when the reactions were carried out in bromobenzene. The 7-methyl substituted pyranopyrrolone (**275b**) reacted with dimethyl acetylenedicarboxylate in good yield, at much lower temperature, in refluxing acetonitrile. However, the same pyranopyrrolone reacted only very sluggishly with ethyl propiolate in refluxing acetonitrile. Eventually, chlorobenzene was settled upon as the solvent of choice. Its moderately high boiling point permitted reasonably fast reaction, while giving rise to less decomposition than the reaction in bromobenzene.

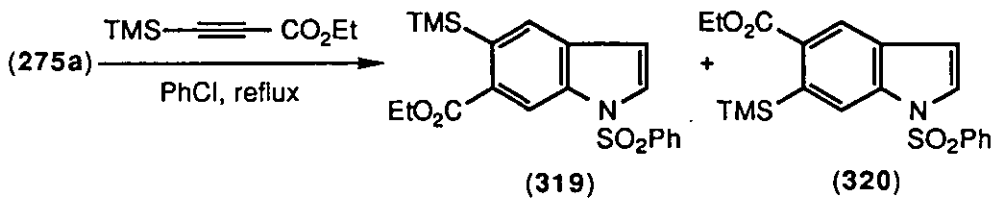
As expected, the unsymmetrical acetylene, ethyl propiolate, was generally not regioselective in its Diels-Alder reactions and gave inseparable mixtures of the indole-5-esters (**318**) and indole-6-esters (**317**).



Compd. (275)	R^1	R^2	Solvent	Time (h)	Compd. (317)/(318)	Combined Yield (%)	Ratio (317):(318)
a	H	H	PhCl	5	a	61	1:1
b	H	Me	PhBr	60	b	56	1.6:1
d	H	Pentyl	PhBr	24	c	59	1:1
e	H	Pr^i	PhCl	48	d	49	1:5
f	Me	Me	PhCl	12	e	80	1:1

The reaction of the pyranopyrrolone (**275b**) with ethyl propiolate showed a slight preference for the formation of the 6-ester (**317b**). The two isomers could be readily distinguished by NMR. The resonance occurring furthest downfield at δ 8.11 was attributed to 4-H of the 5-ester (**318b**). The resonances 4-H and 5-H of the 6-ester (**317b**) were obscured by other peaks, but both are expected to be doublets. Also 7-Me of the 6-ester (**317b**) resonates downfield at δ 2.73 relative to that of the 5-ester (**318b**) (at δ 2.56). The reaction of the pyranopyrrolone (**275e**) with ethyl propiolate gave predominately the 5-ester (**318d**). This is presumably a steric effect of the bulky isopropyl group. Again, the two isomers were distinguished by NMR. 4-H of the 5-ester (**318d**) was observed as a doublet (*J* 1.6 Hz) at δ 8.08. 4-H and 5-H of the 6-ester (**317d**) were observed as doublets (*J* 8 Hz) at δ 7.30 and δ 7.38.

The pyranopyrrolones (**275**) underwent regioselective Diels-Alder reaction with ethyl 3-trimethylsilylpropynoate and gave the 5-trimethylsilylindole-6-esters (**319, 321**) as the major product. The unsubstituted pyranopyrrolone (**275a**) gave a 2.5:1 mixture of the 5-trimethylsilylindole-6-ester (**319**) and the 6-trimethylsilylindole-5-ester (**320**).

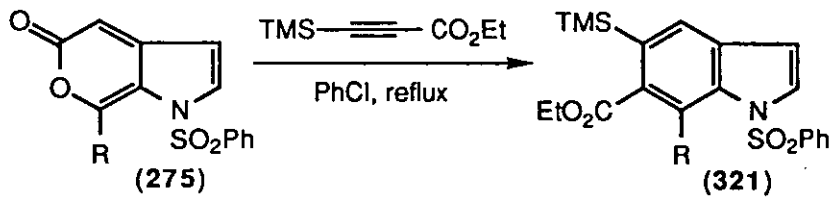


Ratio (**319**):(**320**), 2.5:1

Combined yield 40%

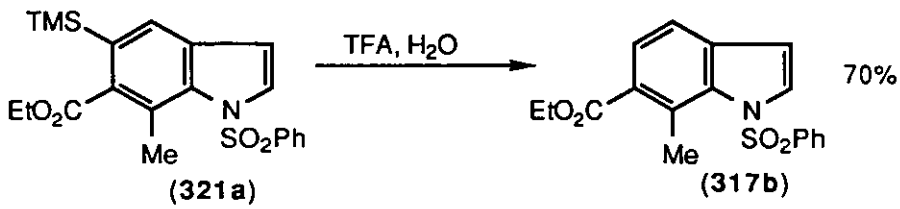
The two isomers were distinguished by the resonances of 4-H and 7-H in their NMR spectrum. 7-H of the 6-ester (**319**), which is situated between two strongly electron withdrawing groups, resonated furthest downfield at δ 8.67. 4-H of the major isomer (**319**) occurred at δ 7.84. 4-H and 7-H of the minor isomer (**320**) coincided as a singlet at δ 8.25.

The 7-alkyl substituted pyranopyrrolones (**275b, d**) gave only a single isomer by 270 MHz NMR. This was assigned as the 5-trimethylsilylindole-6-ester (**321**) due to the resonance of 4-H, which in the case of the 7-methyl compound (**321a**) occurred at δ 7.61 and in the case of the 7-pentyl compound (**321b**) occurred at δ 7.59. 4-H would be expected to resonate much further downfield if the product of Diels-Alder reaction was the 6-trimethylsilylindole-5-ester.



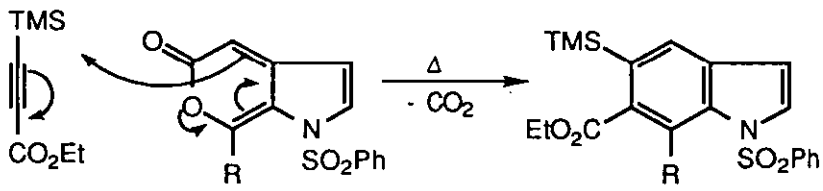
Compd. (**275**)	R	Time (h)	Compd. (**321**)	Yield (%)
b	Me	96	**a**	53
d	Pentyl	120	**b**	12

Confirmation of the structure was obtained by protodesilylation of compound (**321a**) which gave ethyl 7-methyl-1-phenylsulphonylindole-6-carboxylate (**317b**), identical to the major isomer from Diels-Alder reaction of pyranopyrrolone (**275b**) with ethyl propiolate.



(**321a**) (**317b**)

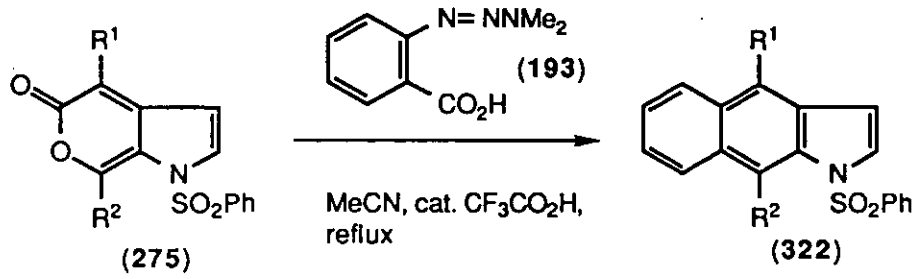
Hence, the regiochemistry of the Diels-Alder reaction is again controlled by the pyrone ring oxygen.



(**275**) (**321**)

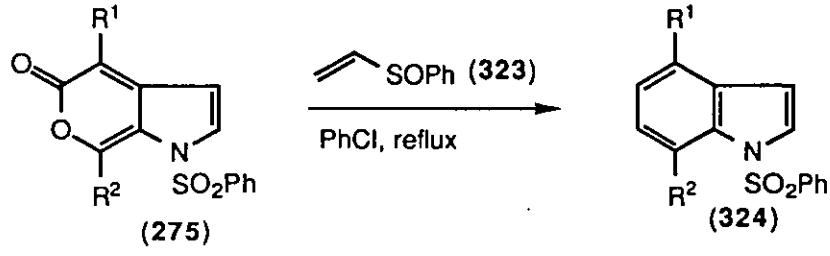
The pyranopyrrolones also reacted with benzyne, generated from 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**),[49] to give benz[*f*]indoles (**322**) in good yield, and with the acetylene equivalent, phenyl vinyl sulphoxide (**323**),[77] to give 5,6-unsubstituted indoles (**324**).

Table 6. Diels-Alder reactions of 1-phenylsulphonylpyrano[3,4-*b*]pyrrol-5(1*H*)-ones (**275**) with benzyne.



Compd. (275)	R^1	R^2	Time (h)	Compd. (322)	Yield (%)
a	H	H	4	**a**	49
b	H	Me	5	**b**	65
d	H	Pentyl	12	**c**	77
f	Me	Me	12	**d**	60

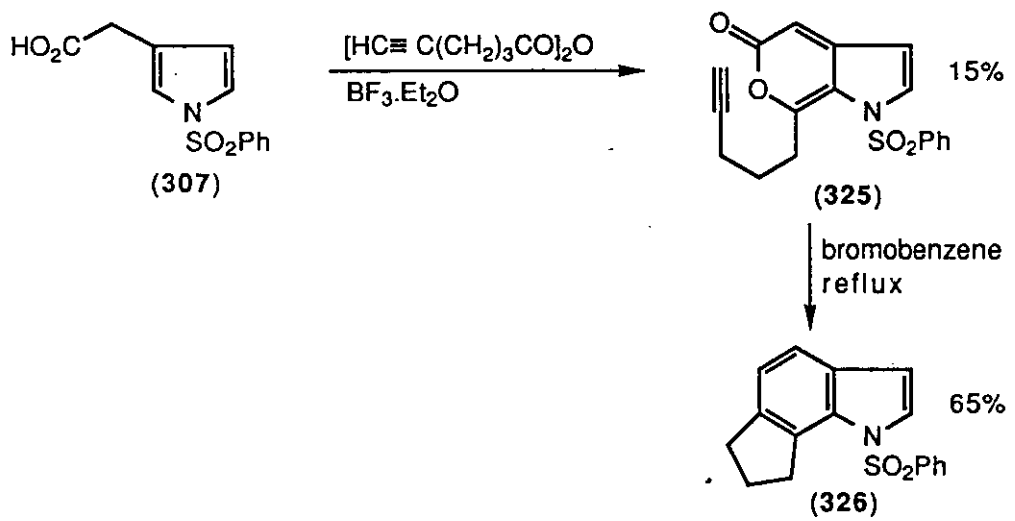
Table 7. Diels-Alder reactions of 1-phenylsulphonylpyrano[3,4-*b*]pyrrol-5(1*H*)-ones (**275**) with phenyl vinyl sulphoxide.



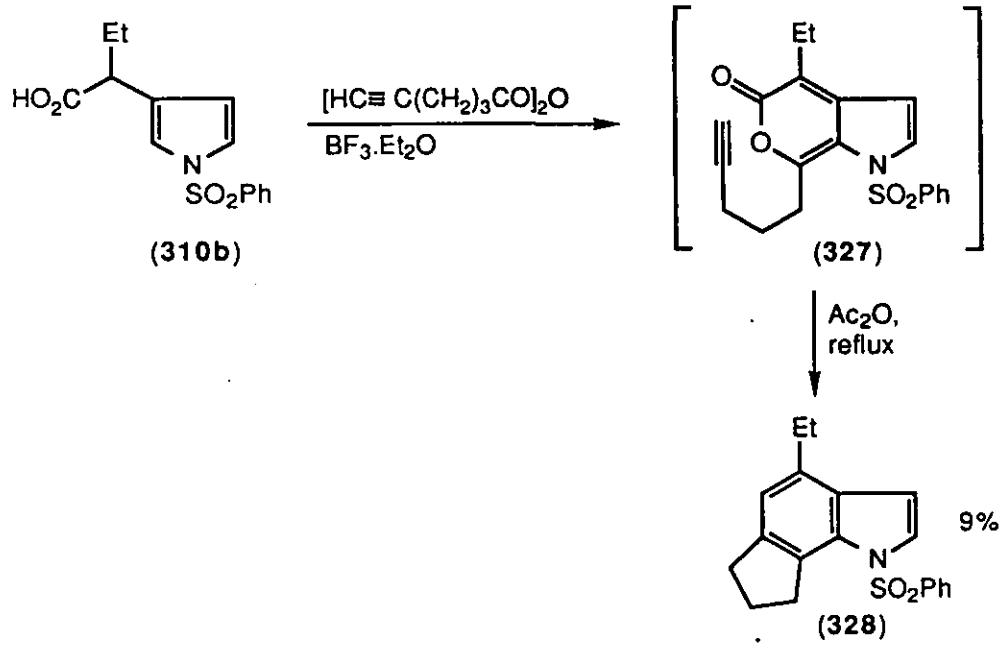
Compd. (275)	R^1	R^2	Time (h)	Compd. (324)	Yield (%)
b	H	Me	48	**a**	60
d	H	Pentyl	72	**b**	44
e	H	Pr^i	144	**c**	20
g	Et	Me	48	**d**	60

4.2.4 Intramolecular Diels-Alder reactions

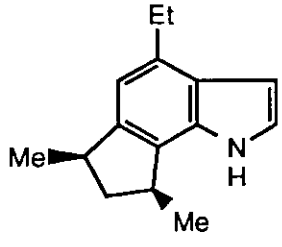
Treatment of 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**) with hex-5-ynoic anhydride in the presence of boron trifluoride diethyl ether gave the pyranopyrrolone (**325**) as an unstable oil in 15% yield. On heating in bromobenzene, the pyranopyrrolone (**325**) underwent smooth intramolecular Diels-Alder reaction to give, after loss of carbon dioxide, 1-phenylsulphonyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole (**326**) in 65% yield.



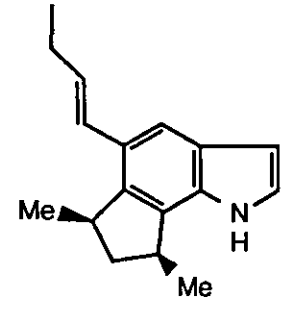
When a similar sequence of reactions was attempted on the ethyl substituted acid (**310b**), isolation of the pyranopyrrolone (**327**) proved difficult. However, heating the crude reaction mixture in acetic anhydride, followed by column chromatography, enabled 4-ethyl-1-phenylsulphonyl-1,6,7,8-tetrahydrocyclopenta[*g*]indole (**328**) to be isolated in 9% yield.



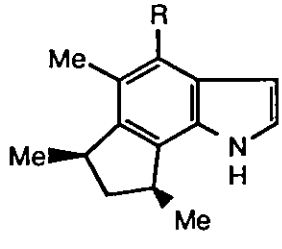
These intramolecular cycloaddition reactions were of interest to us since the tetrahydrocyclopenta[*g*]indole ring system is present in a closely related series of natural products, namely the trikentrins (**329, 330**)[78] and herbindoles (**331**).[79]



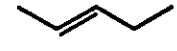
cis-Trikentrin A
(**329**)



cis-Trikentrin B
(**330**)

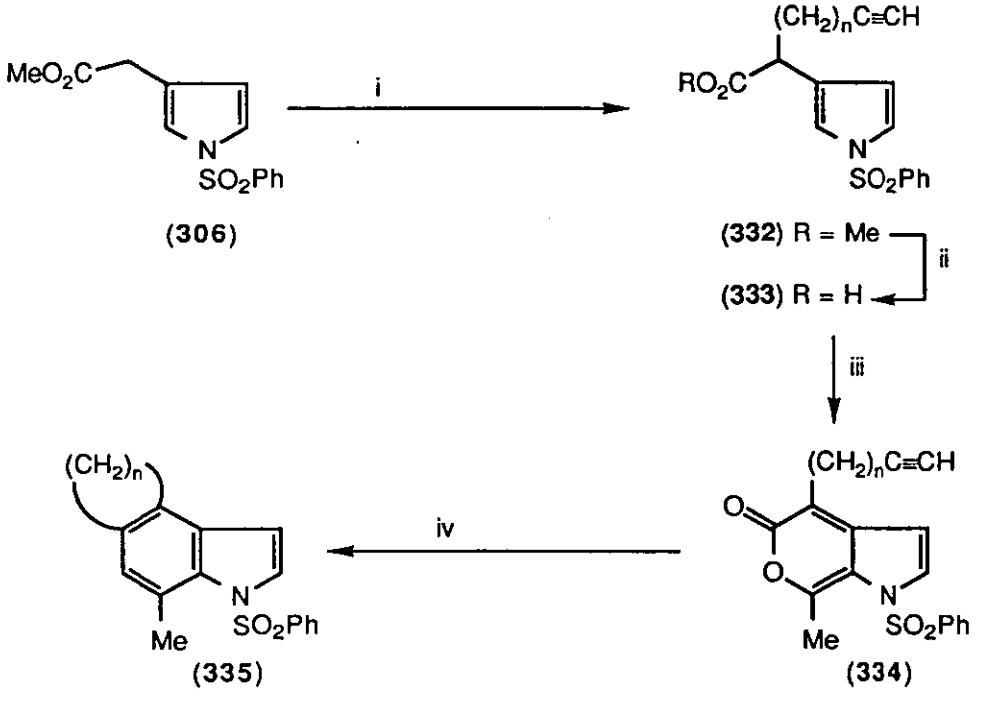


(**331**)

Herbindole A, R = Me
B, R = Et
C, R = 

These compounds are of interest due to their unique structural characteristics and antimicrobial activity. This has led to intense synthetic interest and a number of syntheses of trikentrins have been published recently.[80] However, due to the low yielding pyranopyrrolone formation step, this methodology was not employed further in a trikentrin synthesis.

The 4-substituted pyranopyrrolones (**334**), required for the preparation of cycloalka[*e*]indoles (**335**), were synthesised using the same methodology developed in the thiophene series. Alkylation of methyl 1-phenylsulphonylpyrrol-3-ylacetate (**306**) with 5-iodopentyne (**247**) or 6-iodohexyne (**249**), using lithium isopropylcyclohexylamide as base, gave the α-substituted esters (**332a, b**) in 69% and 70% yield respectively.

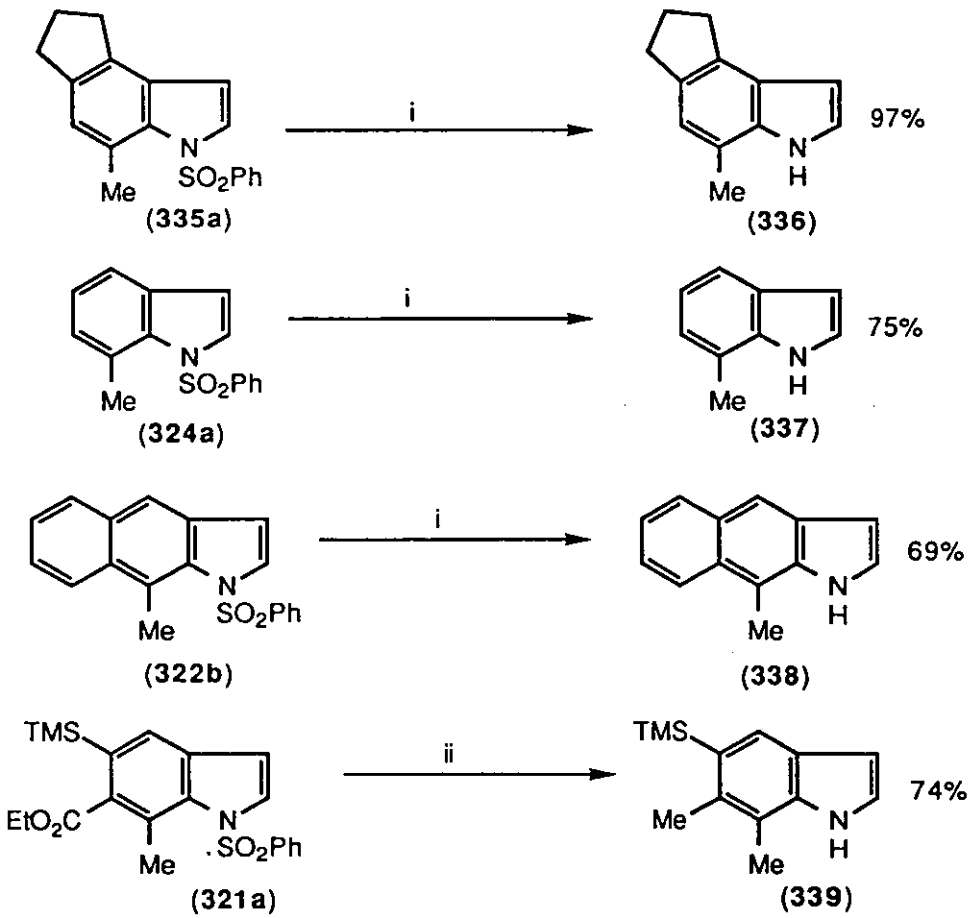


Scheme 16. (**a**, n=3; **b**, n=4) *Reagents* i) LICA, THF, -78°C, then $I(CH_2)_nC{\equiv}CH$; ii) LiOH, aq. THF; iii) Ac_2O, $BF_3.Et_2O$; iv) Toluene (n=3) or bromobenzene (n=4), reflux.

Hydrolysis of the esters (**332**), using lithium hydroxide hydrate in aqueous THF, gave the α-substituted acids (**333a, b**) in 68% and 64% yield respectively. Treatment of the acid (**333a**) with acetic anhydride in the presence of boron trifluoride diethyl ether gave the pyranopyrrolone (**334a**),

as an unstable oil, in 19% yield, which on refluxing in toluene underwent intramolecular cycloaddition to give, after loss of carbon dioxide, 8-methyl-1-phenylsulphonyl-1,4,5,6-tetrahydrocyclopenta[*e*]indole (**335a**) in 68% yield. Similarly, treatment of the acid (**333b**) with acetic anhydride in the presence of boron trifluoride diethyl ether gave the pyranopyrrolone (**334b**) as a stable crystalline solid in 16% yield. On heating in bromobenzene, the pyranopyrrolone (**334b**) underwent intramolecular cycloaddition to give, after loss of carbon dioxide, 9-methyl-1-phenylsulphonyl-4,5,6,7-tetrahydrobenz[*e*]indole (**335b**) in 78% yield.

4.2.5 . Removal of 1-phenylsulphonyl group

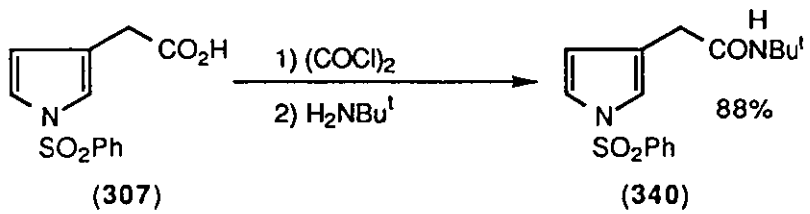


Scheme 17. *Reagents* i) 20% KOH in H_2O, DME, MeOH (1:1:1), reflux; ii) $LiAlH_4$, dioxan, reflux.

Since we were interested in developing this chemistry as a new route to indoles, it was necessary at some stage to remove the 1-phenylsulphonyl group. This could be accomplished by alkaline hydrolysis,[80d] using potassium hydroxide in a 1:1:1 mixture of methanol, 1,2-dimethoxyethane and water, to give the indoles (**336**), (**337**), and (**338**) in 97%, 75%, and 69% yield respectively (Scheme 17). The spectra of indole (**337**) showed good agreement with those of the known 7-methylindole.[81] Alternatively, the 1-phenylsulphonyl group could be reductively removed by reaction with lithium aluminium hydride in refluxing dioxan. This procedure also resulted in the reduction of an ester functionality to a methyl group. Hence, compound (**321a**) was reduced to the indole (**339**) in 74% yield.

4.2.6 Other attempted routes to the pyrano[3,4-*b*]pyrrolones

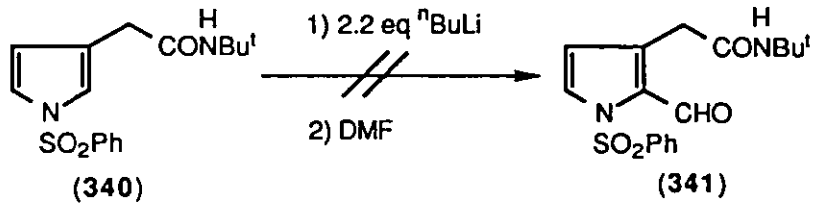
One drawback to the use of pyrano[3,4-*b*]pyrrolones (**275**) in the synthesis of indoles is that the preparation of the pyrano[3,4-*b*]pyrrolones themselves could only be accomplished at best in moderate yield. Hence, we decided to explore other routes to the pyrano[3,4-*b*]pyrrolone ring system. As in the thiophene series, we attempted to use the t-butyl amide functionality as a directing group for *ortho* lithiation which would hopefully provide us with a regioselective method for 2-acylation. Treatment of 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**) with oxalyl chloride, followed by an excess of t-butylamine gave the amide (**340**) in 88% yield.



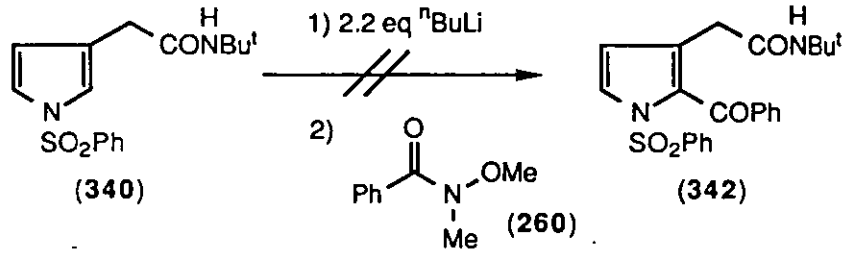
(**307**) (**340**)

However, treatment of the amide (**340**) with 2.2 equivalents of n-butyllithium, followed by quenching with DMF or the *N*-methoxy-*N*-methylamide (**260**)[63] did not afford the desired 2-acylated compounds (**341**) or (**342**). Only

decomposition of the dianion was observed upon warming to room temperature.

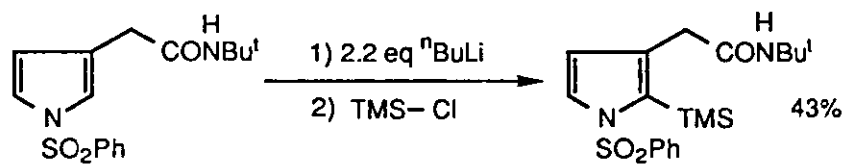


(340) (341)



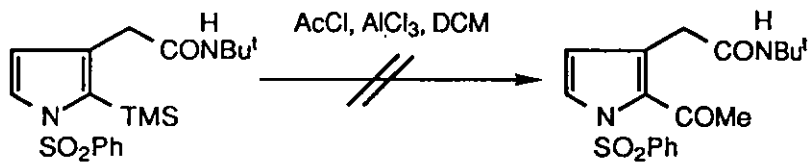
(340) (260) (342)

However, quenching of the dianion, formed by treatment of the amide (**340**) with 2.2 equivalents of n-butyllithium, was possible using the more reactive electrophilic species, trimethylsilyl chloride. Hence, the 2-trimethylsilyl compound (**343**) was obtained in 43% yield.



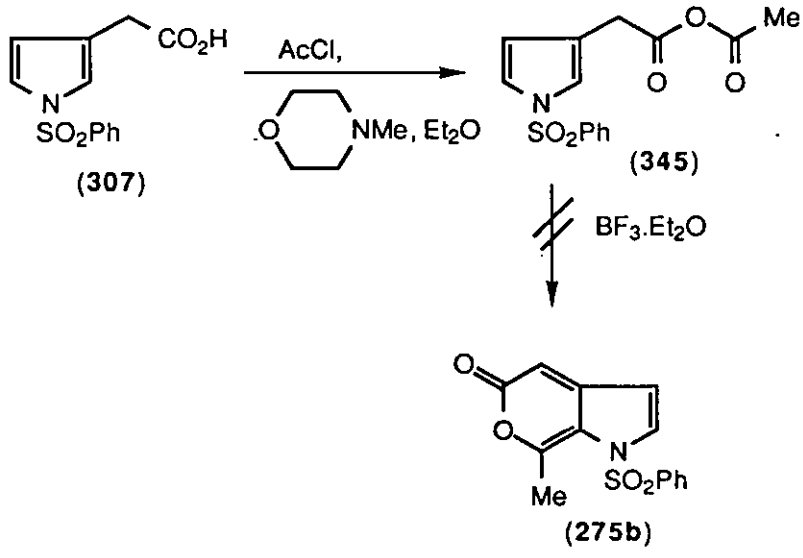
(340) (343)

Unfortunately, *ipso*-substitution on compound (**343**), using a mixture of acetyl chloride and aluminium chloride in dichloromethane, was unsuccessful. A complex mixture of products resulted and none of the 2-acetylated compound (**344**) was isolated.



(343) (344)

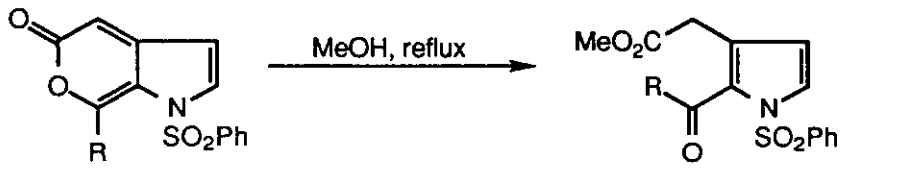
It was assumed that pyranopyrrolone formation probably occurred via cyclisation of a mixed anhydride of type (**345**). Therefore, the mixed anhydride (345) was prepared by treatment of 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**) with acetyl chloride in the presence of *N*-methylmorpholine.[82] However, upon treatment of the anhydride with boron trifluoride diethyl ether, no pyranopyrrolone (**275b**) was observed. Only the starting acid, 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**), was recovered after aqueous work-up.



This casts some doubt upon the involvement of the mixed anhydride (**345**) in pyranopyrrolone formation. It is also possible, that pyranopyrrolone formation occurs via an initial 2-acylation of 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**), followed by cyclodehydration. A possible reason for the low yields of pyranopyrrolones could be competing 5-acylation. However, it has not been possible to prove this by isolating a 5-acyl compound from the mixture of acidic side products accompanying pyranopyrrolone formation.

Another possible route to pyranopyrrolones involves 2-acylation of methyl 1-phenylsulphonylpyrrol-3-ylacetate (**306**), followed by hydrolysis and cyclodehydration. Acetylation of methyl 1-phenylsulphonylpyrrol-3-ylacetate (**306**), using acetyl chloride and tin (IV) chloride, gave one major acetylated product. However, the aromatic pyrrole proton resonances did not appear to be

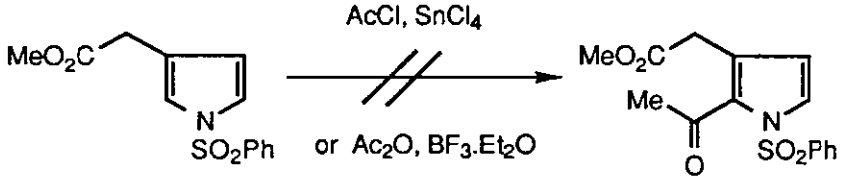
consistent with 2,3-substitution. By heating the pyranopyrrolones (**275b, c**) in refluxing methanol, it was possible to prepare the 2-acyl compounds (**346a, b**) unambiguously in 70% and 94% yield respectively.



(**275**)

(**346**) **a**, R = Me 70%
b, R = Et 94%

This proved that the product of acetylation of (**306**), with acetyl chloride and tin (IV) chloride, is not the 2-acetyl isomer (**346a**). Similarly, acetylation of methyl 1-phenylsulphonylpyrrol-3-ylacetate (**306**), using acetic anhydride and boron trifluoride diethyl ether, gave only a small amount of the 2-acetyl compound (**346a**).

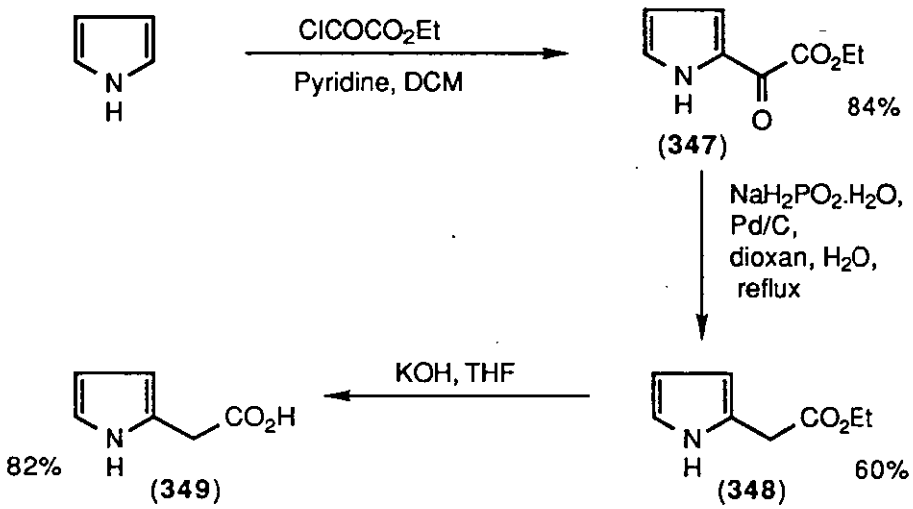


(**306**) (**346a**)

4.3 Pyrano[4,3-*b*]pyrrol-6(1*H*)-ones

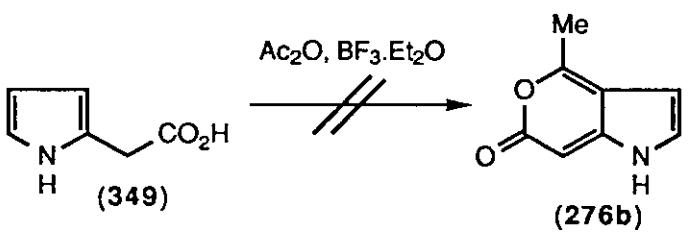
4.3.1 Preparation of pyrrol-2-ylacetic acid

Acylation of pyrrole using, ethyl oxalyl chloride and pyridine in dichloromethane at -78°C, gave ethyl pyrrol-2-ylglyoxalate (**347**).[83] Reduction of the glyoxalate to ethyl pyrrol-2-ylacetate (**348**) was accomplished by refluxing in aqueous dioxan containing palladium on activated carbon and sodium hypophosphite hydrate.[84] Alkaline hydrolysis gave pyrrol-2-ylacetic acid (**349**).[84]

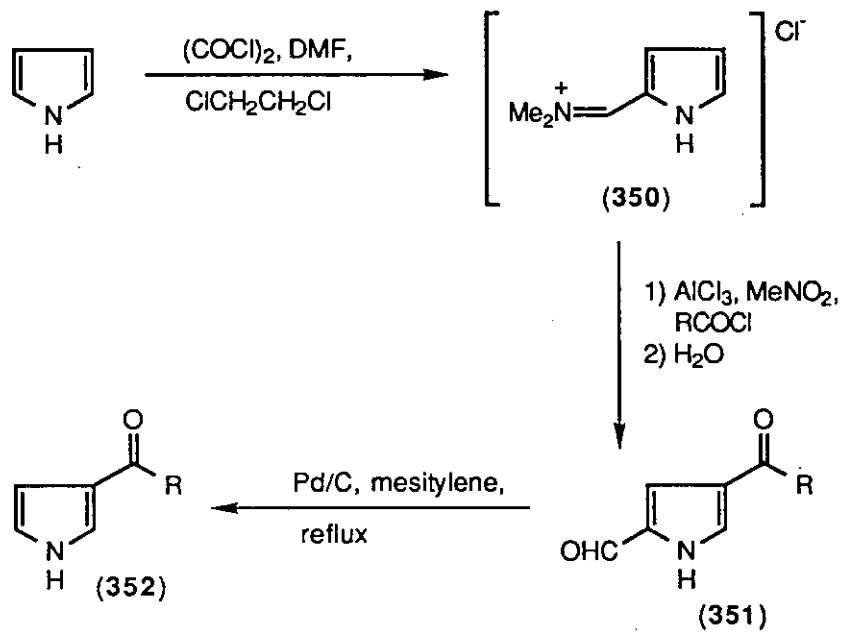


4.3.2 Preparation of pyrano[4,3-*b*]pyrrol-6(1*H*)-ones

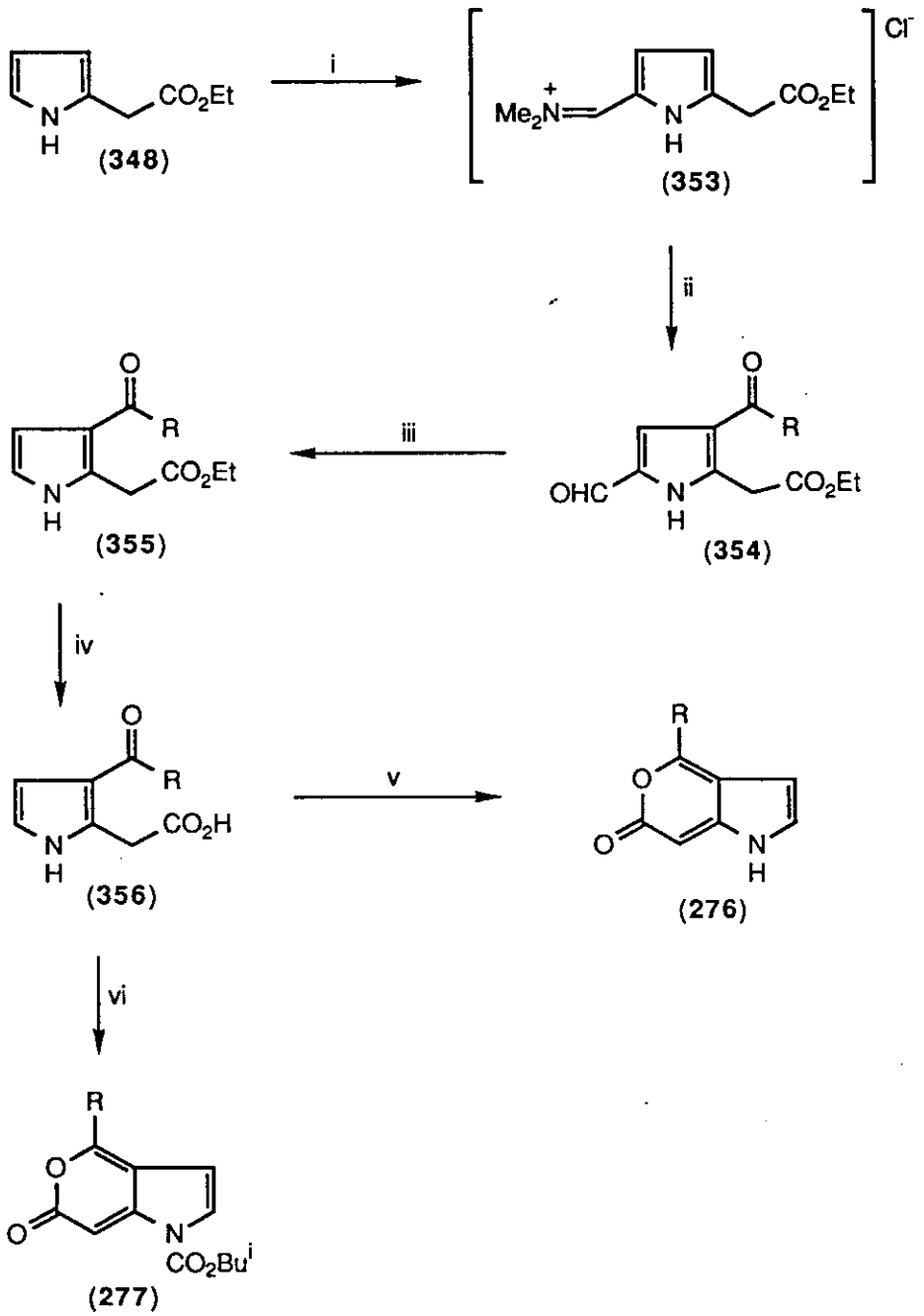
Reaction of pyrrol-2-ylacetic acid (**349**) with acetic anhydride in the presence of boron trifluoride diethyl ether did not result in the formation of 4-methylpyrano[4,3-*b*]pyrrol-6(1*H*)-one (**276b**).



Hence, a different approach involving 3-acylation of ethyl pyrrol-2-ylacetate (**348**) was required. 3-Acyl pyrroles (**352**) have been produced in the past by using the pyrrole Vilsmeier complex (**350**) to direct acylation into the 3-position.[85] The 2-formyl pyrroles (**351**) are obtained upon aqueous work-up. Decarbonylation of the 2-formyl pyrroles occurred readily upon refluxing in mesitylene containing palladium on activated carbon to give the 3-acyl pyrroles (**352**).[86]



The same sequence of reactions could be carried out on ethyl pyrrol-2-ylacetate (**348**). Thus, treatment of ethyl pyrrol-2-ylacetate, with the Vilsmeier salt obtained by reaction of oxalyl chloride with DMF, gave an intermediate pyrrole Vilsmeier complex (**353**) which could be acetylated with acetyl chloride, followed by aqueous work-up to give ethyl 3-acetyl-5-formylpyrrol-2-ylacetate (**354b**) in 92% yield. Similarly, benzoylation of the pyrrole Vilsmeier complex (**353**), using benzoyl chloride gave ethyl 3-benzoyl-5-formylpyrrol-2-ylacetate (**354c**) in 40% yield. Finally, it was found that the pyrrole Vilsmeier complex (**353**) could be formylated, using dichloromethyl methyl ether, to give ethyl 3,5-diformylpyrrol-2-ylacetate (**354a**) in 60% yield. Decarbonylation of the 3-acetyl-5-formylpyrrole (**354b**) was accomplished, by refluxing in mesitylene containing palladium on activated carbon, to give ethyl 3-acetylpyrrol-2-ylacetate (**355b**) in 96% yield.



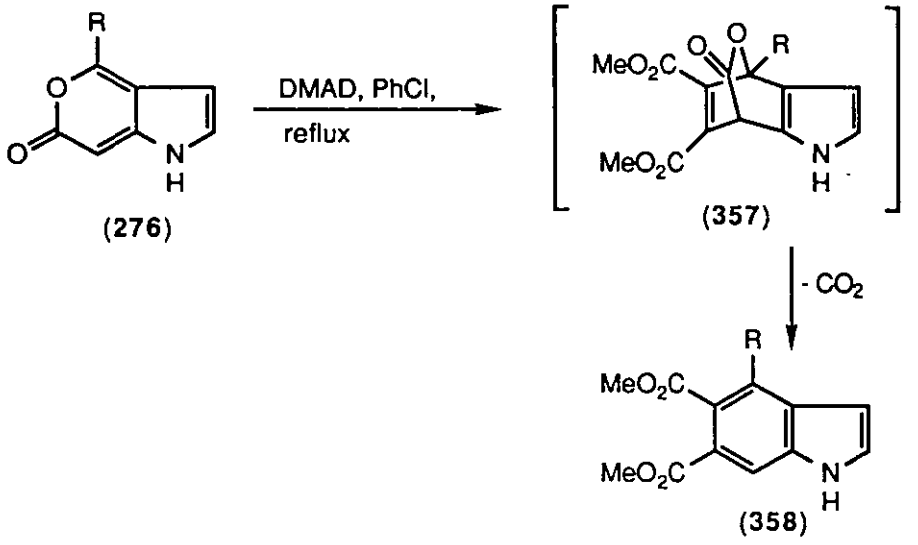
Scheme 18. (**a**, R = H; **b**, R = Me; **c**, R = Ph) *Reagents* i) $(COCl)_2$, DMF, $ClCH_2CH_2Cl$; ii) a) $MeNO_2$, $AlCl_3$, RCOCl (R = Me or Ph) or Cl_2CHOMe (R = H); b) H_2O; iii) Pd/C, mesitylene, reflux; iv) KOH, H_2O, THF, MeOH; v) $ClCO_2Bu^i$ (1.05 eq.), Et_3N, THF; vi) $ClCO_2Bu^i$ (2.2 eq.), Et_3N, THF.

Similarly, the 3-benzoyl-5-formylpyrrole (**354c**) was decarbonylated to give ethyl 3-benzoylpyrrol-2-ylacetate (**355c**) in 90% yield. Decarbonylation of the 3,5-diformylpyrrole (**354a**) proved more difficult since the 3-formyl group was also susceptible to decarbonylation, leading to the formation of ethyl pyrrol-3-ylacetate (**348**). Fortunately, the 5-formyl group was slightly more reactive than the 3-formyl group. Hence, ethyl 3-formylpyrrol-2-ylacetate (**355a**) could be obtained in 63% yield if the reaction was stopped after 5 h. Alkaline hydrolysis of the esters (**355**) gave the acids (**356a, b, c**) in 83%, 88%, and 94% yield respectively.

Treatment of the acids (**356**) with one equivalent of isobutyl chloroformate in dry THF containing an excess of triethylamine gave the pyrano[4,3-*b*]pyrrol-6(1*H*)-ones (**276a, b**), unsubstituted on nitrogen, in 68% and 85% yield respectively. Alternatively, treatment of the acids (**356**) with two equivalents of isobutyl chloroformate in dry THF containing an excess of triethylamine gave the isobutyl 6-oxopyrano[4,3-*b*]pyrrole-1-carboxylates (**277a, b, c**) in 84%, 86%, and 92% yield respectively.

4.3.3 Intermolecular Diels-Alder reactions of the pyrano[4,3-*b*]pyrrol-6(1*H*)-ones

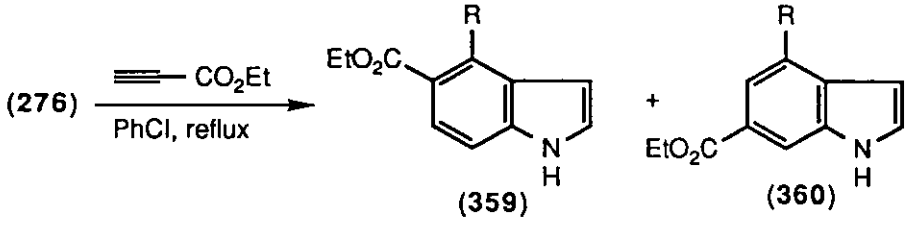
The pyrano[4,3-*b*]pyrrol-6(1*H*)-ones (**276**) underwent Diels-Alder reaction upon heating with the electron deficient dienophile, DMAD, to give, after loss of carbon dioxide, the indole-5,6-diesters (**358**). Again, the initial carbon dioxide bridged adducts (**357**) were not isolated.



(276) (357) (358)

Compd. (276)	R	Time (h)	Compd. (358)	Yield (%)
a	H	1.5	**a**	82
b	Me	4	**b**	63

Diels-Alder reaction of the pyrano[4,3-*b*]pyrrol-6(1*H*)-ones (**276**) with ethyl propiolate was not regioselective and gave essentially equal amounts of the indole-5-esters (**359**) and the indole-6-esters (**360**).



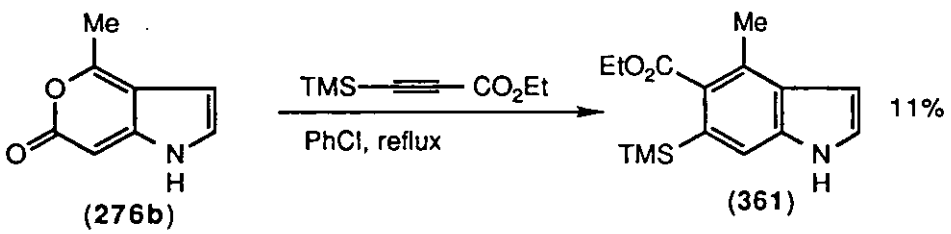
(359) (360)

Compd. (276)	R	Time (h)	Compd. (359)/(360)	Yield (%)	Ratio (359):(360)
a	H	4	**a**	51	1:1.8
b	Me	24	**b**	79	1:1

In the case of the unsubstituted pyranopyrrolone (**276a**), there was a slight preference for the formation of the 6-ester (**360a**). The minor aromatic peaks showed fairly good agreement with those of the known ethyl indole-5-carboxylate (although the spectrum was run in CCl_4).[87] Therefore, further

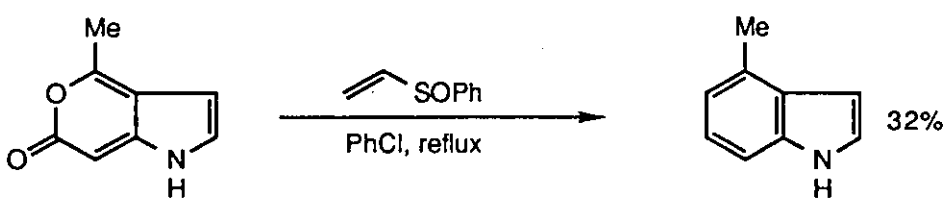
proof was obtained by comparison with the known methyl indole-5-carboxylate (spectrum run in $CDCl_3$).[88]

4-Methylpyrano[4,3-*b*]pyrrol-6(1*H*)-one (**276b**) reacted less readily with the less reactive dienophiles, ethyl 3-trimethylsilylpropynoate and phenyl vinyl sulphoxide. Diels-Alder reaction of the pyranopyrrolone (**276b**) with ethyl 3-trimethylsilylpropynoate gave ethyl 4-methyl-6-trimethylsilylindole-5-carboxylate (**361**) in only 11% yield. The low yield was due to thermal decomposition of the pyranopyrrolone occurring faster than Diels-Alder reaction.



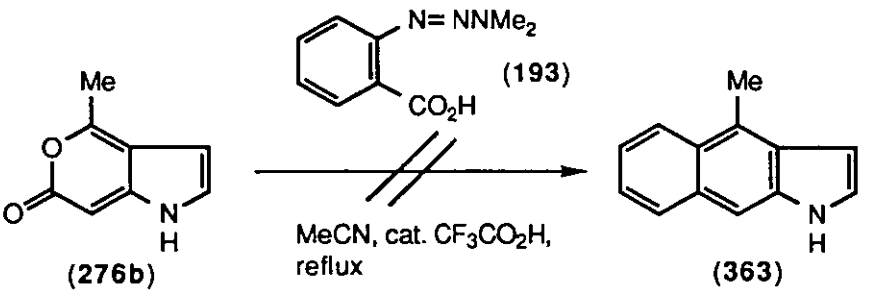
(**276b**) (**361**)

Diels-Alder reaction of the pyranopyrrolone (**276b**) with phenyl vinyl sulphoxide gave the known 4-methylindole (**362a**)[89] in 32% yield.



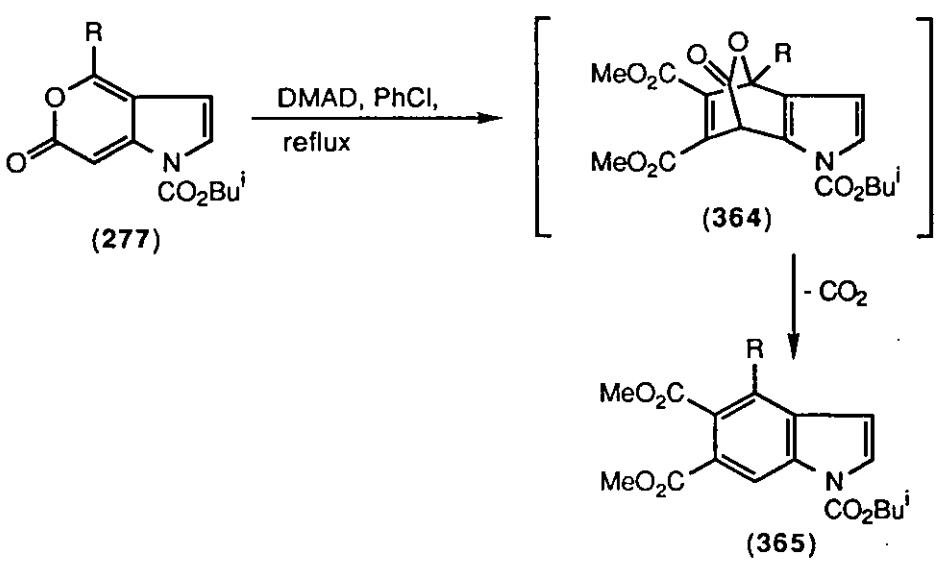
(**276b**) (**362a**)

However, Diels-Alder reaction of the pyranopyrrolone (**276b**) with benzyne did not result in the formation of 4-methylbenz[*f*]indole (**363**). Side reactions led to a mixture of products, which could not be fully characterised, and baseline material.



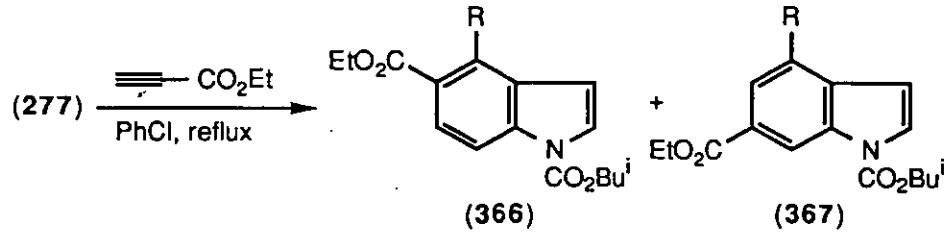
4.3.4 Intermolecular Diels-Alder reactions of the isobutyl 6-oxopyrano[4,3-*b*]pyrrole-1-carboxylates

The isobutyl 6-oxopyrano[4,3-*b*]pyrrole-1-carboxylates (**277**) also underwent ready Diels-Alder reaction with DMAD to give, after loss of carbon dioxide, the indole-1,5,6-triesters (**365**). Again, the carbon dioxide bridged adducts (**364**) were not isolated.



Compd. (277)	R	Time (h)	Compd. (365)	Yield (%)
a	H	2	**a**	99
b	Me	18	**b**	88

Diels-Alder reaction of the oxopyrano[4,3-*b*]pyrrole-1-carboxylates (**277**) with ethyl propiolate was not regioselective and gave essentially equal amounts of the indole-1,5-diesters (**366**) and the indole-1,6-diesters (**367**).

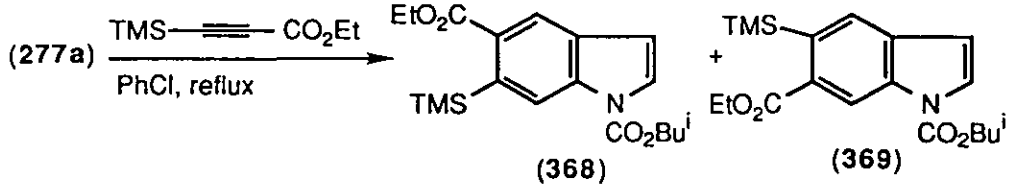


(**366**) (**367**)

Compd. (277)	R	Time (h)	Compd. (366)/(367)	Yield (%)	Ratio (366):(367)
a	H	4	**a**	81	1:1
b	Me	20	**b**	75	1.2:1

In the case of 4-methyl-6-oxopyrano[4,3-*b*]pyrrole-1-carboxylate (**277b**), there was a slight preference for the formation of the 1,5-diester (**366b**), which was characterised by the presence of two doublets (*J* 8.8 Hz) at δ 7.93 and δ 8.04 corresponding to 6-H and 7-H. Whereas, 7-H of the 1,6-diester (**367b**) appeared as a broad singlet at δ 8.71.

The Diels-Alder reaction with ethyl 3-trimethylsilylpropynoate showed greater regioselectivity. The unsubstituted oxopyrano[4,3-*b*]pyrrole-1-carboxylate (**277a**) gave the 6-trimethylsilylindole-1,5-diester (**368**) and the 5-trimethylsilylindole-1,6-diester (**369**) in a ratio of 7:1 in 90% combined yield.

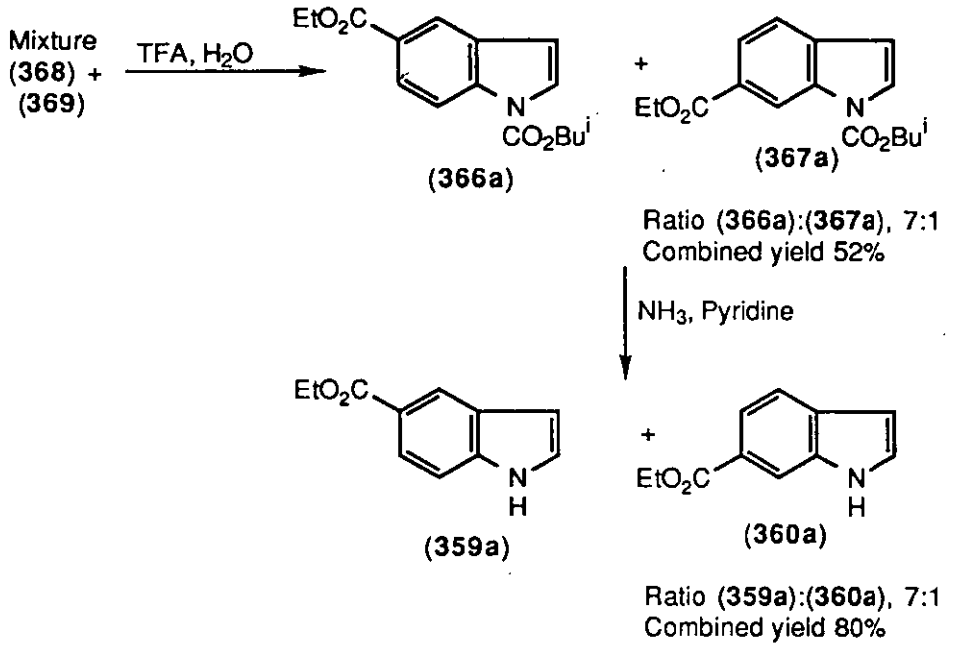


(**368**) (**369**)

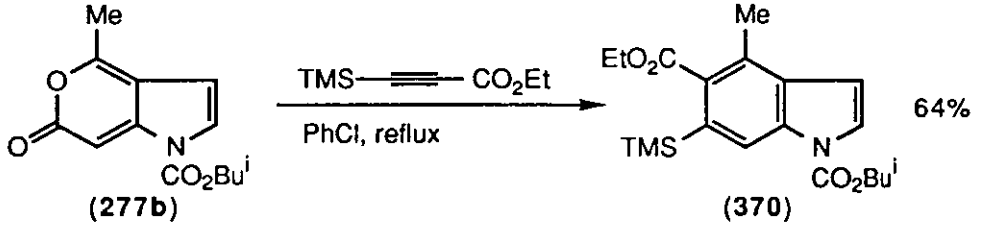
Ratio (**368**):(**369**), 7:1

Combined yield 90%

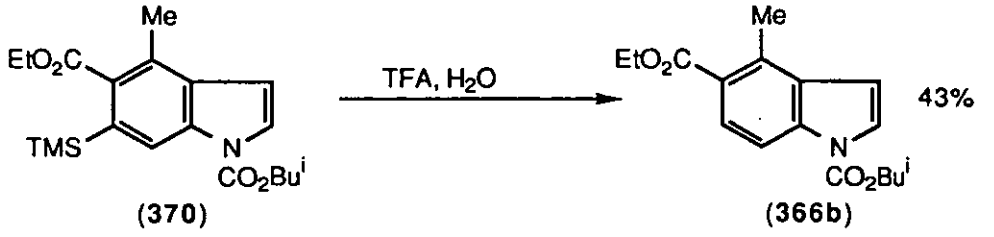
The structures (**368**) and (**369**) were confirmed by protodesilylation, followed by hydrolysis of the isobutyl carbamate functionality, and comparison of the mixture of indole esters (**359a**) and (**360a**) with the known indole-5-carboxylates.[87,88]



Diels-Alder reaction of 4-methyl-6-oxopyrano[4,3-*b*]pyrrole-1-carboxylate (**277b**) with ethyl 3-trimethylsilylpropynoate gave only one isomer by 250 MHz ^{1}H NMR. This was assigned as the 6-trimethylsilylindole-1,5-diester (**370**).

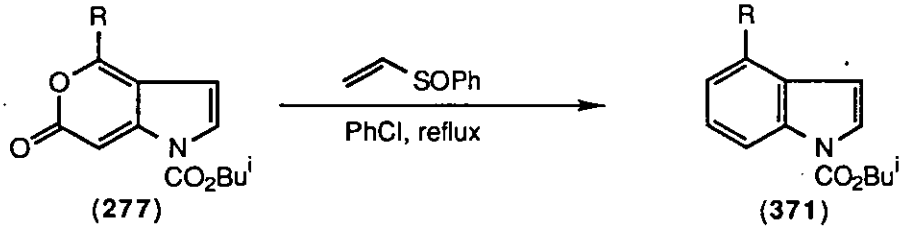


The structure (**370**) was confirmed by protodesilylation, using aqueous trifluoroacetic acid, to give the indole-1,5-diester (**366b**), identical to the major product from the Diels-Alder reaction of 4-methyl-6-oxopyrano[4,3-*b*]pyrrole-1-carboxylate (**277b**) with ethyl propiolate.



(370) (366b)

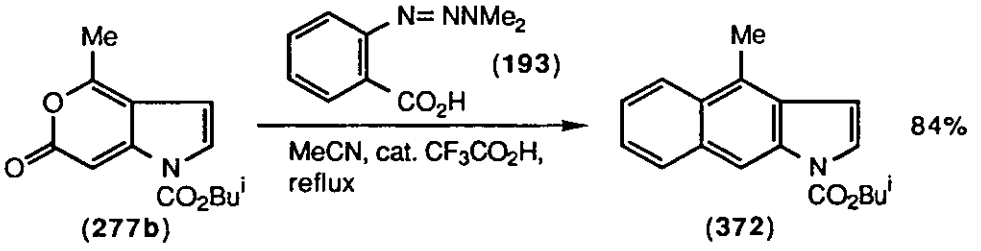
The oxopyrano[4,3-*b*]pyrrole-1-carboxylates (**277**) also reacted with the acetylene equivalent, phenyl vinyl sulphoxide, to give the 4-substituted indoles (**371a, b**) in 85% and 91% yield respectively. The preparation of the 4-aryl indole (**371b**) is particularly useful since 4-aryl indoles are relatively difficult to prepare by other routes.



(277) (371)

Compd. (277)	R	Time (h)	Compd. (371)	Yield (%)
b	Me	144	**a**	85
c	Ph	192	**b**	91

4-Methyl-6-oxopyrano[4,3-*b*]pyrrole-1-carboxylate (**277b**) reacted with benzyne, generated from 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**), to give the 4-methylbenz[*f*]indole (**372**) in 84% yield.

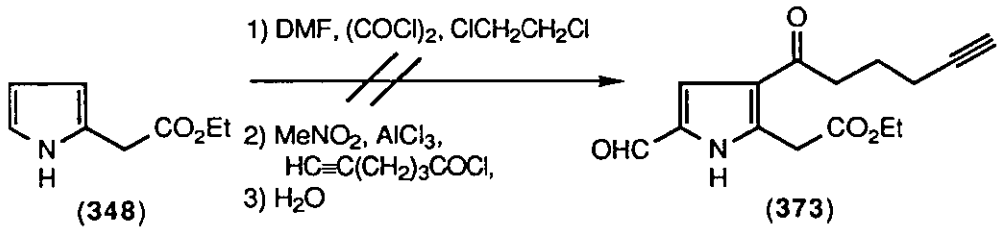


(277b) (372)

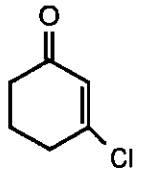
Hence, the 6-oxopyrano[4,3-*b*]pyrrole-1-carboxylates (**277**) react well with a range of electron deficient alkynes, phenyl vinyl sulphoxide, and benzyne. However, the pyrano[4,3-*b*]pyrrol-6(1*H*)-ones (**276**) only react in good yield with DMAD and ethyl propiolate. On reaction of the pyranopyrrolones (**276**) with the less reactive dienophiles, ethyl 3-trimethylsilylpropynoate and phenyl vinyl sulphoxide, formation of a considerable amount of dark coloured baseline material was observed upon prolonged heating. It appears that the isobutyl ester substituent increases the thermal stability of the pyranopyrrolones (**277**) relative to the pyranopyrrolones (**276**).

4.3.5 Attempted intramolecular Diels-Alder reactions of the pyrano[4,3-*b*]pyrrol-6(1*H*)-ones

Attempted acylation of the pyrrole Vilsmeier complex (**353**) of ethyl pyrrol-2-ylacetate (**348**), prepared as described above, with hex-5-ynoyl chloride did not give the 3-acyl-5-formylpyrrole (**373**). The only isolated compound was the cyclohexanone (**203**), produced by cyclisation of the acid chloride.



(**348**) (**373**)

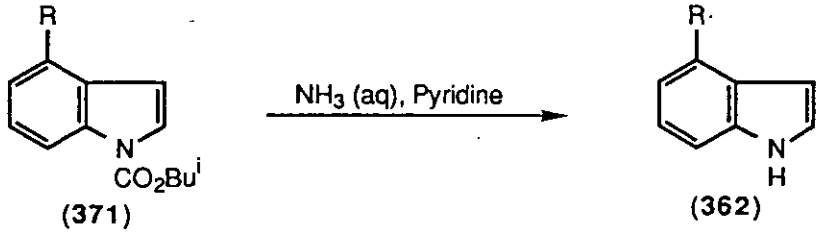


(**203**)

No further work was carried out on the preparation of suitable substrates for intramolecular Diels-Alder reaction.

4.3.6 Hydrolysis of the isobutyl carbamate functionality

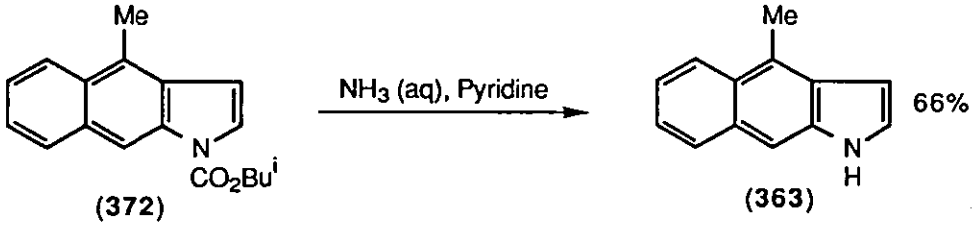
Isobutyl carbamates are readily hydrolysed using a mixture of aqueous ammonia and pyridine.[90] Hydrolysis of the indole-1-esters (**370**)-(**372**) was especially useful since the pyrano[4,3-*b*]pyrrol-6(1*H*)-ones (**276**) only underwent Diels-Alder reaction with DMAD and ethyl propiolate in good yield. Isobutyl 4-methylindole-1-carboxylate (**371a**) was converted into 4-methylindole (**362a**)[89] in 78% yield, by treatment with aqueous ammonia in pyridine. Similarly, isobutyl 4-phenylindole-1-carboxylate (**371b**) gave 4-phenylindole (**362b**)[71] in 78% yield.



(**371**) (**362**)

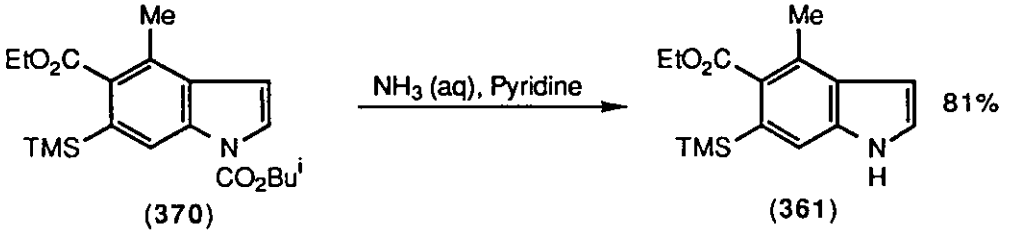
Compd. (371)	R	Time (h)	Compd. (362)	Yield (%)
a	Me	24	**a**	78
b	Ph	72	**b**	78

Hydrolysis of isobutyl 4-methylbenz[*f*]indole-1-carboxylate (**372**), using a mixture of aqueous ammonia in pyridine, gave 4-methylbenz[*f*]indole (**363**) in 66% yield.



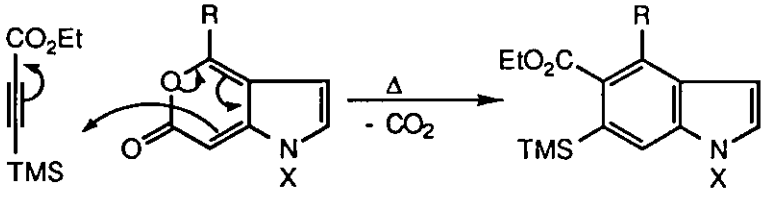
(**372**) (**363**)

Similarly, hydrolysis of 5-ethyl 1-isobutyl 4-methyl-6-trimethylsilylindole-1,5-dicarboxylate (**370**) gave ethyl 4-methyl-6-trimethylsilylindole-5-carboxylate (**361**) in 81% yield, identical to the product of Diels-Alder reaction of 4-methylpyrano[4,3-*b*]pyrrol-6(1*H*)-one (**276b**) with ethyl 3-trimethylsilylpropynoate, thus confirming the regiochemistry of this Diels-Alder reaction.



(**370**) (**361**)

Hence, the direction of addition of the 6-oxopyrano[4,3-*b*]pyrrole-1-carboxylates (**277**) and the pyrano[4,3-*b*]pyrrol-6(1*H*)-ones (**276**) to ethyl 3-trimethylsilylpropynoate is opposite to that of the 1-phenylsulphonylpyrano[3,4-*b*]pyrrol-5(1*H*)-ones (**275**). This can again be explained in terms of the direction of addition being controlled by the pyrone ring oxygen.



(**276**) X = H
(**277**) X = CO_2Bu^i

(**361**) X = H, R = Me
(**368**) X = CO_2Bu^i, R = H
(**370**) X = CO_2Bu^i, R = Me

4.4 Conclusions

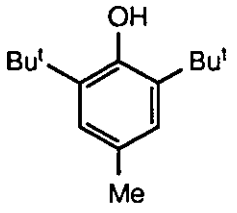
The 1-phenylsulphonylpyrano[3,4-*b*]pyrrol-5(1*H*)-ones (**275**) and the isobutyl 6-oxopyrano[4,3-*b*]pyrrole-1-carboxylates (**277**) are stable pyrrole-2,3-quinodimethane type dienes which react with electron-deficient alkynes to give, after loss of carbon dioxide, indoles. Reaction also occurs readily with benzyne, to give benz[*f*]indoles, and with phenyl vinyl sulphoxide, to give 5,6-unsubstituted indoles. The pyrano[3,4-*b*]pyrrol-5(1*H*)-ones undergo intramolecular Diels-Alder reaction to give cycloalka[*e*]- and cycloalka[*g*]indoles. Hence, a wide variety of substitution patterns is available in the benzene ring.

CHAPTER 5

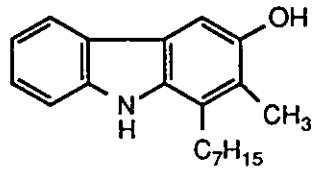
Carazostatin

5.1 Introduction

Radical scavenging agents are potentially useful therapeutic agents in that they may alleviate tissue damage due to generation of free radicals, such as superoxide, and the subsequent oxidative disintegration of all membranes.[91-93] Indeed antioxidants such as butylated hydroxytoluene (BHT) (**374**) and related compounds are known to inhibit free radical induced lipid peroxidation *in vitro*.[94] Recently Japanese workers have isolated a novel radical scavenger from *Streptomyces chromofuscus* which is much more active than BHT. Using a combination of spectroscopic techniques, the compound, named carazostatin, was identified as 1-heptyl-3-hydroxy-2-methylcarbazole (**375**).[95]



(**374**)

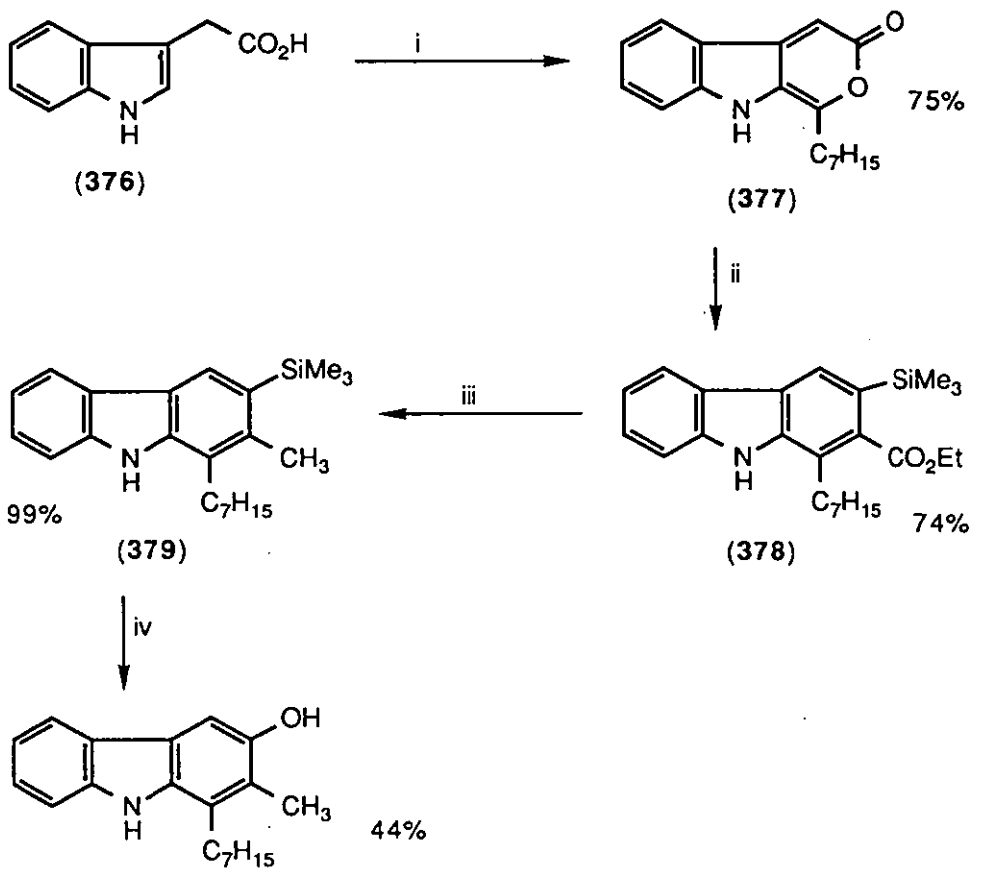


Carazostatin (**375**)

5.2 Synthesis of carazostatin

The synthesis of carazostatin (**375**) is based on a versatile Diels-Alder route to polysubstituted carbazoles,[38,39] developed in our laboratory, and employed in the synthesis of hyellazole and the carbazomycins.[96] Thus reaction of indol-3-ylacetic acid (**376**) with octanoic anhydride in the presence of boron trifluoride diethyl ether gave 1-heptylpyrano[3,4-*b*]indol-3-one (**377**) in 75% yield. Diels-Alder reaction of the pyranoindolone (**377**) with commercially available ethyl 3-trimethylsilylpropynoate was, as expected, completely regioselective and gave, after loss of carbon dioxide, the carbazole (**378**) in 74% yield. The ester group in carbazole (**378**) was reduced directly to a methyl group in 99% yield by heating with excess lithium aluminium hydride in dioxan. The resulting 1,2-dialkyl-3-trimethylsilylcarbazole (**379**) was converted into carazostatin (**375**) by mercuriodesilylation, using mercuric acetate in acetic acid, followed by hydroboration, using borane-tetrahydrofuran complex, oxidation, using

alkaline hydrogen peroxide, and hydrolysis in dilute hydrochloric acid (44% overall), a sequence of reactions which has been previously used in the synthesis of the carbazomycins.[96] The spectroscopic data of synthetic carazostatin (**375**) closely matched those described for the natural product.[95]



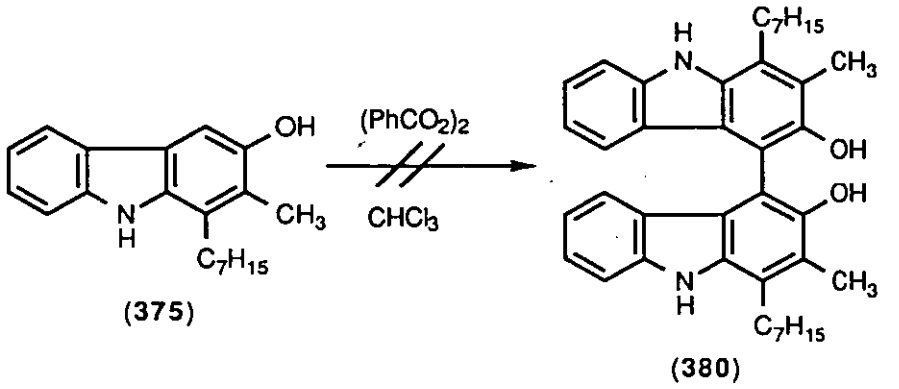
Carazostatin (**375**)

Scheme 19. *Reagents* i) $(C_7H_{15}CO)_2O$, $BF_3.Et_2O$; ii) $Me_3SiC{\equiv}CCO_2Et$, PhBr, reflux; iii) $LiAlH_4$, dioxan, reflux; iv) a) $Hg(OAc)_2$, AcOH; b) $BH_3.THF$; c) H_2O_2, aq. NaOH; d) aq. HCl.

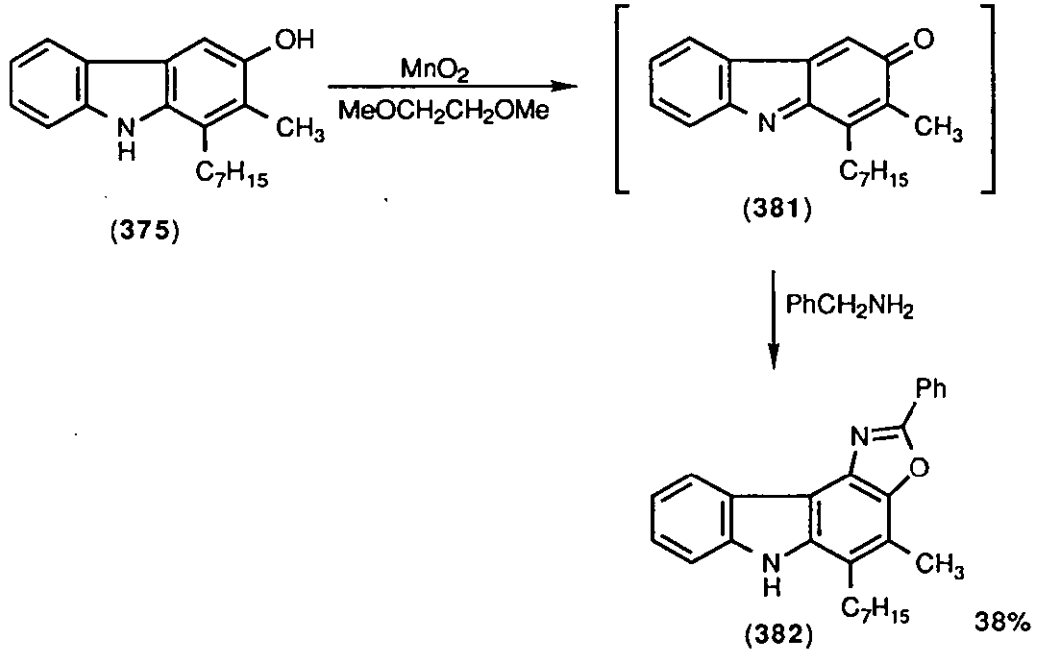
5.3 Oxidation of Carazostatin

In view of its reported role as an antioxidant, we briefly investigated the oxidation of carazostatin. Indeed solutions of carazostatin readily decompose in air, presumably by oxidation, to give dark coloured material. Deliberate oxidation of carazostatin with dibenzoyl peroxide, which by analogy with similar

oxidations of other 3-hydroxycarbazoles[96] might be expected to give the 4,4'-bicarbazole (**380**), was unsatisfactory and produced complex mixtures.

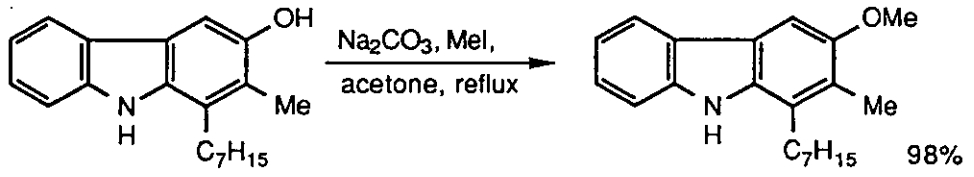


On the other hand, if we assume that the initial process is the formation of the iminoquinone (**381**), this should be intercepted by reaction with nucleophiles. In support of this, when the oxidation was carried out by the addition of manganese (IV) oxide in the presence of benzylamine, the oxazolocarbazole (**382**) was obtained in 38% yield, in a reaction which mimics that of the anticancer agent 9-hydroxyellipticine under similar oxidative conditions.[97]

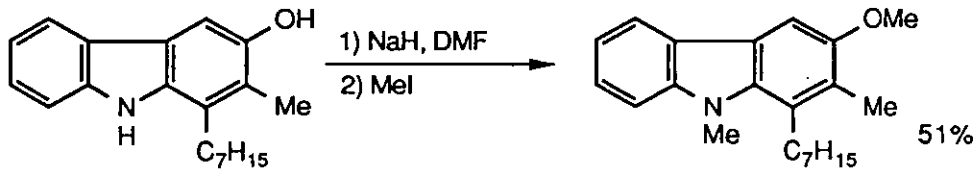


5.4 Electrochemistry

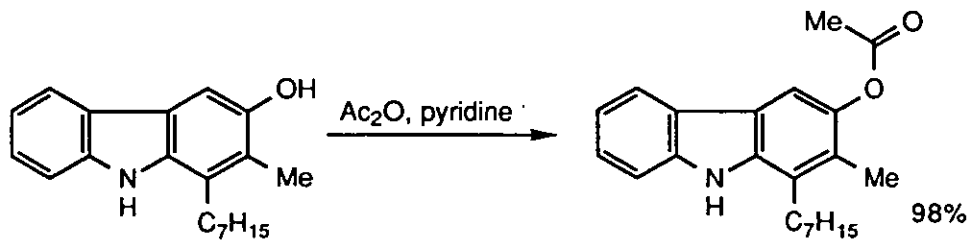
More relevant perhaps than chemical oxidation of carazostatin is a comparison of its oxidation potential with known antioxidants such as BHT (**374**), and to this end, in collaboration with Dr. Roger Mortimer in this department, we carried out an electrochemical study on BHT, carazostatin, and its *O*-methyl (**383**), *N*,*O*-dimethyl (**384**), and *O*-acetyl (**385**) derivatives, prepared by standard methods. Thus, treatment of carazostatin with sodium carbonate and methyl iodide in refluxing acetone gave the *O*-methyl derivative (**383**) in 98% yield. Similarly, treatment of carazostatin with an excess of sodium hydride in DMF followed by quenching with methyl iodide gave the *N*,*O*-dimethyl derivative (**384**) in 51% yield. Treatment of carazostatin with acetic anhydride in pyridine gave the *O*-acetyl derivative (**385**) in 98% yield.



(**375**) (**383**)

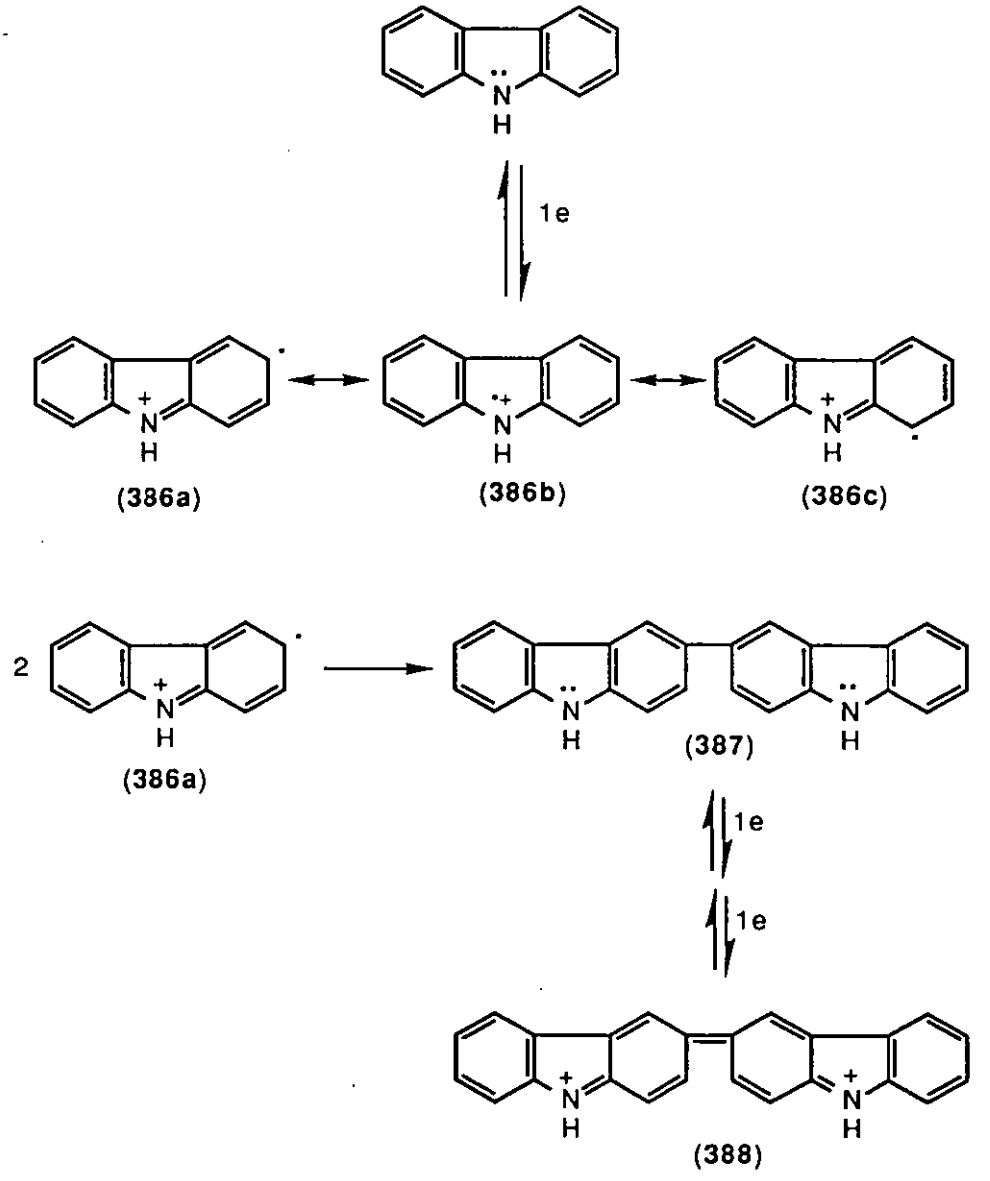


(**375**) (**384**)

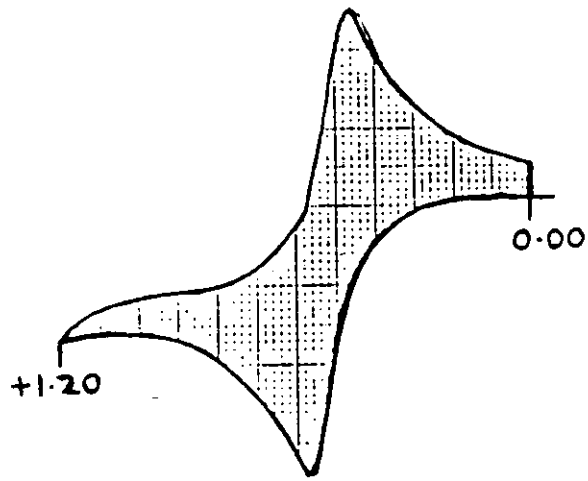


(**375**) (**385**)

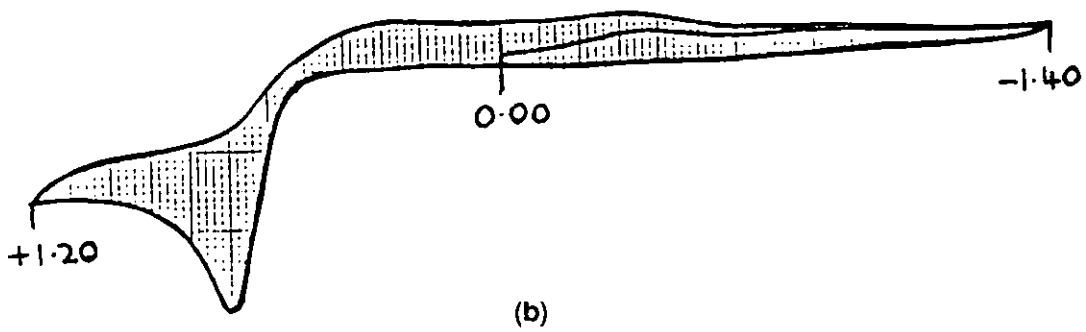
Electrochemical studies of carazostatin and BHT.- The electrochemical oxidation pathway of carbazole, the parent molecule to carazostatin, is initiated by a one electron transfer to form the radical cation (**386**).[98-100] Study of a wide range of *N*-substituted and ring substituted carbazoles has shown that the 3, 6, and 9 (N) positions are extremely reactive; if these sites are not blocked by inert substituents the cation radicals (**386**) generated react rapidly by deprotonation and dimerisation.[99] Of the two dicarbazyls formed, the 3,3' isomer (**387**) is the predominant product and is more easily oxidised than carbazole, so at the applied potential the dicarbazyl (**387**) undergoes two further one electron oxidations in an ECE mechanism.



Thus, as expected, the electrochemical oxidation of carazostatin gave an irreversible wave (Figure 1).



(a)



(b)

Figure 1. Voltammograms of **a**) Ferrocene and **b**) Carazostatin, using a platinum working electrode. Scan rate 50 mV s^{-1}.

Table 8 shows anodic peak potentials ($E_{p,a}$) at a sequence of scan rates contrasted with values for BHT electrochemical oxidation (via the phenoxonium ion), with ferrocene formal potentials (E^f) as reference.

Table 8. Electrochemical data for carazostatin, BHT and ferrocene

	Carazostatin	BHT	Ferrocene
Scan rate/mV s^{-1}	$(E_{p,a})^{a,c}$/V *vs.* s.s.c.e		$(E^f)^{b,c}$/V *vs.* s.s.c.e
20	+0.68	+1.22	+0.52
50	+0.70	+1.26	+0.52
100	+0.73	+1.28	+0.53
200	+0.75	+1.30	+0.53
500	+0.80	+1.38	+0.53

[a]$E_{p,a}$ = anodic peak potential

[b]Formal potential $E^f = 0.5(E_{p,c} + E_{p,a})$, where $E_{p,c}$ = cathodic peak potential

[c]Values quoted were (± 0.01)

For carazostatin and BHT, a positive shift in $E_{p,a}$ is observed with increasing scan rate because the coupled chemical reaction reduces the concentration of product at the surface from the value it would have had for a simple electron transfer reaction. The less positive $E_{p,a}$ values for carazostatin compared to BHT support the observation of Kato *et al.*[95] that the former is a more active antioxidant. This increased activity we interpret as being due to the iminoquinone formation pathway favoured by the presence of the 3-hydroxy substituent.

Interestingly, the electrochemical oxidation of carazostatin at the glassy carbon electrode showed quasi-reversible voltammetry, indicating stabilisation of the product by adsorption onto the carbon surface.

Electrochemical studies of carazostatin derivatives (**383-385**).- Table 9 shows anodic peak potentials ($E_{p,a}$) at a sequence of scan rates for derivatives (**383-385**).

Table 9. Electrochemical data for carazostatin derivatives (**383-385**)

	383	**384**	**385**
	O-methyl	*N,O*-dimethyl	*O*-acetyl
Scan rate/mV s^{-1}	$(E_{p,a})^{a,b}$/V *vs.* s.s.c.e		
20	+0.98	+1.10	+1.22
40	+0.99	+1.08	+1.24
100	+1.02	+1.06	+1.24
200	+1.04	+1.07	+1.27
400	+1.06	+1.07	+1.29

[a]$E_{p,a}$ = anodic peak potential

[b]Values quoted were (± 0.01)

All three compounds are less active than carazostatin. This observation can be interpreted in terms of the decreasing ability of the substituents to stabilise the radical cation as Table 9 is traversed. For (**383**) and (**385**) a positive shift in $E_{p,a}$ is again observed with increasing scan rate. In contrast, compound (**384**) shows no trend in $E_{p,a}$ with increase in scan rate. Furthermore, at the higher scan rates, current for the electrochemical reduction of the radical cation is observed. Also $i_p/\sqrt{}$(scan rate) decreases more rapidly with increasing scan rate for compound (**384**) than for the other compounds showing that the dimerisation through C-6 or C-4 is slower.

5.5 Conclusions

Carazostatin (**375**) has been efficiently prepared, in four steps, from indol-3-ylacetic acid. Studies on the reactivity of carazostatin have shown it to be readily oxidised chemically, using manganese (IV) oxide, and electrochemically, where carazostatin was found to be more readily oxidised than BHT.

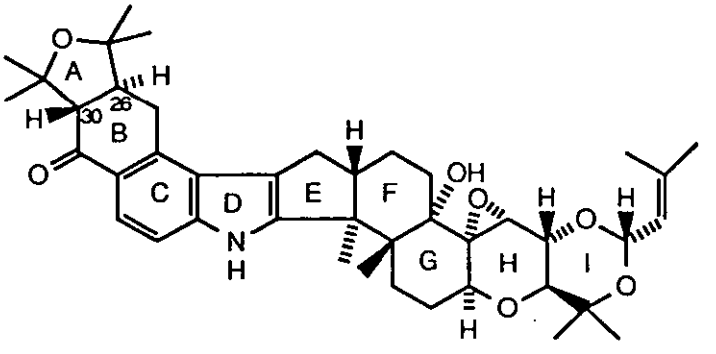
CHAPTER 6

Lolitrem studies

6.1 Introduction

Ryegrass staggers is a nervous disorder of sheep, cattle, horses, and deer grazing perennial ryegrass (*Lolium perenne*) dominant pastures.[101,102] The disorder, characterised by severe inco-ordination and hypersensitivity to external stimuli is of considerable importance to agriculture in New Zealand and Australia. It has been reported that an *Acremonium* species, an endophytic fungus which infects ryegrass is associated with the production of the neurotoxins which cause ryegrass staggers.[103]

Extensive investigations into the cause of ryegrass staggers led to the isolation and purification of four potent neurotoxins named lolitrems A, B, C, and D from toxic ryegrass and ryegrass seed.[104,105] The structure of the major neurotoxin, lolitrem B (**389**), was assigned based on a detailed study of its high field ^{1}H and ^{13}C NMR spectra.[106]



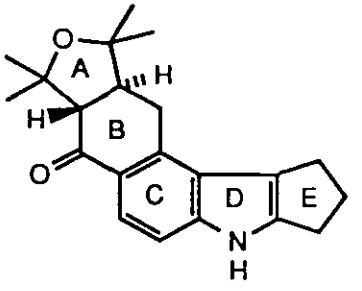
Lolitrem B (**389**)

Although the trans-fusion of rings A and B follows from a vicinal (H,H) coupling of 14.3 Hz for the C-26 and C-30 protons, the relative and absolute configuration of these two chiral centres remains unknown.

It is evident that the lolitrems are related to the known tremorgenic mycotoxins, *viz* aflatrem,[107] the penitrems,[108] and janthitrems[109] in terms of structure, biogenesis and biological effects.[110] The structural differences in rings A and B of the lolitrems, penitrems, and janthitrems are due to different isoprenylations which in turn lead to the unique ring structures. In the case of the lolitrems, an additional mevalonate unit leads to the formation of ring I.

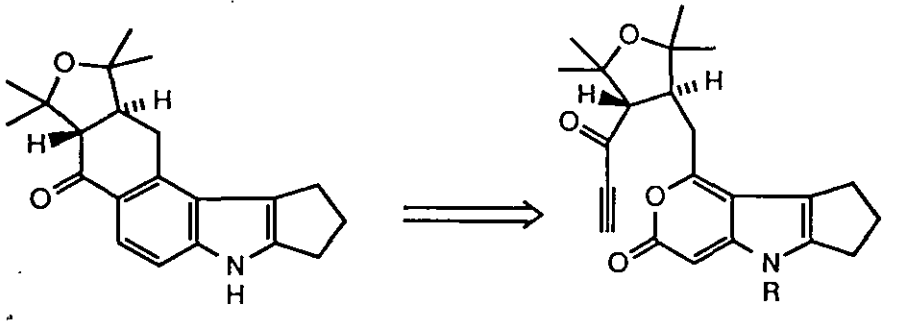
6.2 Model studies

All of the tremorgenic indoles possess similar structures to lolitrem B (**389**) in the right hand portion (rings E-I) of the molecule. The main differences occur in the left hand portion (rings A-B). Much synthetic work has already been carried out on the synthesis of ring systems necessary for the construction of the right hand portion of lolitrem B.[111] However no synthetic work has appeared on the synthesis of the A and B rings of lolitrem B. Therefore, we decided to begin by attempting a synthesis of the pentacyclic compound (**390**).

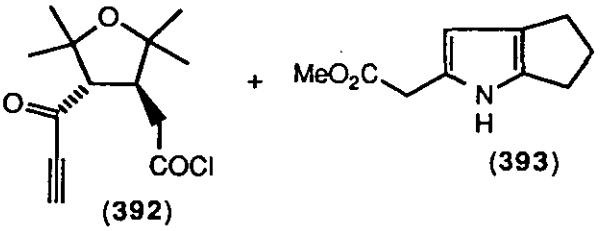


(390)

Disconnections.-



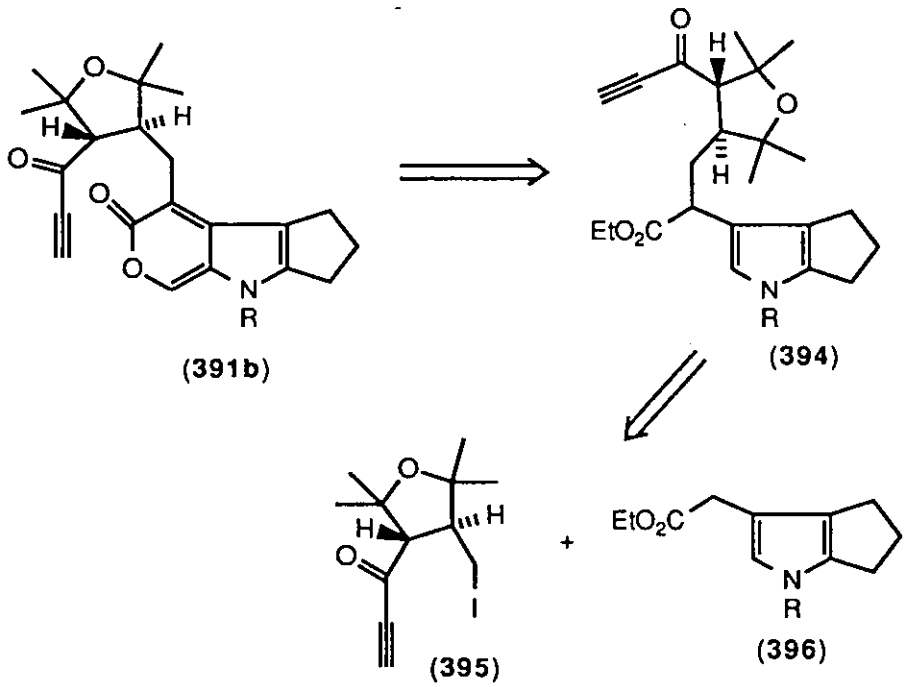
(390) **(391a)**



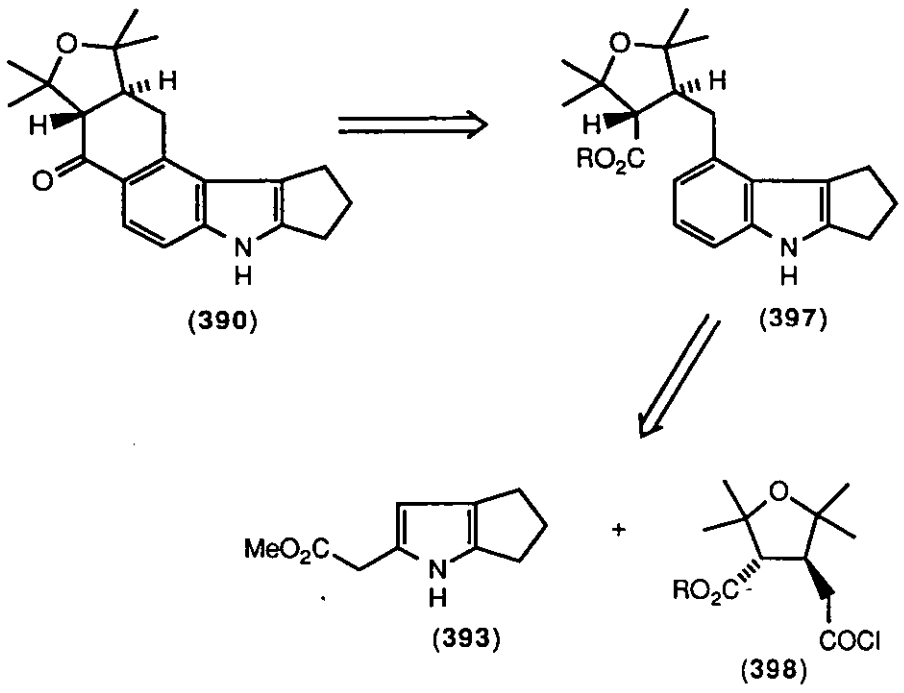
(392) **(393)**

The pentacyclic indole (**390**) could be formed via intramolecular Diels-Alder reaction of the pyranopyrrolone (**391a**), which can in turn be disconnected to the pyrrole (**393**) and the tetrahydrofuran (**392**). Acylation of the pyrrole (**393**) at the vacant 3-position, using the acid chloride (**392**), followed by hydrolysis and cyclodehydration should give the pyranopyrrolone (**391a**).

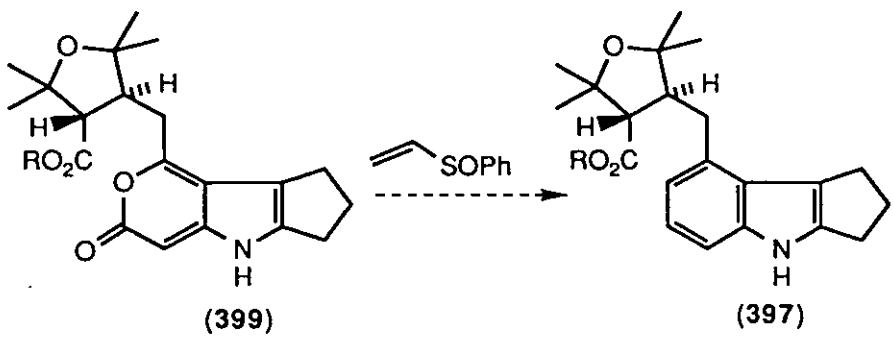
The pentacyclic indole (**390**) could also be formed via intramolecular Diels-Alder reaction of the isomeric pyranopyrrolone (**391b**). The pyranopyrrolone (**391b**) could be disconnected to the ester (**394**), which could be formed by alkylation of the pyrrole ester (**396**) with the alkynyl iodide (**395**). Formylation of the pyrrole (**394**) at the vacant 2-position, followed by hydrolysis and cyclodehydration should give the pyranopyrrolone (**391b**).



Alternatively, the B ring of the indole (**390**) could be formed by an intramolecular Friedel-Crafts reaction of the indole (**397**). Indole (**397**) can also be disconnected to the pyrrole (**393**) and the tetrahydrofuran (**398**). Acylation of the pyrrole (**393**), using the acid chloride (**398**), followed by hydrolysis and cyclodehydration, would be expected to give the pyranopyrrolone (**399**).

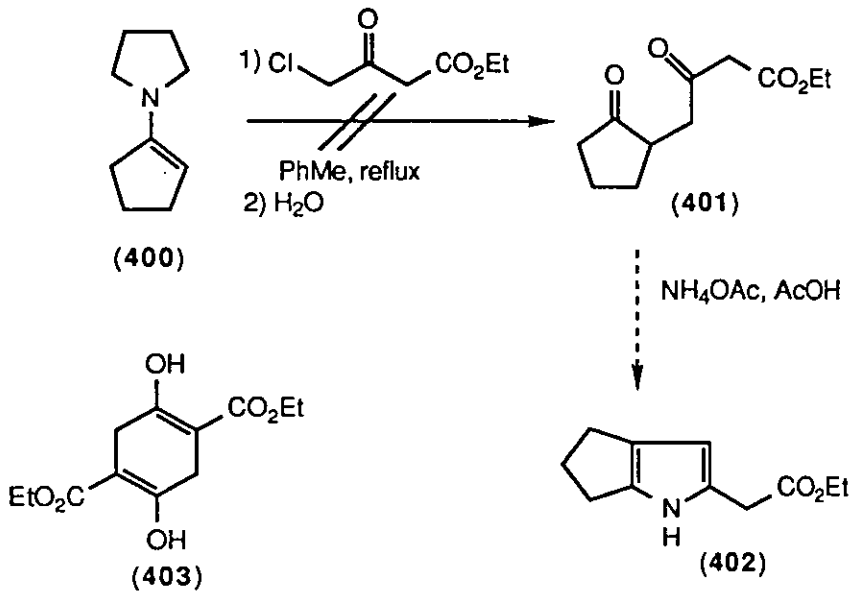


The pyranopyrrolone (**399**) should undergo Diels-Alder reaction with the acetylene equivalent phenyl vinyl sulphoxide to give the indole (**397**). Hydrolysis of compound (**397**), followed by acid chloride formation should allow cyclisation, via intramolecular Friedel-Crafts reaction, to give the indole (**390**).



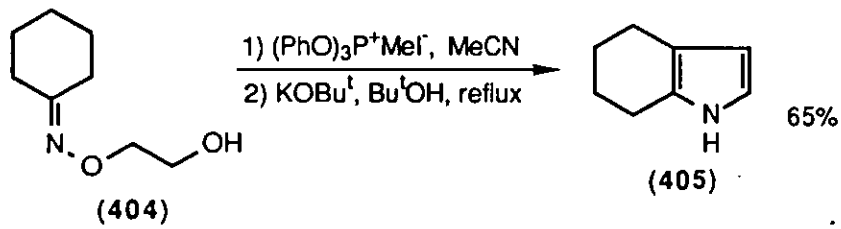
6.3 Synthesis of the pyrrole fragment

We initially intended to synthesise the ethyl ester (**402**) by ring closure of the 1,4-diketone (**401**), using ammonium acetate. However, reaction of the enamine (**400**) with ethyl 4-chloroacetoacetate did not give the diketone (**401**). The only product isolated appeared to be the cyclic enol (**403**) from dimerisation of ethyl 4-chloroacetoacetate.[112]

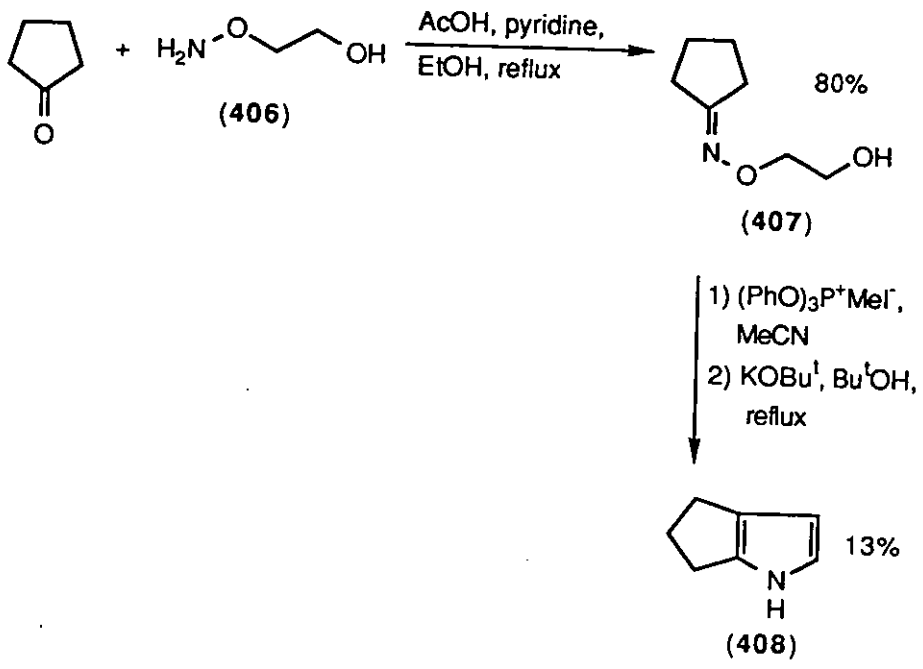


We then decided to prepare the 'parent' cyclopenta[*b*]pyrrole (**408**), and introduce the acetic ester functionality by one of the standard methods shown in earlier Chapters.

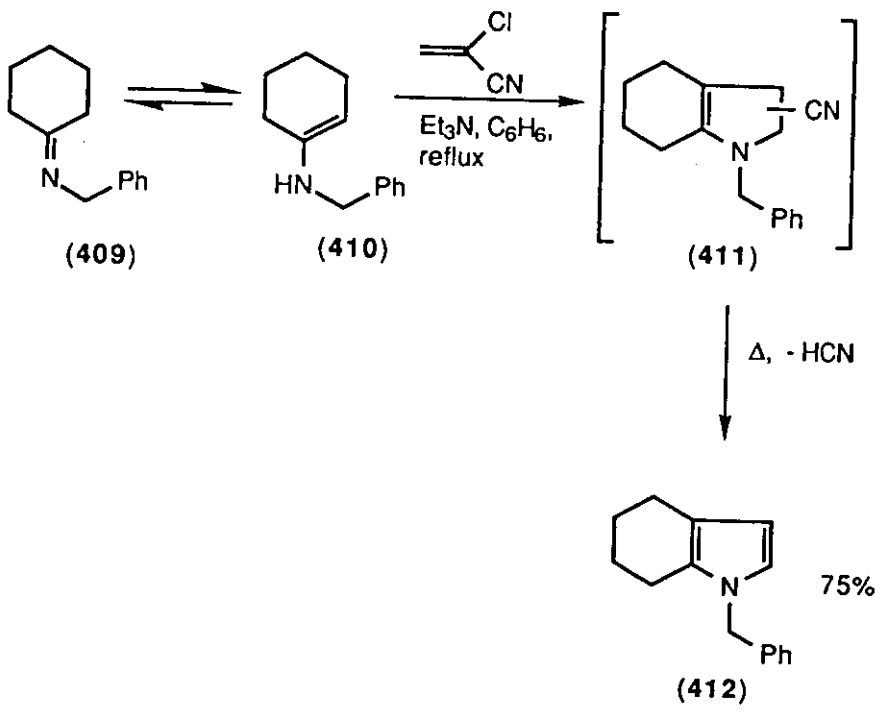
4,5,6,7-Tetrahydroindole (**405**) has been prepared in good yield from the *O*-(2-hydroxyethyl)-ketoxime (**404**).[113]



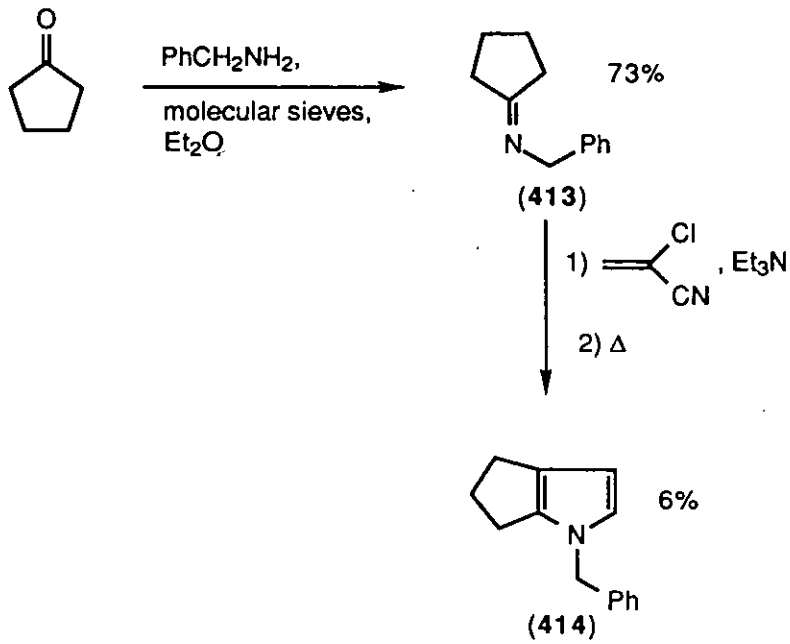
However, when we extended the reaction to the cyclopenta[*b*]pyrrole (**408**), the yield was only 13%.



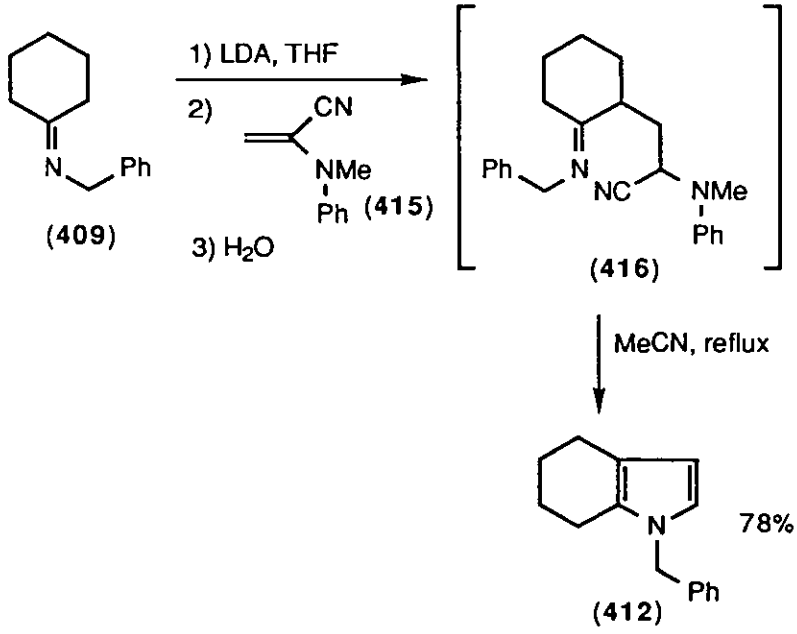
1-Benzyl-4,5,6,7-tetrahydroindole (**412**) has been prepared in good yield by reaction of the imine (**409**) with 2-chloroacrylonitrile, followed by pyrolysis of the intermediate (**411**).[114]



However, this route gave the 1-benzylcyclopenta[*b*]pyrrole (**414**) in only 6% yield.



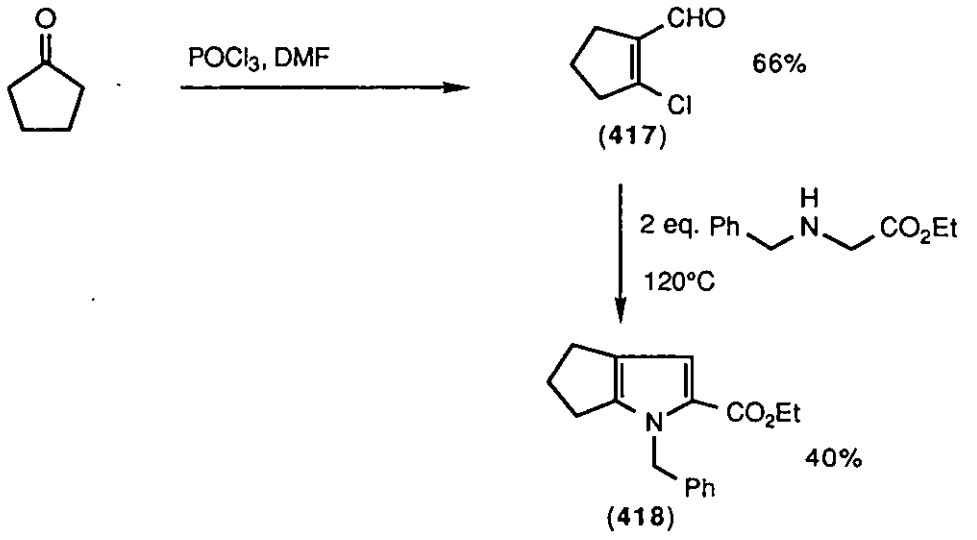
A similar sequence of reactions involved treatment of the imine (**409**) with LDA, followed by 2-(*N*-methylanilino)acrylonitrile (**415**), then water, and finally thermolysis in refluxing acetonitrile to give the 1-benzyltetrahydroindole (**412**).[115]



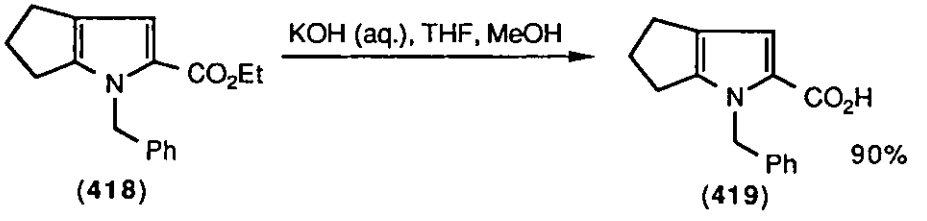
However, when this sequence of reactions was repeated on the imine (**413**), no 1-benzylcyclopenta[*b*]pyrrole (**414**) was observed by TLC.

We then decided to prepare the pyrrole (**418**), which has been reported in the literature,[116] since the desired 1-benzylcyclopenta[*b*]pyrrole (**414**) should be readily available via hydrolysis and decarboxylation.

Treatment of cyclopentanone with phosphorus oxychloride in DMF gave the β-chloroaldehyde (**417**).[117] Reaction of the β-chloroaldehyde (**417**) with two equivalents of *N*-benzylglycine ethyl ester at 120°C gave the pyrrole (**418**).[116]

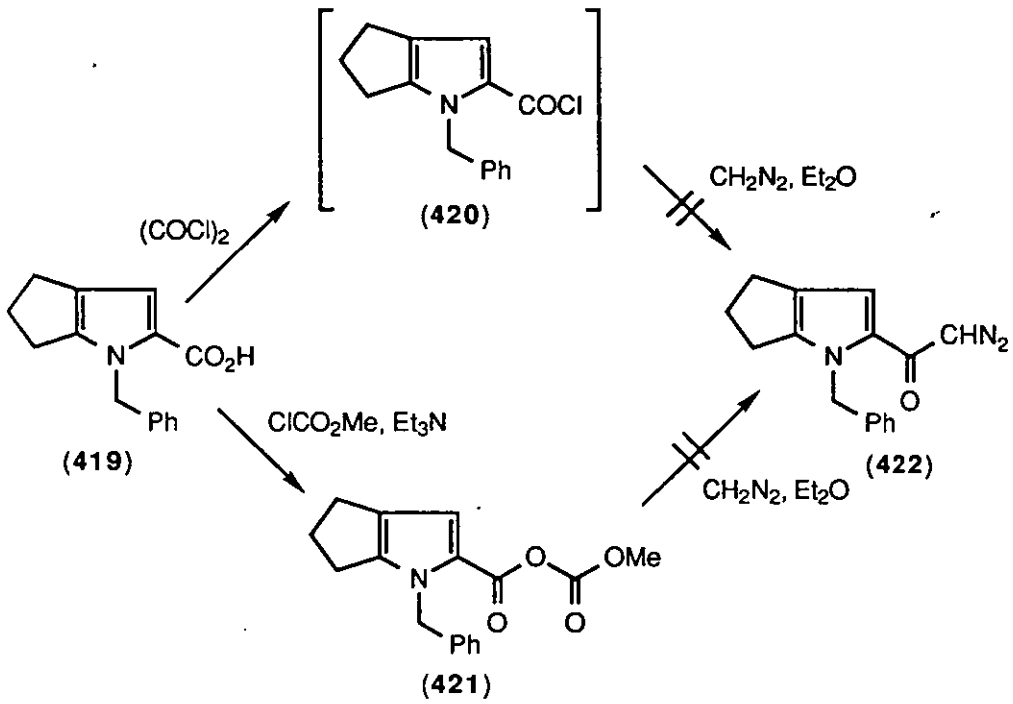


Alkaline hydrolysis of the ester (**418**), using aqueous potassium hydroxide in tetrahydrofuran and methanol, gave the acid (**419**) in 90% yield.

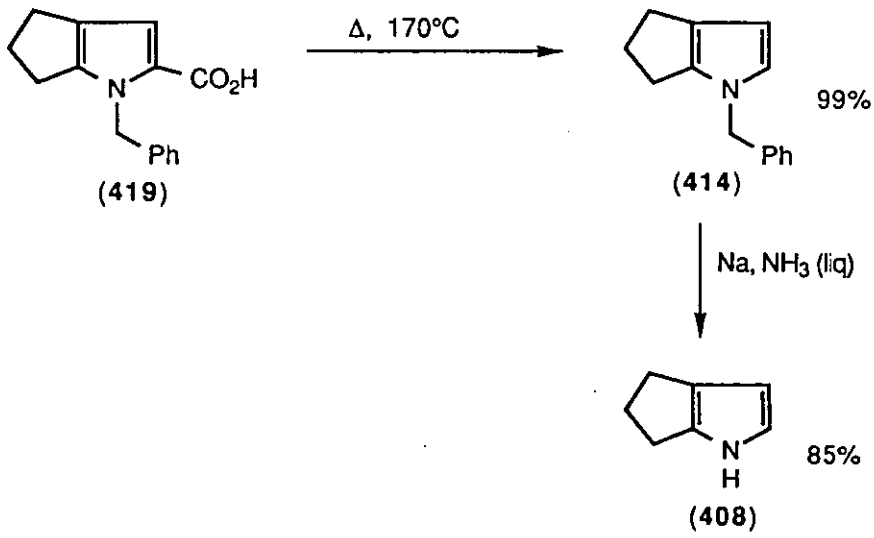


Attempts to perform an Arndt-Eistert procedure on the acid (**419**) were unsuccessful. Neither the acid chloride (**420**), formed by treatment of the acid (**419**) with oxalyl chloride, nor the mixed anhydride (**421**), formed by treatment of the acid (**419**) with methyl chloroformate in the presence of

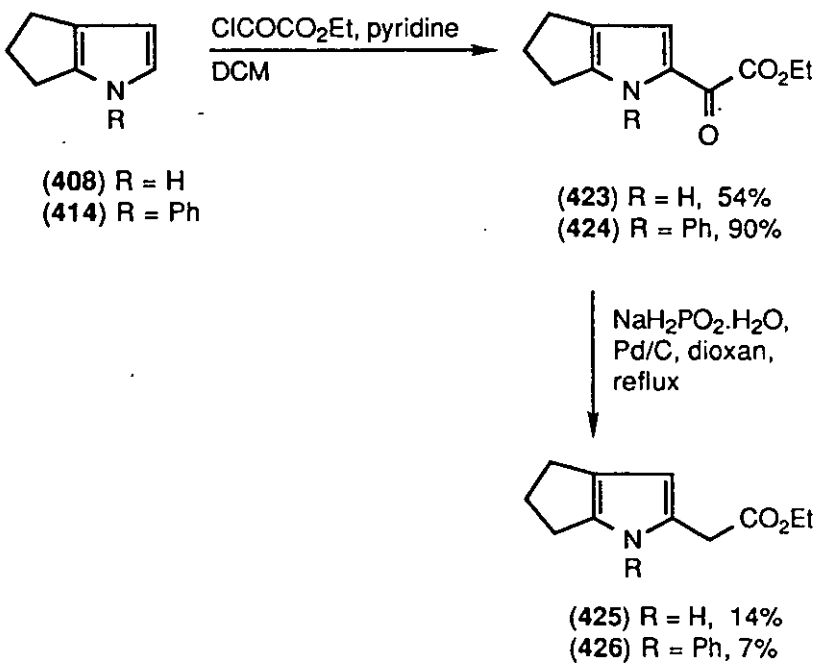
triethylamine, reacted with diazomethane.



However, decarboxylation of the acid (**419**) occurred smoothly at its melting point to give the 1-benzylcyclopenta[*b*]pyrrole (**414**) in 99% yield. Compound (**414**) could be debenzylated, by treatment with sodium in liquid ammonia, to give the cyclopenta[*b*]pyrrole (**408**) in 85% yield.



The pyrroles (**408**) and (**414**) were 2-acylated, by treatment with ethyl oxalyl chloride and pyridine in dry dichloromethane, to give the glyoxalates (**423**) and (**424**) in yields of 54% and 90% respectively. However, attempted reduction of the glyoxalates (**423**) and (**424**), using sodium hypophosphite and palladium on activated carbon in refluxing dioxan, gave the pyrroles (**425**) and (**426**) in yields of only 14% and 7% respectively although, in the case of the benzyl substituted compound (**424**), starting material was recovered in 69% yield.

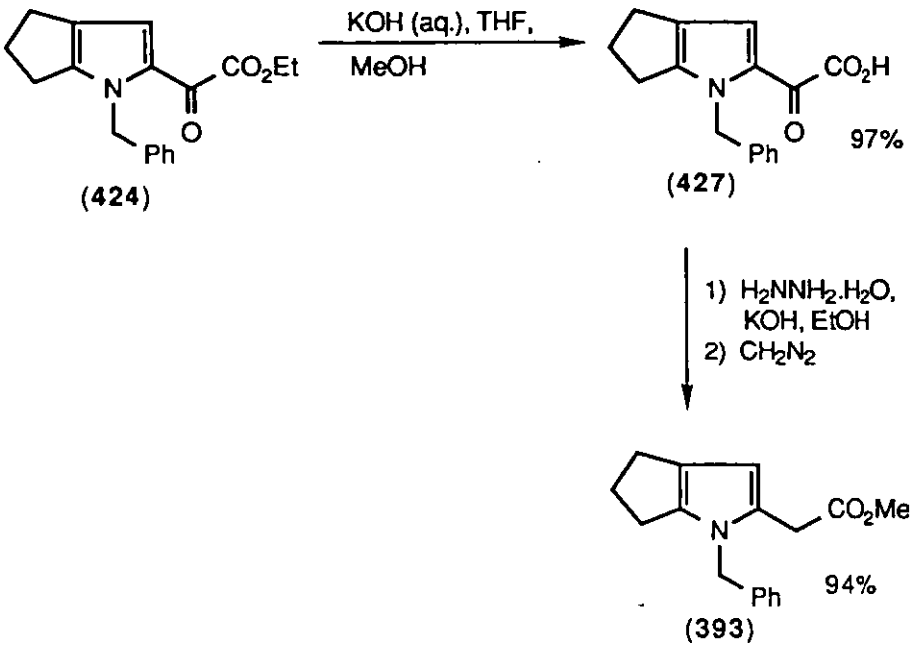


(**408**) R = H
(**414**) R = Ph

(**423**) R = H, 54%
(**424**) R = Ph, 90%

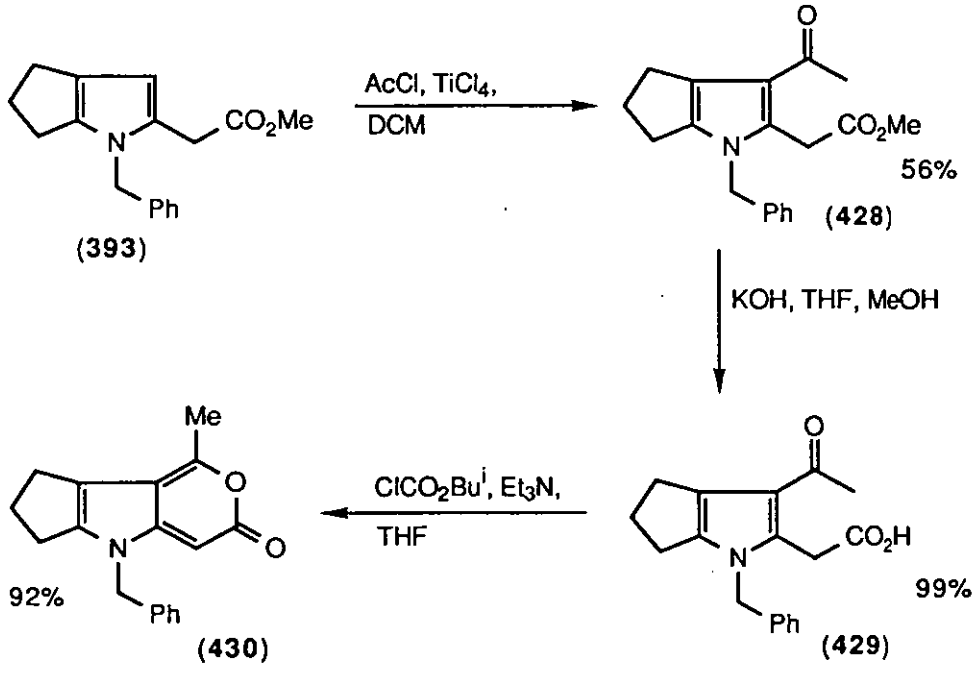
(**425**) R = H, 14%
(**426**) R = Ph, 7%

However, the glyoxalate (**424**) could be hydrolysed, using aqueous potassium hydroxide in tetrahydrofuran and methanol, to give the acid (**427**) in 97% yield. Wolff-Kishner reduction of the acid (**427**), using ethanolic potassium hydroxide and hydrazine hydrate, followed by esterification, using diazomethane, gave the ester (**393**) in 94% yield.



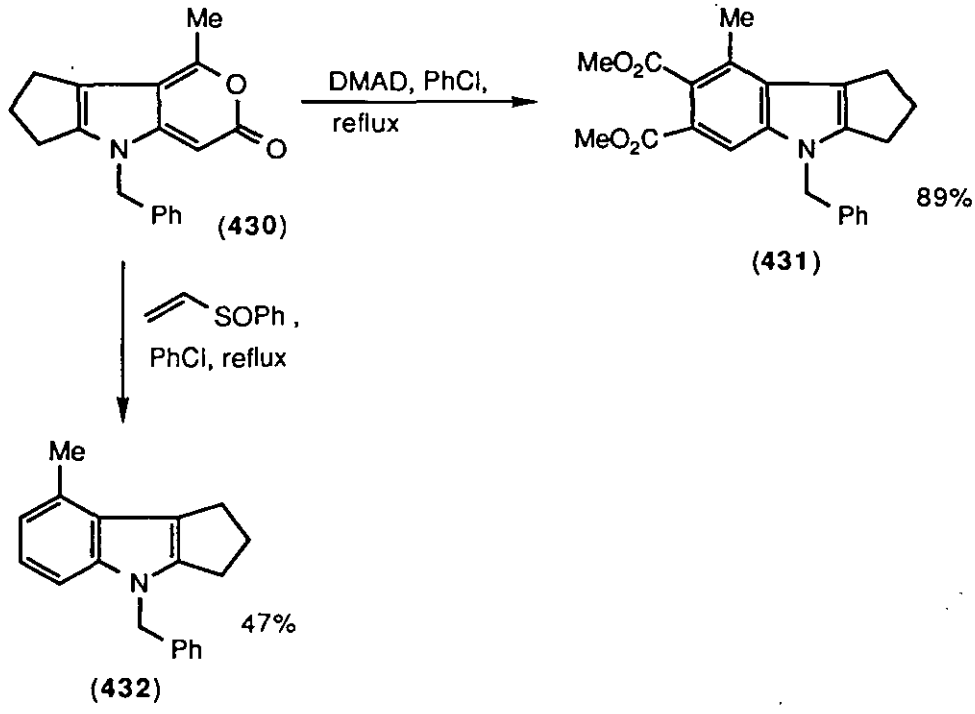
6.4 Pyranopyrrolone studies

In order to test whether the ester (**393**) could be converted into a pyranopyrrolone and Diels-Alder reactions carried out, we decided to prepare the simple methyl substituted pyranopyrrolone (**430**).



The ester (**393**) could be acetylated, using acetyl chloride in the presence of tin (IV) chloride or titanium (IV) chloride, to give the 3-acetylpyrrole (**428**) in 37% and 56% yield respectively. Alkaline hydrolysis of the ester (**428**), using aqueous potassium hydroxide in tetrahydrofuran and methanol, gave the acid (**429**) in 99% yield. Treatment of the acid (**429**), with isobutyl chloroformate and triethylamine in tetrahydrofuran, gave the pyranopyrrolone (**430**) in 92% yield.

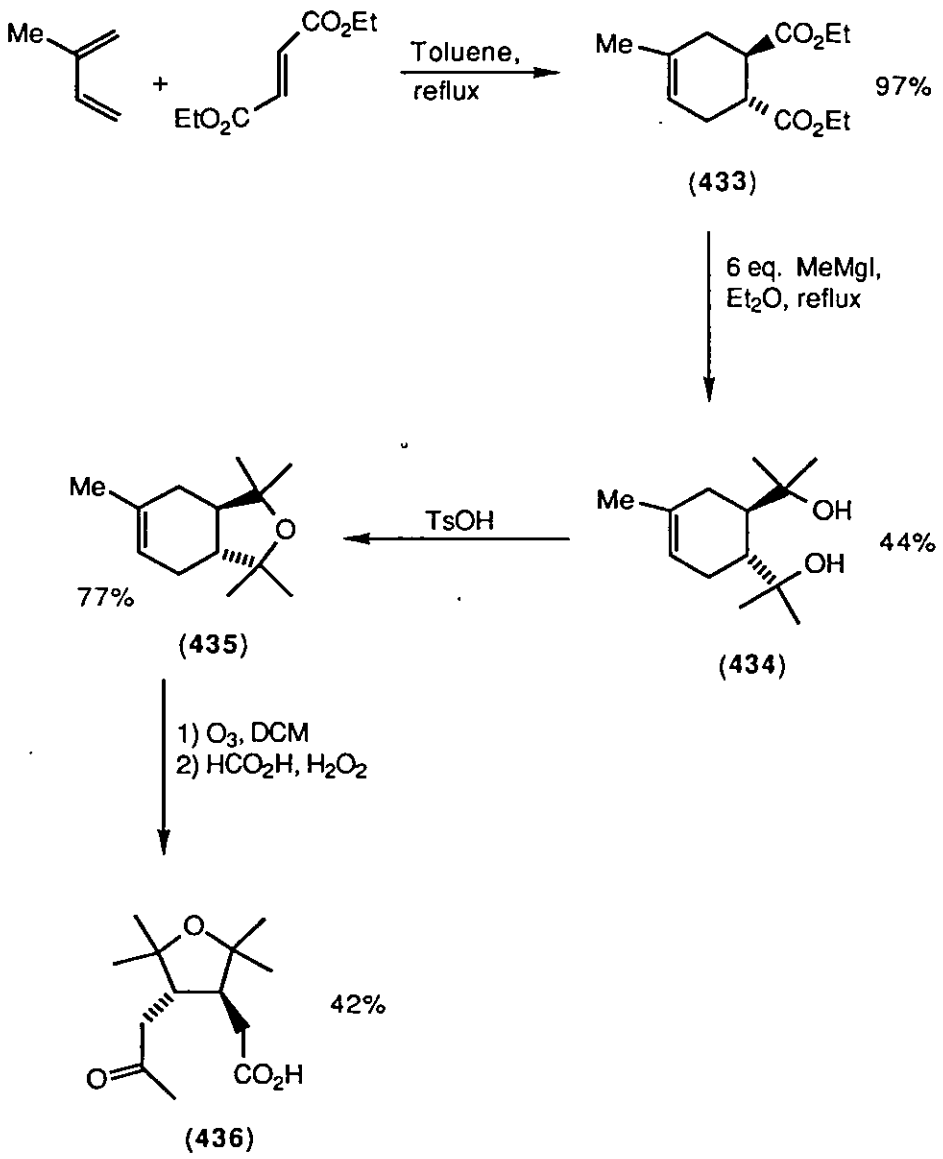
On heating with DMAD in refluxing chlorobenzene, the pyranopyrrolone (**430**) underwent Diels-Alder reaction to give, after loss of carbon dioxide, the indole (**431**) in 89% yield. Similarly, heating with phenyl vinyl sulphoxide in refluxing chlorobenzene gave the indole (**432**) in 47% yield.



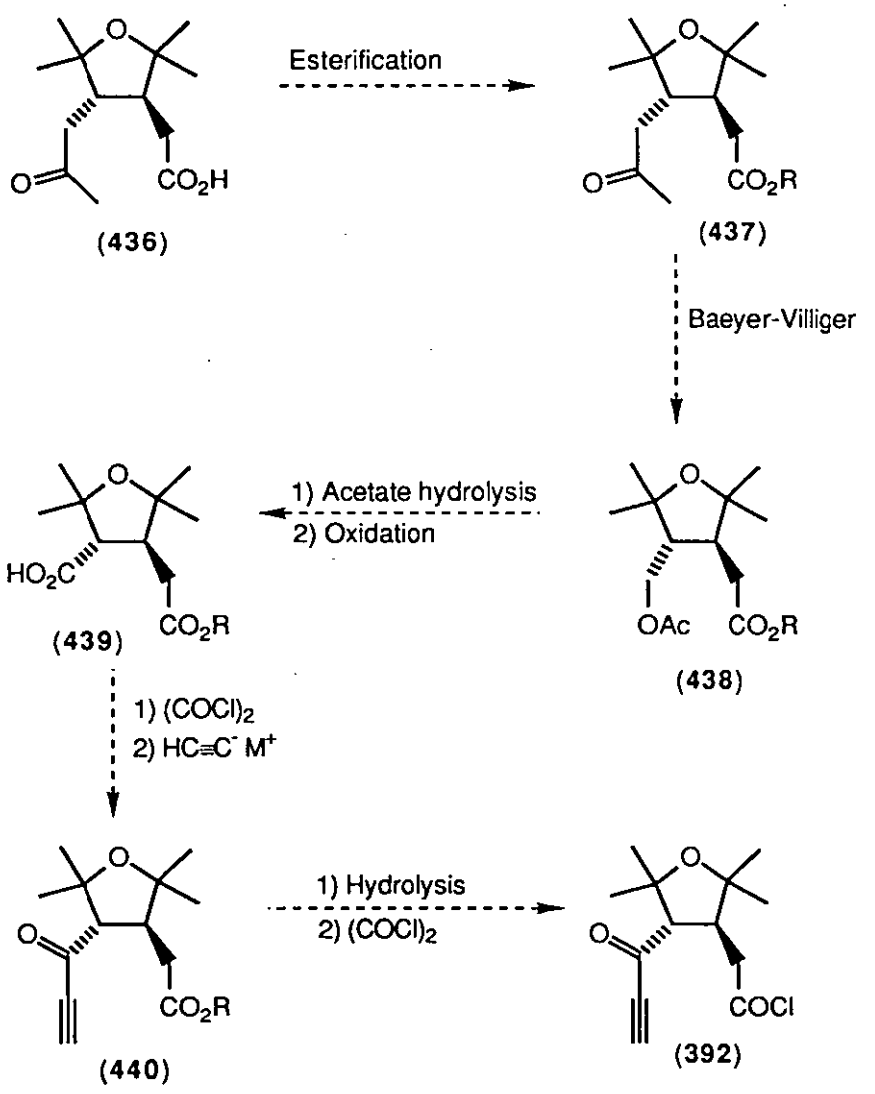
The fact that the Diels-Alder reaction with phenyl vinyl sulphoxide only went in 47% yield suggests that the more bulky pyranopyrrolone (**399**) is not likely to react satisfactorily with phenyl vinyl sulphoxide. Hence, the intramolecular Diels-Alder route is likely to produce the best results.

6.5 Tetrahydrofuran studies

Diels-Alder reaction of isoprene with diethyl fumarate gave the cyclohexene (**433**) in 97% yield. The ester groups in the cyclohexene are both equatorial hence conversion into the diol proved difficult. This result has been observed with similar systems.[118] However, heating the diester (**433**) with six equivalents of methyl magnesium iodide in refluxing ether gave the diol (**434**) in 44% yield. Heating the diol with *p*-toluenesulphonic acid resulted in cyclisation to the tetrahydrofuran (**435**) in 77% yield. Ozonolysis, followed by oxidative work-up gave the keto-acid (**436**) in 42% yield.



In order to convert the keto-acid (**436**) into the tetrahydrofuran (**392**) necessary for the acylation of the pyrrole (**393**), degradation of the ketone side chain is required. It is envisaged that this could be accomplished by esterification, of the acid, followed by Baeyer-Villiger reaction of the ketone to give the diester (**438**). Selective hydrolysis of the acetate followed by oxidation would give the acid (**439**). Conversion to the acid chloride, followed by addition of acetylide would give compound (**440**) having the correct substitution in the left hand chain. Hydrolysis of the ester functionality, followed by acid chloride formation would give the tetrahydrofuran (**392**) suitable for acylation of the pyrrole (**393**).



6.6 Conclusions

The pyrrole (**393**) has been prepared by a lengthy route. Preliminary studies have shown that the pyrrole (**393**) can be 3-acylated and the pyranopyrrolone (**430**) formed by the usual method. The pyranopyrrolone (**430**) underwent Diels-Alder reaction with DMAD and phenyl vinyl sulphoxide to give the indoles (**431**) and (**432**) respectively. Although the pyrrole (**393**) was available in multigram quantities, development of a shorter pyrrole synthesis would be useful. Further work is required on the conversion of the keto-acid (**436**) into the tetrahydrofuran (**392**), required for acylation of the pyrrole (**393**). Improvement of the Grignard and ozonolysis steps would be useful, in order to facilitate production of larger quantities of the keto-acid (**436**).

CHAPTER 7

Experimental section

7.1 General Information

Solvents and reagents.- Ether refers to diethyl ether and light petroleum refers to the petroleum fraction boiling in the range 40-60°C. Dichloromethane, ether, ethyl acetate, and light petroleum were distilled through a 36 cm Vigreux column prior to use. Ether was dried by distillation from calcium chloride and storing over sodium wire. THF and dioxan were dried by distillation from sodium-benzophenone ketyl. Benzene was dried by standing over sodium wire for several days. Toluene was dried by distillation from calcium hydride and storing over sodium wire. Dichloromethane was dried by distillation from phosphorus pentoxide. DMF and DMSO were dried by stirring over calcium hydride, distilling at reduced pressure, and storing over 4 A molecular sieves under nitrogen. Pyridine, triethylamine, and *N*-isopropylcyclohexylamine were dried by distillation from potassium hydroxide pellets and storing over potassium hydroxide under nitrogen. Boron trifluoride diethyl ether was distilled from calcium hydride at reduced pressure and stored under nitrogen. DMAD and ethyl propiolate were distilled prior to use. Unless otherwise stated all other reagents were used as supplied.

Chromatography.- Analytical TLC was carried out using Merck Kieselgel 60 F_{254} aluminium backed plates and visualised under UV light, with molybdate solution, or with Ehrlich's reagent. Column chromatography was carried out using Merck Kieselgel 60 H or Sorbsil C 60 silica.

Spectra.- Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1710 FT spectrometer or a Pye-Unicam PU 9516 spectrometer linked to an IBM computer. UV spectra were recorded on a Shimadzu UV-160 or a Philips PU 8740 UV/VIS scanning spectrophotometer. ^{1}H NMR spectra were recorded on a Jeol GSX 270 (operating at 270 MHz) or on a Bruker 250 AC (operating at 250 MHz). ^{13}C NMR spectra were recorded on a Bruker 250 AC (operating at 62.9 MHz). Mass spectra were recorded on a VG Micromass 7070B instrument, a Kratos MS80 instrument, or a VG Analytical ZAB-E instrument, in the electron impact mode at 70 eV, using a direct insertion probe. Chemical ionisation spectra were recorded using the latter instrument.

Electrochemistry.- Sets of voltammograms at a sequence of scan rates were obtained in duplicate using either Thompson Electrochem or Princeton Applied Research instrumentation. A three-electrode system was employed with 1 cm^2 platinum flag (for the data in Tables 8 and 9) or 0.5 cm diameter glassy carbon disc working electrodes. The platinum working electrode was pretreated before each set of voltammograms by anodisation, then cathodisation, for 5 min each in 0.5 M sulphuric acid at 100 mA, then washed thoroughly with de-ionised water and dried. The glassy carbon disc working electrode was polished with 2.0 μm alumina, washed with de-ionised water and dried. The reference electrode was a sodium chloride saturated calomel electrode (s.s.c.e.) with a platinum-mesh counter electrode. Solution concentrations were 1 x 10^{-3} M in freshly distilled DMF containing 0.1 M tetrabutylammonium tetrafluoroborate as supporting electrolyte. Measurements were conducted at ambient laboratory temperatures (22 ± 2°C) in solutions freed of oxygen by bubbling with solvent-saturated nitrogen.

Other information.- Melting points were determined using a Reichert Kofler hot stage apparatus or an Electrothermal digital melting point apparatus and are uncorrected.

7.2 Experimental for Chapter 2

Preparation of benzothieno[2,3-c]*pyran-3-ones*

Ethyl 2-Formylbenzothiophen-3-ylacetate (**177a**).- Tin (IV) chloride (4.5 ml, 38.3 mmol) was added dropwise to a stirred solution of ethyl benzothiophen-3-ylacetate (**171**) (4.21 g, 19.1 mmol) in dry dichloromethane (50 ml) at -10°C under nitrogen. Dichloromethyl methyl ether (2.1 ml, 23.0 mmol) was added dropwise, the mixture allowed to warm to 0°C, and stirred overnight. The mixture was poured into dilute hydrochloric acid and extracted with dichloromethane. The extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was recrystallised (dichloromethane-light petroleum) to give the *title compound* (**177a**) (1.68 g, 35%), m.p. 95-99°C (Found: C, 62.9; H, 4.8; S, 12.6. $C_{13}H_{12}O_3S$ requires C, 62.9; H, 4.9; S, 12.9%); ν_{max}(Nujol) 1 718 and 1 657 cm^{-1}; δ(270 MHz; $CDCl_3$) 10.33 (1 H, s, CHO), 7.98-7.94 (1 H, m), 7.91-7.87 (1 H, m), 7.56-7.46 (2 H, m), 4.25 (2 H, s, CH_2CO_2Et), 4.17 (2 H, q, *J* 7 Hz, ester CH_2), and 1.23 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 248 (M^+, 66%), 220 (11), 206 (56), 202 (31), 175 (100), 161 (16), and 147 (70).

2-*Formylbenzothiophen*-3-*ylacetic acid* (**178a**).- A mixture of the formyl ester (**177a**) (1.65 g, 6.67 mmol) and potassium hydroxide solution (2 M; 20 ml) in THF (18 ml) and methanol (2 ml) was stirred at room temperature for 3 h. The mixture was diluted with water (50 ml), extracted with ether, and the ether layer discarded. The aqueous layer was acidified and extracted with ether. The ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give the *title compound* (**178a**) (1.34 g, 91%), m.p. 155-160°C (Found: C, 60.0; H, 3.6; S, 14.8. $C_{11}H_8O_3S$ requires C, 60.0; H, 3.7; S, 14.6%); ν_{max}(Nujol) 1 718 and 1 624 cm^{-1}; δ[270 MHz; $(CD_3)_2CO$] 10.42 (1 H, s, CHO), 8.09 (1 H, dd, *J* 7, 1 Hz), 8.03 (1 H , dd, *J* 7, 1 Hz), 7.61-7.49 (2 H, m, 5-H + 6-H), and 4.45 (2 H, s, CH_2CO_2H); *m/z* 220 (M^+, 10%), 202 (4), 176 (100), 175 (74), and 147 (75).

Benzothieno[2,3-c]*pyran*-3-*one* (**169a**).- A solution of the formyl acid (**178a**) (69 mg, 0.31 mmol) in acetic anhydride (15 ml) was heated under reflux for 3 h. The mixture was concentrated under reduced pressure and the residue chromatographed (ether) to give the *title compound* (**169a**) (34 mg, 54%), m.p. 150-160°C (decomp.) (Found: C, 65.3; H, 3.25; S, 15.6. $C_{11}H_6O_2S$ requires C, 65.3; H, 3.0; S, 15.85%); ν_{max}(Nujol) 3 057, 1 691, and 1 624 cm^{-1}; λ_{max}(EtOH) 220 (ε 18 400), 238 (17 380), 290 (5 790), and 425 nm (2 930); δ(270 MHz; $CDCl_3$) 7.91 (1 H, d, *J* 7 Hz), 7.84 (1 H, d, *J* 1.2 Hz, 1-H), 7.61-7.53 (2 H, m), 7.41-7.35 (1 H, m), and 6.78 (1 H, d, *J* 1.5 Hz, 4-H); *m/z* 202 (M^+, 100%), 174 (54), 146 (44), and 102 (23).

Ethyl 2-*Acetylbenzothiophen*-3-*ylacetate* (**177b**).- Acetyl chloride (240 mg, 3.0 mmol) was added to a stirred solution of ethyl benzothiophen-3-ylacetate (**171**) (220 mg, 1.0 mmol) in dry dichloromethane (25 ml) at 0°C under nitrogen. Tin (IV) chloride (1 M; 6 ml) in dichloromethane was added dropwise, the mixture allowed to warm to room temperature, and stirred for 48 h. Water (25 ml) was added and the mixture stirred for 30 min. More water (50 ml) was added and the dichloromethane layer was separated, washed with brine, dried ($MgSO_4$), and evaporated. The residue was recrystallised (ether-light petroleum) to give the *title compound* (**177b**) (113 mg, 43%), m.p. 98-99°C (Found: C, 63.8; H, 5.3; S, 12.0. $C_{14}H_{14}O_3S$ requires C, 64.1; H, 5.4; S, 12.2%); ν_{max}(CCl_4) 1 741 and 1 678 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.85 (2 H, m), 7.48 (2 H, m), 4.35 (2 H, s, CH_2CO_2Et), 4.16 (2 H, q, *J* 8 Hz, ester CH_2), 2.64 (3 H, s, CH_3CO), and 1.24 (3 H, t, *J* 8 Hz, ester CH_3); *m/z* 262 (M^+, 47%), 218 (32), 216 (100), 189 (84), 188 (87), 175 (19), 147 (44), 128 (16), 115 (14), and 102 (19).

2-*Acetylbenzothiophen*-3-*ylacetic acid* (**178b**).- A mixture of the ester (**177b**) (50 mg, 0.19 mmol) and potassium hydroxide solution (2 M, 5 ml) in THF (9 mL) and methanol (1 ml) was stirred at room temperature for 3 h. The mixture was diluted with water (30 ml) and extracted with ether (25 ml). The ether extract was discarded, the water layer acidified to pH1, and extracted with ether (3 x 25 ml). The ether extracts were washed with water, brine, dried

($MgSO_4$), and evaporated to give the *title compound* (**178b**) (36 mg, 81%), m.p. 220-224°C (Found: M^+, 234.0346. $C_{12}H_{10}O_3S$ requires M, 234.0351); ν_{max}(Nujol) 1 711 and 1 666 cm^{-1}; δ[270 MHz; $(CD_3)_2CO$] 8.1-8.0 (2 H, m), 7.6-7.5 (2 H, m), 4.40 (2 H, s, CH_2CO_2H), and 2.62 (3 H, s, CH_3CO); *m/z* 234 (M^+, 21%), 216 (13), 190 (75), 175 (100), 147 (48), and 43 (66).

1-*Methylbenzothieno*[2,3-c]*pyran*-3-*one* (**169b**). *Method A*.- The keto acid (**178b**) (20 mg, 0.09 mmol) was dissolved in acetic anhydride (5 ml) and the mixture heated under reflux for 12 h. The mixture was concentrated under reduced pressure and the residue dissolved in ethyl acetate, washed with sodium hydrogen carbonate solution, brine, dried ($MgSO_4$), and evaporated to give the *title compound* (**169b**) (12 mg, 65%), identical to the sample prepared by method B (see below).

Method B.- Freshly distilled boron trifluoride diethyl ether (1 ml) was added dropwise to a stirred solution of benzothiophen-3-ylacetic acid (**176**) (710 mg, 3.7 mmol) in acetic anhydride (1 ml). The mixture was stirred at room temperature for 3 h, before being diluted with ether (25 ml). The yellow precipitate was filtered off, washed with ether, water, and ether again, and dried under vacuum to give the *title compound* (**169b**) (530 mg, 66%), m.p. 225-226°C (Found: C, 66.6; H, 3.7; S, 14.1. $C_{12}H_8O_2S$ requires C, 66.65; H, 3.7; S, 14.8%); ν_{max}(Nujol) 1 712 cm^{-1}; λ_{max}(EtOH) 221 (ε 12 510), 236 (12 460), 291 (3 250), 316 (2 150), 409 (4 950), and 430 nm (5 310); δ[270 MHz; $(CD_3)_2CO$] 8.16 (1 H, d, *J* 7.5 Hz), 7.80 (1 H, d, *J* 7.5 Hz), 7.65 (1 H, t, *J* 7.5 Hz), 7.45 (1 H, t, *J* 7.5 Hz), 6.75 (1 H, s, 4-H), and 2.42 (3 H, s, 1-Me); *m/z* 216 (M^+, 100%), 201 (3), 188 (75), 173 (4), 160 (21), 145 (26), and 115 (15).

1-*Pentylbenzothieno*[2,3-c]*pyran*-3-*one* (**169c**).- Freshly distilled boron trifluoride diethyl ether (1 ml) was added dropwise to a stirred solution of benzothiophen-3-ylacetic acid (**176**) (650 mg, 3.4 mmol) in hexanoic anhydride (2 ml) at 0°C. The mixture was warmed to room temperature and stirred for 4 h. Water (20 ml) and pyridine (1 ml) were added, the mixture

stirred for 15 min, and extracted with ether (3 x 25 ml). The combined ether extracts were washed with sodium hydrogen carbonate solution, brine, and dried ($MgSO_4$). The ether was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**169c**) (330 mg, 36%), m.p. 89-90°C (Found: C, 70.4; H, 5.9; S, 11.5. $C_{16}H_{16}O_2S$ requires C, 70.6; H, 5.9; S, 11.8); ν_{max}($CHCl_3$) 1 707 cm^{-1}; λ_{max}(EtOH) 221 (ε 16 240), 240 (18 920), 290 (6 820), 410 (4 390), and 432 nm (4 720); δ(270 MHz; $CDCl_3$) 7.89 (1 H, d, *J* 8 Hz), 7.63-7.52 (2 H, m), 7.37 (1 H, m), 6.63 (1 H, s, 4-H), 2.69 (2 H, t, *J* 7.6 Hz, allylic CH_2), 1.82 (2 H, m), 1.35 (4 H, m), and 0.90 (3 H, m, pentyl CH_3); *m/z* 272 (M^+, 94%), 244 (16), 216 (17), 201 (29), 187 (100), 173 (14), 145 (62), and 115 (22).

Diels-Alder Reactions of Benzothieno[2,3-c]*pyran*-3-*ones*

Reaction of benzothieno[2,3-c]*pyran*-3-*one* (**169a**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranone (**169a**) (59 mg, 0.29 mmol) and dimethyl acetylenedicarboxylate (83 mg, 0.58 mmol) in bromobenzene (10 ml) was heated under reflux for 5 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give *dimethyl dibenzothiophene*-2,3-*dicarboxylate* (**181a**) (69 mg, 79%), m.p. 102-104°C (Found: C, 64.0; H, 3.9; S, 10.6. $C_{16}H_{12}O_4S$ requires C, 64.0; H, 4.0; S, 10.7%); ν_{max}(Nujol) 1 736 and 1 719 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.53 (1 H, s), 8.22 (2 H, m), 7.90 (1 H, m), 7.54 (2 H, m), 3.98 (3 H, s, CO_2Me), and 3.97 (3 H, s, CO_2Me); *m/z* 300 (M^+, 81%), 269 (100), and 149 (66).

Reaction of benzothieno[2,3-c]*pyran*-3-*one* (**169a**) *with ethyl propiolate*.- A mixture of the pyranone (**169a**) (23 mg, 0.11 mmol) and ethyl propiolate (56 mg, 0.57 mmol) in bromobenzene (10 ml) was heated under reflux for 36 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a mixture of *ethyl dibenzothiophene*-2-*carboxylate* (**182a**) and *ethyl dibenzothiophene*-3-*carboxylate* (**183a**) (19 mg, 65%) in the ratio of 1 to 1, (Found: C, 70.2; H, 4.5; S, 12.2. $C_{15}H_{12}O_2S$ requires C, 70.3; H, 4.7; S, 12.5); ν_{max}(Nujol) 1 716 cm^{-1}; δ(270 MHz;

$CDCl_3$) 8.85 (1 H, d, *J* 1.7 Hz, 4-H, 3-ester), 8.57 (1 H, s, 1-H, 2-ester), 8.27-8.11 (m), 7.91-7.85 (m), 7.55-7.49 (m), 4.46 (2 H, q, *J* 7 Hz, ester CH_2, 3-ester), 4.44 (2 H, q, *J* 7 Hz, ester CH_2, 2-ester), 1.46 (3 H, t, *J* 7 Hz, ester CH_3, 3-ester), and 1.45 (3 H, t, *J* 7 Hz, ester CH_3, 2-ester); *m/z* 256 (M^+, 100%), 228 (19), 211 (82), 183 (38), and 139 (26).

Reaction of benzothieno[2,3-c]*pyran*-3-*one* (**169a**) *with ethyl* 3-*trimethylsilylpropynoate*.- A mixture of the pyranone (**169a**) (26 mg, 0.13 mmol) and ethyl 3-trimethylsilylpropynoate (44 mg, 0.26 mmol) in bromobenzene (10 ml) was heated under reflux for 36 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4) to give a mixture of ethyl 3-trimethylsilyldibenzothiophene-2-carboxylate (**188**) and ethyl 2-trimethylsilyldibenzothiophene-3-carboxylate (**189**) (29 mg, 69%) in the ratio of 6 to 1. Recrystallisation from dichloromethane-light petroleum gave pure *ethyl* 3-*trimethylsilyldibenzothiophene*-2-*carboxylate* (**188**), m.p. 151-154°C (Found: C, 65.8; H, 5.9; S, 10.0. $C_{18}H_{20}O_2SSi$ requires C, 65.8; H, 6.1; S, 9.8%); ν_{max}(Nujol) 1 708 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.57 (1 H, s), 8.46 (1 H, s), 8.23 (1 H, m), 7.89 (1 H, m), 7.53-7.49 (2 H, m), 4.43 (2 H, q, *J* 7 Hz, ester CH_2), 1.45 (3 H, t, *J* 7 Hz, ester CH_3), and 0.43 (9 H, s, Me_3Si); *m/z* 328 (M^+, 5%), 313 (92), 285 (100), and 269 (14).

Reaction of 1-*methylbenzothieno*[2,3-c]*pyran*-3-*one* (**169b**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranone (**169b**) (130 mg, 0.6 mmol) and dimethyl acetylenedicarboxylate (170 mg, 1.2 mmol) in bromobenzene (20 ml) was heated under reflux for 8 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give *dimethyl* 1-*methyldibenzothiophene*-2,3-*dicarboxylate* (**181b**) (176 mg, 93%), m.p. 147°C (Found: C, 64.7; H, 4.4; S, 10.0. $C_{17}H_{14}O_4S$ requires C, 64.95; H, 4.5; S, 10.2%); ν_{max}(Nujol) 1 725 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.65 (1 H, s, 4-H), 8.25-8.19 (1 H, m), 7.93-7.85 (1 H, m), 7.57-7.48 (2 H, m), 4.03 (3 H, s, CO_2Me), 3.97 (3 H, s, CO_2Me), and 2.57 (3 H, s, 1-Me); *m/z* 314 (M^+, 98%), 283 (100), 282 (99), 267 (17), 255 (5), 240 (10), 224 (86), and 196 (39).

Reaction of 1-*methylbenzothieno*[2,3-c]*pyran*-3-*one* (**169b**) *with ethyl propiolate*.- A mixture of the pyranone (**169b**) (110 mg, 0.5 mmol) and ethyl propiolate (250 mg, 2.5 mmol) in bromobenzene (20 ml) was heated under reflux for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a mixture of *ethyl* 1-*methyldibenzothiophene*-2-*carboxylate* (**182b**) and *ethyl* 1-*methyldibenzothiophene*-3-*carboxylate* (**183b**) (109 mg, 79%) in the ratio of 1.5 to 1, m.p. 47-53°C (Found: M^+ 270.0713. $C_{16}H_{14}O_2S$ requires *M*, 270.0714); ν_{max}(Nujol) 1 715 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.66 (1 H, s, 4-H, minor), 8.23-8.18 (1 H, m, minor), 8.16-8.11 (1 H, m, major), 8.05-7.85 (m), 7.55-7.40 (m), 4.46 (2 H, q, *J* 7 Hz, ester CH_2, minor), 4.43 (2 H, q, *J* 7 Hz, ester CH_2, major), 2.85 (3 H, s, 1-Me, major), 2.60 (3 H, s, 1-Me, minor), 1.47 (3 H, t, *J* 7 Hz, ester CH_3, minor), and 1.44 (3 H, t, *J* 7 Hz, ester CH_3, major); *m/z* 270 (M^+, 100%), 255 (4), 242 (15), 225 (71), and 197 (41).

Reaction of 1-*methylbenzothieno*[2,3-c]*pyran*-3-*one* (**169b**) *with methyl phenylpropiolate*.- A mixture of the pyranone (**169b**) (98 mg, 0.45 mmol) and methyl phenylpropiolate (180 mg, 1.13 mmol) in bromobenzene (15 ml) was heated under reflux for 6 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give (i) *methyl* 1-*methyl*-3-*phenyldibenzothiophene*-2-*carboxylate* (**184a**) (57 mg, 38%), m.p. 124-126°C (Found: C, 75.7; H, 4.8. $C_{21}H_{16}O_2S$ requires C, 75.9; H, 4.85%); ν_{max}(Nujol) 1 723 and 1 259 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.15 (1 H, d, *J* 7 Hz, 5-H), 8.01 (1 H, s, 4-H), 7.90 (1 H, d, *J* 7.5 Hz, 8-H), 7.51-7.38 (7 H, m), 3.62 (3 H, s, CO_2Me), and 2.64 (3 H, s, 1-Me); *m/z* 332 (M^+, 100%), 301 (37), 286 (6), 271 (19), and 258 (14); and (ii) *methyl* 1-*methyl*-2-*phenyldibenzothiophene*-3-*carboxylate* (**185a**) (49 mg, 33%), m.p. 129-131°C (Found: C, 75.7; H, 5.0. $C_{21}H_{16}O_2S$ requires C, 75.9; H, 4.85%); ν_{max}(Nujol) 1 727 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.56 (1 H, s, 4-H), 8.21 (1 H, m), 7.90 (1 H, m), 7.53-7.38 (6 H, m), 7.23 (1 H, m), 3.61 (3 H, s, CO_2Me), and 2.34 (3 H, s, 1-Me); *m/z* 332 (M^+, 100%), 301 (36), 286 (7), 271 (20), and 258 (11).

Reaction of 1-*methylbenzothieno*[2,3-c]*pyran*-3-*one* (**169b**) *with methyl tetrolate*.- A mixture of the pyranone (**169b**) (90 mg, 0.42 mmol) and methyl tetrolate (163 mg, 1.67 mmol) in bromobenzene (15 ml) was heated under reflux for 7 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give a mixture of *methyl* 1,3-*dimethyldibenzothiophene*-2-*carboxylate* (**186a**) and *methyl* 1,2-*dimethyldibenzothiophene*-3-*carboxylate* (**187a**) (66 mg, 59%) in the ratio of 5 to 1, m.p. 80-83°C (Found: C, 70.8; H, 5.15. $C_{16}H_{14}O_2S$ requires C, 71.1; H, 5.2%); ν_{max}(Nujol) 1 720 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.49 (1 H, s, 4-H, minor), 8.12 (m), 7.87 (m), 7.85 (1 H, s, 4-H, major), 7.45 (m), 3.98 (3 H, s, CO_2Me, major), 3.97 (3 H, s, CO_2Me, minor), 2.64 (3 H, s, minor), 2.57 (3 H, s, minor), 2.55 (3 H, s, 1-Me, major), and 2.50 (3 H, s, 3-Me, major); *m/z* 270 (M^+, 100%), 239 (36), 238 (20), 211 (22), and 210 (27).

Reaction of 1-*methylbenzothieno*[2,3-c]*pyran*-3-*one* (**169b**) *with ethyl* 3-*trimethylsilylpropynoate*.- A mixture of the pyranone (**169b**) (110 mg, 0.5 mmol) and ethyl 3-trimethylsilylpropynoate (260 mg, 1.5 mmol) in bromobenzene (20 ml) was heated under reflux for 70 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give, after recrystallisation (hexane), *ethyl* 1-*methyl*-3-*trimethylsilyldibenzothiophene*-2-*carboxylate* (**190a**) (117 mg, 67%), m.p. 101-103°C, (Found: C, 66.5; H, 6.45; S, 9.1. $C_{19}H_{22}O_2SSi$ requires C, 66.6; H, 6.5; S, 9.4%); ν_{max}(Nujol) 1 714 and 846 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.23 (1 H, s, 4-H), 8.22-8.17 (1 H, m), 7.92-7.86 (1 H, m), 7.52-7.46 (2 H, m), 4.45 (2 H, q, *J* 7.5 Hz, ester CH_2), 2.62 (3 H, s, 1-Me), 1.44 (3 H, t, *J* 7.5 Hz, ester CH_3), and 0.38 (9 H, s, Me_3Si); *m/z* 342 (M^+, 5%), 327 (99), 299 (100), 283 (11), 253 (5), 239 (6), 225 (10), 211 (10), 197 (6), 155 (9), and 149 (8).

Protodesilylation of the dibenzothiophene (**190a**).- The dibenzothiophene (**190a**) (20 mg, 0.058 mmol) was dissolved in a mixture of trifluoroacetic acid (2 ml) and water (1 ml) and heated to 70°C for 2 h. The mixture was diluted with water (30 ml) and extracted with ether. The ether extracts were

washed with sodium hydrogen carbonate solution, water, brine, dried ($MgSO_4$), and evaporated to give *ethyl 1-methyldibenzothiophene-2-carboxylate* (**182b**) (12 mg, 76%), m.p. 74-79°C (Found: M^+, 270.0718. $C_{16}H_{14}O_2S$ requires M, 270.015); ν_{max}(Nujol) 1 708 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.18 (1 H, m), 8.02 (2 H, s, 3-H + 4-H), 7.90 (1 H, m), 7.50 (2 H, m), 4.43 (2 H, q, *J* 8 Hz, ester CH_2), 2.87 (3 H, s, 1-Me), and 1.44 (3 H, t, *J* 8 Hz, ester CH_3); *m/z* 270 (M^+, 100%), 241 (16), 225 (51), 224 (23), 197 (30), and 196 (13).

Reaction of 1-methylbenzothieno[2,3-c]*pyran-3-one* (**169b**) *with methyl 4-hydroxypent-2-ynoate*.- A mixture of the pyranone (**169b**) (120 mg, 0.55 mmol) and methyl 4-hydroxypent-2-ynoate (140 mg, 1.10 mmol) in bromobenzene (20 ml) was heated under reflux for 80 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give 1,4-*dimethylfuro*[3,4-b]*dibenzothiophene-3-one* (**192a**) (68 mg, 46%), m.p. 229-231°C, (Found: M^+ 268.0557. $C_{16}H_{12}O_2S$ requires M, 268.0558); ν_{max}(Nujol) 1 750 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.22 (1 H, d, *J* 8 Hz, 9-H), 7.98 (1 H, s, 10-H), 7.93 (1 H, d, *J* 8 Hz, 6-H), 7.60-7.47 (2 H, m, 7-H +8-H), 5.63 (1 H, q, *J* 7 Hz, 1-H), 2.96 (3 H, s, 4-Me), and 1.67 (3 H, d, *J* 7 Hz, 1-Me); *m/z* 268 (M^+, 70%), 253 (60), 225 (100), and 197 (25).

Reaction of 1-methylbenzothieno[2,3-c]*pyran-3-one* (**169b**) *with benzyne*.- A mixture of the pyranone (**169b**) (76 mg, 0.35 mmol) and 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**) (136 mg, 0.70 mmol) in bromobenzene (15 ml) was heated under reflux for 12 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give, after recrystallisation (dichloromethane - light petroleum), 6-*methylbenzo*[b]*dibenzothiophene*(**194**) (34 mg, 39%), m.p. 98-101°C (Found: C, 82.35; H, 4.8. $C_{17}H_{12}S$ requires C, 82.2; H, 4.9%); ν_{max}(Nujol) 3 067, 1 456, 1 381, 878, 756, and 724 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.52 (1 H, s, 11-H), 8.26 (1 H, m), 8.12 (1 H, d, *J* 8 Hz), 8.05 (1 H, d, *J* 8 Hz), 7.85 (1 H, m), 7.59-7.47 (4 H, m), and 2.92 (3 H, s, 6-Me); *m/z* 248 (M^+, 100%) and 247 (37).

Reaction of 1-*pentylbenzothieno*[2,3-c]*pyran*-3-*one* (**169c**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranone (**169c**) (80 mg, 0.29 mmol) and dimethyl acetylenedicarboxylate (84 mg, 0.59 mmol) in bromobenzene (15 ml) was heated under reflux for 14 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *dimethyl* 1-*pentyldibenzothiophene*-2,3-*dicarboxylate* (**181c**) (74 mg, 68%), m.p. 60-61°C (Found: C, 68.4; H, 5.9; S, 8.6. $C_{21}H_{22}O_4S$ requires C, 68.1; H, 6.0; S, 8.65); $\nu_{max}(CCl_4)$ 1 730 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.66 (1 H, s, 4-H), 8.20 (1 H, m), 7.90 (1 H, m), 7.55 (2 H, m), 4.02 (3 H, s, CO_2Me), 3.98 (3 H, s, CO_2Me), 2.91 (2 H, t, *J* 8.5 Hz, benzylic CH_2), 1.80 (2 H, m), 1.40 (4 H, m), and 0.92 (3 H, t, *J* 6.5 Hz, pentyl CH_3); *m/z* 370 (M^+, 51%), 339 (35), 338 (49), 295 (100), 147 (32), 111 (45), 71 (13), and 57 (30).

Reaction of 1-*pentylbenzothieno*[2,3-c]*pyran*-3-*one* (**169c**) *with ethyl propiolate*.- A mixture of the pyranone (**169c**) (80 mg, 0.29 mmol) and ethyl propiolate (144 mg, 1.47 mmol) in bromobenzene (20 ml) was heated under reflux for 36 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a mixture of *ethyl* 1-*pentyldibenzothiophene*-2-*carboxylate* (**182c**) and *ethyl* 1-*pentyldibenzothiophene*-3-*carboxylate* (**183c**) (52 mg, 54%) in the ratio of 1 to 1, (Found: C, 73.3; H, 6.8; S, 9.9. $C_{20}H_{22}O_2S$ requires C, 73.6; H, 6.8; S, 9.8%); ν_{max}(film) 1 718 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.70 (1 H, d, *J* 2 Hz, 4-H, 3-ester), 8.23 (1 H, m), 8.15 (1 H, m), 8.00 (2 H, s, 3-H +4-H, 2-ester), 7.95 (1 H, d, *J* 2 Hz, 2-H, 3-ester), 7.90-7.85 (2 H, m), 7.55-7.45 (4 H, m), 4.50-4.40 (4 H, m, ester CH_2, both isomers), 3.25 (2 H, t, *J* 8 Hz, benzylic CH_2, 2-ester), 2.93 (2 H, t, *J* 8 Hz, benzylic CH_2, 3-ester), 1.90-1.75 (4 H, m), 1.60-1.40 (14 H, m), and 1.0-0.9 (6 H, m, pentyl CH_3, both isomers); *m/z* 326 (M^+, 100%), 281 (23), 269 (24), 241 (42), and 197 (43).

Reaction of 1-*pentylbenzothieno*[2,3-c]*pyran*-3-*one* (**169c**) *with methyl phenylpropiolate*.- A mixture of the pyranone (**169c**) (60 mg, 0.22 mmol) and methyl phenylpropiolate (90 mg, 0.55 mmol) in bromobenzene (7 ml) was

heated under reflux for 11 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give a mixture of *methyl* 1-*pentyl*-3-*phenyldibenzothiophene*-2-*carboxylate* (**184b**) and *methyl* 1-*pentyl*-2-*phenyldibenzothiophene*-3-*carboxylate* (**185b**) (60 mg, 70%) in the ratio of 1.6 to 1 (Found: C, 77.3; H, 6.3. $C_{25}H_{24}O_2S$ requires C, 77.3; H, 6.2%); $\nu_{max}(CHCl_3)$ 1 723 and 1 262 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.54 (1 H, s, 4-H, minor), 8.21 (1 H, m, minor), 8.15 (1 H, m, 5-H, major), 8.00 (1 H, s, 4-H, major), 7.89 (m), 7.52-7.40 (m), 7.20 (1 H, m, minor), 3.594 (3 H, s, CO_2Me, minor), 3.590 (3 H, s, CO_2Me, major), 2.98 (2 H, m, benzylic CH_2, major), 2.69 (2 H, m, benzylic CH_2, minor), 1.90 (2 H, m, major), 1.40 (m), 1.20 (m), 0.93 (3 H, t, *J* 7 Hz, pentyl CH_3, major), 0.80 (3 H, t, *J* 7 Hz, pentyl CH_3, minor); *m/z* 388 (M^+, 100%), 357 (10), 331 (14), 299 (22), and 271 (27).

Reaction of 1-*pentylbenzothieno*[2,3-c]*pyran*-3-*one* (**169c**) *with methyl tetrolate*.- A mixture of the pyranone (**169c**) (62 mg, 0.29 mmol) and methyl tetrolate (89 mg, 0.91 mmol) in bromobenzene (10 ml) was heated under reflux for 11 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give a mixture of *methyl* 3-*methyl*-1-*pentyldibenzothiophene*-2-*carboxylate* (**186b**) and *methyl* 2-*methyl*-1-*pentyldibenzothiophene*-3-*carboxylate* (**187b**) (25 mg, 34%) in the ratio of 6 to 1 (Found: C, 73.8; H, 7.0. $C_{20}H_{22}O_2S$ requires C, 73.6; H, 6.8%); $\nu_{max}(CHCl_3)$ 1 723 and 1 271 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.48 (1 H, s, 4-H, minor), 8.15-8.10 (m), 7.90-7.85 (m), 7.85 (1 H, s, 4-H, major), 7.5-7.4 (m), 3.96 (s, CO_2Me, both isomers), 2.95 (2 H, m, benzylic CH_2, minor), 2.85 (2 H, m, benzylic CH_2, major), 2.64 (3 H, s, 2-Me, minor), 2.45 (3 H, s, 3-Me, major), 1.8-1.7 (m), 1.5-1.3 (m), and 1.0-0.9 (m, pentyl CH_3, both isomers); *m/z* 326 (M^+, 100%), 295 (15), 269 (39), and 251 (11).

Reaction of 1-*pentylbenzothieno*[2,3-c]*pyran*-3-*one* (**169c**) *with ethyl* 3-*trimethylsilylpropynoate*.- A mixture of the pyranone (**169c**) (40 mg, 0.15 mmol) and ethyl 3-trimethylsilylpropynoate (50 mg, 0.29 mmol) in

bromobenzene (10 ml) was heated under reflux for 7 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:5)] to give *ethyl* 1-*pentyl*-3-*trimethylsilyldibenzothiophene*-2-*carboxylate* (**190b**) (34 mg, 60%) as a yellow oil, (Found: C, 69.4; H, 7.5; S, 8.1. $C_{23}H_{30}O_2SSi$ requires C, 69.3; H, 7.6; S, 8.0%); ν_{max}(film) 1 722 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.23 (1 H, s, 4-H), 8.20 (1 H, m), 7.90 (1 H, m), 7.45 (2 H, m), 4.42 (2 H, q, *J* 8 Hz, ester CH_2), 2.92 (2 H, t, *J* 8 Hz, benzylic CH_2), 1.80 (2 H, m), 1.40 (7 H, m), 0.94 (3 H, t, *J* 6 Hz, pentyl CH_3), and 0.38 (9 H, s, Me_3Si); *m/z* 398 (M^+, 8%), 383 (100), 355 (37), and 297 (16).

Reaction of 1-*pentylbenzothieno*[2,3-c]*pyran*-3-*one* (**169c**) *with methyl* 4-*hydroxypent*-2-*ynoate*.- A mixture of the pyranone (**169c**) (47 mg, 0.17 mmol) and methyl 4-hydroxypent-2-ynoate (44 mg, 0.35 mmol) in bromobenzene (10 ml) was heated under reflux for 8 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give 1-*methyl*-4-*pentylfuro*[3,4-b]*dibenzothiophene*-3-*one* (**192b**) (31 mg, 55%), m.p. 138-139°C, (Found: C, 73.8; H, 6.1; S, 9.6. $C_{20}H_{20}O_2S$ requires C, 74.0; H, 6.2; S, 9.9%); ν_{max}(Nujol) 1 744 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.18 (1 H, dd, *J* 8, 2 Hz, 9-H), 7.93 (1 H, s, 10-H), 7.88 (1 H, dd, *J* 8, 2 Hz, 6-H), 7.50 (2 H, m, 7-H + 8-H), 5.62 (1 H, q, *J* 8 Hz, 1-H), 3.38 (2 H, t, *J* 8 Hz, benzylic CH_2), 1.80 (2 H, m), 1.72 (3 H, d, *J* 8 Hz, 4-Me), 1.40 (4 H, m), and 0.90 (3 H, t, *J* 7 Hz, pentyl CH_3); *m/z* 324 (M^+, 100%), 281 (66), 268 (56), 267 (55), and 225 (33).

Preparation of benzothieno[3,2-c]*pyran*-3-*ones*

Ethyl 3-*Formylbenzothiophen*-2-*ylacetate* (**210a**).- Tin (IV) chloride (1.3 ml, 11.3 mmol) was added dropwise to a stirred solution of ethyl benzothiophen-2-ylacetate (**209**) (831 mg, 3.77 mmol) in dry dichloromethane (10 ml) at -20°C under nitrogen. Dichloromethyl methyl ether (0.41 ml, 4.52 mmol) was added dropwise, the mixture allowed to warm to 0°C, and stirred overnight. The mixture was poured into dilute hydrochloric acid and extracted with dichloromethane. The extracts were washed with water, brine, dried ($MgSO_4$),

and evaporated. The residue was chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**210a**) (713 mg, 76%) as a yellow oil (Found: C, 63.0; H, 4.85; S, 12.8. $C_{13}H_{12}O_3S$ requires C, 62.9; H, 4.9; S, 12.9%); ν_{max}(film) 3 061, 2 763, 1 739, and 1 672 cm^{-1}; δ(270 MHz; $CDCl_3$) 10.39 (1 H, s, CHO), 8.54 (1 H, d, *J* 8 Hz), 7.82 (1 H, d, *J* 7.5 Hz), 7.52-7.39 (2 H, m), 4.31 (2 H, s, CH_2CO_2Et), 4.23 (2 H, q, *J* 7 Hz, ester CH_2), and 1.29 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 248 (M^+, 72%), 220 (4), 206 (68), 202 (59), 191 (15), 175 (100), and 147 (82).

Benzothieno[3,2-c]*pyran*-3-*one* (**170a**).- A mixture of the formyl ester (**210a**) (421 mg, 1.70 mmol) and potassium hydroxide solution (2 M; 4 ml) in THF (9 ml) and methanol (1 ml) was stirred at room temperature for 3 h. The mixture was diluted with water (10 ml), extracted with ether, and the ether layer discarded. The aqueous layer was acidified and extracted with ether. The ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give 3-formylbenzothiophen-2-ylacetic acid (**211a**). The crude acid was dissolved in acetic anhydride (30 ml) and heated under reflux for 3 h. The mixture was concentrated under reduced pressure and the residue chromatographed (ether) to give the *title compound* (**170a**) (145 mg, 42%), m.p. 165°C (decomp.) (Found: M^+, 202.0087. $C_{11}H_6O_2S$ requires *M*, 202.0089); ν_{max}(Nujol) 3 062, 1 703, 1 635, and 1 536 cm^{-1}; λ_{max}(EtOH) 220 (ε 19 560), 232 (20 900), 255 (11 650), 266 (13 380), 272 (14 080), and 278 nm (11 420); δ(270 MHz; $CDCl_3$) 8.26 (1 H, d, *J* 1.5 Hz, 1-H), 7.70 (1 H, m), 7.55 (1 H, m), 7.44-7.36 (2 H, m), and 6.52 (1 H, d, *J* 1.2 Hz, 4-H); *m/z* 202 (M^+, 100%), 174 (49), 146 (42), 145 (36), and 102 (22).

Ethyl 3-*Acetylbenzothiophen*-2-*ylacetate* (**210b**).- A solution of ethyl benzothiophen-2-ylacetate (**209**) (415 mg, 1.88 mmol) in dry dichloromethane (5 ml) was added dropwise to a stirred mixture of tin (IV) chloride (0.65 ml, 5.6 mmol) and acetyl chloride (0.16 ml, 2.3 mmol) in dry dichloromethane (10 ml) under nitrogen. The mixture was stirred overnight at room temperature, diluted with water (20 ml), and extracted with dichloromethane. The dichloromethane extracts were washed with water, brine,

dried ($MgSO_4$), evaporated, and the residue chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**210b**) (228 mg, 46%) as a yellow oil (Found: C, 64.0; H, 5.4. $C_{14}H_{14}O_3S$ requires C, 64.1; H, 5.4%); ν_{max}(film) 1 739 and 1 669 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.03 (1 H, d, *J* 8 Hz), 7.81 (1 H, d, *J* 8 Hz), 7.45-7.37 (2 H, m), 4.20 (2 H, q, *J* 7 Hz, ester CH_2), 4.13 (2 H, s, CH_2CO_2Et), 2.70 (3 H, s, CH_3CO), and 1.28 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 262 (M^+, 84%), 216 (100), and 188 (71).

1-*Methylbenzothieno*[3,2-c]*pyran*-3-*one* (**170b**).- Freshly distilled boron trifluoride diethyl ether (0.25 ml) was added dropwise to a stirred solution of benzothiophen-2-ylacetic acid (**208**) (221 mg, 1.15 mmol) in acetic anhydride (0.5 ml). The mixture was stirred at room temperature for 3 h before being diluted with ether (20 ml). The precipitate was filtered off, washed with ether, sodium hydrogen carbonate solution, water, and ether again, and dried under vacuum to give the *title compound* (**170b**) (143 mg, 58%), m.p. 160-164°C (Found: M^+ 216.0239. $C_{12}H_8O_2S$ requires *M*, 216.0245); ν_{max}(Nujol) 1 708 cm^{-1}; λ_{max}(EtOH) 219 (ε 52 390), 234 (78 690), 266 (64 690), 273 (70 450), 307 (10 320), 319 (10 860), and 364 nm (11 040); δ [270 MHz; $(CD_3)_2CO$] 7.90 (1 H, m), 7.72 (1 H, m), 7.44 (2 H, m), 6.44 (1 H, d, *J* 0.7 Hz, 4-H), and 2.78 (3 H, s, 1-Me); *m/z* 216 (M^+, 100%), 201 (11), 188 (80), and 145 (35).

Diels-Alder Reactions of Benzothieno[3,2-c]*pyran*-3-*ones*

Reaction of benzothieno[3,2-c]*pyran*-3-*one* (**170a**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranone (**170a**) (12 mg, 0.06 mmol) and dimethyl acetylenedicarboxylate (17 mg, 0.12 mmol) in bromobenzene (5 ml) was heated under reflux for 7 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give *dimethyl dibenzothiophene*-2,3-*dicarboxylate* (**213a**) = (**181a**) (13 mg, 73%), identical to the previous sample.

Reaction of benzothieno[3,2-c]*pyran*-3-*one* (**170a**) *with ethyl propiolate*.- A mixture of the pyranone (**170a**) (51 mg, 0.25 mmol) and ethyl

propiolate (124 mg, 1.26 mmol) in bromobenzene (10 ml) was heated under reflux for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a mixture of *ethyl dibenzothiophene*-2-*carboxylate* (**214a**) = (**182a**) and *ethyl dibenzothiophene*-3-*carboxylate* (**215a**) = (**183a**) (48 mg, 74%) in the ratio of 1 to 1.6, m.p. 43-59°C, spectral data given previously.

Reaction of benzothieno[3,2-c]*pyran*-3-*one* (**170a**) *with ethyl* 3-*trimethylsilylpropynoate*.- A mixture of the pyranone (**170a**) (69 mg, 0.34 mmol) and ethyl 3-trimethylsilylpropynoate (174 mg, 1.02 mmol) in bromobenzene (15 ml) was heated under reflux for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give a mixture of *ethyl* 3-*trimethylsilyldibenzothiophene*-2-*carboxylate* (**220**) = (**188**) and *ethyl* 2-*trimethylsilyldibenzothiophene*-3-*carboxylate* (**221**) = (**189**) in the ratio 1 to 10, m.p. 85-87°C (Found: C, 65.7; H, 6.1; S, 9.6. $C_{18}H_{20}O_2SSi$ requires C, 65.8; H, 6.1; S, 9.8%); ν_{max}(Nujol) 1 713, 1 248, 843, and 761 cm^{-1}; δ(270 MHz; $CDCl_3$) (data for (**221**) only) 8.82 (1 H, s, 4-H), 8.23 (1 H, m, 5-H), 8.17 (1 H, s, 1-H), 7.87 (1 H, m), 7.51-7.48 (2 H, m), 4.47 (2 H, q, *J* 7 Hz, ester CH_2), 1.49 (3 H, t, *J* 7 Hz, ester CH_3), and 0.44 (9 H, s, Me_3Si); *m/z* 328 (M^+, 11%), 313 (100), and 285 (94).

Reaction of 1-*Methylbenzothieno*[3,2-c]*pyran*-3-*one* (**170b**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranone (**170b**) (183 mg, 0.85 mmol) and dimethyl acetylenedicarboxylate (241 mg, 1.69 mmol) in bromobenzene (25 ml) was heated under reflux for 9 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give *dimethyl* 4-*methyldibenzothiophene*-2,3-*dicarboxylate* (**213b**) (195 mg, 73%), m.p. 153°C (Found: C, 64.7; H, 4.4; S, 10.3. $C_{17}H_{14}O_4S$ requires C, 64.95; H, 4.5; S, 10.2%); ν_{max}(Nujol) 1 729 and 1 714 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.46 (1 H, m), 8.43 (1 H, s, 1-H), 7.93 (1 H, m), 7.54 (2 H, m), 4.02 (3 H, s, CO_2Me), 3.95 (3 H, s, CO_2Me), and 2.89 (3 H, s, 4-Me); *m/z* 314 (M^+, 100%), 283 (87), 282 (86), 224 (73), and 196 (34).

Reaction of 1-*Methylbenzothieno*[3,2-c]*pyran*-3-*one* (**170b**) *with ethyl propiolate*.- A mixture of the pyranone (**170b**) (91 mg, 0.42 mmol) and ethyl propiolate (210 mg, 2.1 mmol) in bromobenzene (15 ml) was heated under reflux for 40 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a mixture of *ethyl* 4-*methyldibenzothiophene*-2-*carboxylate* (**214b**) and *ethyl* 4-*methyldibenzothiophene*-3-*carboxylate* (**215b**) (86 mg, 76%) in the ratio of 1 to 1.9, m.p. 53-58°C, (Found: C, 71.2; H, 5.1; S, 11.7. $C_{16}H_{14}O_2S$ requires C, 71.1; H, 5.2; S, 11.9%); ν_{max}(Nujol) 3 061 and 1 713 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.51-8.48 (1 H, m, major), 8.44 (1 H, m, major), 7.94-7.88 (4 H, m, minor), 7.85 (1 H, d, *J* 8.5 Hz, major), 7.74 (1 H, dd, *J* 8, 0.5 Hz, major), 7.54-7.48 (m), 4.43 (q, *J* 7 Hz, ester CH_2, both isomers), 3.14 (3 H, s, 4-Me, major), 2.97 (3 H, s, 4-Me, minor), 1.45 (3 H, t, *J* 7 Hz, ester CH_3, minor), and 1.44 (3 H, t, *J* 7 Hz, ester CH_3, major); *m/z* 270 (M^+, 100%), 241 (12), 225 (59), 197 (36), and 149 (55).

Reaction of 1-*Methylbenzothieno*[3,2-c]*pyran*-3-*one* (**170b**) *with methyl phenylpropiolate*.- A mixture of the pyranone (**170b**) (51 mg, 0.24 mmol) and methyl phenylpropiolate (94 mg, 0.59 mmol) in bromobenzene (5 ml) was heated under reflux for 8 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give a mixture of *methyl* 4-*methyl*-3-*phenyldibenzothiophene*-2-*carboxylate* (**216**) and *methyl* 4-*methyl*-2-*phenyldibenzothiophene*-3-*carboxylate* (**217**) (52 mg, 66%) in the ratio of 1 to 3, m.p. 136-149°C (Found: C, 75.6; H, 4.85. $C_{21}H_{16}O_2S$ requires C, 75.9; H, 4.85%); ν_{max}($CHCl_3$) 1 724 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.45 (m), 8.24 (1 H, s, 1-H, minor), 7.90 (m), 7.75 (1 H, s, 1-H, major), 7.52-7.39 (m), 3.63 (3 H, s, CO_2Me, major), 3.58 (3 H, s, CO_2Me, minor), 2.94 (3 H, s, 4-Me, major), and 2.67 (3 H, s, 4-Me, minor); *m/z* 332 (M^+, 100%), 301 (39), 286 (8), 271 (23), 258 (14), and 239 (3).

Reaction of 1-*Methylbenzothieno*[3,2-c]*pyran*-3-*one* (**170b**) *with methyl tetrolate*.- A mixture of the pyranone (**170b**) (52 mg, 0.24 mmol) and methyl tetrolate (94 mg, 0.96 mmol) in bromobenzene (5 ml) was heated under

reflux for 8 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give a mixture of methyl 3,4-dimethyldibenzothiophene-2-carboxylate (**218**) and methyl 2,4-dimethyldibenzothiophene-3-carboxylate (**219**) (23 mg, 35%) in the ratio of 1 to 10. Recrystallisation (dichloromethane-light petroleum) gave pure *methyl 2,4-dimethyldibenzothiophene-3-carboxylate* (**219**), m.p. 120-123°C (Found: C, 71.15; H, 5.5. $C_{16}H_{14}O_2S$ requires C, 71.1; H, 5.2%); $\nu_{max}(CHCl_3)$ 1 724 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.35 (1 H, m), 7.87 (1 H, m), 7.58 (1 H, s, 1-H), 7.45 (2 H, m), 3.99 (3 H, s, CO_2Me), 2.84 (3 H, s), and 2.44 (3 H, s); *m/z* 270 (M^+, 100%), 255 (3), 239 (54), 238 (25), 211 (22), and 210 (23).

Reaction of 1-Methylbenzothieno[3,2-c]pyran-3-one (**170b**) *with ethyl 3-trimethylsilylpropynoate*.- A mixture of the pyranone (**170b**) (107 mg, 0.5 mmol) and ethyl 3-trimethylsilylpropynoate (170 mg, 1 mmol) in bromobenzene (15 ml) was heated under reflux for 8 days.. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give, after recrystallisation (hexane), *ethyl 4-methyl-2-trimethylsilyldibenzothiophene-3-carboxylate* (**222**) (52 mg, 31%), m.p. 97-99°C (Found: C, 66.5; H, 6.5; S, 9.4. $C_{19}H_{22}O_2SSi$ requires C, 66.6; H, 6.5; S, 9.4%); ν_{max}(Nujol) 1 719, 1 256, 1 169, and 841 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.42-8.39 (1 H, m, 5-H), 7.94 (1 H, s, 1-H), 7.92-7.89 (1 H, m), 7.52-7.47 (2 H, m), 4.45 (2 H, q, *J* 7 Hz, ester CH_2), 2.89 (3 H, s, 4-Me), 1.45 (3 H, t, *J* 7 Hz, ester CH_3), and 0.36 (9 H, s, Me_3Si); *m/z* 342 (M^+, 14%), 327 (100), 299 (98), and 283 (8).

Desulphurisation reactions

Desulphurisation of dimethyl 1-methyldibenzothiophene-2,3-dicarboxylate (**181b**).-The dibenzothiophene (**181b**) (74 mg, 0.24 mmol) was dissolved in methanol (9 ml) and tetrahydrofuran (3 ml) and the solution cooled to 0°C. Nickel (II) chloride hexahydrate (783 mg, 3.30 mmol, 14 equiv) was added followed by sodium borohydride (374 mg, 9.89 mmol, 42 equiv) in small portions. The mixture was allowed to warm to room temperature and stirred for

24 h. Further nickel (II) chloride (14 equiv) followed by sodium borohydride (42 equiv) was added and the mixture refluxed for 2 h. The mixture was filtered through Celite, evaporated, and the residue chromatographed [ether-light petroleum (1:1)] to give *dimethyl 3-methylbiphenyl-4,5-dicarboxylate* (**225**) (62 mg, 93%), m.p. 88-91°C (Found: C, 71.55; H, 5.7. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.7%); ν_{max}(Nujol) 1 740, 1 606, 1 440, 1 332, 1 272, 1 162, and 758 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.05 (1 H, d, *J* 1.5 Hz, 6-H), 7.63-7.57 (3 H, m), 7.50-7.36 (3 H, m), 3.97 (3 H, s, CO_2Me), 3.92 (3 H, s, CO_2Me), and 2.43 (3 H, s, 3-Me); *m/z* 284 (M^+, 48%), 253 (100), 252 (73), 194 (87), and 165 (43).

Desulphurisation of dimethyl 4-methyldibenzothiophene-2,3-dicarboxylate (**213b**).-The dibenzothiophene (**213b**) (55 mg, 0.18 mmol) was dissolved in methanol (9 ml) and tetrahydrofuran (3 ml) and the solution cooled to 0°C. Nickel (II) chloride hexahydrate (582 mg, 2.45 mmol, 14 equiv) was added followed by sodium borohydride (278 mg, 7.35 mmol, 42 equiv) in small portions. The mixture was allowed to warm to room temperature and stirred for 1 h. Further nickel (II) chloride (14 equiv) followed by sodium borohydride (42 equiv) was added and the mixture stirred for 5 h. The mixture was filtered through Celite, evaporated, and the residue chromatographed [ether-light petroleum (1:1)] to give *dimethyl 2-methylbiphenyl-3,4-dicarboxylate* (**227**) (41 mg, 83%), m.p. 59-60°C (Found: C, 71.65; H, 5.6. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.7%); ν_{max}(Nujol) 1 736, 1 722, 1 434, and 1 294 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.90 (1 H, d, *J* 8.5 Hz, 5-H), 7.48-7.25 (6 H, m), 3.98 (3 H, s, CO_2Me), 3.92 (3 H, s, CO_2Me), and 2.21 (3 H, s, 2-Me); *m/z* 284 (M^+, 15%), 253 (61), 252 (91), 251 (100), 166 (43), and 165 (48).

7.3 Experimental for Chapter 3

Preparation of Thieno[2,3-c]*pyran-3-ones*

Formylation of ethyl 3-thienylacetate (**234**)- To a solution of ethyl 3-thienylacetate (**234**) (2.146 g, 12.61 mmol) and tin(IV) chloride (7.38 ml, 63.03 mmol) in dry dichloromethane (40 ml) at 0°C under nitrogen was added dichloromethyl methyl ether (1.37 ml, 15.13 mmol) dropwise with stirring. The mixture was stirred overnight, acidified with dilute hydrochloric acid, and extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give a mixture of *ethyl 2-formyl-3-thienylacetate* (**235a**) and *ethyl 2-formyl-4-thienylacetate* (2.269 g, 91%) in the ratio 1 to 1, characterised as a mixture, (Found: C, 54.4; H, 5.1. $C_9H_{10}O_3S$ requires C, 54.5; H, 5.1%); ν_{max}(film) 3 094, 1 734, 1 669, and 1 190 cm^{-1}; δ(270 MHz; $CDCl_3$) 10.02 (1 H, d, *J* 0.7 Hz, CHO), 9.89 (1 H, d, *J* 1.2 Hz, CHO), 7.73 (1 H, d, *J* 1.5 Hz, 2,4-isomer), 7.69 (1 H, d, *J* 4.9 Hz, 5-H, 2,3-isomer), 7.59 (1 H, d, *J* 0.7 Hz, 2,4-isomer), 7.13 (1 H, d, *J* 4.9 Hz, 4-H, 2,3-isomer), 4.19 (2 H, q, *J* 7 Hz, ester CH_2), 4.18 (2 H, q, *J* 7 Hz, ester CH_2), 4.00 (2 H, s, CH_2CO_2Et, 2,3-isomer), 3.67 (2 H, s, CH_2CO_2Et, 2,4-isomer), 1.28 (3 H, t, *J* 7 Hz, ester CH_3), and 1.27 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 198 (M^+, 23%), 170 (20), 153 (11), 152 (7), 125 (100), and 97 (42).

2-Formyl-3-thienylacetic acid (**236a**) *and 2-Formyl-4-thienylacetic acid.*- A 1:1 mixture of ethyl 2-formyl-3-thienylacetate (**235a**) and ethyl 2-formyl-4-thienylacetate (1.98 g, 9.98 mmol) and aqueous potassium hydroxide solution (2 M; 25 ml) in tetrahydrofuran (27 ml) and methanol (3 ml) was stirred at room temperature for 2 h. The mixture was diluted with water (50 ml) and extracted with ether. The ether extract was discarded and the aqueous layer acidified and extracted with ether. The ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give *2-formyl-3-thienylacetic acid* (**236a**) and *2-formyl-4-thienylacetic acid* in the ratio 1 to 1 (1.544 g, 91%), characterised as a mixture, (Found: M^+ 170.0021.

$C_7H_6O_3S$ requires *M*, 170.0038.); ν_{max}(film) 3 200-2 400, 1 713, and 1 654 cm^{-1}; δ[270 MHz; $(CD_3)_2CO$] 10.09 (1 H, d, *J* 1 Hz, CHO), 9.94 (1 H, d, *J* 1.2 Hz, CHO), 7.93-7.91 (m, both isomers), 7.84 (1 H, s, 2,4-isomer), 7.23 (1 H, d, *J* 5.1 Hz, 4-H, 2,3-isomer), 4.12 (2 H, s, CH_2CO_2H, 2,3-isomer), and 3.76 (2 H, s, CH_2CO_2H, 2,4-isomer); *m/z* 170 (M^+, 48%), 152 (6), 142 (11), 125 (100), and 97 (56).

Thieno[2,3-c]*pyran*-3-*one* (**228a**).- To a 1:1 mixture of 2-formyl-3-thienylacetic acid (**236a**) and 2-formyl-4-thienylacetic acid (1.028 g, 6.04 mmol) and triethylamine (1.83 g, 18.13 mmol) in dry tetrahydrofuran (100 ml) at 0°C was added isobutyl chloroformate (0.99 g, 7.25 mmol) dropwise with stirring. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into brine (200 ml) and extracted with ethyl acetate. The combined organic extracts were evaporated and the residue chromatographed (ether) to give the *title compound* (**228a**) (268 mg, 29%), m.p. 110°C (darkens) (Found: C, 55.4; H 2.6. $C_7H_4O_2S$ requires C, 55.25; H, 2.65%); ν_{max}(Nujol) 3 118, 3 073, 1 765, 1 704, 1 684, 1 620, and 1 537 cm^{-1}; λ_{max}(EtOH) 219 (ε 17 120) and 400 nm (4 450); δ[270 MHz; $(CD_3)_2CO$] 8.31 (1 H, dd, *J* 1.5, 0.7 Hz, 1-H), 7.92 (1 H, d, *J* 5.6 Hz, 6-H), 6.94 (1 H, dd, *J* 5.6, 0.5 Hz, 5-H), and 6.38 (1 H, d, *J* 1.5 Hz, 4-H); *m/z* 152 (M^+, 100%), 124 (87), 96 (64), and 70 (28).

Acetylation of ethyl 3-*thienylacetate* (**234**).- Tin(IV) chloride (2.0 ml, 17 mmol) was added dropwise to a stirred solution of ethyl 3-thienylacetate (**234**) (0.965 g, 5.67 mmol) and acetyl chloride (0.48 ml, 6.80 mmol) in dry dichloromethane (30 ml) under nitrogen. The mixture was stirred overnight, poured into dilute hydrochloric acid, and extracted with ether. The combined ether extracts were washed with sodium hydrogen carbonate, water, brine, and dried ($MgSO_4$). Concentration *in vacuo* and chromatography [ether-light petroleum (3:1)] gave a 6:1 mixture of *ethyl* 2-*acetyl*-3-*thienylacetate* (**235b**) and *ethyl* 2-*acetyl*-4-*thienylacetate* (0.940 g, 78%), m.p. 42-55°C, characterised as a mixture, (Found: C, 56.2; H, 5.5; S, 15.2. $C_{10}H_{12}O_3S$ requires C, 56.6; H, 5.7; S, 15.1%); ν_{max}(Nujol) 1 732 and 1 662 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.63 (1 H, d, *J* 1.6 Hz, minor), 7.44 (1 H, d,

J 5 Hz, 5-H, major), 7.43 (1 H, d, *J* 1.6 Hz, minor), 7.05 (1 H, d, *J* 5 Hz, 4-H, major), 4.17 (2 H, q, *J* 7.5 Hz, ester CH_2, minor), 4.16 (2 H, q, *J* 7.5 Hz, ester CH_2, major), 4.04 (2 H, s, CH_2CO_2Et, major), 3.81 (2 H, s, CH_2CO_2Et, minor), 2.52 (3 H, s, CH_3CO, minor), 2.51 (3 H, s, CH_3CO, major), 1.27 (3 H, t, *J* 7.5 Hz, ester CH_3, minor), and 1.26 (3 H, t, *J* 7.5 Hz, ester CH_3, major); *m/z* 212 (M^+, 61%), 197 (10), 166 (82), 139 (100), 125 (27), 111 (13), and 97 (27).

2-Acetyl-3-thienylacetic acid (**236b**) and *2-acetyl-4-thienylacetic acid*.- A 6:1 mixture of ethyl 2-acetyl-3-thienylacetate (**235b**) and ethyl 2-acetyl-4-thienylacetate (0.754 g, 3.55 mmol) was dissolved in tetrahydrofuran-methanol (9:1; 10 ml) and potassium hydroxide solution(2 M; 5 ml) added dropwise with stirring and external cooling. The mixture was stirred at room temperature for 2 h, diluted with water, extracted with ether, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give *2-acetyl-3-thienylacetic acid* (**236b**) and *2-acetyl-4-thienylacetic acid* as a 6:1 mixture (0.490 g, 75%), m.p. 130-152°C, characterised as a mixture, (Found: C, 52.35; H, 4.3; S, 17.1. $C_8H_8O_3S$ requires C, 52.2; H, 4.4; S, 17.4%); ν_{max}(Nujol) 3 200-2 600 (br), 1 713, and 1 659 cm^{-1}; δ[270 MHz; $(CD_3)_2CO$] 7.80 (1 H, d, *J* 1.5 Hz, minor), 7.71 (1 H, d, *J* 6 Hz, 5-H, major), 7.68 (1 H, m, minor), 7.18 (1 H, d, *J* 6 Hz, 4-H, major), 4.06 (2 H, s, CH_2CO_2H, major), 3.71 (2 H, s, CH_2CO_2H, minor), 2.52 (3 H, s, CH_3CO, minor), and 2.49 (3 H, s, CH_3CO, major); *m/z* 184 (M^+, 34%), 169 (58), 141 (100), 125 (78), 97 (42), and 43 (61).

1-*Methylthieno*[2,3-c]*pyran*-3-*one* (**228b**).- A 6:1 mixture of 2-acetyl-3-thienylacetic acid (**236b**) and 2-acetyl-4-thienylacetic acid (400 mg, 2.17 mmol) in acetic anhydride (20 ml) was heated to reflux for 4 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in ether (60 ml), washed with sodium hydrogen carbonate, water, brine, dried ($MgSO_4$), and evaporated to give the *title compound* (**228b**) (278 mg, 77%), m.p. 120-125°C (decomp.) (lit.,[48] 137-141°C); ν_{max}(Nujol) 1 711, 1 689, 1 624,

and 1 557 cm^{-1}; λ_{max}(EtOH) 219 (ε 7 100), 273 (9 700), and 402 nm (1 700); δ[270 MHz; $(CD_3)_2CO$] 7.87 (1 H, d, *J* 6 Hz, 6-H), 6.92 (1 H, d, *J* 6 Hz, 5-H), 6.19 (1 H, s, 4-H), and 2.45 (3 H, s, 1-Me); *m/z* 166 (M^+, 100%), 151 (14), 138 (93), 123 (19), 110 (28), and 95 (23).

Ethyl 2-(3-*thienyl*)*propanoate* (**237a**).- n-Butyllithium (1.5 M in hexane; 4.6 ml) was added dropwise to a solution of *N*-isopropylcyclohexylamine (968 mg, 6.86 mmol) in dry tetrahydrofuran (30 ml) at -78°C under nitrogen. The mixture was allowed to warm to 0°C, stirred for 5 min, and then recooled to -78°C. Ethyl 3-thienylacetate (1.061 g, 6.23 mmol) in dry tetrahydrofuran (15 ml) was added dropwise. The mixture was allowed to warm to room temperature and added dropwise to a solution of methyl iodide (2.65 g, 18.7 mmol) in dry dimethyl sulphoxide (3 ml) under nitrogen. The resulting solution was stirred at room temperature overnight. Water (100 ml) was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue chromatographed [ether-light petroleum (1:4)] to give the *title compound* (**237a**) (963 mg, 84%) as a colourless oil (Found: C, 58.5; H, 6.6. $C_9H_{12}O_2S$ requires C, 58.7; H, 6.6%); ν_{max}(film) 3 107, 1 734, and 1 182 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.27 (1 H, dd, *J* 5, 3 Hz, 5-H), 7.12 (1 H, m, 2-H), 7.06 (1 H, dd, *J* 5, 1.3 Hz, 4-H), 4.13 (2 H, q, *J* 7 Hz, with additional fine splitting, ester CH_2), 3.82 (1 H, q, *J* 7 Hz, C*H*CO_2Et), 1.50 (3 H, d, *J* 7 Hz, C*H*$_3$CH), and 1.23 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 184 (M^+, 29%) and 111 (100).

2-(3-*Thienyl*)*propanoic acid* (**238a**).- A mixture of the ester (**237a**) (957 mg, 5.19 mmol) and aqueous potassium hydroxide solution (2 M; 25 ml) in tetrahydrofuran (27 ml) and methanol (3 ml) was stirred at room temperature for 2 h. The mixture was diluted with water (50 ml), extracted with ether, and the ether layer discarded. The aqueous layer was acidified and extracted with ether. The ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give the *title compound* (**238a**) (705 mg, 87%) as a yellow oil (Found: C, 54.0; H, 5.1. $C_7H_8O_2S$ requires C, 53.8; H, 5.2%);

ν_{max}(film) 3 400-2 400 and 1 708 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.29 (1 H, dd, *J* 5, 3 Hz, 5-H), 7.16 (1 H, m, 2-H), 7.08 (1 H, dd, *J* 5, 1.2 Hz, 4-H), 3.86 (1 H, q, *J* 7.3 Hz, C*H*CO_2H), and 1.53 (3 H, d, *J* 7.3 Hz, CH_3CH); *m/z* 156 (M^+, 35%) and 111 (100).

1,4-*Dimethylthieno*[2,3-c]*pyran*-3-*one* (**228c**).- Boron trifluoride diethyl ether (0.7 ml, 5.7 mmol) was added dropwise to a stirred solution of the acid (**238a**) (681 mg, 4.36 mmol) in acetic anhydride (1.6 ml, 17.4 mmol) at 0°C. The mixture was allowed to warm to room temperature and stirred for 3 h. Water (50 ml) was added and the mixture extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give the *title compound* (**228c**) (193 mg, 25%) as a yellow solid, m.p. 143-146°C (Found: C, 59.7; H, 4.35. $C_9H_8O_2S$ requires C, 60.0; H, 4.5%); ν_{max}(Nujol) 3 101, 1 680, 1 627, 1 559, and 781 cm^{-1}; λ_{max}(EtOH) 223 (ε 21 340) and 404 nm (7 200); δ (270 MHz; $CDCl_3$) 7.47 (1 H, d, *J* 5.6 Hz, 6-H), 6.85 (1 H, d, *J* 5.6 Hz, 5-H), 2.45 (3 H, s, 1-Me), and 2.23 (3 H, s, 4-Me); *m/z* 180 (M^+, 100%), 152 (94), 151 (83), 137 (83), and 109 (22).

Ethyl 2-(3-*thienyl*)*pentanoate* (**237b**).- n-Butyllithium (1.5 M; 3.67 ml) was added dropwise to a solution of *N*-isopropylcyclohexylamine (0.90 ml, 5.5 mmol) in dry tetrahydrofuran (20 ml) at -78°C under nitrogen. The mixture was allowed to warm to 0°C, stirred for 5 minutes and then recooled to -78°C. Ethyl 3-thienylacetate (851 mg, 5.00 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to warm to room temperature and added dropwise to a solution of n-propyl iodide (1.0 ml, 10.25 mmol) in dry DMSO (4 ml) under nitrogen. The resulting solution was stirred at room temperature overnight. Water (100 ml) was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give the *title compound* (**237b**) (908 mg, 86%) as a colourless oil (Found: C, 62.3; H, 7.7.

$C_{11}H_{16}O_2S$ requires C, 62.2; H, 7.6%); ν_{max}(film) 3 107, 2 960, 1 734, and 1 178 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.25 (1 H, dd, *J* 4.5, 3 Hz, 5-H), 7.13 (1 H, m, 2-H), 7.06 (1 H, dd, *J* 5, 1.5 Hz, 4-H), 4.19-4.07 (2 H, m, ester CH_2), 3.69 (1 H, t, *J* 7.7 Hz, $CHCO_2Et$), 2.08-1.94 (1 H, m), 1.82-1.68 (1 H, m), 1.34-1.22 (2 H, m, $CH_3CH_2CH_2$), 1.23 (3 H, t, *J* 7.1 Hz, ester CH_3), and 0.92 (3 H, t, *J* 7.2 Hz, $CH_3CH_2CH_2$); *m/z* 212 (M^+, 16%), 170 (28), 139 (30), and 97 (100).

2-(3-*Thienyl*)*pentanoic acid* (**238b**).- A mixture of the ester (**237b**) (862 mg, 4.06 mmol) and aqueous potassium hydroxide (2 M; 10 ml) in tetrahydrofuran (9 ml) and methanol (1 ml) was stirred at room temperature for 12 h. The mixture was diluted with water (50 ml), extracted with ether, and the ether layer discarded. The aqueous layer was acidified and extracted with ether. The combined ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give the *title compound* (**238b**) (635 mg, 85%) as a colourless oil (Found: C, 58.8; H, 6.8. $C_9H_{12}O_2S$ requires C, 58.7; H, 6.6%); ν_{max}(film) 3 200-2 400 and 1 708 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.28 (1 H, dd, *J* 5, 3 Hz, 5-H), 7.15 (1 H, dd, *J* 2.7, 1 Hz, 2-H), 7.07 (1 H, dd, *J* 5.1, 1.2 Hz, 4-H), 3.72 (1 H, t, *J* 7.7 Hz, $CHCO_2H$), 2.07-1.95 (1 H, m), 1.84-1.70 (1 H, m), 1.34-1.28 (2 H, m, $CH_3CH_2CH_2$), and 0.92 (3 H, t, *J* 7.3 Hz, $CH_3CH_2CH_2$); *m/z* 184 (M^+, 27%), 142 (55), and 97 (100).

1-*Methyl*-4-*propylthieno*[2,3-c]*pyran*-3-*one* (**228d**).- Boron trifluoride diethyl ether (0.55 ml) was added dropwise to a stirred solution of the acid (**238b**) (551 mg, 2.99 mmol) in acetic anhydride (1.1 ml) and ether (2 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 3 h. Water was added and the mixture extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give the *title compound* (**228d**) (189 mg, 30%), m.p. 66-72°C (Found: C, 63.6; H, 5.9. $C_{11}H_{12}O_2S$ requires C, 63.3; H, 5.8%); ν_{max}(Nujol) 3 104, 3 072, 1 690, 1 633, and 1 562 cm^{-1}; λ_{max}(EtOH) 222 (ε 26 320), 224 (26 390), and 406 nm (9 870); δ(270 MHz; $CDCl_3$) 7.46 (1 H, d, *J* 5.9 Hz, 6-

H), 6.87 (1 H, d, *J* 5.6 Hz, 5-H), 2.63 (2 H, t, *J* 7.6 Hz, $CH_3CH_2CH_2$), 2.45 (3 H, s, 1-Me), 1.67-1.58 (2 H, m, $CH_3CH_2CH_2$), and 0.96 (3 H, t, *J* 7.3 Hz, $CH_3CH_2CH_2$); *m/z* 208 (M^+, 13%), 179 (17), 153 (100), and 111 (37).

Diels-Alder reactions of Thieno[2,3-c]*pyran*-3-*ones*

Reaction of thieno[2,3-c]*pyran*-3-*one* (**228a**) *with dimethyl acetylenedicarboxylate*.- A mixture of thieno[2,3-*c*]pyran-3-one (**228a**) (58 mg, 0.38 mmol) and dimethyl acetylenedicarboxylate (108 mg, 0.76 mmol) in bromobenzene (6 ml) was heated under reflux for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *dimethyl benzothiophene*-5,6-*dicarboxylate* (**231a**) (73 mg, 77%), m.p. 74-75°C (Found: C, 57.6; H, 3.9. $C_{12}H_{10}O_4S$ requires C, 57.6; H, 4.0%); ν_{max}($CHCl_3$) 1 724 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.29 (1 H, s), 8.18 (1 H, s), 7.67 (1 H, d, *J* 5.4 Hz, 2-H), 7.43 (1 H, d, *J* 5.1 Hz, 3-H), and 3.94 (6 H, s, CO_2Me); *m/z* 250 (M^+, 55%) and 219 (100).

Reaction of thieno[2,3-c]*pyran*-3-*one* (**228a**) *with ethyl propiolate*.- A mixture of the pyranone (**228a**) (63 mg, 0.41 mmol) and ethyl propiolate (203 mg, 2.07 mmol) in bromobenzene (6 ml) was refluxed for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a mixture of *ethyl benzothiophene*-6-*carboxylate* (**232a**) and *ethyl benzothiophene*-5-*carboxylate* (**233a**) (63 mg, 74%) in the ratio 1.3 to 1, characterised as a mixture, (Found: C, 64.0; H, 5.1. $C_{11}H_{10}O_2S$ requires C, 64.1; H,4.9%); ν_{max}(film) 3 102, 1 713, and 1 278 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.62 (1 H, dd, *J* 1.5, 0.7 Hz, 7-H, 6-ester), 8.54 (1 H, s, 4-H, 5-ester), 8.05-8.00 (m, both isomers) 7.92 (1 H, d, *J* 8.3 Hz, 7-H, 5-ester), 7.86 (1 H, d, *J* 8.3 Hz, 6-ester), 7.64 (1 H, d, *J* 5.4 Hz, 2-H, 6-ester), 7.52 (1 H, d, *J*, 5.4 Hz, 2-H, 5-ester), 7.43 (1 H, d, *J* 5.6 Hz, 3-H, 5-ester), 7.39 (1 H, dd, *J* 5.6, 0.7 Hz, 3-H, 6-ester), 4.42 (q, *J* 7.1 Hz, ester CH_2, both isomers), and 1.43 (t, *J* 7.1 Hz, ester CH_3, both isomers); *m/z* 206 (M^+, 61%), 191 (6), 178 (18), 161 (100), and 133 (33).

Reaction of thieno[2,3-c]*pyran*-3-*one* (**228a**) *with ethyl* 3-*trimethylsilylpropynoate*.- A mixture of the pyranone (**228a**) (90 mg, 0.59 mmol) and ethyl 3-trimethylsilylpropynoate (302 mg, 1.77 mmol) in bromobenzene (10 ml) was refluxed for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give a mixture of *ethyl* 5-*trimethylsilylbenzothiophene*-6-*carboxylate* (**240a**) and *ethyl* 6-*trimethylsilylbenzothiophene*-5-*carboxylate* (**241a**) (95 mg, 58%) in the ratio 4 to 1, m.p. 90-91°C, characterised as a mixture, (Found: C, 60.5; H, 6.6. $C_{14}H_{18}O_2SSi$ requires C, 60.4; H, 6.5%) ν_{max}(Nujol) 3 086, 3 065, 1 703, 1 278, and 842 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.61 (1 H, s, 7-H, major), 8.52 (1 H, s, 4-H, minor), 8.18 (1 H, s, 7-H, minor), 8.13 (1 H, s, 4-H, major), 7.60 (1 H, d, *J* 5.4 Hz, 2-H, major), 7.53 (1 H, d, *J* 5.4 Hz, 2-H, minor), 7.40 (m, 3-H, both isomers), 4.41 (q, *J* 7.1 Hz, ester CH_2, both isomers), 1.44 (t, *J* 7.1 Hz, ester CH_3, both isomers), and 0.38 (s, Me_3Si, both isomers); *m/z* 278 (M^+, 2%), 263 (87), 235 (100), and 219 (15).

Protodesilylation of ethyl-5-*trimethylsilylbenzothiophene*-6-*carboxylate* (**240a**) *and ethyl*-6-*trimethylsilylbenzothiophene*-5-*carboxylate* (**241a**).- A 4:1 mixture of ethyl-5-trimethylsilylbenzothiophene-6-carboxylate (**240a**) and ethyl-6-trimethylsilylbenzothiophene-5-carboxylate (**241a**) (17 mg) was heated at 70°C for 2 h in a mixture of trifluoroacetic acid (2 ml) and water (1 ml). The mixture was diluted with water (30 ml) and extracted with ether. The ether extracts were washed with saturated aqueous sodium hydrogen carbonate solution (until the washings remained basic), water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a mixture of *ethyl benzothiophene*-6-*carboxylate* (**232a**) and *ethyl benzothiophene*-5-*carboxylate* (**233a**) (10 mg, 79%) in the ratio 4 to 1 as a colourless oil, data already given.

Reaction of 1-*methylthieno*[2,3-c]*pyran*-3-*one* (**228b**) *with ethyl* 3-*trimethylsilylpropynoate*.- A solution of the pyranone (**228b**) (66 mg, 0.4 mmol) and ethyl 3-trimethylsilylpropynoate (203 mg, 1.19 mmol) in bromobenzene (10 ml) was refluxed for 20 h. The solvent was removed and the

residue chromatographed [ether-light petroleum (1:3)] to give a 9:1 mixture of *ethyl 7-methyl-5-trimethylsilylbenzothiophene-6-carboxylate* (**240b**) and *ethyl-7-methyl-6-trimethylsilylbenzothiophene-5-carboxylate* (**241b**) (84 mg, 72%), m.p. 45-50°C, (Found C, 61.5; H, 6.9. $C_{15}H_{20}O_2SSi$ requires C, 61.6; H, 6.9); ν_{max}(Nujol) 3 090, 1 722, 1 687, 1 290, and 841 cm^{-1}; δ(270 MHz; $CDCl_3$) (major isomer) 7.91 (1 H, s, 4-H), 7.50 (1 H, d, *J* 5.4 Hz, 2-H), 7.36 (1 H, d, *J* 5.4 Hz, 3-H), 4.42 (2 H, q, *J* 7 Hz, ester CH_2), 2.61 (3 H, s, 7-Me), 1.42 (3 H, t, *J* 7 Hz, ester CH_3), and 0.34 (9 H, s, Me_3Si); *m/z* 292 (M^+, 15%), 277 (100), and 249 (93).

Protodesilylation of ethyl 7-methyl-5-trimethylsilylbenzothiophene-6-carboxylate (**240b**).- Ethyl 7-methyl-5-trimethylsilylbenzothiophene-6-carboxylate (**240b**) (22 mg, 0.075 mmol) in aqueous trifluoroacetic acid (1:2; 3 ml) was heated at 70°C for 2 h and then allowed to stand overnight. The mixture was diluted with water (30 ml) and extracted with ether. The combined ether extracts were washed with half saturated sodium hydrogen carbonate solution (until the washings remained basic) and then washed with water, brine, and dried ($MgSO_4$). Evaporation of the solvent followed by chromatography [dichloromethane - light petroleum (1:1)] gave *ethyl 7-methylbenzothiophene-6-carboxylate* (**232b**) (15 mg, 91%), m.p. 33-35°C, ν_{max}(Nujol) 1 718 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.94 (1 H, d, *J* 8.3 Hz), 7.69 (1 H, d, *J* 8.3 Hz), 7.59 (1 H, d, *J* 5.4 Hz, 2-H), 7.38 (1 H, d, *J* 5.4 Hz, 3-H), 4.39 (2 H, q, *J* 7 Hz, ester CH_2), 2.88 (3 H, s, 7-Me), and 1.43 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 220 (M^+, 96%), 191 (21), 175 (100), and 147 (50).

Reaction of 1,4-dimethylthieno[2,3-c]pyran-3-one (**228c**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranone (**228c**) (26 mg, 0.14 mmol) and dimethyl acetylenedicarboxylate (41 mg, 0.28 mmol) in bromobenzene (5 ml) was heated under reflux for 12 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *dimethyl 4,7-dimethylbenzothiophene-5,6-dicarboxylate* (**231c**) (37 mg, 92%), m.p. 66-67°C (Found: C, 60.3; H, 5.1. $C_{14}H_{14}O_4S$ requires C, 60.4; H, 5.1%); ν_{max}(Nujol) 3 088, 1 718, 1 268, and 1 212 cm^{-1}; δ(270

MHz; $CDCl_3$) 7.61 (1 H, d, *J* 5.6 Hz, 2-H), 7.50 (1 H, d, *J* 5.6 Hz, 3-H), 3.90 (6 H, s, CO_2Me), 2.65 (3 H, s), and 2.64 (3 H, s); *m/z* 278 (M^+, 54%), 247 (88), 246 (100), and 188 (73).

Reaction of 1,4-*dimethylthieno*[2,3-c]*pyran*-2-*one* (**228c**) *with ethyl propiolate*.- A mixture of the pyranone (**228c**) (36 mg, 0.20 mmol) and ethyl propiolate (98 mg, 1.00 mmol) in bromobenzene (5 ml) was heated under reflux for 12 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a mixture of *ethyl* 4,7-*dimethylbenzothiophene*-5-*carboxylate* (**232c**) and *ethyl* 4,7-*dimethylbenzothiophene*-6-*carboxylate* (**233c**) (45 mg, 96%) in the ratio of 1 to 1, (Found: C, 66.7; H, 5.8. $C_{13}H_{14}O_2S$ requires C, 66.6; H, 6.0%); ν_{max}(film) 3 082, 1 713, 1 263, 1 232, and 1 155 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.72 (1 H, s), 7.66 (1 H, s), 7.60 (1 H, d, *J*, 5.6 Hz), 7.56 (1 H, d, *J* 5.6 Hz), 7.48 (1 H, d, *J* 5.6 Hz), 7.43 (1 H, d, *J* 5.6 Hz), 4.39 (4 H, q, *J* 7.1 Hz, ester CH_2, both isomers), 2.85 (3 H, s), 2.83 (3 H, s), 2.61 (3 H, s), 2.56 (3 H, s), and 1.43 (6 H, t, *J* 7.1 Hz, ester CH_3, both isomers); *m/z* 234 (M^+, 100%), 219 (3), 205 (37), 189 (71), and 161 (40).

Reaction of 1-*methyl*-4-*propylthieno*[2,3-c]*pyran*-3-*one* (**228d**)*with dimethyl acetylenedicarboxylate*.- A mixture of the pyranone (**228d**) (41 mg, 0.2 mmol) and dimethyl acetylenedicarboxylate (56 mg, 0.39 mmol) in bromobenzene (5 ml) was refluxed for 3 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *dimethyl* 7-*methyl*-4-*propylbenzothiophene*-5,6-*dicarboxylate* (**231d**) (40 mg, 66%), m.p. 56-58°C (Found: C, 62.7; H, 5.9. $C_{16}H_{18}O_4S$ requires C, 62.7; H, 5.9%); ν_{max}(Nujol) 3 114, 1 729, 1 266, and 1 206 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.61 (1 H, d, *J* 5.6 Hz, 2-H), 7.50 (1 H, d, *J* 5.6 Hz, 3-H), 3.90 (3 H, s, CO_2Me), 3.89 (3 H, s, CO_2Me), 2.99 (2 H, t, *J* 8 Hz, benzylic CH_2), 2.64 (3 H, s, 7-Me), 1.74-1.65 (2 H, m, $CH_2CH_2CH_3$), and 0.99 (3 H, t, *J* 7.3 Hz, propyl CH_3); *m/z* 306 (M^+, 49%), 275 (68), 274 (100), and 259 (61).

Reaction of 1-*methyl*-4-*propylthieno*[2,3-c]*pyran*-3-*one* (**228d**)*with ethyl propiolate.*- A mixture of the pyranone (**228d**) (48 mg, 0.23 mmol) and ethyl propiolate (113 mg, 1.15 mmol) in bromobenzene (5 ml) was refluxed for 3 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give *ethyl 7-methyl*-4-*propylbenzothiophene*-6-*carboxylate* (**232d**) and *ethyl 7-methyl*-4-*propylbenzothiophene*-5-*carboxylate* (**233d**) (37 mg, 61%) in the ratio 1.2 to 1, characterised as a mixture, (Found: C, 68.65; H, 6.9. $C_{15}H_{18}O_2S$ requires C, 68.7; H, 6.9%); ν_{max}(film) 3 081, 2 960, 1 713, 1 260, 1 234, and 1 153 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.71 (1 H, s, 5-H, major), 7.63 (1 H, s, 6-H, minor), 7.59 (1 H, d, *J* 5.6 Hz, 2-H, major), 7.55 (1 H, d, *J* 5.6 Hz, 2-H, minor), 7.49-7.45 (m, 3-H, both isomers), 4.40 (2 H, q, *J* 7.1 Hz, ester CH_2, major), 4.39 (2 H, q, *J* 7.1 Hz, ester CH_2, minor), 3.25 (2 H, t, *J* 7.9 Hz, benzylic CH_2, minor), 2.91 (2 H, t, *J* 7.7 Hz, benzylic CH_2, major), 2.83 (3 H, s, 7-Me, major), 2.56 (3 H, d, *J* 0.7 Hz, 7-Me, minor), 1.79-1.67 (m, $CH_2CH_2CH_3$, both isomers), 1.43 (3 H, t, *J* 7.1 Hz, ester CH_3, major), 1.42 (3 H, t, *J* 7.1 Hz, ester CH_3, minor), 1.04 (3 H, t, *J* 7.1 Hz, propyl CH_3, minor), and 1.00 (3 H, t, *J* 7.3 Hz, propyl CH_3, major); *m/z* 262 (M^+, 100%), 233 (69), 217 (39), 205 (45), and 187 (29).

Reaction of 1-*pentylthieno*[2,3-c]*pyran*-3-*one* (**228e**) *with ethyl* 3-*trimethylsilylpropynoate.*- A mixture of the pyranone (**228e**)[48] (87 mg, 0.39 mmol) and ethyl 3-trimethylsilylpropynoate (200 mg, 1.18 mmol) in bromobenzene (10 ml) was refluxed for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give *ethyl*-7-*pentyl*-5-*trimethylsilylbenzothiophene*-6-*carboxylate* (**240c**) and *ethyl*-7-*pentyl*-6-*trimethylsilylbenzothiophene*-5-*carboxylate* (**241c**) as a 12:1 mixture (32 mg, 23%), (Found: M^+, 348.1579. $C_{19}H_{28}O_2SSi$ requires *M*, 348.1579); ν_{max}(film) 1 723, 1 261, and 842 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.90 (1 H, s, 4-H), 7.48 (1 H, d, *J* 5.4 Hz, 2-H), 7.34 (1 H, d, *J* 5.4 Hz, 3-H), 4.40 (2 H, q, *J* 7 Hz, ester CH_2), 2.92 (2 H, m, benzylic CH_2), 1.77 (2 H, m), 1.35-1.45 (7 H, m), 0.90 (3 H, t, *J* 7 Hz, pentyl CH_3), and 0.33 (9 H, s, Me_3Si); *m/z* 348 (M^+, 10%), 333 (100), 319 (2), 305 (36), and 295 (14).

Acylation of ethyl 3-*thienylacetate* (**234**) *with hex*-5-*ynoyl chloride*.- Oxalyl chloride (0.63 ml, 7.25 mmol) and hex-5-ynoic acid (0.541 g, 4.83 mmol) in dry ether (20 ml) were stirred at room temperature overnight, concentrated *in vacuo*, dissolved in dry dichloromethane (25 ml), and added to anhydrous zinc chloride (1.97 g, 14.49 mmol). Ethyl 3-thienylacetate (0.766 g, 4.50 mmol) in dry dichloromethane (5 ml) was added and the mixture stirred at room temperature overnight. The reaction mixture was poured into dilute hydrochloric acid and extracted with ether. The combined ether extracts were washed with dilute aqueous sodium hydrogen carbonate solution, brine, dried ($MgSO_4$), evaporated, and the residue chromatographed [ether-light petroleum(3:1)] to give a 5:1 mixture of *ethyl* 2-*hex*-5-*ynoyl*-3-*thienylacetate* (**242**) and *ethyl* 2-*hex*-5-*ynoyl*-4-*thienylacetate* (0.51 g, 43%), m.p. 45-52°C (Found: C, 63.4; H, 6.2; S, 11.9. $C_{14}H_{16}O_3S$ requires C, 63.6; H, 6.1; S, 12.1%); ν_{max}(Nujol) 3 266, 3 111, 3 082, 1 728, 1 687, 1 647, and 1 524 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.68 (1 H, d, *J* 1.5 Hz, 5-H, minor), 7.45 (1 H, d, *J* 6 Hz, 5-H, major), 7.44 (1 H, d, *J* 1.5 Hz, 3-H, minor), 7.07 (1 H, d, *J* 6 Hz, 4-H, major), 4.17 (2 H, q, *J* 7 Hz, ester CH_2, minor), 4.16 (2 H, q, *J* 7 Hz, ester CH_2, major), 4.05 (2 H, s, CH_2CO_2Et, major), 3.63 (2 H, s, CH_2CO_2Et, minor), 3.04 (2 H, t, *J* 8 Hz, CH_2CO, minor), 3.01 (2 H, t, *J* 8 Hz, CH_2CO, major), 2.29 (m, propargylic CH_2, both isomers), 1.94 (m, acetylenic CH + CH_2CH_2CO, both isomers), 1.27 (3 H, t, *J* 7 Hz, ester CH_3, minor), and 1.25 (3 H, t, *J* 7 Hz, ester CH_3, major); *m/z* 264 (M^+, 4%), 219 (45), 212 (60), 197 (12), 190 (29), 177 (37), 166 (81), 151 (16), and 141 (100).

2-*Hex*-5-*ynoyl*-3-*thienylacetic acid* (**243**).- The mixture of ethyl 2-hex-5-ynoyl-3-thienylacetate (**242**) and ethyl 2-hex-5-ynoyl-4-thienylacetate (0.202 g, 0.77 mmol) was dissolved in tetrahydrofuran-methanol (9:1; 10 ml) and potassium hydroxide solution (2 M; 5 ml) was added dropwise, with external cooling, to the stirred solution. When the addition was complete, the mixture was stirred at room temperature for 2 h, diluted with water (50 ml), extracted with ether, and this extract discarded. The aqueous phase was acidified with dilute

hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give a 5:1 mixture of 2-hex-5-ynoyl-3-thienylacetic acid (**243**) and 2-hex-5-ynoyl-4-thienylacetic acid (0.149 g, 82%). Recrystallisation from ether gave the *title compound* (**243**) (119 mg, 66%), m.p. 95-97°C (Found: C, 60.85; H, 5.1. $C_{12}H_{12}O_3S$ requires C, 61.0; H, 5.1%); ν_{max}(Nujol) 3 278, 3 103, 1 708, 1 666, and 1 526 cm^{-1}; δ[270 MHz; $(CD_3)_2CO$] 7.71 (1 H, d, *J* 6 Hz, 5-H), 7.18 (1 H, d, *J* 6 Hz, 4-H), 4.06 (2 H, s, CH_2CO_2H), 3.02 (2 H, t, *J* 7.5 Hz, CH_2CO), 2.37 (1 H, t, *J* 3 Hz, acetylenic CH), 2.28 (2 H, td, *J* 7.5, 3 Hz, propargylic CH_2), and 1.88 (2 H, quintet, *J* 7 Hz, CH_2CH_2CO); *m/z* 237 (MH^+, 3%), 236 (M^+, 1%), 218 ($M-H_2O$, 2%), 184 (40) 177 (23), 169 (9), 166 (26), 141 (100), 138 (21), and 125 (16).

7,8-*Dihydroindeno*[4,5-b]*thiophene* (**245**).- 2-Hex-5-ynoyl-3-thienylacetic acid (**243**) (100 mg, 0.42 mmol) was refluxed in acetic anhydride (20 ml) under nitrogen for 5 h. The mixture was concentrated and the residue chromatographed [ether-light petroleum (1:3)] to give the *title compound* (**245**) (57 mg, 77%) as a colourless oil, (Found: C, 75.9; H, 6.0; S, 18.1. $C_{11}H_{10}S$ requires C, 75.8; H, 5.8; S, 18.4%); ν_{max}(film) 3 053, 2 953, 2 842, 1 592, 1 571, 1 459, and 1 437 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.64 (1 H, d, *J* 8 Hz, 4-H), 7.37 (2 H, m, 2-H +3-H), 7.29 (1 H, d, *J* 8 Hz, 5-H), 3.12 (2 H, t, *J* 7 Hz, benzylic CH_2), 3.11 (2 H, t, *J* 7 Hz, benzylic CH_2), and 2.25 (2 H, quintet, *J* 7 Hz, $CH_2CH_2CH_2$); *m/z* 174 (M^+, 100%), 173 (71), 171 (16), 147 (7), 129 (11), 115 (3), 86 (6), 74 (3), and 45 (6).

5-*Iodopent*-1-*yne* (**247**).- A mixture of 5-chloropent-1-yne (850 mg, 8.29 mmol) and sodium iodide (6.2 g, 41.44 mmol) in methyl ethyl ketone (30 ml) was refluxed for 15 h. After cooling, the mixture was filtered. The filtrate was diluted with water and extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated to give the *title compound* (**247**) (1.182 g, 73%) sufficiently pure for use without further purification, ν_{max}(film) 3 296, 2 119, 1 428, 1 222, and 641 cm^{-1}; δ(270 MHz; $CDCl_3$) 3.32 (2 H, t, *J* 6.7 Hz, CH_2I), 2.34 (2 H, td, *J* 6.6, 2.7 Hz, propargylic CH_2), 2.05-1.96 (2 H, m, CH_2CH_2I), and 1.99 (1

H, t, *J* 2.7 Hz, acetylenic CH); *m/z* 194 (M^+, 61%), 169 (12), 127 (11), and 67 (100).

Ethyl 2-(3-*thienyl*)*hept*-6-*ynoate* (**250a**).- n-Butyllithium (1.5 M; 2.60 ml) was added dropwise to a solution of *N*-isopropylcyclohexylamine (0.64 ml, 3.90 mmol) in dry tetrahydrofuran (20 ml) at -78°C under nitrogen. The mixture was allowed to warm to 0°C, stirred for 5 min, and then recooled to -78°C. Ethyl 3-thienylacetate (604 mg, 3.55 mmol) in dry tetrahydrofuran (5 ml) was added dropwise. The mixture was warmed to room temperature and added dropwise to a solution of 5-iodopent-1-yne (1.15 g, 5.93 mmol) in dry DMSO (4 ml) under nitrogen. The resulting solution was stirred overnight. Water (100 ml) was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give the *title compound* (**250a**) (0.639 g, 76%) as a colourless oil, (Found: C, 66.0; H, 6.9. $C_{13}H_{16}O_2S$ requires C, 66.1; H, 6.8%); ν_{max}(film) 3 293, 3 105, 2 953, 2 117, 1 732, and 1 152 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.27 (1 H, dd, *J* 4.6, 2.7 Hz, 5-H), 7.14 (1 H, m, 2-H), 7.06 (1 H, dd, *J* 4.9, 1.2 Hz, 4-H), 4.20-4.08 (2 H, m, ester CH_2), 3.69 (1 H, t, *J* 7.7 Hz, C*H*CO_2Et), 2.20 (2 H, td, *J* 7.1, 2.7 Hz, propargylic CH_2), 2.16-2.06 (1 H, m), 1.95 (1 H, t, *J* 2.7 Hz, acetylenic CH), 1.95-1.87 (1 H, m), 1.54-1.47 (2 H, m, C≡CCH_2CH_2), and 1.23 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 236 (M^+, 8%), 163 (96), and 97 (100).

2-(3-*Thienyl*)*hept*-6-*ynoic acid* (**251a**).- A mixture of ethyl 2-(3-thienyl)hept-6-ynoate (**250a**) (551 mg, 2.33 mmol) and aqueous potassium hydroxide solution (2 M; 10 ml) in tetrahydrofuran (9 ml) and methanol (1 ml) was stirred at room temperature for 24 h. The mixture was diluted with water (50 ml), extracted with ether, and the ether layer discarded. The aqueous layer was acidified and extracted with ether. The ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give the *title compound* (**251a**) (456 mg, 94%) as a colourless oil, (Found: C, 63.7; H, 6.0. $C_{11}H_{12}O_2S$ requires C, 63.4; H, 5.8%); ν_{max}(film) 3 295, 3 200-2 400, 2 117, and 1 708 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.29 (1 H, dd, *J* 5,3 Hz, 5-H),

7.17 (1 H, dd, *J* 3, 1 Hz, 2-H), 7.07 (1 H, dd, *J* 5, 1.3 Hz, 4-H), 3.73 (1 H, t, *J* 7.7 Hz, C*H*CO_2H), 2.20 (2 H, td, *J* 6.8, 2.7 Hz, propargylic CH_2), 2.17-2.11 (1 H, m), 1.98-1.92 (1 H, m), 1.95 (1 H, t, *J* 2.7 Hz, acetylenic CH), and 1.56-1.49 (2 H, m, C≡CCH_2CH_2); *m/z* 208 (M^+, 17%), 163 (100), and 97 (96).

1-*Methyl*-4-(*pent*-1-*yn*-5-*yl*)*thieno*[2,3-c]*pyran*-3-*one* (**252a**).- Boron trifluoride diethyl ether (0.35 ml) was added dropwise to a stirred solution of the acid (**251a**) (382 mg, 1.83 mmol) in acetic anhydride (0.7 ml) and ether (1 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 3 h. Water was added and the mixture extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed.[ether-light petroleum (4:1)] to give the *title compound* (**252a**) (96 mg, 23%), m.p. 90-92°C (Found: C, 67.5; H, 5.2. $C_{13}H_{12}O_2S$ requires C, 67.2; H, 5.2%) ν_{max}(Nujol) 3 251, 3 227, 3 105, 3 081, 2 111, 1 679, 1 633, and 1 557 cm^{-1}; λ_{max}(EtOH) 223 (ε 26 050) and 407 nm (10 210); δ(270 MHz; $CDCl_3$) 7.49 (1 H, d, *J* 5.9 Hz, 6-H), 6.97 (1 H, d, *J* 5.6 Hz, 5-H), 2.79 (2 H, t, *J* 7.5 Hz, allylic CH_2), 2.46 (3 H, s, 1-Me), 2.23 (2 H, td, *J* 6.9, 2.7 Hz, propargylic CH_2), 2.00 (1 H, t, *J* 2.7 Hz, acetylenic CH), and 1.84 (2 H, quintet, *J* 7 Hz, C≡CCH_2CH_2); *m/z* 232 (M^+, 2%), 188 (100), 187 (46), and 173 (53).

4-*Methyl*-6,7-*dihydroindeno*[5,4-b]*thiophene* (**253a**).- A solution of the pyranone (**252a**) (35 mg, 0.15 mmol) in bromobenzene (10 ml) was refluxed for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give the *title compound* (**253a**) (23 mg, 81%), m.p. 30-32°C (Found: M^+, 188.0660. $C_{12}H_{12}S$ requires *M*, 188.0660); ν_{max}(Nujol) 3 100, 3 016, 1 448, 861, 760, and 692 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.44 (1 H, d, *J* 5:4 Hz, 2-H), 7.30 (1 H, d, *J* 5.6 Hz, 3-H), 7.08 (1 H, s, 6-H), 3.14 (2 H, t, *J* 7.4 Hz, benzylic CH_2), 3.02 (2 H, t, *J* 7.3 Hz, benzylic CH_2), 2.55 (3 H, s, 7-Me), and 2.20 (2 H, quintet, *J* 7.5 Hz, $CH_2C\mathit{H}_2CH_2$); *m/z* 188 (M^+, 100%), 187 (46), and 173 (52).

6-(p-*Toluenesulphonyloxy)hex*-1-*yne* (**248**).- A mixture of hex-5-yn-1-ol (681 mg, 6.94 mmol) and tosyl chloride (2.65 g, 13.88 mmol) in pyridine (5 ml) was stirred at 0°C for 6 h. Water was added and the mixture extracted with ether. The combined ether extracts were washed with saturated aqueous copper(II) sulphate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated to give the *title compound* (**248**) (1.715 g, 98%) as a colourless oil, sufficiently pure for use without further purification, ν_{max}(film) 3 294, 1 359, 1 190, and 1 176 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.79 (2 H, d, *J* 8.3 Hz, 2-H),7.35 (2 H, d, *J* 8.5 Hz, 3-H), 4.06 (2 H, t, *J* 6.2 Hz, CH_2O), 2.45 (3 H, s, 4-Me), 2.17 (2 H, td, *J* 6.8, 2.7 Hz, propargylic CH_2), 1.92 (1 H, t, *J* 2.7 Hz, acetylenic CH), 1.81-1.75 (2 H, m), and 1.58-1.53 (2 H, m); *m/z* 252 (M^+, 0.2%), 155 (50), and 91 (100).

6-*Iodohex*-1-*yne* (**249**).- A mixture of 6-(*p*-toluenesulphonyloxy)hex-1-yne (1.63 g, 6.46 mmol) and sodium iodide (1.94 g, 12.94 mmol) in acetone (20 ml) was stirred at room temperature for 24 h. Water was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give the *title compound* (1.201 g, 89%) as a colourless liquid, ν_{max}(film) 3 297, 2 118, 1 213 and 640 cm^{-1}; δ(270 MHz; $CDCl_3$) 3.21 (2 H, t, *J* 6.8 Hz, CH_2I), 2.23 (2 H, td, *J* 6.8, 2.7 Hz, propargylic CH_2), 1.98-1.90 (3 H,m), and 1.64 (2 H, quintet, *J* 7.4 Hz); *m/z* 208 (M^+, 9%), 127 (6), and 81 (100).

Ethyl 2-(3-*thienyl*)*oct*-7-*ynoate* (**250b**).- n-Butyllithium (1.5 M; 1.75 ml) was added dropwise to a solution of *N*-isopropylcyclohexylamine (0.43 ml, 2.61 mmol) in dry tetrahydrofuran (15 ml) under nitrogen at -78°C. The mixture was allowed to warm to 0°C, stirred for 5 min, and recooled to -78°C. A solution of ethyl 3-thienylacetate (404 mg, 2.37 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to warm to room temperature and added to a solution of 6-iodohex-1-yne (1.0 g, 4.8 mmol) in dry DMSO (4 ml) under nitrogen. The mixture was stirred overnight. Water was added and the resulting mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was

evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give the *title compound* (**250b**) (404 mg, 68%) as a colourless oil, (Found: M^+, 250.1028. $C_{14}H_{18}O_2S$ requires M, 250.1028); ν_{max}(film) 3 295, 3 105, 2 117, and 1 733 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.27 (1 H, dd, *J* 5.2, 2.6 Hz, 5-H), 7.13 (1 H, m, 2-H), 7.06 (1 H, dd, *J* 5.0, 1.3 Hz, 4-H), 4.14 (2 H, m, ester CH_2), 3.68 (1 H, t, *J* 7.6 Hz, $CHCO_2Et$), 2.17 (2 H, td, *J* 7, 2.7 Hz, propargylic CH_2), 2.14-2.00 (1 H, m), 1.92 (1 H, t, *J* 2.7 Hz, acetylenic CH), 1.91-1.75 (1 H, m), 1.58-1.49 (2 H, m), 1.44-1.33 (2 H, m), and 1.23 (3 H, t, *J* 7.2 Hz, ester CH_3); *m/z* 250 (M^+, 4%), 177 (20), 170 (24), and 97 (100).

2-(3-*Thienyl*)*oct*-7-*ynoic acid* (**251b**).- A mixture of ethyl 2-(3-thienyl)oct-7-ynoate (**250b**) (360 mg, 1.44 mmol) and aqueous potassium hydroxide solution (2 M; 10 ml) in tetrahydrofuran (9 ml) and methanol (1 ml) was stirred at room temperature for 24 h. The mixture was diluted with water (30 ml), extracted with ether, and the ether layer discarded. The aqueous layer was acidified and extracted with ether. The combined ether extracts were washed with water, brine, dried ($MgSO_4$), and evaporated to give the *title compound* (**251b**) (299 mg, 93%), m.p. 62-64°C (Found: C, 64.9; H, 6.35. $C_{12}H_{14}O_2S$ requires C, 64.8; H, 6.35%); ν_{max}(Nujol) 3 300-2 400, 3 295, 2 117, and 1 708 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.29 (1 H, dd, *J* 4.9, 2.9 Hz, 5-H), 7.16 (1 H, m, 2-H), 7.07 (1 H, dd, *J* 4.9, 1.3 Hz, 4-H), 3.71 (1 H, t, *J* 7.8 Hz, $CHCO_2H$), 2.17 (2 H, td, *J* 6.8, 2.7 Hz, propargylic CH_2), 2.10-2.01 (1 H, m), 1.92 (1 H, t, *J* 2.7 Hz, acetylenic CH), 1.85-1.77 (1 H, m), 1.58-1.49 (2 H, m), and 1.44-1.36 (2 H, m); *m/z* 222 (M^+, 12%), 177 (31), 142 (47), and 97 (100).

4-(*Hex*-1-*yn*-6-*yl*)-1-*methylthieno*[2,3-c]*pyran*-3-*one* (**252b**).- Boron trifluoride diethyl ether (0.19 ml, 1.54 mmol) was added dropwise to a stirred solution of 2-(3-thienyl)oct-7-ynoic acid (**251b**) (263 mg, 1.18 mmol) in acetic anhydride (0.45 ml, 4.77 mmol) at 0°C. The mixture was allowed to warm to room temperature and stirred for 3 h. Water was added and the mixture extracted with ether. The combined ether extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water, brine, and dried

($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give the *title compound* (**252b**) (30 mg, 10%), m.p. 105-109°C (Found: C, 68.2; H, 5.8. $C_{14}H_{14}O_2S$ requires C, 68.3; H, 5.7%); ν_{max}(Nujol) 3 243, 1 677, 1 632, and 1 558 cm^{-1}; λ_{max}(EtOH) 223 (ε 23 050) and 406 nm (8 480); δ(270 MHz; $CDCl_3$) 7.48 (1 H, d, *J* 5.9 Hz, 6-H), 6.88 (1 H, d, *J* 5.6 Hz, 5-H), 2.67 (2 H, t, *J* 7.1 Hz, allylic CH_2), 2.45 (3 H, s, 1-Me), 2.23 (2 H, td, *J* 6.8, 2.6 Hz, propargylic CH_2), 1.93 (1 H, t, *J* 2.6 Hz, acetylenic CH), 1.73-1.69 (2 H, m), and 1.62-1.56 (2 H, m); *m/z* 246 (M^+, 26%), 179 (48), 151 (100), and 43 (85).

4-*Methyl*-6,7,8,9-*tetrahydronaphtho*[2,1-b]*thiophene* (**253b**).- A solution of the pyranone (**252b**) (24 mg, 0.097 mmol) in bromobenzene (10 ml) was refluxed for 2 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give the *title compound* (**253b**) (14 mg, 71%), m.p. 32-33°C (Found: C, 76.9; H, 7.3. $C_{13}H_{14}S$ requires C, 77.2; H, 7.0%); ν_{max}(Nujol) 3 098, 1 444, 758, and 688 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.43 (1 H, d, *J* 5.6 Hz, 2-H), 7.38 (1 H, d, *J* 5.6 Hz, 3-H), 6.91 (1 H, s, 6-H), 3.02 (2 H, t, *J* 6 Hz, benzylic CH_2), 2.86 (2 H, t, *J* 5.9 Hz, benzylic CH_2), 2.52 (3 H, s, 7-Me), and 1.93-1.84 (4 H, m, $CH_2CH_2CH_2CH_2$); *m/z* 202 (M^+, 100%), 187 (30), and 174 (61).

Investigation of alternative routes to thieno[2,3-c]*pyran*-3-*ones*

N-*t-Butyl*-3-*thienylacetamide* (**254**).- Oxalyl chloride (5 ml) was added to a suspension of 3-thienylacetic acid (2.115 g, 14.88 mmol) in dry benzene (5 ml) and the mixture stirred until effervescence ceased. The solution was evaporated under reduced pressure and the residue dissolved in dry benzene (10 ml). This solution was added to a stirred solution of t-butylamine (5 ml, 47.5 mmol) in dry benzene (50 ml) at 0°C. The mixture was stirred at room temperature for 1 h, poured into water, and extracted with ether. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue recrystallised (light petroleum) to give the *title compound* (**254**) (2.77 g, 94%), m.p. 107-108°C (Found: C, 60.95; H, 7.75; N, 7.1. $C_{10}H_{15}NOS$ requires C, 60.9; H, 7.7; N, 7.1%); ν_{max}(Nujol) 3 304,

3 077, 1 646, and 1 557 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.32 (1 H, dd, *J* 4.9, 2.9 Hz, 5-H), 7.11 (1 H, m, 2-H), 6.99 (1 H, dd, *J* 5.0, 1.3 Hz, 4-H), 5.3-5.2 (1 H, br, NH), 3.50 (2 H, s, $CH_2CONHBu^t$), and 1.29 (9 H, s, t-Bu); *m/z* 197 (M^+, 4%), 98 (87), 97 (45), and 57 (100).

N-*t-Butyl*-2-*formyl*-3-*thienylacetamide* (**255**).- To a solution of the amide (**254**) (337 mg, 1.71 mmol) in dry tetrahydrofuran (10 ml) at -78°C under nitrogen was added n-butyllithium (1.5 M, 2.50 ml) dropwise with stirring. The mixture was allowed to warm to room temperature, dimethylformamide (125 mg, 1.71 mmol) added, and the mixture stirred overnight. The reaction was quenched with ice and dilute hydrochloric acid and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the crude product (185 mg, 48%). Recrystallisation (dichloromethane-light petroleum) gave the *title compound* (**255**) (140 mg, 36%), m.p. 130-133°C (Found: C, 58.5; H, 6.9; N, 6.15. $C_{11}H_{15}NO_2S$ requires C, 58.6; H, 6.7; N, 6.2%); ν_{max}(Nujol) 3 300, 1 663, 1 644, and 1 553 cm^{-1}; δ(270 MHz; $CDCl_3$) 9.92 (1 H, s, CHO), 7.72 (1 H, d, *J* 4.9 Hz, 5-H), 7.19 (1 H, d, *J* 5.1 Hz, 4-H), 6.0 (1 H, br, NH), 3.81 (2 H, s, $CH_2CONHBu^t$), and 1.30 (9 H, s, t-Bu); *m/z* 225 (M^+, 3%), 153 (6), 126 (100), and 97 (7).

N-*t-Butyl*-2-*trimethylsilyl*-3-*thienylacetamide* (**256**).- n-Butyllithium (1.55 M, 4.22 ml) was added dropwise to a solution of the amide (**254**) (587 mg, 2.98 mmol) in dry tetrahydrofuran (15 ml) under nitrogen at -78°C. The mixture was stirred for 1.5 h, trimethylsilyl chloride (0.76 ml, 5.96 mmol) was added, and the mixture allowed to warm to room temperature. After stirring overnight, saturated ammonium chloride solution was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**256**) (699 mg, 87%), m.p. 129-132°C (Found: C, 57.9; H, 8.7; N, 5.3. $C_{13}H_{23}NOSSi$ requires C, 57.9; H, 8.6; N, 5.2%); ν_{max}(Nujol) 3 274, 3 079, 1 650, 1 562, and 841 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.55 (1 H, d, *J* 4.6 Hz, 5-

H), 7.05 (1 H, d, *J* 4.6 Hz, 4-H), 5.1 (1 H, br, NH), 3.59 (2 H, s, $CH_2CONHBu^t$), 1.25 (9 H, s, t-Bu), and 0.35 (9 H, s, Me_3Si); *m/z* 269 (M^+, 1%), 254 (96), 198 (100), 169 (43), 155 (43), 73 (51), and 57 (89).

Reaction of N-*t-butyl*-2-*trimethylsilyl*-3-*thienylacetamide* (**256**) *with acetyl chloride.*- A mixture of acetyl chloride (15 mg, 0.19 mmol) and aluminium chloride (119 mg, 0.89 mmol) in dry dichloromethane (5 ml) was stirred for 10 minutes. The amide (**256**) (40 mg, 0.15 mmol) was added and the mixture stirred overnight. Water was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed to give (a) N-*t-butyl*-5-*acetyl*-2-*trimethylsilyl*-3-*thienylacetamide* (**258**) (17 mg, 37%), m.p. 144-149°C [Found: MH^+ (CI, NH_3), 312.1454. $C_{15}H_{25}NO_2SSi$ requires *M*H, 312.1454); ν_{max}(Nujol) 3 279, 3 075, 1 666, 1 645, 1 556, and 842 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.63 (1 H, s, 4-H), 5.1 (1 H, br, NH), 3.55 (2 H, s, $CH_2CONHBu^t$), 2.55 (3 H, s, CH_3CO), 1.30 (9 H, s, t-Bu), and 0.37 (9 H, s, Me_3Si); *m/z* 311 (M^+, 0.1%), 269 (45), 240 (59), 212 (41), 140 (100), 125 (72), and 57 (72); and (b) N-*t-butyl*-2-*acetyl*-4-*thienylacetamide* (**259**) (15 mg, 42%), m.p. 103-107°C (Found: C, 60.4; H, 7.3; N, 5.9. $C_{12}H_{17}NO_2S$ requires C, 60.2; H, 7.2; N, 5.85%); ν_{max}(Nujol) 3 282, 3 086, 1 661, 1 646, and 1 559 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.63 (1 H, s, 5-H), 7.42 (1 H, s, 3-H), 5.3 (1 H, br, NH), 3.47 (2 H, s, $CH_2CONHBu^t$), 2.55 (3 H, s, CH_3CO), and 1.33 (9 H, s, t-Bu); *m/z* 239 (M^+, 2%), 140 (100), 97 (14), and 57 (53).

Preparation of 6-*bromo*-1-*methylthieno*[3,2-c]*pyran*-3-*one*

Ethyl 5-*Bromo*-2-*thienylacetate* (**263**).- Ethyl 2-thienylacetate (**262b**) (3.185 g, 18.74 mmol) and *N*-bromosuccinimide (3.52 g, 19.76 mmol) in chloroform-acetic acid (1:1 v/v; 25 ml) were stirred at room temperature overnight. The mixture was diluted with an equal volume of water and the organic layer separated, washed with potassium hydroxide solution, water, brine, and dried ($MgSO_4$). After evaporation of the solvent the residual oil was

chromatographed [toluene-light petroleum(1:3)] to give the *title compound* (**263**) (3.282 g, 70%) as a yellow oil, (Found: M^+, 247.9507. $C_8H_9BrO_2S$ requires *M*, 247.9507); ν_{max}(film) 1 741 cm^{-1}; δ(270 MHz; $CDCl_3$) 6.89 (1 H, d, *J* 3.7 Hz, 4-H), 6.68 (1 H, dt, *J* 3.7, 1 Hz, 3-H), 4.18 (2 H, q, *J* 7 Hz, ester CH_2), 3.75 (2 H, d, *J* 1 Hz, CH_2CO_2Et), and 1.28 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 250 (M^+, 30%), 248 (M^+, 29), 177 (96), and 175 (100).

Ethyl 3-*Acetyl*-5-*bromo*-2-*thienylacetate* (**264**).- To a solution of acetyl chloride (0.43 ml, 6.1 mmol) and tin(IV) chloride (2.85 ml, 24.4 mmol) in 1,2-dichloroethane (20 ml) under nitrogen was added a solution of ethyl 5-bromo-2-thienylacetate (**263**) (1.011 g, 4.06 mmol) in 1,2-dichloroethane (5 ml). The mixture was warmed to 50°C, stirred for 36 h, poured into dilute hydrochloric acid, and extracted with dichloromethane. The combined dichloromethane extracts were washed with water, brine, and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**264**) (448 mg, 38%), m.p. 38-42°C (Found: C, 41.15; H, 3.55. $C_{10}H_{11}BrO_3S$ requires C, 41.25; H, 3.8%); ν_{max}(Nujol) 1 732 and 1 669 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.34 (1 H, s, 4-H), 4.19 (2 H, q, *J* 7 Hz, ester CH_2), 4.13 (2 H, s, CH_2CO_2Et), 2.47 (3 H, s, CH_3CO), and 1.28 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 292 (M^+, 23%), 290 (M^+, 22), 246 (86), 244 (80), 219 (82), 217 (73), and 43 (100).

3-*Acetyl*-5-*bromo*-2-*thienylacetic acid* (**265**).- To a solution of ethyl 3-acetyl-5-bromo-2-thienylacetate (**264**) (375 mg, 1.29 mmol) in methanol (3 ml) was added potassium hydroxide (2 M; 3 ml) dropwise with stirring and external cooling. The reaction mixture was then stirred at room temperature for 2 h. Water (20 ml) was added, the mixture extracted with ether, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). Evaporation of solvent gave the *title compound* (**265**) (292 mg, 86%) as a brown oil which could not be purified further, ν_{max}(Nujol) 3 200-2 400 (br), 3 085, 1 721, and 1 664 cm^{-1}; δ[270 MHz; $(CD_3)_2CO$] 7.59 (1 H, s, 4-H), 4.20 (2 H, s, CH_2CO_2H), and 2.48 (3 H, s,

CH_3CO); *m/z* 264 (M^+, 9%), 262 (M^+, 8), 246 (12), 244 (12), and 43 (100).

6-*Bromo*-1-*methylthieno*[3,2-c]*pyran*-3-*one* (**266**).- To a solution of the ester (**264**) (781 mg, 2.68 mmol) in methanol (10 ml) was added potassium hydroxide (2 M; 7 ml) dropwise with stirring and external cooling. The mixture was warmed to room temperature, stirred for 1 h, diluted with water (30 ml), extracted with ether, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was removed and the crude acid (**265**) was dissolved in acetic anhydride (25 ml) and refluxed for 3 h. The solvent was removed under reduced pressure and ether (25 ml) added. The precipitate was collected and washed with ether to give the *title compound* (**266**) (402 mg, 61%), m.p. 225°C (decomp.) (Found: C, 39.3; H, 1.9. $C_8H_5BrO_2S$ requires C, 39.2; H, 2.1%); ν_{max}(Nujol) 1 709 cm^{-1}; λ_{max}(EtOH) 227 (ε 20 090), 291 (2 990), and 374 nm (1 390); δ[270 MHz; $(CD_3)_2SO$] 7.48 (1 H, s, 7-H), 6.57 (1 H, s, 4-H), and 2.49 (3 H, s, 1-Me); *m/z* 246 (M^+, 85%), 244 (M^+, 87), 218 (81), 216 (79), and 43 (100).

Diels-Alder Reactions

Reaction of 6-*Bromo*-1-*methylthieno*[3,2-c]*pyran*-3-*one* (**266**) *with dimethyl acetylenedicarboxylate*.- The pyranone (**266**) (39 mg, 0.16 mmol) and dimethyl acetylenedicarboxylate (45 mg, 0.32 mmol) in bromobenzene (10 ml) were refluxed for 24 h under nitrogen. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *dimethyl* 2-*bromo*-4-*methylbenzothiophene*-5,6-*dicarboxylate* (**268**) (38 mg, 70%), m.p. 159-161°C, (Found: C, 45.6; H, 3.0. $C_{13}H_{11}BrO_4S$ requires C, 45.5; H, 3.2%); ν_{max}(Nujol) 1 737 and 1 713 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.28 (1 H, s, 7-H), 7.47 (1 H, s, 3-H), 3.98 (3 H, s, CO_2Me), 3.91 (3 H, s, CO_2Me), and 2.52 (3 H, s, 4-Me); *m/z* 344 (M^+, 39%), 342 (M^+, 36), 313 (72), 312 (100), 311 (68), 310 (96), 254 (55), and 252 (53).

Reaction of 6-*Bromo*-1-*methylthieno*[3,2-c]*pyran*-3-*one* (**266**)*with ethyl propiolate.*- The pyranone (**266**) (42 mg, 0.17 mmol) and ethyl propiolate (84 mg, 0.86 mmol) in bromobenzene (10 ml) were refluxed for 48 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give a 1.4:1 mixture of *ethyl*-2-*bromo*-4-*methylbenzothiophene*-5-*carboxylate* (**269**) and *ethyl*-2-*bromo*-4-*methylbenzothiophene*-6-*carboxylate* (**270**) (34 mg, 66%), m.p. 35-39°C (Found: M^+, 297.9663. $C_{12}H_{11}BrO_2S$ requires M, 297.9663); ν_{max}(Nujol) 3 091 and 1 718 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.27 (1 H, s, minor), 7.82 (1 H, d, *J* 8.5 Hz, major), 7.79 (1 H, s, minor), 7.57 (1 H, d, *J* 8.5 Hz major), 7.51 (1 H, s, major, 3-H), 7.42 (1 H, s, minor, 3-H), 4.44 -4.35 (m, ester CH_2, both isomers), 2.79 (3 H, s, 4-Me, major), 2.57 (3 H, s, 4-Me, minor), and 1.41 (t, *J* 7 Hz, ester CH_3, both isomers); *m/z* 300 (M^+, 100%), 298 (M^+, 98), 255 (92), 253 (89), 227 (41), and 225 (43).

Reaction of 6-*Bromo*-1-*methylthieno*[3,2-c]*pyran*-3-*one* (**266**) *with ethyl* 3-*trimethylsilylpropynoate.*- The pyranone (**266**) (47 mg, 0.19 mmol) and ethyl 3-trimethylsilylpropynoate (98 mg, 0.58 mmol) in bromobenzene (10 ml) were refluxed for 4 days. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give *ethyl* 2-*bromo*-4-*methyl*-6-*trimethylsilylbenzothiophene*-5-*carboxylate* (**271**) (48 mg, 67%), m.p. 46-49°C (Found: M^+, 370.0058. $C_{15}H_{19}BrO_2SSi$ requires M, 370.0059); ν_{max}(Nujol) 1 722, 1 249, and 840 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.77 (1 H, s, 7-H), 7.42 (1 H, s, 3-H), 4.40 (2 H, q, *J* 7 Hz, ester CH_2), 2.53 (3 H, s, 4-Me), 1.41 (3 H, t, *J* 7 Hz, ester CH_3), and 0.32 (9 H, s, Me_3Si); *m/z* 372 (M^+, 3%), 370 (M^+, 3), 357 (97), 355 (87), 329 (100), and 327 (98).

7.4 Experimental for Chapter 4

Preparation of 1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*ones*

Formylation of *Methyl* 1-*Phenylsulphonylpyrrol*-3-*ylacetate* (**306**).- To a solution of the ester (**306**) (2.212 g, 7.92 mmol) and tin (IV) chloride (4.6 ml, 39.60 mmol) in dry dichloromethane (50 ml) at 0°C under nitrogen was added dichloromethyl methyl ether (0.93 ml, 10.3 mmol) dropwise with stirring. The mixture was allowed to warm to room temperature and stirred overnight. Dilute hydrochloric acid was added and the mixture extracted with ether. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give a mixture of *methyl 2-formyl*-1-*phenylsulphonylpyrrol*-3-*ylacetate* (**311**) and *methyl 2-formyl*-1-*phenylsulphonylpyrrol*-4-*ylacetate* (2.239 g, 92%) in the ratio 1 to 1 as a yellow oil (Found: C, 54.75; H, 4.15; N, 4.6. $C_{14}H_{13}NO_5S$ requires C, 54.7; H, 4.3; N, 4.6%); ν_{max}(film) 1 740, 1 670, 1 376, and 1 176 cm^{-1}; δ(270 MHz; $CDCl_3$) 10.23 (1 H, s, CHO), 9.93 (1 H, s, CHO), 7.95-7.84 (m), 7.69-7.51 (m), 7.12 (1 H, d, *J* 2 Hz, 3-H, 2,4-isomer), 6.44 (1 H, d, *J* 3.2 Hz, 4-H, 2,3-isomer), 3.87 (2 H, s, CH_2CO_2Me, 2,3-isomer), 3.72 (3 H, s, CO_2Me), 3.68 (3 H, s, CO_2Me), and 3.51 (2 H, s, CH_2CO_2Me, 2,4-isomer); *m/z* 307 (M^+, 10%), 279 (15), 275 (2), 248 (7), 220 (9), 184 (9), 166 (21), 141 (27), and 77 (100).

2-*Formyl*-1-*phenylsulphonylpyrrol*-3-*ylacetic acid* (**312**) and 2-*Formyl*-1-*phenylsulphonylpyrrol*-4-*ylacetic acid*.- A mixture of methyl 2-formyl-1-phenylsulphonylpyrrol-3-ylacetate (**311**) and methyl 2-formyl-1-phenylsulphonylpyrrol-4-ylacetate (2.078 g, 6.76 mmol) and lithium hydroxide monohydrate (1.42 g, 33.8 mmol) in tetrahydrofuran (30 ml) and water (30 ml) was stirred at 0°C for 1 h. Water (100 ml) was added, the mixture extracted with ethyl acetate and the ethyl acetate layer discarded. The aqueous layer was acidified and extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated to give 2-*formyl*-1-*phenylsulphonylpyrrol*-3-*ylacetic acid*

(**312**) and *2-formyl-1-phenylsulphonylpyrrol-4-ylacetic acid* (1.586 g, 80%) in the ratio 1 to 1 as a yellow oil (Found: M^+, 293.0358. $C_{13}H_{11}NO_5S$ requires M, 293.0358); ν_{max}(film) 3 200-2 400, 1 714, 1 669, 1 376, and 1 178 cm^{-1}; δ[270 MHz; $(CD_3)_2CO$] 10.18 (1 H, s, CHO), 9.94 (1 H, s, CHO), 8.07-8.02 (m), 7.79-7.65 (m), 7.21 (1 H, d, *J* 2 Hz, 3-H, 2,4-isomer), 6.57 (1 H, d, *J* 3.2 Hz, 4-H, 2,3-isomer), 3.84 (2 H, s, CH_2CO_2H, 2,3-isomer), and 3.57 (2 H, s, CH_2CO_2H, 2,4-isomer); *m/z* 293 (M^+, 5%), 275 (1), 249 (9), 153 (21), 141 (16), 108 (63), and 77 (100).

1-*Phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275a**).- Triethylamine (2.15 ml, 15.33 mmol) was added to a solution of 2-formyl-1-phenylsulphonylpyrrol-3-ylacetic acid (**312**) and 2-formyl-1-phenylsulphonylpyrrol-4-ylacetic acid (1.50 g, 5.11 mmol) in tetrahydrofuran (100 ml) at 0°C. Isobutyl chloroformate (1.46 ml, 11.24 mmol) in tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was poured into brine, extracted with ethyl acetate, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**275a**) (294 mg, 21%), m.p. 129-135°C (decomp.) (Found: C, 56.5; H, 3.3; N, 5.1. $C_{13}H_9NO_4S$ requires C, 56.7; H, 3.3; N, 5.1%); $\nu_{max}(CH_2Cl_2)$ 1 718 cm^{-1}; λ_{max}(EtOH) 215 (ε 19 500), 261 (5 300), and 380 nm (7 000); δ[270 MHz; $(CD_3)_2SO$] 8.52 (1 H, dd, *J* 1.4, 0.7 Hz, 7-H), 8.02 (2 H, d, *J* 8 Hz), 7.99 (1 H, d, *J* 3.5 Hz, 2-H), 7.77 (1 H, t, *J* 8 Hz), 7.65 (2 H, t, *J* 8 Hz), 6.05 (1 H, d, *J* 3.5 Hz, 3-H), and 6.15 (1 H, d, *J* 1.2 Hz, 4-H); *m/z* 275 (M^+, 84%), 247 (5), 141 (37), 134 (100), and 77 (86).

7-Methyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol*-5(1H)-*one* (**275b**).- Boron trifluoride diethyl ether (0.2 ml) was added dropwise to a stirred, ice-cooled mixture of 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**) (360 mg, 1.35 mmol) and acetic anhydride (0.5 ml) in ether (3 ml). The mixture was stirred at room temperature for 6 h, diluted with ether, and filtered. The solid was washed with ether, sodium hydrogen carbonate solution,

water, and dried under vacuum to give the *title compound* (**275b**) (168 mg, 43%), m.p. 157-162°C (Found: C, 58.1; H, 3.8; N, 4.8. $C_{14}H_{11}NO_4S$ requires C, 58.1; H, 3.8; N, 4.8%); ν_{max}(Nujol) 1 704 cm^{-1}; δ[270 MHz; $(CD_3)_2CO$] 7.84 (2 H, d, *J* 7 Hz), 7.79 (1 H, d, *J* 3.9 Hz, 2-H), 7.72 (1 H, t, *J* 7.5 Hz), 7.62 (2 H, t, *J* 7.5 Hz), 6.50 (1 H, d, *J* 3.7 Hz, 3-H), 5.83 (1 H, s, 4-H), and 2.66 (3 H, s, 7-Me); *m/z* 289 (M^+, 18%), 148 (100), 77 (30) and 43 (39).

7-*Ethyl*-1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275c**).- Boron trifluoride diethyl ether (1.05 ml, 8.5 mmol) was added dropwise to a stirred, ice-cooled mixture of 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**) (1.50 g, 5.65 mmol) and propionic anhydride (1.8 ml, 14.1 mmol) in ether (12 ml). The mixture was stirred at room temperature for 48 h, partitioned between water and ethyl acetate, and the aqueous phase extracted with ethyl acetate. The combined extracts were washed with sodium hydrogen carbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**275c**) (609 mg, 36%), m.p. 92-95°C (Found: C, 59.15; H, 4.3; N, 4.6. $C_{15}H_{13}NO_4S$ requires C, 59.4; H, 4.3; N, 4.6%); ν_{max}($CHCl_3$) 1 702, 1 570, 1 378, and 1 176 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.65-7.47 (6 H, m), 6.28 (1 H, d, *J* 3.9 Hz, 3-H), 5.89 (1 H, s, 4-H), 3.07 (2 H, q, *J* 7.4 Hz, CH_2CH_3), and 1.26 (3 H, t, *J* 7.4 Hz, CH_2CH_3); *m/z* 303 (M^+, 15%), 162 (97), and 77 (100).

7-*Pentyl*-1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275d**).- Boron trifluoride diethyl ether (0.15 ml) was added dropwise to a solution of the acid (**307**)(200 mg, 0.76 mmol) in hexanoic anhydride (0.35 ml) and ether (2 ml) at room temperature and the resulting mixture was stirred for 24 h. Water was added and the mixture extracted with ether. The combined extracts were washed with saturated sodium hydrogen carbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**275d**) (85 mg, 33%), m.p. 79-82°C (Found: C, 62.6; H, 5.5; N, 4.15. $C_{18}H_{19}NO_4S$ requires C, 62.6; H, 5.5; N, 4.1%); ν_{max}($CHCl_3$) 1 708, 1 381, and 1 177 cm^{-1}; λ_{max}(EtOH) 209 (ε 21

400), 211 (21 800), and 376 nm (9 980); δ(270 MHz; $CDCl_3$) 7.68-7.61 (3 H, m), 7.60 (1 H, d, *J* 3.9 Hz, 2-H), 7.53-7.48 (2 H, m), 6.27 (1 H, d, *J* 3.9 Hz, 3-H), 5.88 (1 H, s, 4-H), 3.02 (2 H, t, *J* 7.8 Hz, allylic CH_2), 1.65 (2 H, m), 1.30 (4 H, m), and 0.89 (3 H, t, *J* 7 Hz, pentyl CH_3); *m/z* 345 (M^+, 53%), 204 (33), 192 (38), 176 (19), 148 (100), and 77 (80).

7-*Isopropyl*-1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275e**).- Boron trifluoride diethyl ether (0.6 ml, 4.7 mmol) was added dropwise to a solution of the acid (**307**) (624 mg, 2.35 mmol) in isobutyric anhydride (1.2 ml, 7.1 mmol) and ether (2 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 20 h. Water was added and the mixture extracted with ethyl acetate. The combined extracts were washed with saturated sodium hydrogen carbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**275e**) (144 mg, 19%), m.p. 136-142°C (Found: C, 60.2; H, 4.7; N, 4.3. $C_{16}H_{15}NO_4S$ requires C, 60.55; H, 4.8; N, 4.4%); ν_{max}($CHCl_3$) 1 708, 1 568, 1 380, 1 172, and 1 130 cm^{-1}; λ_{max}(EtOH) 376 (ε 9 830) nm; δ(250 MHz; $CDCl_3$) 7.66-7.62 (4 H, m), 7.55-7.49 (2 H, m), 6.29 (1 H, d, *J* 3.9 Hz, 3-H), 5.90 (1 H, s, 4-H), 3.84 (1 H, heptet, *J* 6.7 Hz, isopropyl CH), and 1.22 (6 H, d, *J* 6.7 Hz, isopropyl CH_3); *m/z* 317 (M^+, 36%), 176 (56), 77 (93), and 69 (100).

Methyl 2-(1-*Phenylsulphonylpyrrol*-3-*yl*)*propanoate* (**309a**).- n-Butyllithium (1.5 M, 1.67 ml) was added dropwise to a solution of *N*-isopropylcyclohexylamine (0.41 ml, 2.51 mmol) in dry tetrahydrofuran (15 ml) at -78°C under nitrogen. The mixture was warmed to 0°C, stirred for 5 mins, and recooled to -78°C. A solution of the ester (**306**)(637 mg, 2.28 mmol) in dry tetrahydrofuran (5 ml) was added dropwise and the resulting solution stirred at -78°C for 2 h. Methyl iodide (2 ml) was added, the mixture allowed to warm to room temperature, and stirred overnight. Water (50 ml) was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**309a**) (620 mg, 93%) as a colourless oil (Found: C, 57.2; H, 5.4;

N, 4.65. $C_{14}H_{15}NO_4S$ requires C, 57.3; H, 5.15; N, 4.8%); ν_{max}(film) 3 140, 1 738, 1 371, 1 176, 1 063 and 729 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.85 (2 H, d, *J* 8 Hz), 7.58 (1 H, t, *J* 7 Hz), 7.50 (2 H, t, *J* 7 Hz), 7.12-7.05 (2 H, m, 2-H + 5-H), 6.28 (1 H, dd, *J* 3.2, 1.7 Hz, 4-H), 3.66 (3 H, s, CO_2Me), 3.59 (1 H, q, *J* 7 Hz, $CHCO_2Me$), and 1.41 (3 H, d, *J* 7 Hz, CH_3CH); *m/z* 293 (M^+, 26%), 234 (100), 141 (20), and 77 (51).

2-(1-*Phenylsulphonylpyrrol*-3-*yl*)*propionic acid* (**310a**).- A mixture of the ester (**309a**) (530 mg, 1.81 mmol) and lithium hydroxide hydrate (380 mg, 9.03 mmol) in tetrahydrofuran (5 ml) and water (5 ml) was stirred at room temperature for 20 h. Water (20 ml) was added, the mixture extracted with ethyl acetate, and this extract discarded. The aqueous layer was acidified and extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated to give the *title compound* (**310a**) (489 mg, 97%), m.p. 100-104°C (Found: M^+, 279.0565. $C_{13}H_{13}NO_4S$ requires *M*, 279.0565); ν_{max}(Nujol) 3 200-2 400, 1 713, 1 371, 1 176, 1 110, 1 064, and 729 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.87-7.83 (2 H, m), 7.63-7.57 (1 H, m), 7.54-7.47 (2 H, m), 7.12-7.08 (2 H, m, 2-H + 5-H), 6.31 (1 H, dd, *J* 4.2, 2.0 Hz, 4-H), 3.61(1 H, q, *J* 7.3 Hz, $CHCO_2H$), and 1.44 (3 H, d, *J* 7.3 Hz, CH_3CH); *m/z* 279 (M^+, 40%), 234 (100), 141 (26), 94 (28), and 77 (77).

4,7-*Dimethyl*-1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275f**).- Boron trifluoride diethyl ether (0.41 ml, 3.3 mmol) was added dropwise to a stirred solution of the acid (**310a**) (467 mg, 1.67 mmol) in acetic anhydride (0.63 ml, 6.7 mmol) and ether (2 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 15 h. Water (30 ml) was added and the mixture extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water , brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**275f**) (129 mg, 25%), m.p. 193-196 °C (Found: C, 59.2; H, 4.2; N, 4.5. $C_{15}H_{13}NO_4S$ requires C, 59.4; H, 4.3; N, 4.6%); ν_{max}(Nujol) 1 690, 1 379, and 1 182 cm^{-1}; λ_{max}(EtOH) 214 (ε 21 780), 325 (3 110), 369 (9 400), and 377 nm (8

550); δ(270 MHz; $CDCl_3$) 7.68-7.60 (3 H, m), 7.56 (1 H, d, *J* 3.9 Hz, 2-H) 7.53-7.50 (2 H, m), 6.32 (1 H, d, *J* 3.9 Hz, 3-H), 2.65 (3 H, d, *J* 0.7 Hz, 7-Me), and 2.04 (3 H, s, 4-Me); *m/z* 303 (M^+, 14%), 162 (100), 92 (31), 77 (25), and 43 (39).

Methyl 2-(1-*phenylsulphonylpyrrol*-3-*yl*)*butanoate* (**309b**).- n-Butyllithium (1.45 M, 7.20 ml) was added to a solution of *N*-isopropylcyclohexylamine (1.47 g, 10.44 mmol) in dry tetrahydrofuran (50 ml) under nitrogen at -78°C. The mixture was allowed to warm to 0°C, stirred for 5 minutes, and recooled to -78°C. The ester (**306**) (2.65 g, 9.49 mmol) in dry tetrahydrofuran (20 ml) was added dropwise and the mixture stirred for 2 h. Ethyl iodide (5 ml) was added and the mixture allowed to warm to room temperature. After stirring overnight, the mixture was poured into brine and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**309b**) (2.425 g, 83%) as a colourless oil (Found: C, 58.7; H, 5.6; N, 4.3. $C_{15}H_{17}NO_4S$ requires C, 58.6; H, 5.6; N, 4.6%); ν_{max}(film) 3 140, 1 734, 1 370, 1 178, and 1 064 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.86-7.82 (2 H, m), 7.60-7.57 (1 H, m), 7.53-7.47 (2 H, m), 7.11-7.06 (2 H, m, 2-H + 5-H), 6.28 (1 H, dd, *J* 3.2, 1.7 Hz, 4-H), 3.65 (3 H, s, CO_2Me), 3.35 (1 H, t, *J* 7.5 Hz, $CHCO_2Me$), 1.96-1.88 (1 H, m), 1.75-1.64 (1 H, m), and 0.85 (3 H, t, *J* 7.4 Hz, CH_2CH_3); *m/z* 307 (M^+, 26%), 278 (9), 248 (100), 141 (22), 106 (14), and 77 (68).

2-(1-*Phenylsulphonylpyrrol*-3-*yl*)*butanoic acid* (**310b**).- A mixture of the ester (**309b**) (2.217 g, 7.21 mmol) and lithium hydroxide hydrate (1.51 g, 36.06 mmol) in tetrahydrofuran (10 ml) and water (10 ml) was stirred at room temperature for 24 h. Water was added, the mixture extracted with ethyl acetate, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue triturated with light petroleum to give the *title compound* (**310b**) (1.736 g, 82%), m.p. 80°C (Found: C, 57.1; H, 5.1; N, 4.7. $C_{14}H_{15}NO_4S$

requires C, 57.3; H, 5.15; N, 4.8%); ν_{max}(film) 1 700, 1 462, 1 374, 1 170, and 1 064 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.85-7.82 (2 H, m), 7.60 (1 H, t, *J* 7 Hz), 7.49 (2 H, t, *J* 7.5 Hz), 7.10 (2 H, m, 2-H + 5-H), 6.29 (1 H, t, *J* 2.4 Hz, 4-H), 3.35 (1 H, t, *J* 7.5 Hz, $CHCO_2H$), 2.01-1.90 (1 H, m), 1.77-1.66 (1 H, m), and 0.87 (3 H, t, *J* 7.4 Hz, CH_2CH_3); *m/z* 293 (M^+, 43%), 264 (14), 248 (93), 220 (7), 141 (34), and 77 (100).

4-*Ethyl*-7-*methyl*-1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275g**).- Boron trifluoride diethyl ether (0.16 ml, 1.34 mmol) was added dropwise to a solution of the acid (**310b**) (196 mg, 0.67 mmol) in acetic anhydride (0.25 ml, 2.67 mmol) and ether (1 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred overnight. Water was added and the mixture extracted with ethyl acetate. The combined extracts were washed with saturated sodium hydrogen carbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give a yellow oil, trituration of which with ether-light petroleum gave the *title compound* (**275g**) (63 mg, 30%), m.p. 178-181°C (Found: M^+, 317.0706. $C_{16}H_{15}NO_4S$ requires *M*, 317.0722); ν_{max}(Nujol) 1 686, 1 652, 1 582, 1 374, 1 176, and 1 132 cm^{-1}; λ_{max}(EtOH) 377 (ε 9 110) nm; δ(250 MHz; $CDCl_3$) 7.69-7.60 (3 H, m), 7.57 (1 H, d, *J* 4.1 Hz, 2-H), 7.54-7.47 (2 H, m), 6.34 (1 H, d, *J* 3.8 Hz, 3-H), 2.65 (3 H, s, 7-Me), 2.47 (2 H, q, *J* 7.5 Hz, CH_2CH_3), and 1.08 (3 H, t, *J* 7.5 Hz, CH_2CH_3); *m/z* 317 (M^+, 20%), 176 (100), 77 (37), and 43 (35).

Formylation of *Methyl* 2-(1-*phenylsulphonylpyrrol*-3-*yl*)*butanoate* (**309b**).- To a solution of the ester (**309b**) (136 mg, 0.44 mmol) and tin (IV) chloride (0.26 ml, 2.21 mmol) in dry dichloromethane (4 ml) at 0°C under nitrogen was added dichloromethyl methyl ether (0.05 ml, 0.58 mmol) with stirring. The mixture was stirred at 0°C for 5 h, and then allowed to warm to room temperature. Dilute hydrochloric acid was added and the mixture extracted with ether. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give a mixture of *methyl* 2-(2-*formyl*-1-*phenylsulphonylpyrrol*-3-*yl*)*butanoate* (**313**) and *methyl* 2-(2-*formyl*-

1-*phenylsulphonylpyrrol*-4-*yl*)*butanoate* (**314**) (116 mg, 78%) in the ratio 1 to 2 as a yellow oil (Found: C, 57.4; H, 5.2; N, 4.0. $C_{16}H_{17}NO_5S$ requires C, 57.3; H, 5.1; N, 4.2%); ν_{max}(film) 3 124, 1 738, 1 672, 1 448, 1 374, 1 192, and 1 090 cm^{-1}; δ(250 MHz; $CDCl_3$) 10.20 (1 H, s, CHO, minor), 9.92 (1 H, s, CHO, major), 7.95-7.85 (m, both isomers), 7.70-7.63 (m, both isomers), 7.58-7.52 (m, both isomers), 7.15 (1 H, d, *J* 1.9 Hz, 3-H, major), 6.54 (1 H, d, *J* 3.3 Hz, 4-H, minor), 4.33 (1 H, t, *J* 7.4 Hz, C*H*CO_2Me, minor), 3.70 (3 H, s, CO_2Me, major), 3.65 (3 H, s, CO_2Me, minor), 3.44 (1 H, t, *J* 7.6 Hz, C*H*CO_2Me, major), 2.06-1.90 (m, both isomers), 1.81-1.68 (m, both isomers), 0.90 (3 H, t, *J* 7.3 Hz, CH_2CH_3, major), and 0.84 (3 H, t, *J* 7.4 Hz, CH_2CH_3, minor); *m/z* 335 (M^+, 13%), 303 (8), 276 (40), 248 (8), 212 (10), 194 (10), 141 (29), and 77 (100).

Diels-Alder reactions of 1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*ones*

Reaction of 1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275a**) *with dimethyl acetylenedicarboxylate.*- A mixture of the pyranopyrrolone (**275a**) (41 mg, 0.15 mmol) and dimethyl acetylenedicarboxylate (42 mg, 0.30 mmol) in chlorobenzene (5 ml) was refluxed for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give *dimethyl* 1-*phenylsulphonylindole*-5,6-*dicarboxylate* (**316a**) (32 mg, 58%), m.p. 129-130°C (Found: C, 57.65; H, 4.0; N, 3.8. $C_{18}H_{15}NO_6S$ requires C, 57.9; H, 4.05; N, 3.75%); ν_{max}($CHCl_3$) 1 724, 1 307, and 1 118 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.40 (1 H, s, 7-H), 7.91-7.87 (3 H, m), 7.72 (1 H, d, *J* 3.7 Hz, 2-H), 7.59-7.56 (1 H, m), 7.50-7.45 (2 H, m), 6.74 (1 H, d, *J* 3.7 Hz, 3-H), 3.95 (3 H, s, CO_2Me), and 3.90 (3 H, s, CO_2Me); *m/z* 373 (M^+, 100%), 342 (61), 201 (77), 141 (15), and 77 (45).

Reaction of 1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275a**) *with ethyl propiolate.*- A mixture of the pyranopyrrolone (**275a**) (45 mg, 0.16 mmol) and ethyl propiolate (80 mg, 0.80 mmol) in chlorobenzene (5 ml) was refluxed for 5 h. The solvent was evaporated and the residue

chromatographed [ether-light petroleum (2:1)] to give a mixture of *ethyl* 1-*phenylsulphonylindole*-5-*carboxylate* (**318a**) and *ethyl* 1-*phenylsulphonylindole*-6-*carboxylate* (**317a**) (33 mg, 61%) in the ratio 1 to 1, m.p. 98-105 °C (Found: C, 62.0; H, 4.55; N, 4.15. $C_{17}H_{15}NO_4S$ requires C, 62.0; H, 4.6; N, 4.25%); ν_{max}(Nujol) 3 142, 1 713, 1 376, 1 289, and 1 175 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.69 (1 H, s, 7-H, 6-ester), 8.27 (1 H, s, 4-H, 5-ester), 8.02 (2 H, s), 7.95-7.87 (m, both isomers), 7.71 (1 H, d, *J* 3.7 Hz, 2-H), 7.63 (1 H, d, *J* 3.7 Hz, 2-H), 7.57-7.42 (m, both isomers), 6.73 (1 H, d, *J* 3.7 Hz, 3-H), 6.70 (1 H, dd, *J* 3.7, 1.0 Hz, 3-H), 4.42 (2 H, q, *J* 7.1 Hz, ester CH_2), 4.38 (2 H, q, *J* 7.1 Hz, ester CH_2), 1.43 (3 H, t, *J* 7.1 Hz, ester CH_3), and 1.39 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 329 (M^+, 100%), 284 (29), 188 (19), and 77 (57).

Reaction of 1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275a**) *with ethyl* 3-*trimethylsilylpropynoate*.- A mixture of the pyranopyrrolone (**275a**) (102 mg, 0.37 mmol) and ethyl 3-trimethylsilylpropynoate (189 mg, 1.11 mmol) in chlorobenzene (10 ml) was refluxed for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give a mixture of *ethyl* 1-*phenylsulphonyl*-5-*trimethylsilylindole*-6-*carboxylate* (**319**) and *ethyl* 1-*phenylsulphonyl*-6-*trimethylsilylindole*-5-*carboxylate* (**320**) (59 mg, 40%) in the ratio 2.5 to 1 (Found: M^+, 401.1117. $C_{20}H_{23}NO_4SSi$ requires *M*, 401.1117); ν_{max}(Nujol) 3 142, 3 068, 1 718, 1 377, 1 283, 1 174, and 1 142 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.67 (1 H, s, 7-H, major), 7.94-7.88 (m, both isomers), 7.84 (1 H, s, 4-H, major), 7.67 (1 H, d, *J* 3.7 Hz, 2-H, major), 7.65 (1 H, d, *J* 3.9 Hz, 2-H, minor), 7.57-7.44 (m, both isomers), 6.71 (1 H, d, *J* 3.7 Hz, 3-H, minor), 6.70 (1 H, dd, *J* 3.7, 0.7 Hz, 3-H, major), 4.43 (2 H, q, *J* 7.1 Hz, ester CH_2, major), 4.37 (2 H, q, *J* 7.1 Hz, ester CH_2, minor), 1.46 (3 H, t, *J* 7.1 Hz, ester CH_3, major), 1.39 (3 H, t, *J* 7.1 Hz, ester CH_3, minor), 0.37 (9 H, s, Me_3Si, minor), and 0.33 (9 H, s, Me_3Si, major); *m/z* 401 (M^+, 2%), 386 (100), 358 (40), 217 (43), and 77 (13).

Reaction of 1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275a**) *with benzyne*.- A mixture of the pyranopyrrolone (**275a**) (53 mg, 0.19

mmol), 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**) (74 mg, 0.39 mmol), and trifluoroacetic acid (1 drop) in acetonitrile (10 ml) was refluxed for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give 1-*phenylsulphonylbenz*[f]*indole* (**322a**) (29 mg, 49%), m.p. 127-129 °C (Found: C, 70.4; H, 4.2; N, 4.5. $C_{18}H_{13}NO_2S$ requires C, 70.3; H, 4.3; N, 4.6%); ν_{max}(Nujol) 3 128, 1 372, 1 175, and 1 099 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.46 (1 H, s, 9-H), 8.01-7.97 (2 H, m), 7.92-7.88 (3 H, m), 7.68 (1 H, d, *J* 3.7 Hz, 2-H), 7.50-7.37 (5 H, m), and 6.79 (1 H, d, *J* 3.9 Hz, 3-H); *m/z* 307 (M^+, 48%), 166 (100), and 139 (25).

Reaction of 7-methyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275b**) *with dimethyl acetylenedicarboxylate*.- a) A mixture of the pyranopyrrolone (**275b**) (66 mg, 0.23 mmol), and dimethyl acetylenedicarboxylate (65 mg, 0.46 mmol) in bromobenzene (10 ml) was heated under reflux for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give *dimethyl 7-methyl-1-phenylsulphonylindole-5,6-dicarboxylate* (**316b**) (53 mg, 60%), m.p. 108-112°C, (Found: C, 58.8; H, 4.4; N, 3.5. $C_{19}H_{17}NO_6S$ requires C, 58.9; H, 4.4; N, 3.6%); ν_{max}(Nujol) 1 729, 1 278, and 1 188 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.11 (1 H, s, 4-H), 7.92 (1 H, d, *J* 3.4 Hz, 2-H), 7.66 (2 H, d, *J* 8 Hz), 7.57 (1 H, t, *J* 7.5 Hz), 7.47 (2 H, t, *J* 7.5 Hz), 6.76 (1 H, d, *J* 3.4 Hz, 3-H), 3.92 (3 H, s, CO_2Me), 3.88 (3 H, s, CO_2Me), and 2.49 (3 H, s, 7-Me); *m/z* 387 (M^+, 34%), 356 (14), and 77 (100).

b) A mixture of the pyranopyrrolone (**275b**) (16 mg, 0.055 mmol), and dimethyl acetylenedicarboxylate (15 mg, 0.11 mmol) in acetonitrile (2 ml) was heated under reflux for 15 h. The solvent was evaporated and the residue chromatographed to give *dimethyl 7-methyl-1-phenylsulphonylindole-5,6-dicarboxylate* (**316b**) (15 mg, 70%), data given above.

Reaction of 7-methyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275b**) *with ethyl propiolate*.- A mixture of the pyranopyrrolone (**275b**) (42 mg, 0.15 mmol) and ethyl propiolate (71 mg, 0.73 mmol) in

bromobenzene (10 ml) was refluxed for 60 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give a mixture of *ethyl 7-methyl-1-phenylsulphonylindole-6-carboxylate* (**317b**) and *ethyl 7-methyl-1-phenylsulphonylindole-5-carboxylate* (**318b**) (28 mg, 56%) in the ratio 1.6 to 1 as a yellow oil (Found: C, 63.2; H, 5.1; N, 4.4. $C_{18}H_{17}NO_4S$ requires C, 63.0; H, 5.0; N, 4.1%); ν_{max}(film) 1 714, 1 367, 1 294, 1 174, and 1 130 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.11 (1 H, s, 4-H, minor), 7.86-7.83 (m), 7.71-7.64 (m), 7.57-7.34 (m), 6.77 (1 H, d, *J* 4 Hz, 3-H, minor), 6.67 (1 H, d, *J* 3.9 Hz, 3-H, major), 4.38-4.31 (m, ester CH_2, both isomers), 2.73 (3 H, s, 7-Me, major), 2.56 (3 H, s, 7-Me, minor), 1.41-1.33 (m, ester CH_3, both isomers); *m/z* 343 (M^+, 100%), 298 (15), and 202 (54).

Reaction of 7-methyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275b**) *with ethyl 3-trimethylsilylpropynoate*.- A mixture of the pyranopyrrolone (**275b**) (216 mg, 0.75 mmol) and ethyl 3-trimethylsilylpropynoate (510 mg, 3.00 mmol) in chlorobenzene (20 ml) was refluxed for 96 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *ethyl 7-methyl-1-phenylsulphonyl-5-trimethylsilylindole-6-carboxylate* (**321a**) (165 mg, 53%), m.p. 122-127°C (Found: C, 60.7; H, 6.1; N, 3.2. $C_{21}H_{25}NO_4SSi$ requires C, 60.7; H, 6.1; N, 3.4%); ν_{max}($CHCl_3$) 1 718, 1 368, and 1 174 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.83 (1 H, d, *J* 3.9 Hz, 2-H), 7.67 (2 H, d, *J* 8 Hz), 7.61 (1 H, s, 4-H), 7.56 (1 H, t, *J* 8 Hz), 7.46 (2 H, t, *J* 8 Hz), 6.68 (1 H, d, *J* 3.4 Hz, 3-H), 4.34 (2 H, q, *J* 7 Hz, ester CH_2), 2.48 (3 H, s, 7-Me), 1.36 (3 H, t, *J* 7 Hz, ester CH_3), and 0.28 (9 H, s, Me_3Si); *m/z* 415 (M^+, 7%), 400 (100), 372 (10), 259 (34), 231 (35), and 77 (16).

Protodesilylation of ethyl 7-methyl-1-phenylsulphonyl-5-trimethylsilylindole-6-carboxylate (**321a**).- A solution of the 5-trimethylsilylindole (**321a**) (19 mg, 0.046 mmol) in trifluoroacetic acid (2 ml) and water (1 ml) was heated at 70 °C for 2 h. The mixture was diluted with water (30 ml) and extracted with ether. The combined ether extracts were washed with saturated aqueous sodium hydrogen carbonate solution (until the

washings remained basic), water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give *ethyl 7- methyl-1-phenylsulphonylindole-6-carboxylate* (**317b**) (11 mg, 70%) as a colourless oil, ν_{max}(film) 1 713, 1 366, 1 173 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.84 (1 H, d, *J* 3.9 Hz, 2-H), 7.67-7.63 (3 H, m), 7.55 (1 H, t, *J* 7 Hz), 7.45-7.34 (3 H, m), 6.67 (1 H, d, *J* 3.7 Hz, 3-H), 4.34 (2 H, q, *J* 7 Hz, ester CH_2), 2.73 (3 H, s, 7-Me), and 1.38 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 343 (M^+, 100%), 298 (21), 202 (62), 174 (29), 156 (42), 141 (15), 77 (41).

Reaction of 7-methyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275b**) *with benzyne.*- A mixture of the pyranopyrrolone (**275b**) (58 mg, 0.2 mmol), 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**) (116 mg, 0.6 mmol), and trifluoroacetic acid (1 drop) in acetonitrile (10 ml) was heated under reflux for 5 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give 9-*methyl*-1-*phenylsulphonylbenz*[f]*indole*(**322b**) (42 mg, 65%), (Found: C, 71.1; H, 4.7; N, 4.3. $C_{19}H_{15}NO_2S$ requires C, 71.0; H, 4.7; N, 4.4%); ν_{max}(film) 3 070, 1 583, 1 447, 1 364, 1 186, and 726 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.16 (1 H, d, *J* 8 Hz), 7.84 (1 H, d, *J* 8 Hz), 7.73 (1 H, s, 4-H), 7.66 (1 H, d, *J* 3.9 Hz, 2-H), 7.57-7.40 (5 H, m), 7.31-7.25 (2 H, m), 6.71 (1 H, d, *J* 3.9 Hz, 3-H), and 3.05 (3 H, s, 9-Me); *m/z* 321 (M^+, 18%) and 180 (100).

Reaction of 7-methyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275b**) *with phenyl vinyl sulphoxide.*- A mixture of the pyranopyrrolone (**275b**) (90 mg, 0.31 mmol) and phenyl vinyl sulphoxide (142 mg, 0.93 mmol) in chlorobenzene (5 ml) was heated under reflux for 48 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *7-methyl-1-phenylsulphonylindole* (**324a**) (51 mg, 60%) as a colourless oil (Found: C, 66.4; H, 4.9; N, 5.0. $C_{15}H_{13}NO_2S$ requires C, 66.4; H, 4.8; N, 5.2%); ν_{max}($CHCl_3$) 1 586, 1 446, 1 364, and 1 166 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.79 (1 H, d, *J* 3.8 Hz, 2-H), 7.68-7.64 (2 H, m), 7.54-7.51 (1 H, m), 7.46-7.38 (3 H, m), 7.12 (1 H, t, *J* 7.8 Hz, 5-H), 7.01 (1 H, d, *J* 6.8 Hz, 6-H), 6.70 (1 H, d, *J* 3.7 Hz, 3-H), and 2.52

(3 H, s, 3-Me); *m/z* 271 (M^+, 32%), 130 (100), and 77 (39).

Reaction of 7-pentyl-1-phenylsulphonylpyrano[3,4-b]pyrrol-5(1H)-one (**275d**) *with dimethyl acetylenedicarboxylate.*- A mixture of the pyranopyrrolone (**275d**) (44 mg, 0.13 mmol) and dimethyl acetylenedicarboxylate (36 mg, 0.25 mmol) in bromobenzene (5 ml) was refluxed for 18 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give *dimethyl 7-pentyl-1-phenylsulphonylindole-5,6-dicarboxylate* (**316c**) (29 mg, 51%), m.p. 103-106°C (Found: M^+, 443.1404. $C_{23}H_{25}NO_6S$ requires *M*, 443.1403); $\nu_{max}(CHCl_3)$ 1 724, 1 297, and 1 190 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.07 (1 H, s, 4-H), 7.93 (1 H, d, *J* 3.9 Hz, 2-H), 7.64-7.55 (3 H, m), 7.47-7.41 (2 H, m), 6.76 (1 H, d, *J* 3.7 Hz, 3-H), 3.91 (3 H, s, CO_2Me), 3.87 (3 H, s, CO_2Me), 2.99 (2 H, m, benzylic CH_2), 1.6 (2 H, m), 1.2 (4 H, m), and 0.85 (3 H, m, pentyl CH_3); *m/z* 443 (M^+, 20%), 412 (31), 411 (28), 368 (66), 270 (40), 149 (100), and 77 (40).

Reaction of 7-pentyl-1-phenylsulphonylpyrano[3,4-b]pyrrol-5(1H)-one (**275d**) *with ethyl propiolate.*- A mixture of the pyranopyrrolone (**275d**) (34 mg, 0.10 mmol) and ethyl propiolate (48 mg, 0.49 mmol) in bromobenzene (3 ml) was refluxed for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give a mixture of *ethyl 7-pentyl-1-phenylsulphonylindole-5-carboxylate* (**318c**) and *ethyl 7-pentyl-1-phenylsulphonylindole-6-carboxylate* (**317c**) (23 mg, 59%) in the ratio 1 to 1 (Found: M^+, 399.1504. $C_{22}H_{25}NO_4S$ requires *M*, 399.1504); $\nu_{max}(CHCl_3)$ 1 713, 1 369, and 1 174 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.07 (1 H, d, *J* 1.7 Hz, 4-H, 5-ester), 7.86 (1 H, d, *J* 3.7 Hz, 2-H), 7.84 (1 H, d, *J* 3.9 Hz, 2-H), 7.77 (1 H, d, *J* 1.7 Hz, 6-H, 5-ester), 7.65-7.52 (m, both isomers), 7.46-7.39 (m, both isomers), 7.34 (1 H, d, *J* 8 Hz, 6-ester), 6.76 (1 H, d, *J* 3.7 Hz, 3-H), 6.68 (1 H, d, *J* 3.9 Hz, 3-H), 4.41-4.30 (m, ester CH_2, both isomers), 3.32 (2 H, t, *J* 8 Hz, benzylic CH_2, 6-ester), 2.98 (2 H, t, *J* 8 Hz, benzylic CH_2, 5-ester), 1.54-1.11 (m, both isomers), and 0.90-0.78 (m, pentyl CH_3, both isomers); *m/z* 399 (M^+, 100%), 354 (44), 202 (43), 174 (45), and 77 (36).

Reaction of 7-pentyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275d**) *with ethyl 3-trimethylsilylpropynoate*.- A mixture of the pyranopyrrolone (**275d**) (60 mg, 0.17 mmol) and ethyl 3-trimethylsilylpropynoate (88 mg, 0.52 mmol) in chlorobenzene (15 ml) was refluxed for 120 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *ethyl 7-pentyl-1-phenylsulphonyl-5-trimethylsilylindole-6-carboxylate* (**321b**) (10 mg, 12%) as a colourless oil (Found: M^+, 471.1900. $C_{25}H_{33}NO_4SSi$ requires M, 471.1900); $\nu_{max}(CCl_4)$ 1 726, 1 374, 1 265, and 1 177 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.84 (1 H, d, *J* 3.9 Hz, 2-H), 7.66-7.62 (2 H, m), 7.59 (1 H, s, 4-H), 7.55-7.53 (1 H, m), 7.47-7.44 (2 H, m), 6.68 (1 H, d, *J* 3.8 Hz, 3-H), 4.34 (2 H, q, *J* 7 Hz, ester CH_2), 2.99 (2 H, t, *J* 8 Hz, benzylic CH_2), 1.40 (2 H, m), 1.37 (3 H, t, *J* 7 Hz, ester CH_3), 1.20 (4 H, m), 0.86 (3 H, t, *J* 7 Hz, pentyl CH_3), and 0.27 (9 H, s, Me_3Si); *m/z* 471 (M^+, 5%), 456 (100), 259 (17), 230 (14), and 77 (11).

Reaction of 7-pentyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275d**) *with benzyne*.- A mixture of the pyranopyrrolone (**275d**) (64 mg, 0.19 mmol), 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**) (72 mg, 0.37 mmol), and trifluoroacetic acid (1 drop) in acetonitrile (10 ml) was refluxed for 12 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give *9-pentyl-1-phenylsulphonylbenz*[f]*indole* (**322c**) (54 mg, 77%), m.p. 80-82°C (Found: C, 73.4; H, 6.2; N, 3.7. $C_{23}H_{23}NO_2S$ requires C, 73.2; H, 6.1; N, 3.7%); ν_{max}(Nujol) 1 448, 1 364, 1 175, and 1 092 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.14 (1 H, d, *J* 8 Hz), 7.86 (1 H, d, *J* 7 Hz), 7.79 (1 H, d, *J* 3.9 Hz, 2-H), 7.78 (1 H, s, 4-H), 7.63-7.60 (2 H, m), 7.51-7.31 (5 H, m), 6.74 (1 H, d, *J* 3.9 Hz, 3-H), 3.54 (2 H, t, *J* 8 Hz, benzylic CH_2), 1.56-1.50 (2 H, m), 1.35-1.25 (4 H, m), and 0.88 (3 H, t, *J* 7 Hz, pentyl CH_3); *m/z* 377 (M^+, 25%), and 180 (100).

Reaction of 7-pentyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275d**) *with phenyl vinyl sulphoxide*.- A mixture of the pyranopyrrolone (**275d**) (84 mg, 0.24 mmol) and phenyl vinyl sulphoxide (111 mg, 0.73

mmol) in chlorobenzene (5 ml) was refluxed for 72 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give *7-pentyl-1-phenylsulphonylindole* (**324b**) (35 mg, 44%), m.p. 60-61°C (Found: C, 69.6; H, 6.4; N, 4.3. $C_{19}H_{21}NO_2S$ requires C, 69.7; H, 6.5; N, 4.3%); ν_{max}($CHCl_3$) 3 156, 1 446, 1 370, and 1 168 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.77 (1 H, d, *J* 3.8 Hz, 2-H), 7.66-7.62 (2 H, m), 7.54-7.51 (1 H, m), 7.45-7.35 (3 H, m), 7.16 (1 H, t, *J* 7.4 Hz, 5-H), 7.08 (1 H, d, *J* 7.3 Hz, 6-H), 6.69 (1 H, d, *J* 3.8 Hz, 3-H), 2.96 (2 H, t, *J* 7.9 Hz, benzylic CH_2), 1.50-1.44 (2 H, m), 1.26-1.21 (4 H, m), and 0.86 (3 H, t, *J* 6.6 Hz, pentyl CH_3); *m/z* 327 (M^+, 33%), 130 (100), and 77 (21).

Reaction of 7-isopropyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275e**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranopyrrolone (**275e**) (57 mg, 0.18 mmol) and dimethyl acetylenedicarboxylate (51 mg, 0.36 mmol) in chlorobenzene (5 ml) was refluxed for 30 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give *dimethyl 7-isopropyl-1-phenylsulphonylindole-5,6-dicarboxylate* (**316d**) (44 mg, 59%), m.p. 109-113°C (Found: C, 60.5; H, 5.1; N, 3.3. $C_{21}H_{21}NO_6S$ requires C, 60.7; H, 5.1; N, 3.4%); ν_{max}(Nujol) 3 164, 1 730, 1 450, 1 376, 1 298, and 1 266 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.08 (1 H, s, 4-H), 7.93 (1 H, d, *J* 3.8 Hz, 2-H), 7.66 (2 H, d, *J* 7.3 Hz), 7.60 (1 H, t, *J* 7.3 Hz), 7.49 (2 H, t, *J* 7.4 Hz), 6.73 (1 H, d, *J* 3.8 Hz, 3-H), 4.01 (1 H, heptet, *J* 7.1 Hz, isopropyl CH), 3.88 (6 H, s, CO_2Me), and 1.09 (6 H, d, *J* 7.1 Hz, isopropyl CH_3); *m/z* 415 (M^+, 14%), 384 (13), 242 (100), 183 (18), and 77 (37).

Reaction of 7-isopropyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5(1H)-one* (**275e**) *with ethyl propiolate*.- A mixture of the pyranopyrrolone (**275e**) (57 mg, 0.18 mmol) and ethyl propiolate (88 mg, 0.90 mmol) in chlorobenzene (10 ml) was refluxed for 48 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give a mixture of *ethyl 7-isopropyl-1-phenylsulphonylindole-5-carboxylate* (**318d**) and *ethyl 7-isopropyl-1-phenylsulphonylindole-6-carboxylate* (**317d**) (33 mg, 49%) in the ratio 5 to 1. Recrystallisation from light petroleum gave pure

ethyl 7-isopropyl-1-phenylsulphonylindole-5-carboxylate (**318d**), m.p. 106-111°C (Found: C, 64.5; H, 5.7; N, 3.75. $C_{20}H_{21}NO_4S$ requires C, 64.7; H, 5.7; N, 3.8%); ν_{max}(Nujol) 1 712, 1 376, and 1 176 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.08 (1 H, d, *J* 1.6 Hz, 4-H), 7.90-7.88 (2 H, m), 7.65-7.62 (2 H, m), 7.57-7.55 (1 H, m), 7.49-7.44 (2 H, m), 6.77 (1 H, d, *J* 3.7 Hz, 3-H), 4.38 (2 H, q, *J* 7.1 Hz, ester CH_2), 3.89 (1 H, heptet, *J* 6.7 Hz, isopropyl CH), 1.40 (3 H, t, *J* 7.1 Hz, ester CH_3), and 1.03 (6 H, d, *J* 6.8 Hz, isopropyl CH_3); *m/z* 371 (M^+, 100%), 229 (35), 184 (54), 157 (44), and 77 (70).

Reaction of 7-isopropyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5*(1H)-*one* (**275e**) *with phenyl vinyl sulphoxide.*- A mixture of the pyranopyrrolone (**275e**) (90 mg, 0.28 mmol) and phenyl vinyl sulphoxide (130 mg, 0.85 mmol) in chlorobenzene (5 ml) was refluxed for 144 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *7-isopropyl-1-phenylsulphonylindole* (**324c**) (17 mg, 20%), m.p. 49-50°C (Found: M^+, 299.0988. $C_{17}H_{17}NO_2S$ requires *M*, 299.0980); ν_{max}($CHCl_3$) 1 446, 1 374, 1 354, 1 168, 1 122, and 1 104 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.79 (1 H, d, *J* 3.8 Hz, 2-H), 7.65-7.61 (2 H, m), 7.57-7.51 (1 H, m), 7.47-7.41 (2 H, m), 7.40-7.35 (1 H, m, 4-H), 7.23-7.19 (2 H, m, 5-H + 6-H), 6.69 (1 H, d, *J* 3.9 Hz, 3-H), 3.89 (1 H, heptet, *J* 6.7 Hz, isopropyl CH), and 1.02 (6 H, d, *J* 6.7 Hz, isopropyl CH_3); *m/z* 299 (M^+, 71%), 284 (13), 158 (100), 143 (28), 130 (21), 118 (39), and 77 (38).

Reaction of 4,7-dimethyl-1-phenylsulphonylpyrano[3,4-b]*pyrrol-5*(1H)-*one* (**275f**) *with dimethyl acetylenedicarboxylate.*- A mixture of the pyranopyrrolone (**275f**) (30 mg, 0.10 mmol) and dimethyl acetylenedicarboxylate (28 mg, 0.20 mmol) in chlorobenzene (5 ml) was refluxed for 12 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give *dimethyl 4,7-dimethyl-1-phenylsulphonylindole-5,6-dicarboxylate* (**316e**) (28 mg, 71%) as a colourless oil (Found: M^+, 401.0933. $C_{20}H_{19}NO_6S$ requires *M*, 401.0933); ν_{max}($CHCl_3$) 1 729, 1 372, and 1 175 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.91 (1 H, d, *J* 3.9 Hz, 2-H), 7.67-7.63 (2 H, m), 7.61-7.55 (1 H,

m), 7.49-7.43 (2 H, m), 6.80 (1 H, d, *J* 3.9 Hz, 3-H), 3.86 (3 H, s, CO_2Me), 3.84 (3 H, s, CO_2Me), 2.53 (3 H, s, ArMe), and 2.50 (3 H, s, ArMe); *m/z* 401 (M^+, 23%), 370 (17), 369 (14), 304 (21), 228 (100), and 77 (25).

Reaction of 4,7-*dimethyl*-1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275f**) *with ethyl propiolate*.- A mixture of the pyranopyrrolone (**275f**) (34 mg, 0.11 mmol) and ethyl propiolate (55 mg, 0.56 mmol) in chlorobenzene (5 ml) was refluxed for 12 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give a mixture of *ethyl* 4,7-*dimethyl*-1-*phenylsulphonylindole*-5-*carboxylate* (**318e**) and *ethyl* 4,7-*dimethyl*-1-*phenylsulphonylindole*-6-*carboxylate* (**317e**) (32 mg, 80%) in the ratio 1 to 1 as a colourless oil (Found: C, 63.9; H, 5.5; N, 3.95. $C_{19}H_{19}NO_4S$ requires C, 63.85; H, 5.4; N, 3.9%); ν_{max}($CHCl_3$) 1 709, 1 371, and 1 175 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.85 (1 H, d, *J* 3.9 Hz, 2-H), 7.84 (1 H, d, *J* 3.9 Hz, 2-H), 7.68-7.63 (m, both isomers), 7.59-7.52 (m, both isomers), 7.48-7.40 (m, both isomers), 6.87 (1 H, d, *J* 3.9 Hz, 3-H), 6.71 (1 H, d, *J* 3.9 Hz, 3-H), 4.35 (2 H, q, *J* 7 Hz, ester CH_2), 4.34 (2 H, q, *J* 7 Hz, ester CH_2), 2.71 (3 H, s, ArMe), 2.66 (3 H, s, ArMe), 2.50 (3 H, s, ArMe), 2.44 (3 H, s, ArMe), 1.38 (3 H, t, *J* 7 Hz, ester CH_3), and 1.37 (3 H, t, *J* 7 Hz, ester CH_3); *m/z* 357 (M^+, 100%), 312 (17), 216 (89), 188 (26), 170 (73), and 77 (32).

Reaction of 4,7-*dimethyl*-1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**275f**) *with benzyne*.- A mixture of the pyranopyrrolone (**275f**) (36 mg, 0.12 mmol), 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**) (46 mg, 0.24 mmol), and trifluoroacetic acid (1 drop) in acetonitrile (10 ml) was refluxed for 12 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give 4,9-*dimethyl*-1-*phenylsulphonylbenz*[f]*indole* (**322d**) (24 mg, 60%), m.p. 154-156°C (Found: C, 71.4; H, 5.0; N, 4.05. $C_{20}H_{17}NO_2S$ requires C, 71.6; H, 5.1 N, 4.1%); ν_{max}(Nujol) 1 367 and 1 176 cm^{-1}; δ(270 MHz; $CDCl_3$) 8.21-8.17 (1 H, m), 8.07-8.03 (1 H, m), 7.65 (1 H, d, *J* 3.9 Hz, 2-H), 7.56-7.51 (3 H, m), 7.40 (1 H, t, *J* 7.3 Hz), 7.31-7.27 (3 H, m), 6.83 (1 H, d, *J* 3.6 Hz,

3-H), 3.02 (3 H, s, ArMe), and 2.70 (3 H, s, ArMe); *m/z* 335 (M^+, 22%) and 194 (100).

Reaction of 4-*ethyl*-7-*methyl*-1-*phenylsulphonylpyrano*[3,4-b]-*pyrrol*-5(1H)-*one* (**275g**) *with phenyl vinyl sulphoxide*.- A mixture of the pyranopyrrolone (**275g**) (63 mg, 0.20 mmol) and phenyl vinyl sulphoxide (121 mg, 0.79 mmol) in chlorobenzene (5 ml) was refluxed for 48 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give 4-*ethyl*-7-*methyl*-1-*phenylsulphonylindole* (**324d**) (36 mg, 60%) as a yellow oil (Found: C, 68.3; H, 5.8; N, 4.7. $C_{17}H_{17}NO_2S$ requires C, 68.2; H, 5.7; N, 4.7%); ν_{max}(film) 1 446, 1 364, 1 176, and 1 120 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.80 (1 H, d, *J* 4.0 Hz, 2-H), 7.69-7.65 (2 H, m), 7.55-7.52 (1 H, m), 7.48-7.40 (2 H, m), 6.95 (2 H, s, 5-H + 6-H), 6.77 (1 H, d, *J* 3.8 Hz, 3-H), 2.83 (2 H, q, *J* 7.6 Hz, CH_2CH_3), 2.47 (3 H, s, 7-Me), and 1.28 (3 H, t, *J* 7.5 Hz, CH_2CH_3); *m/z* 299 (M^+, 30%), 158 (100), 143 (19), and 77 (15).

Intramolecular Diels-Alder reactions

7-(*Pent*-1-*yn*-5-*yl*)-1-*phenylsulphonylpyrano*[3,4-b]*pyrrol*-5(1H)-*one* (**325**).-Boron trifluoride diethyl ether (0.15 ml) was added dropwise to a solution of the acid (**307**) (193 mg, 0.73 mmol) in hex-5-ynoic anhydride (174 mg, 0.84 mmol) and ether (2 ml) at room temperature. The mixture was stirred for 24 h. Water was added and the mixture extracted with ethyl acetate. The combined extracts were washed with saturated sodium hydrogen carbonate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**325**) (38 mg, 15%) as a yellow oil, ν_{max}($CHCl_3$) 3 308, 1 709, 1 574, 1 381, and 1 177 cm^{-1}; λ_{max}(EtOH) 215 (ε 18 500) and 374 nm (3 070); δ(270 MHz; $CDCl_3$) 7.70-7.62 (3 H, m), 7.60 (1 H, d, *J* 3.9 Hz, 2-H), 7.54-7.48 (2 H, m), 6.27 (1 H, d, *J* 3.7 Hz, 3-H), 5.90 (1 H, s, 4-H), 3.17 (2 H, t, *J* 7.5 Hz, allylic CH_2), 2.28 (2 H, td, *J* 7, 1.5 Hz, propargylic CH_2), 1.98 (1 H, t, *J* 1.5 Hz, acetylenic CH), and 1.95 (2 H, m, $C{\equiv}CCH_2CH_2$); *m/z* 341 (M^+, 0.2%), 297 (65), 156 (100), and 77 (32).

1-*Phenylsulphonyl*-1,6,7,8-*tetrahydrocyclopenta*[g]*indole* (**326**).- A solution of the pyranopyrrolone (**325**) (30 mg, 0.09 mmol) in bromobenzene was refluxed for 5 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**326**) (17 mg, 65%), m.p. 128-131°C (lit.,[70] 133-134°C) (Found: C, 69.0; H, 5.3; N, 4.55. Calc for $C_{17}H_{15}NO_2S$ C, 68.7; H, 5.1; N, 4.7%); $\nu_{max}(CHCl_3)$ 1 377, 1 361, 1 173, and 728 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.73-7.68 (2 H, m), 7.66 (1 H, d, *J* 3.9 Hz, 2-H), 7.53-7.50 (1 H, m), 7.48-7.40 (2 H, m), 7.34 (1 H, d, *J* 8 Hz, 4-H), 7.14 (1 H, d, *J* 8 Hz, 5-H), 6.68 (1 H, d, *J* 3.9 Hz, 3-H), 3.19 (2 H, t, *J* 7.3 Hz, benzylic CH_2), 2.93 (2 H, t, *J* 7.3 Hz, benzylic CH_2), and 2.02 (2 H, quintet, *J* 7.4 Hz, $CH_2CH_2CH_2$); *m/z* 297 (M^+, 80%), 156 (100), and 77 (21).

4-*Ethyl*-1-*phenylsulphonyl*-1,6,7,8-*tetrahydrocyclopenta*[g]*indole* (**328**).- Boron trifluoride diethyl ether (0.25 ml, 2.03 mmol) was added dropwise to a solution of the acid (**310b**) (295 mg, 1.01 mmol) in hex-5-ynoic anhydride (309 mg, 1.50 mmol) and ether (1 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 12 h. Water was added and the mixture extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). Evaporation of the solvent gave the crude pyranopyrrolone (**327**) which was dissolved in acetic anhydride (30 ml) and refluxed for 2 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**328**) (29 mg, 9%), m.p. 92-94°C (Found: C, 70.0; H, 5.9; N, 4.25. $C_{19}H_{19}NO_2S$ requires C, 70.1; H, 5.9; N, 4.3%); $\nu_{max}(CHCl_3)$ 1 445, 1 360, 1 175, and 1 130 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.72-7.67 (3 H, m), 7.52 (1 H, t, *J* 7.5 Hz), 7.42 (2 H, t, *J* 7.8 Hz), 7.00 (1 H, s, 5-H), 6.74 (1 H, t, *J* 3.7 Hz, 3-H), 3.14 (2 H, t, *J* 7.3 Hz, benzylic CH_2), 2.91 (2 H, t, *J* 7.5 Hz, benzylic CH_2), 2.83 (2 H, q, *J* 7.6 Hz, CH_3CH_2), 2.00 (2 H, quintet, *J* 7.4 Hz, $CH_2CH_2CH_2$), and 1.27 (3 H, t, *J* 7.5 Hz, CH_3CH_2); *m/z* 325 (M^+, 43%), 184 (100), 155 (25), and 77 (35).

Methyl 2-(1-*phenylsulphonylpyrrol*-3-*yl*)*hept*-6-*ynoate* (**332a**).- n-Butyllithium (1.5 M, 0.80 ml) was added dropwise to a solution of *N*-

isopropylcyclohexylamine (170 mg, 1.20 mmol) in dry tetrahydrofuran (10 ml) at -78°C under nitrogen. The mixture was warmed to 0°C, stirred for 5 mins and recooled to -78°C. A solution of the ester (**306**) (305 mg, 1.09 mmol) in dry tetrahydrofuran (5 ml) was added dropwise, and the resulting solution stirred at -78°C for 2 h. 5-Iodopent-1-yne (434 mg, 2.24 mmol) in dry tetrahydrofuran (5 ml) was added, the mixture allowed to warm to room temperature, and stirred overnight. Water (30 ml) was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give the *title compound* (**332a**) (261 mg, 69%) as a colourless oil. (Found: C, 62.85; H, 5.7; N, 4.0. $C_{18}H_{19}NO_4S$ requires C, 62.6; H, 5.5; N, 4.1%); ν_{max}(film) 3 295, 2 952, 2 117, 1 734, 1 372, 1 176, and 1 064 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.85 (2 H, d, *J* 7 Hz), 7.60 (1 H, t, *J* 7.2 Hz), 7.50 (2 H, t, *J* 7.4 Hz), 7.10-7.08 (2 H, m, 2-H + 5-H), 6.28 (1 H, m, 4-H), 3.65 (3 H, s, CO_2Me), 3.46 (1 H, t, *J* 7.6 Hz, $CHCO_2Me$), 2.16 (2 H, td, *J* 7.1, 2.7 Hz, propargylic CH_2), 2.05-1.97 (1 H, m), 1.94 (1 H, t, *J* 2.7 Hz, acetylenic CH), 1.84-1.76 (1 H, m), and 1.44 (2 H, quintet, *J* 7.3 Hz, $C{\equiv}CCH_2CH_2$); *m/z* 345 (M^+, 1%), 204 (72), and 77 (100).

2-(1-*Phenylsulphonylpyrrol*-3-*yl*)*hept*-6-*ynoic acid* (**333a**).- A mixture of the ester (**332a**) (822 mg, 2.38 mmol) and lithium hydroxide hydrate (500 mg, 11.90 mmol) in tetrahydrofuran (2.5 ml) and water (2.5 ml) was stirred at room temperature for 24 h. Water (30 ml) was added, the mixture extracted with ethyl acetate, and this extract discarded. The aqueous layer was acidified and extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated to give the *title compound* (**333a**) (536 mg, 68%) as a colourless oil (Found: M^+, 331.0878. $C_{17}H_{17}NO_4S$ requires *M*, 331.0878); ν_{max}(film) 3 296, 3 200-2 400, 2 117, 1 708, 1 371, 1 176, 1 104, and 1 065 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.86-7.83 (2 H, m), 7.61-7.58 (1 H, m), 7.53-7.48 (2 H, m), 7.11 (2 H, d, *J* 2.4 Hz, 2-H + 5-H), 6.30 (1 H, t, *J* 2.4 Hz, 4-H), 3.47 (1 H, t, *J* 7.6 Hz, $CHCO_2H$), 2.17 (2 H, td, *J* 7, 2.7 Hz, propargylic CH_2), 2.07-2.02 (1 H, m), 1.94 (1 H, t, *J* 2.7 Hz, acetylenic CH), 1.84-1.81 (1 H,

m), and 1.50-1.44 (2 H, m, C≡CCH_2CH_2); *m/z* 331 (M^+, 1%), 286 (5), 190 (100), and 77 (92).

7-*Methyl*-4-(*pent*-1-*yn*-5-*yl*)-1-*phenylsulphonylpyrano*[3,4-b]-*pyrrol*-5(1H)-*one* (**334a**).- Boron trifluoride diethyl ether (0.33 ml, 2.7 mmol) was added dropwise to a stirred solution of the acid (**333a**) (440 mg, 1.33 mmol) in acetic anhydride (0.50 ml, 5.3 mmol) and ether (1 ml) at 0°C. The mixture was stirred at 0°C for 1 h and then at room temperature for 4 h. Water (30 ml) was added and the mixture extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water , brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**334a**) (89 mg, 19%) as a yellow oil; ν_{max}(film) 3 296, 2 933, 1 699, 1 584, 1 374, 1 176, and 1 083 cm^{-1}; λ_{max}(EtOH) 216 (ε 16 740), 325 (1 520), 369 (5 840), and 378 nm (5 670); δ(270 MHz; $CDCl_3$) 7.69-7.61 (3 H, m), 7.56 (1 H, d, *J* 3.9 Hz, 2-H) 7.53-7.47 (2 H, m), 6.44 (1 H, d, *J* 3.9 Hz, 3-H), 2.65 (3 H, s, 7-Me), 2.59 (2 H, t, *J* 7 Hz, allylic CH_2), 2.07 (2 H, td, *J* 6.8, 2.7 Hz, propargylic CH_2), 1.94 (1 H, t, *J* 2.7 Hz, acetylenic CH), and 1.78-1.68 (2 H, m, C≡CCH_2CH_2); *m/z* 311 (33), 170 (100), 155 (17), and 77 (9).

8-*Methyl*-1-*phenylsulphonyl*-1,4,5,6-*tetrahydrocyclopenta*[e]*indole* (**335a**).- A solution of the pyranopyrrolone (**334a**) (72 mg, 0.20 mmol) in toluene (20 ml) was refluxed for 1 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)]to give the *title compound* (**335a**) (43 mg, 68%), m.p. 108-110°C (Found: C, 69.45; H, 5.4; N, 4.4. $C_{18}H_{17}NO_2S$ requires C, 69.4; H, 5.5; N, 4.5%); ν_{max}(Nujol) 1 350, 1 171, and 1 127 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.78 (1 H, d, *J* 3.7 Hz, 2-H), 7.68-7.64 (2 H, m), 7.56-7.50 (1 H, m), 7.46-7.39 (2 H, m), 6.90 (1 H, s, 7-H), 6.62 (1 H, d, *J* 3.9 Hz, 3-H), 3.01 (2 H, t, *J* 7.4 Hz, benzylic CH_2), 2.92 (2 H, t, *J* 7.3 Hz, benzylic CH_2), 2.49 (3 H, s, 8-Me), and 2.15 (2 H, quintet, *J* 7 Hz, CH_2CH_2CH_2); *m/z* 311 (M^+, 34%), 170 (100), 155 (18), and 77 (12).

Methyl 2-(1-*phenylsulphonylpyrrol*-3-*yl*)*oct*-7-*ynoate* (**332b**).- n-Butyllithium (1.5 M, 0.60 ml) was added dropwise to a solution of *N*-isopropylcyclohexylamine (127 mg, 0.90 mmol) in dry tetrahydrofuran (10 ml) at -78°C under nitrogen. The mixture was warmed to 0°C, stirred for 5 mins, and recooled to -78°C. A solution of the ester (**306**) (229 mg, 0.82 mmol) in dry tetrahydrofuran (5 ml) was added dropwise and the resulting solution stirred at -78°C for 2 h. 6-Iodohex-1-yne (343 mg, 1.65 mmol) in dry tetrahydrofuran (5 ml) was added, the mixture allowed to warm to room temperature, and stirred overnight. Water (50 ml) was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give the *title compound* (**332b**) (205 mg, 70%) as a colourless oil (Found: C, 63.3; H, 5.9; N, 3.9. $C_{19}H_{21}NO_4S$ requires C, 63.5; H, 5.9; N, 3.9%); ν_{max}(film) 3 295, 2 948, 2 116, 1 735, 1 372, 1 176, and 1 063 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.86-7.82 (2 H, m), 7.63-7.57 (1 H, m), 7.53-7.47 (2 H, m), 7.10-7.05 (2 H, m, 2-H + 5-H), 6.27 (1 H, dd, *J* 3.2, 1.7 Hz, 4-H), 3.64 (3 H, s, CO_2Me), 3.44 (1 H, t, *J* 7.6 Hz, C*H*CO_2Me), 2.13 (2 H, td, *J* 6.8, 2.7 Hz, propargylic CH_2), 1.96-1.85 (1 H, m), 1.91 (1 H, t, *J* 2.7 Hz, acetylenic CH_2), 1.71-1.63 (1 H, m), 1.52-1.44 (2 H, m), and 1.37-1.25 (2 H, m); *m/z* 359 (M^+, 4%), 300 (26), 279 (16), 218 (100), 158 (28), 141 (32), and 77 (96).

2-(1-*Phenylsulphonylpyrrol*-3-*yl*)*oct*-7-*ynoic acid* (**333b**).- A mixture of the ester (**332b**) (725 mg, 2.02 mmol) and lithium hydroxide hydrate (423 mg, 10.08 mmol) in tetrahydrofuran (2.5 ml) and water (2.5 ml) was stirred at room temperature for 24 h. Water (20 ml) was added, the mixture extracted with ethyl acetate, and this extract discarded. The aqueous layer was acidified and extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated to give the *title compound* (**333b**) (450 mg, 64%), m.p. 94-97°C (Found: C, 62.4; H, 5.5; N, 4.0. $C_{18}H_{19}NO_4S$ requires C, 62.6; H, 5.5; N, 4.1%); ν_{max}(Nujol) 3 297, 3 200-2 400, 2 116, 1 708, 1 372, 1 176, 1 104, and 1 063 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.85 (2 H, d, *J* 7.3 Hz), 7.60 (1 H, t, *J* 7.3 Hz), 7.50 (2 H, t, *J* 7.4 Hz), 7.11-7.09 (2 H, m, 2-H + 5-H), 6.28 (1

H, m, 4-H), 3.44 (1 H, t, *J* 7 Hz, C*H*CO_2H), 2.13 (2 H, td, *J* 6.8, 2.7 Hz, propargylic CH_2), 1.94-1.88 (1 H, m), 1.90 (1 H, t, *J* 2.7 Hz, acetylenic CH), 1.70-1.65 (1 H, m), 1.53-1.45 (2 H, m), and 1.40-1.28 (2 H, m); *m/z* 345 (M^+, 3%), 300 (14), 265 (17), 220 (15), 204 (100), 141 (30), and 77 (99).

4-(*Hex*-1-*yn*-6-*yl*)-7-*methyl*-1-*phenylsulphonylpyrano*[3,4-b]-*pyrrol*-5(1H)-*one* (**334b**).- Boron trifluoride diethyl ether (0.27 ml, 2.2 mmol) was added dropwise to a stirred solution of the acid (**333b**) (384 mg, 1.11 mmol) in acetic anhydride (0.42 ml, 4.45 mmol) and ether (1 ml) at 0°C. The mixture was stirred at 0°C for 1 h and then at room temperature for 4 h. Water (30 ml) was added and the mixture extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate solution, water , brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**334b**) (66 mg, 16%), m.p. 105-108°C (Found: C, 65.0; H, 5.2; N, 3.7. $C_{20}H_{19}NO_4S$ requires C, 65.0; H, 5.2; N, 3.8%); ν_{max}(Nujol) 3 296, 2 116, 1 698, 1 586, 1 373, and 1 185 cm^{-1}; λ_{max}(EtOH) 215 (ε 15 460), 217 (15 490), 370 (8 365), and 377 nm (8 650); δ(270 MHz; $CDCl_3$) 7.68-7.60 (3 H, m), 7.56 (1 H, d, *J* 3.9 Hz, 2-H) 7.50 (2 H, t, *J* 7.4 Hz), 6.34 (1 H, d, *J* 3.9 Hz, 3-H), 2.65 (3 H, s, 7-Me), 2.46 (2 H, t, *J* 7.3 Hz, allylic CH_2), 2.16 (2 H, td, *J* 7, 2.7 Hz, propargylic CH_2), 1.92 (1 H, t, *J* 2.7 Hz, acetylenic CH), 1.60-1.55 (2 H, m), and 1.47-1.41 (2 H, m); *m/z* 369 (M^+, 15%), 325 (11), 200 (27), 184 (45), 158 (77), 77 (55), and 43 (100).

9-*Methyl*-1-*phenylsulphonyl*-4,5,6,7-*tetrahydrobenz*[*e*]*indole* (**335b**).- A solution of the pyranopyrrolone (**334b**) (55 mg, 0.15 mmol) in bromobenzene (15 ml) was refluxed for 12 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**335b**) (38 mg, 78%), m.p. 80-82°C (Found: C, 69.9; H, 5.9; N, 4.2. $C_{19}H_{19}NO_2S$ requires C, 70.1; H, 5.9; N, 4.3%); ν_{max}(Nujol) 1 485, 1 358, and 1 175 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.76 (1 H, d, *J* 3.9 Hz, 2-H), 7.66 (2 H, dd, *J* 7.2, 1.6 Hz), 7.51 (1 H, t, *J* 7.3 Hz), 7.45 (2 H, t, *J* 7.5

Hz), 6.73 (1 H, s, 8-H), 6.68 (1 H, d, *J* 3.7 Hz, 3-H), 2.85 (2 H, t, *J* 6 Hz, benzylic CH_2), 2.73 (2 H, t, *J* 6 Hz, benzylic CH_2), 2.44 (3 H, s, 9-Me), and 1.86-1.78 (4 H, m, $CH_2CH_2CH_2CH_2$); *m/z* 325 (M^+, 40%), 184 (100), 169 (13), and 77 (9).

N-*phenylsulphonyl cleavage*

8-*Methyl*-1,4,5,6-*tetrahydrocyclopenta*[e]*indole* (**336**).- A mixture of the *N*-phenylsulphonylindole (**335a**) (28 mg, 0.09 mmol) and potassium hydroxide (0.6 g, 10.7 mmol) in 1,2-dimethoxyethane (1 ml), methanol (1 ml), and water (1 ml) was refluxed for 15 h. The mixture was allowed to cool to room temperature, diluted with water, and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated to give the *title compound* (**336**) (15 mg, 97%), m.p. 143-146°C (Found: M^+, 171.1048. $C_{12}H_{13}N$ requires *M*, 171.1048); $\nu_{max}(CHCl_3)$ 3 480 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.07 (1 H,br, NH), 7.21 (1 H, t, *J* 2.8 Hz, 2-H), 6.93 (1 H, s, 7-H), 6.47 (1 H, dd, *J* 3.1, 2.1 Hz, 3-H), 3.08 (2 H, t, *J* 7.4 Hz, benzylic CH_2), 2.99 (2 H, t, *J* 7.3 Hz, benzylic CH_2), 2.48 (3 H, s, 8-Me), and 2.17 (2 H, quintet, *J* 7.3 Hz, $CH_2CH_2CH_2$); *m/z* 171 (M^+, 100%), 156 (67), 142 (10), 128 (10), 115 (8), 84 (11), and 77 (12).

7-*Methylindole* (**337**).- A mixture of the *N*-phenylsulphonylindole (**324a**) (40 mg, 0.15 mmol) and potassium hydroxide (1.2 g, 21.4 mmol) in 1,2-dimethoxyethane (2 ml), methanol (2 ml), and water (2 ml) was refluxed under nitrogen for 24 h. The mixture was allowed to cool to room temperature, diluted with water, and extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**337**) (14.5 mg, 75%), m.p. 81-83°C (lit.,[89b] 82°C), $\nu_{max}(CHCl_3)$ 3 480, 1 426, and 1 338 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.05 (1 H, br, NH), 7.51 (1 H, d, *J* 7.5 Hz, 4-H), 7.20 (1 H, t, *J* 2.8 Hz, 2-H), 7.05-7.01 (2 H, m, 5-H + 6-H), 6.56 (1 H, dd, *J* 3.1, 2.0 Hz, 3-H), and 2.50 (3

H, s, 7-Me); *m/z* 131 (M^+, 78%), 130 (100), 103 (12), and 77 (24).

9-*Methylbenz*[f]*indole* (**338**).- A mixture of the *N*-phenylsulphonylindole (**322b**) (23 mg, 0.07 mmol) and potassium hydroxide (1.2 g, 21.4 mmol) in 1,2-dimethoxyethane (2 ml), methanol (2 ml), and water (2 ml) was refluxed under nitrogen for 24 h. The mixture was allowed to cool to room temperature, diluted with water, and extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**338**) (9 mg, 69%), m.p. 53-55°C (Found: M^+, 181.0891. $C_{13}H_{11}N$ requires *M*, 181.0891); $\nu_{max}(CHCl_3)$ 3 484, and 1 412 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.08 (1 H, d, *J* 8.5 Hz), 8.04 (1 H, s, 4-H), 7.95 (1 H, d, *J* 8.0 Hz), 8.1-7.9 (1 H, br, NH), 7.43-7.34 (3 H, m), 6.67 (1 H, dd, *J* 3.3, 1.9 Hz, 3-H), and 2.82 (3 H, s, 9-Me); *m/z* 181 (M^+, 100%), 180 (87), 152 (21), 91 (11), and 77 (15).

6,7-*Dimethyl*-5-*trimethylsilylindole* (**339**).- The ester (**321a**) (49 mg, 0.12 mmol) was added to a suspension of lithium aluminium hydride (45 mg, 1.2 mmol) in dry dioxane (5 ml) and the mixture refluxed under nitrogen for 24 h. The excess lithium aluminium hydride was destroyed by careful addition of water (0.5 ml) followed by solid sodium hydrogen carbonate until a white granular precipitate resulted. The mixture was diluted with ether (50 ml), filtered through Celite, and the filtrate dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give the *title compound* (**339**) (19 mg, 74%), m.p. 65-72°C (Found: M^+, 217.1270. $C_{13}H_{19}NSi$ requires *M*, 217.1287); ν_{max}(Nujol) 3 412 and 838 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.98 (1 H, br, NH), 7.67 (1 H, s, 4-H), 7.13 (1 H, t, *J* 2.8 Hz, 2-H), 6.51 (1 H, dd, *J* 3.1, 2.0 Hz, 3-H), 2.50 (3 H, s, ArMe), 2.40 (3 H, s, ArMe), and 0.36 (9 H, s, Me_3Si); *m/z* 217 (M^+, 45%), 202 (100), and 144 (11).

Other routes to pyrano[3,4-b]*pyrrol*-5(1H)-*ones*

N-*t-Butyl* 1-*phenylsulphonylpyrrol*-3-*ylacetamide* (**340**).- Oxalyl chloride (2 ml) was added to a suspension of 1-phenylsulphonylpyrrol-3-ylacetic acid (**307**) (1.04 g, 3.93 mmol) in dry benzene (2 ml) and the mixture stirred for 1 h. The solution was evaporated under reduced pressure and the residue dissolved in dry benzene (5 ml). This solution was added to a stirred solution of t-butylamine (5 ml, 47.5 mmol) in dry benzene (20 ml) at 0°C. The mixture was stirred at room temperature for 2 h, poured into water, and extracted with ether. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue recrystallised (light petroleum) to give the *title compound* (**340**) (1.11 g, 88%), m.p. 145-148°C (Found: C, 59.8; H, 6.4; N, 8.7. $C_{16}H_{20}N_2O_3S$ requires C, 60.0; H, 6.3; N, 8.7%); ν_{max}(Nujol) 3 303, 1 656, 1 554, 1 379, and 1 174 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.88-7.84 (2 H, m), 7.64-7.58 (1 H, m), 7.55-7.47 (2 H, m), 7.15 (1 H, dd, *J* 3.2, 2.2 Hz, 5-H), 7.05 (1 H, m, 2-H), 6.22 (1 H, dd, *J* 3.2, 1.5 Hz, 4-H), 5.2 (1 H, br, NH), 3.26 (2 H, s, $CH_2CONHBu^t$), and 1.25 (9 H, s, t-Bu); *m/z* 320 (M^+, 9%), 221 (100), 220 (87), 141 (35), 80 (47), 77 (56), and 57 (71).

N-*t-Butyl*-1-*phenylsulphonyl*-2-*trimethylsilylpyrrol*-3-*ylacetamide* (**343**).- n-Butyllithium (1.55 M, 0.58 ml) was added dropwise to a solution of the amide (**340**) (132 mg, 0.41 mmol) in dry tetrahydrofuran (10 ml) under nitrogen at -78°C. The mixture was stirred for 1.5 h, trimethylsilyl chloride (0.10 ml, 0.82 mmol) was added, and the mixture allowed to warm to room temperature. After stirring overnight, saturated ammonium chloride solution was added and the mixture extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (ether) to give the *title compound* (**343**) (70 mg, 43%), m.p. 107-115°C (Found: C, 58.3; H, 7.35; N, 7.05. $C_{19}H_{28}N_2O_3SSi$ requires C, 58.1; H, 7.2; N, 7.1%); ν_{max}(Nujol) 3 274, 1 642, 1 550, 1 372, 1 174, and 846 cm^{-1}; δ(270 MHz; $CDCl_3$) 7.61-7.47 (6 H, m, 5-H + SO_2Ph), 6.25 (1 H, d, *J* 3.2 Hz, 4-H), 5.2 (1 H, br, NH), 3.45 (2 H, s, $CH_2CONHBu^t$), 1.24 (9 H, s, t-Bu), and 0.32 (9 H, s, Me_3Si); *m/z*

393 (MH^+, 2%), 392 (M^+, 0.3%), 377 (91), 321 (100), and 292 (20).

Methyl 2-acetyl-1-phenylsulphonylpyrrol-3-ylacetate (**346a**).- A solution of the pyranopyrrolone (**275b**) (36 mg, 0.13 mmol) in methanol (3 ml) was refluxed for 2 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give the *title compound* (**346a**) (28 mg, 70%), m.p. 67-68 °C (Found: C, 56.3; H, 4.7; N, 4.4. $C_{15}H_{15}NO_5S$ requires C, 56.1; H, 4.7; N, 4.4%); $\nu_{max}(CHCl_3)$ 3 028, 1 738, and 1 637 cm^{-1} ; δ(270 MHz; $CDCl_3$) 7.84 (2 H, d, *J* 7 Hz), 7.60 (1 H, m), 7.50 (2 H, t, *J* 7 Hz), 7.41 (1 H, d, *J* 3.4 Hz, 5-H), 6.27 (1 H, d, *J* 3.2 Hz, 4-H), 3.68 (3 H, s, CO_2Me), 3.59 (2 H, s, CH_2CO_2Me), and 2.53 (3 H, s, CH_3CO); *m/z* 321 (M^+, 14%), 290 (5), 278 (9), 262 (8), 180 (48), 141 (27), and 77 (100).

Methyl 1-phenylsulphonyl-2-propionylpyrrol-3-ylacetate (**346b**).- A solution of the pyranopyrrolone (**275c**) (680 mg, 2.24 mmol) in methanol (50 ml) and sulphuric acid (0.2 ml) was refluxed for 3 h under nitrogen. After cooling to room temperature, the mixture was concentrated *in vacuo*, diluted with water, and extracted with ether. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give the *title compound* (**346b**) (704 mg, 94%), m.p. 51-53°C (Found: C, 57.3; H, 5.1; N, 4.1. $C_{16}H_{17}NO_5S$ requires C, 57.3; H, 5.1; N, 4.2%); ν_{max}(Nujol) 1 738, 1 674, 1 372, and 1 174 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.83 (2 H, d, *J* 7 Hz), 7.60 (1 H, m), 7.51 (2 H, t, *J* 7.5 Hz), 7.29 (1 H, d, *J* 3.2 Hz, 5-H), 6.26 (1 H, d, *J* 3.3 Hz, 4-H), 3.67 (3 H, s, CO_2Me), 3.51 (2 H, s, CH_2CO_2Me), 2.87 (2 H, q, *J* 7.3 Hz, CH_3CH_2), and 1.18 (3 H, t, *J* 7.3 Hz, CH_3CH_2); *m/z* 335 (M^+, 7%), 306 (12), 278 (37), 194 (11), 141 (25), 106 (45), and 77 (100).

Preparation of pyrano[4,3-b]*pyrrol*-6(1H)-*ones*

Ethyl 3,5-*diformylpyrrol*-2-*ylacetate* (**354a**).- A solution of dimethylformamide (0.73 ml, 9.42 mmol) in 1,2-dichloroethane (15 ml) was cooled in an ice-salt bath. A solution of oxalyl chloride (0.58 ml, 6.67 mmol) in 1,2-dichloroethane (5 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 15 mins. The mixture was cooled in ice and a solution of ethyl pyrrol-2-ylacetate (941 mg, 6.14 mmol) in 1,2-dichloroethane (5 ml) added dropwise. The mixture was allowed to warm to room temperature, stirred for 15 mins, and then recooled in ice. Aluminium chloride (3.64 g, 27.27 mmol) was added and the mixture warmed to room temperature over 10 mins. Nitromethane (1.10 ml, 20.4 mmol) was added, the mixture cooled in ice, and dichloromethyl methyl ether (0.83 ml, 9.22 mmol) added rapidly. The mixture was stirred for 4 h at room temperature, poured into ice-water, and stirred for 5 h. The mixture was extracted with dichloromethane. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed [ether-light petroleum (4:1)] to give the *title compound* (**354a**) (771 m g, 60%), m.p. 74-76°C (Found: C, 57.2; H, 5.3; N, 6.7. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%); ν_{max}(Nujol) 3 212, 1 728, 1 646, and 1 208 cm^{-1}; δ(250 MHz; $CDCl_3$) 10.93 (1 H, br, NH), 9.91 (1 H, s, CHO), 9.56 (1 H, s, CHO), 7.34 (1 H, d, *J* 2.5 Hz, 4-H), 4.22 (2 H, q, *J* 7.1 Hz, ester CH_2), 4.16 (2 H, s, CH_2CO_2Et), and 1.31 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 209 (M^+, 24%), 181 (4), 163 (49), and 136 (100).

Ethyl 3-*formylpyrrol*-2-*ylacetate* (**355a**).- A mixture of the dialdehyde (**354a**) (1.04 g, 4.97 mmol) and palladium on activated carbon (10%, 90 mg) in mesitylene (20 ml) was refluxed for 5 h under nitrogen. The mixture was allowed to cool to room temperature, diluted with dichloromethane, and filtered through Celite. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**355a**) (563 mg, 63%) as a yellow oil (Found: M^+, 181.0739. $C_9H_{11}NO_3$ requires *M*, 181.0739); ν_{max}(film) 3 312 (br), 1 730, and 1 658 cm^{-1}; δ(250 MHz; $CDCl_3$) 9.87 (1 H, s, CHO), 9.85 (1 H, br, NH), 6.74 (1 H, dd, *J* 3.0, 2.5

Hz), 6.60 (1 H, t, *J* 2.9 Hz), 4.22 (2 H, q, *J* 7.1 Hz, ester CH_2), 4.10 (2 H, s, CH_2CO_2Et), and 1.30 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 181 (M^+, 27%), 135 (45), 108 (100), and 80 (20).

3-*Formylpyrrol-2-ylacetic acid* (**356a**).- Potassium hydroxide solution (2M, 15 ml) was added dropwise to a solution of ethyl 3-formylpyrrol-2-ylacetate (**355a**) (321 mg, 1.77 mmol) in tetrahydrofuran (9 ml) and methanol (1 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 2 h. Water was added, the mixture extracted with ether, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), the solvent evaporated, and the residue recrystallised (ethyl acetate-light petroleum) to give the *title compound* (**356a**) (226 mg, 83%), m.p. 170-175°C (decomp.) (Found: MH^+, 154.0504. $C_7H_7NO_3$ requires *M*H, 154.0504); ν_{max}(Nujol) 3 356, 1 710, 1 606, 1 544, 1 464, 1 376, and 1 246 cm^{-1}; δ[250 MHz; $CDCl_3$+$(CD_3)_2SO$] 11.2 (1 H, br, NH), 9.82 (1 H, s, CHO), 6.69 (1 H, t, *J* 2.7 Hz), 6.51 (1 H, t, *J* 2.7 Hz), and 3.94 (2 H, s, CH_2CO_2H); *m/z* 154 (MH^+, 18%),153 (M^+, 12), 135 (26), 109 (82), 108 (100), and 80 (44).

Pyrano[4,3-b]*pyrrol*-6(1H)-*one* (**276a**).- A mixture of 3-formylpyrrol-2-ylacetic acid (**356a**) (234 mg, 1.53 mmol) and triethylamine (0.64 ml, 4.58 mmol) in dry tetrahydrofuran (25 ml) was stirred at 0°C. Isobutyl chloroformate (219 mg, 1.60 mmol) in dry tetrahydrofuran (5 ml) was added dropwise. The mixture was stirred at room temperature for 3 h, poured into brine, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed [ether-methanol (9:1)] to give the *title compound* (**276a**) (140 mg, 68%), m.p. ~70°C (darkens) (Found: C, 62.3; H, 3.7; N, 10.5. $C_7H_5NO_2$ requires C, 62.2; H, 3.7; N, 10.4%); ν_{max}(Nujol) 3 104 (br), 1 678, and 1 588 cm^{-1}; δ[250 MHz; $CDCl_3$ + $(CD_3)_2SO$] 10.4 (1 H, br, NH), 7.97 (1 H, s, 4-H), 6.91 (1 H, dd, *J* 3.7, 2.0 Hz, 2-H), 6.12 (1 H, m, 3-H), and 5.73 (1 H, s, 7-H); *m/z* 135 (M^+, 40%), 107 (29), 79 (51), and 52 (100).

Isobutyl 6-*oxopyrano*[4,3-b]*pyrrole*-1-*carboxylate* (**277a**).- A mixture of 3-formylpyrrol-2-ylacetic acid (**356a**) (153 mg, 1.00 mmol) and triethylamine (0.56 ml, 4.00 mmol) in dry tetrahydrofuran (10 ml) was stirred at 0°C. Isobutyl chloroformate (0.29 ml, 2.20 mmol) in dry tetrahydrofuran (5 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into brine and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed (ether) to give the *title compound* (**277a**) (198 mg, 84%), m.p. 77-78°C (Found: C, 61.1; H, 5.5; N, 6.0. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.6; N, 6.0%); ν_{max}(Nujol) 1 738 and 1 688 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.79 (1 H, s, 4-H), 7.27 (1 H, d, *J* 3.4 Hz, 2-H), 6.74 (1 H, brs, 7-H), 6.23 (1 H, d, *J* 4.1 Hz, 3-H), 4.18 (2 H, d, *J* 6.7 Hz, isobutyl CH_2), 2.10 (1 H, m, isobutyl CH), and 1.02 (6 H, d, *J* 6.7 Hz, isobutyl CH_3); *m/z* 235 (M^+, 12%), 179 (10), 135 (15), 107 (19), 79 (14), 57 (100), 51 (26), and 41 (79).

Ethyl 3-*Acetyl*-5-*formylpyrrol*-2-*ylacetate* (**354b**).- A solution of dimethylformamide (1.71 ml, 22.12 mmol) in 1,2-dichloroethane (30 ml) was cooled in an ice-salt bath. A solution of oxalyl chloride (1.37 ml, 15.66 mmol) in 1,2-dichloroethane (15 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 15 mins. The mixture was cooled in ice and a solution of ethyl pyrrol-2-ylacetate (**348**) (2.21 g, 14.43 mmol) in 1,2-dichloroethane (15 ml) added dropwise. The mixture was allowed to warm to room temperature, stirred for 15 mins, and then recooled in ice. Aluminium chloride (8.54 g, 64.05 mmol) was added and the mixture warmed to room temperature over 10 mins. Nitromethane (2.60 ml, 47.9 mmol) was added, the mixture cooled in ice, and acetyl chloride (1.54 ml, 21.65 mmol) added rapidly. The mixture was stirred for 4 h at room temperature, poured into ice-water (200 ml), and stirred for a further 4 h. The mixture was extracted with dichloromethane. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The resulting solid was recrystallised (dichloromethane-light petroleum) to give the *title compound* (**354b**) (2.95 g, 92%), m.p. 109-111°C (Found: C, 59.1; H, 5.9; N, 6.2. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.9; N, 6.3%); ν_{max}(Nujol) 3 228, 1 730, and 1 642

cm^{-1}; δ(250 MHz; $CDCl_3$) 10.94 (1 H, br, NH), 9.52 (1 H, s, CHO), 7.29 (1 H, s, 4-H), 4.23 (2 H, q, *J* 7.1 Hz, ester CH_2), 4.19 (2 H, s, CH_2CO_2Et), 2.47 (3 H, s, CH_3CO), and 1.30 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 223 (M^+, 32%), 177 (100), 149 (40), 136 (26), and 78 (25).

Ethyl 3-*Acetylpyrrol*-2-*ylacetate* (**355b**).- A mixture of ethyl-3-acetyl-5-formylpyrrol-2-ylacetate (**354b**) (2.548 g, 11.41 mmol) and palladium on activated carbon (5%, 335 mg) in mesitylene (30 ml) was refluxed for 10 h under nitrogen. The mixture was allowed to cool to room temperature, diluted with dichloromethane, and filtered through Celite. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**355b**) (2.143 g, 96%) as a yellow oil (Found: M^+, 195.0892. $C_{10}H_{13}NO_3$ requires *M*, 195.0895); ν_{max}(film) 3 312, 3 120, 1 734, 1 638, and 1 562 cm^{-1}; δ(250 MHz; $CDCl_3$) 9.83 (1 H, br, NH), 6.67 (1 H, m), 6.54 (1 H, t, *J* 2.9 Hz), 4.21 (2 H, q, *J* 7.1 Hz, ester CH_2), 4.16 (2 H, s, CH_2CO_2Et), 2.42 (3 H, s, CH_3CO), and 1.30 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 195 (M^+, 34%), 149 (58), and 122 (100).

3-*Acetylpyrrol*-2-*ylacetic acid* (**356b**).- Potassium hydroxide solution (2M, 15 ml) was added dropwise to a solution of ethyl 3-acetylpyrrol-2-ylacetate (**355b**) (503 mg, 2.58 mmol) in tetrahydrofuran (18 ml) and methanol (2 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 4 h. Water was added, the mixture extracted with ethyl acetate, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), the solvent evaporated, and the residue recrystallised (ethyl acetate-light petroleum) to give the *title compound* (**356b**) (380 mg, 88%), m.p. 175-180°C (decomp.) (Found: C, 57.4; H, 5.4; N, 8.25. $C_8H_9NO_3$ requires C, 57.5; H, 5.4; N, 8.4%); ν_{max}(Nujol) 3 344, 1 706, and 1 632 cm^{-1}; δ[250 MHz; $CDCl_3$+$(CD_3)_2SO$] 10.93 (1 H, br, NH), 6.65 (1 H, m), 6.52 (1 H, t, *J* 2.6 Hz), 4.00 (2 H, s, CH_2CO_2H), and 2.44 (3 H, s, CH_3CO); *m/z* 167 (M^+, 27%), 149 (23), 123 (72), and 108 (100).

4-Methylpyrano[4,3-b]*pyrrol*-6(1H)-*one* (**276b**).- A mixture of 3-acetylpyrrol-2-ylacetic acid (**356b**) (570 mg, 3.41 mmol) and triethylamine (1.43 ml, 10.23 mmol) in dry tetrahydrofuran (60 ml) was stirred at 0°C. Isobutyl chloroformate (489 mg, 3.58 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was stirred at room temperature for 5 h, poured into brine, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed [ether-methanol (9:1)] to give the *title compound* (**276b**) (433 mg, 85%), m.p. 130°C (decomp.) (Found: M^+, 149.0485. $C_8H_7NO_2$ requires M, 149.0477); ν_{max}(Nujol) 3 104, 1 698, 1 662, 1 632, 1 610, 1 584, and 1 534 cm^{-1}; δ(250 MHz; $CDCl_3$) 9.52 (1 H, br, NH), 6.89 (1 H, dd, *J* 3.7, 2.0 Hz, 2-H), 6.15 (1 H, dd, *J* 3.4, 1.6 Hz, 3-H), 5.74 (1 H, s, 7-H), and 2.52 (3 H, s, 4-Me); *m/z* 149 (M^+, 100%), 134 (51), and 121 (37).

Isobutyl 4-methyl-6-oxopyrano[4,3-b]*pyrrole-1-carboxylate* (**277b**).- A mixture of 3-acetylpyrrol-2-ylacetic acid (**356b**) (606 mg, 3.63 mmol) and triethylamine (2.02 ml, 14.50 mmol) in dry tetrahydrofuran (60 ml) was stirred at 0°C. Isobutyl chloroformate (1.03 ml, 7.98 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to warm to room temperature, stirred overnight, poured into brine, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed (ether) to give the *title compound* (**277b**) (779 mg, 86%), m.p. 109-110°C (Found: C, 62.6; H, 6.0; N, 5.5. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.1; N, 5.6%); ν_{max}(Nujol) 1 734, 1 702, 1 658, and 1 584 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.22 (1 H, d, *J* 4.1 Hz, 2-H), 6.59 (1 H, brs, 7-H), 6.22 (1 H, dd, *J* 4.2, 0.8 Hz, 3-H), 4.18 (2 H, d, *J* 6.7 Hz, isobutyl CH_2), 2.46 (3 H, s, 4-Me), 2.11 (1 H, m, isobutyl CH), and 1.03 (6 H, d, *J* 6.7 Hz, isobutyl CH_3); *m/z* 249 (M^+, 24%), 149 (36), 121 (21), 57 (100), 41 (71), and 29 (69).

Ethyl 3-benzoyl-5-formylpyrrol-2-ylacetate (**354c**).- A solution of dimethylformamide (1.66 ml, 21.45 mmol) in 1,2-dichloroethane (20 ml) was cooled in an ice-salt bath. A solution of oxalyl chloride (1.37 ml, 15.7 mmol) in 1,2-dichloroethane (20 ml) was added dropwise. The mixture was allowed to

warm to room temperature and stirred for 15 mins. The mixture was cooled in ice and a solution of ethyl pyrrol-2-ylacetate (**348**) (2.19 g, 14.30 mmol) in 1,2-dichloroethane (20 ml) added dropwise. The mixture was allowed to warm to room temperature, stirred for 15 mins, and then recooled in ice. Aluminium chloride (8.47 g, 63.48 mmol) was added and the mixture warmed to room temperature over 10 mins. Nitromethane (2.57 ml, 47.5 mmol) was added, the mixture cooled in ice, and benzoyl chloride (2.49 ml, 21.45 mmol) added rapidly. The mixture was stirred for 6 h at room temperature, poured into ice-water (200 ml), and stirred overnight. The mixture was extracted with dichloromethane. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The resulting oil was chromatographed [ether-light petroleum (4:1)] to give the *title compound* (**354c**) (1.64 g, 40%), m.p. 112-113°C (Found: C, 67.3; H, 5.2; N, 4.85. $C_{16}H_{15}NO_4$ requires C, 67.4; H, 5.3; N, 4.9%); ν_{max}(Nujol) 3 228, 1 730, 1 644, and 1 630 cm^{-1}; δ(250 MHz; $CDCl_3$) 10.87 (1 H, br, NH), 9.52 (1 H, s, CHO), 7.80 (2 H, d, *J* 8 Hz), 7.61-7.46 (3 H, m), 7.17 (1 H, d, *J* 2.5 Hz, 4-H), 4.26 (2 H, q, *J* 7.1 Hz, ester CH_2), 4.25 (2 H, s, CH_2CO_2Et), and 1.31 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 285 (M^+, 57%), 239 (94), 211 (100), 183 (48), and 77 (46).

Ethyl 3-benzoylpyrrol-2-ylacetate (**355c**).- A mixture of ethyl-3-benzoyl-5-formylpyrrol-2-ylacetate (**354c**) (1.06 g, 3.72 mmol) and palladium on activated carbon (5%, 110 mg) in mesitylene (15 ml) was refluxed for 12 h under nitrogen. The mixture was allowed to cool to room temperature, diluted with dichloromethane, and filtered through Celite. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**355c**) (860 mg, 90%), m.p. 84-85°C (Found: C, 70.0; H, 5.9; N, 5.4. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.45%); ν_{max}(Nujol) 3 208, 1 738, 1 598, and 1 560 cm^{-1}; δ(250 MHz; $CDCl_3$) 9.9 (1 H, br, NH), 7.81 (2 H, d, *J* 8 Hz), 7.52-7.41 (3 H, m), 6.70 (1 H, t, *J* 2.7 Hz), 6.44 (1 H, t, *J* 2.8 Hz), 4.24 (2 H, q, *J* 7.1 Hz, ester CH_2), 4.22 (2 H, s, CH_2CO_2Et), and 1.31 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 257 (M^+, 60%), 211 (85), 184 (93), 183 (100), and 77 (41).

3-*Benzoylpyrrol*-2-*ylacetic acid* (**356c**).- Potassium hydroxide solution (2M, 12 ml) was added dropwise to a solution of ethyl 3-benzoylpyrrol-2-ylacetate (**355c**) (612 mg, 2.38 mmol) in tetrahydrofuran (18 ml) and methanol (2 ml) at 0°C. The mixture was allowed to warm to room temperature and stirred for 4 h. Water was added, the mixture extracted with ether, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), the solvent evaporated, and the residue recrystallised (ether-light petroleum) to give the *title compound* (**356c**) (513 mg, 94%), m.p. 151-152°C (decomp.) (Found: M^+, 229.0739. $C_{13}H_{11}NO_3$ requires M, 229.0739.); ν_{max}(Nujol) 3 260, 1 768, and 1 594 cm^{-1}; δ(250 MHz; $CDCl_3$) 11.04 (1 H, br, NH), 7.68 (2 H, d, *J* 8 Hz), 7.43-7.27 (3 H, m), 6.53 (1 H, t, *J* 2.7 Hz), 6.24 (1 H, t, *J* 2.7 Hz), and 3.85 (2 H, s, CH_2CO_2H); *m/z* 229 (M^+, 5%), 211 (9), 184 (100), 108 (91), and 77 (30).

Isobutyl 6-*oxo*-4-*phenylpyrano*[4,3-b]*pyrrole*-1-*carboxylate* (**277c**).- A mixture of 3-benzoylpyrrol-2-ylacetic acid (**356c**) (411 mg, 1.79 mmol) and triethylamine (1.00 ml, 7.17 mmol) in dry tetrahydrofuran (40 ml) was stirred at 0°C under nitrogen. Isobutyl chloroformate (539 mg, 3.94 mmol) in dry tetrahydrofuran (10 ml) was added dropwise. The mixture was allowed to warm to room temperature, stirred overnight, poured into brine, and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed [ether-light petroleum (3:1)] to give the *title compound* (**277c**) (512 mg, 92%), m.p. 109-110°C (Found: C, 69.3; H, 5.3; N, 4.4. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%); ν_{max}(Nujol) 1 748, 1 700, 1 638, and 1 558 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.85 (2 H, m), 7.56-7.50 (3 H, m), 7.35 (1 H, d, *J* 4.2 Hz, 2-H), 6.79 (1 H, brs, 7-H), 6.59 (1 H, d, *J* 4.2 Hz, 3-H), 4.21 (2 H, d, *J* 6.7 Hz, isobutyl CH_2), 2.13 (1 H, m, isobutyl CH), and 1.04 (6 H, d, *J* 6.7 Hz, isobutyl CH_3); *m/z* 311 (M^+, 13%), 255 (17), 211 (15), 77 (46), 57 (78), and 41 (100).

Diels-Alder reactions of pyrano[4,3-b]*pyrrol*-6(1H)-*ones*

Reaction of pyrano[4,3-b]*pyrrol*-6(1H)-*one* (**276a**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranopyrrolone (**276a**) (36 mg, 0.27 mmol) and dimethyl acetylenedicarboxylate (76 mg, 0.53 mmol) in chlorobenzene (10 ml) was refluxed under nitrogen for 1.5 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give *dimethyl indole*-5,6-*dicarboxylate* (**358a**) (51 mg, 82%), m.p. 82-86°C (Found: C, 61.6; H, 4.7; N, 5.9. $C_{12}H_{11}NO_4$ requires C, 61.8; H, 4.75; N, 6.0%); ν_{max}(Nujol) 3 352, 1 712, 1 328, and 1 254 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.79 (1 H, br, NH), 8.06 (1 H, s), 7.77 (1 H, s), 7.37 (1 H, t, *J* 2.8 Hz, 2-H), 6.64 (1 H, m, 3-H), and 3.91 (6 H, s, CO_2Me); *m/z* 233 (M^+, 36%), and 202 (100).

Reaction of pyrano[4,3-b]*pyrrol*-6(1H)-*one* (**276a**) *with ethyl propiolate*.- A mixture of the pyranopyrrolone (**276a**) (42 mg, 0.31 mmol) and ethyl propiolate (152 mg, 1.55 mmol) in chlorobenzene (8 ml) was refluxed under nitrogen for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give *ethyl indole*-5-*carboxylate* (**359a**) and *ethyl indole*-6-*carboxylate* (**360a**) (30 mg, 51%) in the ratio 1 to 1.7, m.p. 57-63°C (Found: C, 69.6; H, 5.85; N, 7.3. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.9; N, 7.4%); ν_{max}(Nujol) 3 300, 1 684, and 1 296 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.56 (1 H, br, NH, 6-ester), 8.50 (1 H, br, NH, 5-ester), 8.43 (1 H, s, 4-H, 5-ester), 8.18 (1 H, s, 7-H, 6-ester), 7.92 (1 H, dd, *J* 8.6, 1.6 Hz, 6-H, 5-ester), 7.83 (1 H, dd, *J* 8.5, 1.2 Hz, 5-H, 6-ester), 7.66 (1 H, d, *J* 8.3 Hz, 4-H, 6-ester), 7.40 (1 H, d, *J* 8.7 Hz, 7-H, 5-ester), 7.36 (1 H, m, 2-H, 6-ester), 7.27 (1 H, m, 2-H, 5-ester), 6.65 (1 H, m, 3-H, 5-ester), 6.61 (1 H, m, 3-H, 6-ester), 4.40 (q, *J* 7.1 Hz, ester CH_2, both isomers), and 1.41 (t, *J* 7.1 Hz, ester CH_3, both isomers); *m/z* 189 (M^+, 85%), 144 (100), and 116 (24).

Reaction of 4-*methylpyrano*[4,3-b]*pyrrol*-6(1H)-*one* (**276b**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranopyrrolone (**276b**) (49 mg, 0.33 mmol) and dimethyl acetylenedicarboxylate (93 mg, 0.66 mmol)

in chlorobenzene (5 ml) was refluxed under nitrogen for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (3:1)] to give *dimethyl 4-methylindole-5,6-dicarboxylate* (**358b**) (51 mg, 63%), m.p. 156-161°C (Found: C, 63.1; H, 5.3; N, 5.65. $C_{13}H_{13}NO_4$ requires C, 63.15; H, 5.3; N, 5.7%); ν_{max}(Nujol) 3 388 and 1 706 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.65 (1 H, br, NH), 7.95 (1 H, s, 7-H), 7.38 (1 H, t, *J* 2.9 Hz, 2-H), 6.63 (1 H, m, 3-H), 3.96 (3 H, s, CO_2Me), 3.89 (3 H, s, CO_2Me), and 2.54 (3 H, s, 4-Me); *m/z* 247 (M^+, 48%), 216 (100), 215 (94), 157 (70), and 129 (34).

Reaction of 4-methylpyrano[4,3-b]pyrrol-6(1H)-one (**276b**) *with ethyl propiolate*.- A mixture of the pyranopyrrolone (**276b**) (83 mg, 0.56 mmol) and ethyl propiolate (273 mg, 2.78 mmol) in chlorobenzene (12 ml) was refluxed under nitrogen for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give *ethyl 4-methylindole-5-carboxylate* (**359b**) and *ethyl 4-methylindole-6-carboxylate* (**360b**) (89 mg, 79%) in the ratio 1 to 1, m.p. 70-89°C (Found: C, 70.7; H, 6.5; N, 6.8. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%); ν_{max}(Nujol) 3 300 and 1 686 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.47 (1 H, br, NH), 8.38 (1 H, br, NH), 8.02 (1 H, s, 7-H, 6-ester), 7.84 (1 H, d, *J* 8.6 Hz, 6-H, 5-ester), 7.62 (1 H, s, 5-H, 6-ester), 7.34 (1 H, t, *J* 2.8 Hz, 2-H), 7.23 (2 H, m), 6.70 (1 H, m, 3-H), 6.60 (1 H, m, 3-H), 4.37 (4 H, m, ester CH_2, both isomers), 2.85 (3 H, s, 4-Me, 5-ester), 2.59 (3 H, s, 4-Me, 6-ester), and 1.41 (6 H, t, *J* 7.1 Hz, ester CH_3, both isomers); *m/z* 203 (M^+, 87%), 174 (20), 158 (100), and 130 (60).

Reaction of 4-methylpyrano[4,3-b]pyrrol-6(1H)-one (**276b**) *with ethyl 3-trimethylsilylpropynoate*.- A mixture of the pyranopyrrolone (**276b**) (50 mg, 0.34 mmol) and ethyl 3-trimethylsilylpropynoate (171 mg, 1.01 mmol) in chlorobenzene (10 ml) was refluxed under nitrogen for 96 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give *ethyl 4-methyl-6-trimethylsilylindole-5-carboxylate* (**361**) (10 mg, 11%), m.p. 55-56°C (Found: M^+, 275.1342. $C_{15}H_{21}NO_2Si$ requires *M*, 275.1342); ν_{max}($CHCl_3$) 3 476, 1 706, 1 282,

1 252, 856, and 840 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.26 (1 H, br, NH), 7.49 (1 H, s, 7-H), 7.24 (1 H, dd, *J* 3.2, 2.5 Hz, 2-H), 6.60 (1 H, m, 3-H), 4.40 (2 H, q, *J* 7.1 Hz, ester CH_2), 2.60 (3 H, s, 4-Me), 1.41 (3 H, t, *J* 7.1 Hz, ester CH_3), and 0.32 (9 H, s, Me_3Si);*m/z* 275 (M^+, 4%), 260 (82), and 232 (100).

Reaction of 4-*methylpyrano*[4,3-b]*pyrrol*-6(1H)-*one* (**276b**) *with phenyl vinyl sulphoxide.*- A mixture of the pyranopyrrolone (**276b**) (46 mg, 0.31 mmol) and phenyl vinyl sulphoxide (141 mg, 0.93 mmol) in chlorobenzene (5 ml) was refluxed under nitrogen for 24 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give 4-*methylindole* (**362a**) (13 mg, 32%) as a colourless oil, picrate m.p. 187-188°C (lit.,[89b] 188°C); n_D^{23} 1.6041 (lit.,[119] n_D^{20} 1.6060); $\nu_{max}(CHCl_3)$ 3 480 and 1 342 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 8.1 (1 H, br, NH), 7.24-7.19 (2 H, m, 2-H + 7-H), 7.11 (1 H, t, *J* 7 Hz, 6-H), 6.92 (1 H, d, *J* 7 Hz, 5-H), 6.57 (1 H, m, 3-H), and 2.57 (3 H, s, 4-Me); δ_C(62.9 MHz; $CDCl_3$) 135.44 (q), 130.22 (q), 127.75 (q), 123.48, 122.08, 119.91, 108.60, 101.06, and 18.81; *m/z* 131 (M^+, 77%), 130 (100), 103 (11), and 77 (20).

Diels-Alder reactions of 6-*oxopyrano*[4,3-b]*pyrrole*-1-*carboxylates*

Reaction of isobutyl 6-*oxopyrano*[4,3-b]*pyrrole*-1-*carboxylate* (**277a**) *with dimethyl acetylenedicarboxylate.*- A mixture of the pyranopyrrolone (**277a**) (65 mg, 0.28 mmol) and dimethyl acetylenedicarboxylate (78 mg, 0.53 mmol) in chlorobenzene (10 ml) was refluxed for 2 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give 1-*isobutyl* 5,6-*dimethyl indole*-1,5,6-*tricarboxylate* (**365a**) (91 mg, 99%) as a colourless oil (Found: C, 61.2; H, 5.7; N, 4.1. $C_{17}H_{19}NO_6$ requires C, 61.3; H, 5.75; N, 4.2%); ν_{max}(film) 1 726 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.60 (1 H, brs, 7-H), 7.96 (1 H, s, 4-H), 7.79 (1 H, d, *J* 3.7 Hz, 2-H), 6.69 (1 H, d, *J* 3.7 Hz, 3-H), 4.27 (2 H, d, isobutyl CH_2), 3.93 (6 H, s, CO_2Me), 2.17 (1 H, m, *J* 6.6 Hz, isobutyl CH), and 1.08 (6 H, d, *J* 6.7 Hz, isobutyl CH_3); *m/z* 333 (M^+, 54%), 302 (32), 246 (25), 233 (19),

201 (85), 57 (100), and 41 (25).

Reaction of isobutyl 6-*oxopyrano*[4,3-b]*pyrrole*-1-*carboxylate* (**277a**) *with ethyl propiolate*.- A mixture of the pyranopyrrolone (**277a**) (71 mg, 0.30 mmol) and ethyl propiolate (148 mg, 1.51 mmol) in chlorobenzene (10 ml) was refluxed for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give 5-*ethyl* 1-*isobutyl indole*-1,5-*dicarboxylate* (**366a**) and 6-*ethyl* 1-*isobutyl indole*-1,6-*dicarboxylate* (**367a**) (71 mg, 81%) in the ratio 1 to 1, m.p. 40-52°C (Found: C, 66.5; H, 6.65; N, 4.95. $C_{16}H_{19}NO_4$ requires C, 66.4; H, 6.6; N, 4.8%); ν_{max}(Nujol) 1 740, 1 708, 1 230, and 762 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.86 (1 H, brs, 7-H, 6-ester), 8.31 (1 H, d, *J* 1.7 Hz, 4-H, 5-ester), 8.22 (1 H, d, *J* 8.7 Hz, 7-H, 5-ester), 8.04 (1 H, dd, *J* 8.7, 1.7 Hz, 6-H, 5-ester), 7.97 (1 H, dd, *J* 8.2, 1.5 Hz, 5-H, 6-ester), 7.79 (1 H, d, *J* 3.7 Hz, 2-H, 6-ester), 7.68 (1 H, d, *J* 3.7 Hz, 2-H, 5-ester), 7.60 (1 H, d, *J* 8.2 Hz, 4-H, 6-ester), 6.68 (1 H, d, *J* 3.8 Hz, 3-H, 5-ester), 6.65 (1 H, d, *J* 3.7 Hz, 3-H, 6-ester), 4.41 (4 H, q, *J* 6.9 Hz, ethyl CH_2, both isomers), 4.28 (2 H, d, *J* 6.5 Hz, isobutyl CH_2, 6-ester), 4.25 (2 H, d, *J* 6.7 Hz, isobutyl CH_2, 5-ester), 2.22-2.13 (2 H, m, isobutyl CH, both isomers), 1.42 (6 H, t, *J* 7.1 Hz, ethyl CH_3, both isomers), 1.11 (6 H, d, *J* 6.7 Hz, isobutyl CH_3, 6-ester), and 1.07 (6 H, d, *J* 6.7 Hz, isobutyl CH_3, 5-ester); *m/z* 289 (M^+, 60%), 189 (68), 161 (46), 144 (70), 116 (43), 57 (100), and 41 (77).

Reaction of isobutyl 6-*oxopyrano*[4,3-b]*pyrrole*-1-*carboxylate* (**277a**) *with ethyl* 3-*trimethylsilylpropynoate*.- A mixture of the pyranopyrrolone (**277a**) (80 mg, 0.34 mmol) and ethyl 3-trimethylsilylpropynoate (173 mg, 1.02 mmol) in chlorobenzene (10 ml) was refluxed for 20 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:7)] to give 5-*ethyl* 1-*isobutyl* 6-*trimethylsilylindole*-1,5-*dicarboxylate* (**368**) and 6-*ethyl* 1-*isobutyl* 5-*trimethylsilylindole*-1,6-*dicarboxylate* (**369**) (111 mg, 90%) in the ratio 7 to 1, m.p. 32-50°C (Found: C, 63.3; H, 7.7; N, 3.9. $C_{19}H_{27}NO_4Si$ requires C, 63.1; H, 7.5; N, 3.9%); ν_{max}(Nujol) 1 742, 1 718, 1 336, 1 234, 844, and 766 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.86 (1 H, s,

7-H, minor), 8.52 (1 H, s, 7-H, major), 8.32 (1 H, s, 4-H, major), 7.89 (1 H, s, 4-H, minor), 7.76 (1 H, d, *J* 4 Hz, 2-H, minor), 7.70 (1 H, d, *J* 3.7 Hz, 2-H, major), 6.66 (d, *J* 3.7 Hz, 3-H, both isomers), 4.40 (q, *J* 7.1 Hz, ethyl CH_2, both isomers), 4.28 (2 H, d, *J* 6.8 Hz, isobutyl CH_2, minor), 4.25 (2 H, d, *J* 6.8 Hz, isobutyl CH_2, major), 2.19 (m, isobutyl CH, both isomers), 1.43 (t, *J* 7.1 Hz, ethyl CH_3, both isomers), 1.11 (6 H, d, *J* 6.8 Hz, isobutyl CH_3, minor), 1.07 (6 H, d, *J* 6.7 Hz, isobutyl CH_3, major), 0.38 (9 H, s, Me_3Si, major), and 0.35 (9 H, s, Me_3Si, minor); *m/z* 361 (M^+, 1%), 346 (100), 318 (20), 262 (28), and 218 (28).

Protodesilylation of 5-*ethyl* 1-*isobutyl* 6-*trimethylsilylindole*-1,5-*dicarboxylate* (**368**) and 6-*ethyl* 1-*isobutyl* 5-*trimethylsilylindole*-1,6-*dicarboxylate* (**369**).-A mixture of the silylated indoles (**368**) and (**369**) (58 mg, 0.16 mmol) was dissolved in trifluoroacetic acid (2 ml) and water (1 ml) and the mixture refluxed under nitrogen for 2 h. The mixture was allowed to cool to room temperature, diluted with water, and extracted with ether. The combined ether extracts were washed with saturated sodium hydrogen carbonate solution (until the washings remained basic), water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give 5-*ethyl* 1-*isobutyl indole*-1,5-*dicarboxylate* (**366a**) and 6-*ethyl* 1-*isobutyl indole*-1,6-*dicarboxylate* (**367a**) (24 mg, 52%) in the ratio 7 to 1, m.p. 48-60°C, spectral data given above.

Hydrolysis of 5-*ethyl* 1-*isobutyl indole*-1,5-*dicarboxylate* (**366a**) and 6-*ethyl* 1-*isobutyl indole*-1,6-*dicarboxylate* (**367a**).-A mixture of the isobutyl indole-1-esters (**366a**) and (**367a**) (18 mg, 0.06 mmol) in 0.88 ammonia (3 ml) and pyridine (1 ml) was stirred at room temperature for 36 h. Water was added and the mixture extracted with ether. The combined ether extracts were washed with saturated aqueous copper (II) sulphate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give *ethyl indole*-5-*carboxylate* (**359a**) and *ethyl indole*-6-*carboxylate* (**360a**) (9.4 mg, 80%) in the ratio 7 to 1, m.p. 76-85°C, spectral data given above.

Reaction of isobutyl 4-methyl-6-oxopyrano[4,3-b]pyrrole-1-carboxylate (**277b**) *with dimethyl acetylenedicarboxylate*.- A mixture of the pyranopyrrolone (**277b**) (40 mg, 0.16 mmol) and dimethyl acetylenedicarboxylate (46 mg, 0.32 mmol) in chlorobenzene (5 ml) was refluxed for 18 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give 1-*isobutyl* 5,6-*dimethyl* 4-*methylindole*-1,5,6-*tricarboxylate* (**365b**) (49 mg, 88%) as a colourless oil (Found: C, 62.2; H, 6.3; N, 3.8. $C_{18}H_{21}NO_6$ requires C, 62.2; H, 6.1; N, 4.0%); ν_{max}(film) 1 734, 1 424, 1 352, and 1 292 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.73 (1 H, brs, 7-H), 7.81 (1 H, d, *J* 3.8 Hz, 2-H), 6.71 (1 H, dd, *J* 3.7,0.7 Hz, 3-H), 4.27 (2 H, d, *J* 6.5 Hz, isobutyl CH_2), 3.97 (3 H, s, CO_2Me), 3.91 (3 H, s, CO_2Me), 2.51 (3 H, s, 4-Me), 2.18 (1 H, m, isobutyl CH), and 1.09 (6 H, d, *J* 6.7 Hz, isobutyl CH_3); *m/z* 347 (M^+, 28%), 315 (64), 259 (17), 215 (80), 57 (100), 41 (63), and 29 (68).

Reaction of isobutyl 4-methyl-6-oxopyrano[4,3-b]pyrrole-1-carboxylate (**277b**) *with ethyl propiolate*.- A mixture of the pyranopyrrolone (**277b**) (79 mg, 0.32 mmol) and ethyl propiolate (155 mg, 1.58 mmol) in chlorobenzene (10 ml) was refluxed for 20 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give 5-*ethyl* 1-*isobutyl* 4-*methylindole*-1,5-*dicarboxylate* (**366b**) and 6-*ethyl* 1-*isobutyl* 4-*methylindole*-1,6-*dicarboxylate* (**367b**) (72 mg, 75%) in the ratio 1.2 to 1 as a colourless oil (Found: C, 67.25; H, 7.1; N, 4.4. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%); ν_{max}(film) 1 738, 1 712, 1 598, and 1 522 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.71 (1 H, brs, 7-H, 6-ester), 8.04 (1 H, d, *J* 8.8 Hz, 7-H, 5-ester), 7.93 (1 H, d, *J* 8.8 Hz, 6-H, 5-ester), 7.78 (2 H, m, 2-H + 5-H, 6-ester), 7.66 (1 H, d, *J* 3.8 Hz, 2-H, 5-ester), 6.76 (1 H, d, *J* 3.8 Hz, 3-H, 5-ester), 6.67 (1 H, d, *J* 3.7 Hz, 3-H, 6-ester), 4.44 (m, ethyl CH_2, both isomers), 4.27 (2 H, d, *J* 6.5 Hz, isobutyl CH_2, 6-ester), 4.24 (2 H, d, *J* 6.6 Hz, isobutyl CH_2, 5-ester), 2.79 (3 H, s, 4-Me, 5-ester), 2.56 (3 H, s, 4-Me, 6-ester), 2.24-2.11 (m, isobutyl CH, both isomers), 1.42 (t, *J* 7.1 Hz, ethyl CH_3, both isomers), 1.10 (6 H, d, *J* 6.7 Hz, isobutyl CH_3, 6-ester), and 1.07 (6 H, d, *J* 6.7 Hz, isobutyl CH_3, 5-ester); *m/z* 303 (M^+, 39%), 203 (27), 158 (22), 57 (100), 41 (49),

and 29 (60).

Reaction of isobutyl 4-methyl-6-oxopyrano[4,3-b]pyrrole-1-carboxylate (**277b**) *with ethyl 3-trimethylsilylpropynoate*.- A mixture of the pyranopyrrolone (**277b**) (100 mg, 0.40 mmol) and ethyl 3-trimethylsilylpropynoate (206 mg, 1.21 mmol) in chlorobenzene (10 ml) was refluxed for 168 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:5)] to give *5-ethyl 1-isobutyl 4-methyl-6-trimethylsilylindole-1,5-dicarboxylate* (**370**) (97 mg, 64%), m.p. 51-52°C (Found: C, 64.2; H, 8.0; N, 3.7. $C_{20}H_{29}NO_4Si$ requires C, 64.0; H, 7.8; N, 3.7%); ν_{max}(Nujol) 1 738, 1 334, 1 284, 1 142, and 840 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.30 (1 H, brs, 7-H), 7.67 (1 H, d, *J* 3.8 Hz, 2-H), 6.66 (1 H, d, *J* 3.9 Hz, 3-H), 4.40 (2 H, q, *J* 7.1 Hz, ethyl CH_2), 4.23 (2 H, d, *J* 6.7 Hz, isobutyl CH_2), 2.54 (3 H, s, 4-Me), 2.17 (1 H, m, isobutyl CH), 1.41 (3 H, t, *J* 7.1 Hz, ethyl CH_3), 1.07 (6 H, d, *J* 6.7 Hz, isobutyl CH_3), and 0.33 (9 H, s, Me_3Si); *m/z* 375 (M^+, 1%), 360 (100), 332 (20), 276 (26), 232 (19), 57 (24), 41 (34), and 29 (43).

Protodesilylation of 5-ethyl 1-isobutyl 4-methyl-6-trimethylsilylindole-1,5-dicarboxylate (**370**).-The 6-trimethylsilylindole (**370**) (40 mg, 0.11 mmol) was dissolved in trifluoroacetic acid (2 ml) and water (1 ml) and the mixture refluxed under nitrogen for 2 h. The mixture was allowed to cool to room temperature, diluted with water, and extracted with ether. The combined ether extracts were washed with saturated sodium hydrogen carbonate solution (until the washings remained basic), water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give *5-ethyl 1-isobutyl 4-methylindole-1,5-dicarboxylate* (**366b**) (14 mg, 43%) as a colourless oil, spectral data given above.

Reaction of isobutyl 4-methyl-6-oxopyrano[4,3-b]pyrrole-1-carboxylate (**277b**) *with benzyne*.- A mixture of the pyranopyrrolone (**277b**) (73 mg, 0.29 mmol), 2-(3,3-dimethyltriazen-1-yl)benzoic acid (**193**) (113 mg, 0.59 mmol), and trifluoroacetic acid (1 drop) in acetonitrile

(10 ml) was refluxed for 6 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:3)] to give *isobutyl* 4-*methylbenz*[f]*indole*-1-*carboxylate* (**372**) (69 mg, 84%), m.p. 41-45°C (Found: C, 76.6; H, 6.8; N, 4.9. $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%); ν_{max}(Nujol) 1 734 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.53 (1 H, brs, 9-H), 8.10 (1 H, m), 7.97 (1 H, m), 7.73 (1 H, d, *J* 4.0 Hz, 2-H), 7.50-7.42 (2 H,m), 6.80 (1 H, d, *J* 4.0 Hz, 3-H), 4.26 (2 H, d, *J* 6.6 Hz, isobutyl CH_2), 2.86 (3 H, s, 4-Me), 2.19 (1 H, m, isobutyl CH), and 1.09 (6 H, d, *J* 6.7 Hz, isobutyl CH_3); *m/z* 281 (M^+, 66%), 225 (65), 181 (100), 57 (69), and 41 (48).

Reaction of isobutyl 4-*methyl*-6-*oxopyrano*[4,3-b]*pyrrole*-1-*carboxylate* (**277b**) *with phenyl vinyl sulphoxide*.- A mixture of the pyranopyrrolone (**277b**) (90 mg, 0.36 mmol) and phenyl vinyl sulphoxide (165 mg, 1.08 mmol) in chlorobenzene (10 ml) was refluxed for 144 h. The solvent was evaporated and the residue chromatographed [dichloromethane-light petroleum (1:2)] to give *isobutyl* 4-*methylindole*-1-*carboxylate* (**371a**) (71 mg, 85%) as a colourless oil (Found: C, 72.5; H, 7.35; N, 5.9. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%); ν_{max}(film) 1 734, 1 424, 1 348, 1 276, and 1 132 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.02 (1 H, d, *J* 8.3 Hz, 7-H), 7.62 (1 H, d, *J* 3.8 Hz, 2-H), 7.20 (1 H, m, 6-H), 7.05 (1 H, dd, *J* 7.3, 0.8 Hz, 5-H), 6.64 (1 H, d, *J* 3.8 Hz, 3-H), 4.22 (2 H, d, *J* 6.6 Hz, isobutyl CH_2), 2.53 (3 H, s, 4-Me), 2.15 (1 H, m, isobutyl CH), and 1.06 (6 H, d, *J* 6.7 Hz, isobutyl CH_3);*m/z* 231 (M^+, 37%), 175 (27), 158 (16), 131 (98), 130 (69), 57 (100), and 41 (66).

Reaction of isobutyl 6-*oxo*-4-*phenylpyrano*[4,3-b]*pyrrole*-1-*carboxylate* (**277c**) *with phenyl vinyl sulphoxide*.- A mixture of the pyranopyrrolone (**277c**) (204 mg, 0.66 mmol) and phenyl vinyl sulphoxide (499 mg, 3.28 mmol) in chlorobenzene (5 ml) was refluxed under nitrogen for 192 h. The solvent was evaporated and the residue chromatographed [dichloromethane-light petroleum (3:1)] to give *isobutyl* 4-*phenylindole*-1-*carboxylate* (**371b**) (175 mg, 91%) as a colourless oil (Found: C, 77.5; H, 6.6; N, 4.5. $C_{19}H_{19}NO_2$ requires C, 77.8; H,6.5; N, 4.8%); ν_{max}(film) 1

736, 1 418, 1 348, 1 268, and 1 166 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.20 (1 H, d, *J* 8 Hz, 7-H), 7.66 (1 H, d, *J* 3.8 Hz, 2-H), 7.60 (2 H, d, *J* 8 Hz), 7.48-7.41 (4 H, m), 7.31(1 H, d, *J* 8 Hz, 5-H), 6.76 (1 H, d, *J* 3.8 Hz, 3-H), 4.25 (2 H, d, *J* 6.6 Hz, isobutyl CH_2), 2.17 (1 H, m, isobutyl CH), and 1.07 (6 H, d, *J* 6.7 Hz, isobutyl CH_3); *m/z* 293 (M^+, 88%), 237 (38), 193 (100), 165 (39), and 57 (40).

Hydrolysis of indole-1-esters

4-*Methylindole* (**362a**).- A solution of the isobutyl indole-1-ester (**371a**) (25 mg, 0.11 mmol) in 0.88 ammonia (3 ml) and pyridine (1 ml) was stirred at room temperature for 24 h. Water was added and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**362a**) (11 mg, 78%), spectral data given above.

4-*Phenylindole* (**362b**).- A solution of the indole-1-ester (**371b**) (123 mg, 0.42 mmol) in pyridine (2 ml) and 0.88 ammonia (6 ml) was stirred at room temperature for 72 h. The mixture was diluted with water and extracted with ether. The combined extracts were washed with saturated copper (II) sulphate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**362b**) (63 mg, 78%), m.p. 76-77°C (lit.,[70] 58-60°C) (Found: C, 86.8; H, 5.6; N, 7.2. $C_{14}H_{11}N$ requires C, 87.0; H, 5.7; N, 7.25%); ν_{max}(Nujol) 3 412 and 750 cm^{-1}; δ_H(250 MHz; $CDCl_3$) 8.23 (1 H, br, NH), 7.73-7.68 (2 H, m), 7.51-7.44 (2 H, m), 7.41-7.33 (2 H, m), 7.31-7.18 (3 H, m), and 6.74 (1 H, m, 3-H); δ_C(62.9 MHz; $CDCl_3$) 141.21 (q), 136.27 (q), 134.52 (q), 128.78, 128.46, 126.92, 126.18 (q), 124.40, 122.33, 119.77, 110.20, and 102.21; *m/z* 193 (M^+, 100%) and 165 (34).

4-*Methylbenz*[f]*indole* (**363**).-A solution of the indole-1-ester (**372**) (26 mg, 0.09 mmol) in 0.88 ammonia (1.5 ml) and pyridine (0.5 ml) was stirred at room temperature for 30 h. Water was added and the mixture extracted with

ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**363**) (11 mg, 66%), m.p. 96-98°C (Found: M^+, 181.0891. $C_{13}H_{11}N$ requires M, 181.0891); $\nu_{max}(CHCl_3)$ 3 480, 1 406, and 1 320 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.15-8.11 (1 H, m), 8.02 (1 H, br, NH), 7.91-7.86 (1 H, m), 7.70 (1 H, s, 9-H), 7.41-7.34 (3 H, m), 6.74 (1 H, m, 3-H), and 2.93 (3 H, s, 4-Me); *m/z* 181 (M^+, 100%), 180 (92), 152 (22), 91 (11), and 77 (14).

Ethyl 4-*methyl*-6-*trimethylsilylindole*-5-*carboxylate* (**361**).-A solution of the indole-1-ester (**370**) (27 mg, 0.07 mmol) in 0.88 ammonia (3 ml) and pyridine (1 ml) was stirred at room temperature for 48 h. Water was added and the mixture extracted with ether. The combined ether extracts were washed with saturated aqueous copper (II) sulphate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give the *title compound* (**361**) (16 mg, 81%), spectral data given above.

7.5 Experimental for Chapter 5

1-*Heptylpyrano*[3,4-b]*indol*-3-*one* (**377**).- Boron trifluoride diethyl ether (5.1 ml) was added dropwise over 1 h to a stirred solution of indol-3-ylacetic acid (5.40 g, 30.82 mmol) in octanoic anhydride (20.09 g, 74.3 mmol) at 0°C. The mixture was allowed to warm to room temperature and stirred for 1 h. Ether (50 ml) was added and the mixture filtered. The resulting solid was washed with ether (30 ml), triturated with half saturated sodium hydrogen carbonate solution (6 x 30 ml), washed with water (3 x 30 ml), and dried *in vacuo* to give the *title compound* (**377**) (6.54 g, 75%), m.p. 151-153°C (EtOAc) (Found: C, 75.95; H, 7.5; N, 4.8. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.5; N, 4.9%); ν_{max}(Nujol) 3 140 (br), 1 692, 1 626, 1 610, and 1 560 cm^{-1}; λ_{max}(EtOH) 246 (ε 41 090), 269 (21 740), 302 (9 100), and 462 nm (11 140); δ(250 MHz; $CDCl_3$) 7.82 (1 H, d, *J* 7.8 Hz), 7.58 (1 H, br, NH), 7.50 (1 H, t, *J* 7.7 Hz), 7.20 (1 H, d, *J* 8.2 Hz), 7.08 (1 H, t, *J* 7.6 Hz), 6.48 (1 H, s, 4-H), 2.77 (2 H, t, *J* 7.5 Hz, allylic CH_2), 1.81-1.72 (2 H, m), 1.33-1.24 (8 H, m), and 0.84 (3 H, t, *J* 6.6 Hz, heptyl CH_3); *m/z* 283 (M^+, 100%), 212 (31), 198 (37), 184 (65), 170 (41), 156 (29), and 129 (29).

Ethyl 1-*heptyl*-3-*trimethylsilyl*-9H-*carbazole*-2-*carboxylate* (**378**).- A mixture of the pyranoindolone (**377**) (2.00 g, 7.06 mmol) and ethyl 3-trimethylsilylpropynoate (2.45 g, 14.41 mmol) in bromobenzene (200 ml) was refluxed under nitrogen for 60 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give the *title compound* (**378**) (2.13 g, 74%) after recrystallisation (dichloromethane-light petroleum), m.p. 138-139°C (Found: C, 73.35; H, 8.7; N, 3.5. $C_{25}H_{35}NO_2Si$ requires C, 73.3; H, 8.6; N, 3.4%); ν_{max}(Nujol) 3 372, 1 702, 1 464, 1 254, 842, and 742 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.28 (1H, br, NH), 8.23 (1 H, d, *J* 8.1 Hz), 7.94 (1 H, s, 4-H), 7.55-7.44 (2 H, m), 7.29-7.23 (1 H, m), 4.42 (2 H, q, *J* 7.1 Hz, ester CH_2), 3.24 (2 H, t, *J* 8 Hz, benzylic CH_2), 1.79-1.73 (2 H, m), 1.53-1.30 (8 H, m), 1.47 (3 H, t, *J* 7.6 Hz, ester CH_3), 0.88 (3 H, t, *J* 6.6 Hz, heptyl CH_3), and 0.54 (9 H, s, Me_3Si); *m/z* 409 (M^+, 100%), 395 (26), 296 (16), and 73 (16).

1-*Heptyl*-2-*methyl*-3-*trimethylsilyl*-9H-*carbazole* (**379**).- Lithium aluminium hydride (547 mg, 14.4 mmol) was added to a stirred solution of ethyl 1-heptyl-3-trimethylsilyl-9*H*-carbazole-2-carboxylate (**378**) (985 mg, 2.40 mmol) in dry dioxan (75 ml), and the mixture refluxed under nitrogen for 20 h. The mixture was allowed to cool and diluted with ether (100 ml). Water (6 ml) was added carefully, followed by solid sodium hydrogen carbonate until a white granular precipitate resulted. The mixture was filtered through Celite, evaporated, and the residue chromatographed [ether-light petroleum (1:3)] to give the *title compound* (**379**) (840 mg, 99%) as a colourless oil, (Found: C, 78.5; H, 9.6; N, 3.9. $C_{23}H_{33}NSi$ requires C, 78.6; H, 9.5; N, 3.9%); ν_{max}(film) 3 440, 3 056, 1 602, 1 466, 1 326, 842, 756, and 738 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.06-8.03 (2 H, m), 7.89 (1 H, br, NH), 7.44-7.36 (2 H, m), 7.20 (1 H, ~t, *J* 7 Hz), 2.88 (2 H, t, *J* 8.0 Hz, benzylic CH_2), 2.58 (3 H, s, 2-Me), 1.70-1.63 (2 H, m), 1.52-1.30 (8 H, m), 0.89 (3 H, t, *J* 6.7 Hz, heptyl CH_3), and 0.42 (9 H, s, Me_3Si); *m/z* 351 (M^+, 100%), 336 (52), 266 (30), and 194 (19).

1-*Heptyl*-3-*hydroxy*-2-*methyl*-9H-*carbazole* (*Carazostatin*) (**375**).- A solution of mercury(II) acetate (737 mg, 2.31 mmol) in acetic acid (10 ml) was added in one portion to 1-heptyl-2-methyl-3-trimethylsilyl-9*H*-carbazole (**379**) (813 mg, 2.31 mmol). The mixture was stirred at room temperature for 1 h during which time a white precipitate had formed. The solvent was removed under reduced pressure and the resulting solid thoroughly dried *in vacuo*. The crude solid was dissolved in dry THF (60 ml) and borane-tetrahydrofuran complex (1M; 34.65 ml) was added dropwise to the stirred solution at room temperature under nitrogen. After 1 h, a mixture of hydrogen peroxide (30%; 12 ml) and sodium hydroxide (2 M; 12 ml) was carefully added (very exothermic-reflux condenser required), and the mixture stirred for a further 2 min. The mixture was acidified with dilute hydrochloric acid, diluted with water, and extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (dichloromethane) to give the *title compound* (**375**) (298 mg, 44%), m.p. 162-163°C (dichloromethane-light petroleum) (lit.,[95]

149-152°C) (Found: C, 81.2; H, 8.6; N, 4.7. Calc for $C_{20}H_{25}NO$ C, 81.3; H, 8.5; N, 4.7%); ν_{max}(Nujol) 3 472, 3 380, 1 612, 1 592, 1 498, 1 460, 1 436, 1 376, 1 310, 1 232, 1 148, 1 064, 832, 772, 740, 722, and 658 cm^{-1}; λ_{max}(MeOH) 218 (ε 37 300), 235 (35 700), 254 (19 000), 266 (15 100), 303 (20 400), and 342 nm (4 600); δ_H(250 MHz; $CDCl_3$) 7.92 (1 H, d, *J* 7.7 Hz), 7.75 (1 H, br, NH), 7.43-7.33 (2 H, m), 7.32 (1 H, s, 4-H), 7.16 (1 H, ~t, *J* 7 Hz), 4.61 (1 H, br, OH), 2.87 (2 H, t, *J* 7.9 Hz, benzylic CH_2), 2.37 (3 H, s, 2-Me), 1.67-1.58 (2 H, m), 1.47-1.29 (8 H, m), and 0.88 (3 H, t, *J* 6.7 Hz, heptyl CH_3); δ_C(62.9 MHz; $CDCl_3$) 148.1 (q), 139.8 (q), 134.0 (q), 125.2, 124.2 (q), 123.7 (q), 121.4 (q), 120.9 (q), 120.1, 118.9, 110.6, 103.0, 31.9, 30.0, 29.5, 29.3, 28.8, 22.7, 14.1, and 12.0; *m/z* 295 (M^+, 100%) and 210 (92).

5-*Heptyl*-4-*methyl*-2-*phenyloxazolo*[5,4-c]-6H-*carbazole* (**382**).- A mixture of carazostatin (**375**) (31 mg, 0.10 mmol), benzylamine (22 mg, 0.21 mmol), and active manganese(IV) oxide (321 mg, 3.7 mmol) in 1,2-dimethoxyethane (4 ml) was stirred at room temperature for 22 h. The mixture was filtered through Celite, evaporated, and the residue chromatographed (dichloromethane) to give the *title compound* (**382**) (16 mg, 38%), m.p. 185-187°C (dichloromethane-light petroleum) (Found: C, 81.5; H, 7.0; N, 7.0. $C_{27}H_{28}N_2O$ requires C, 81.8; H, 7.1; N, 7.1%); ν_{max}($CHCl_3$) 3 476, 1 616, 1 546, 1 486, and 1 458 cm^{-1}; δ(250 MHz; $CDCl_3$) 8.56 (1 H, d, *J* 7.8 Hz), 8.40-8.37 (2 H, m), 8.07 (1 H, br, NH), 7.57-7.50 (4 H, m), 7.43 (1 H, ~t, *J* 7.5 Hz), 7.32 (1 H, ~t, *J* 7.4 Hz), 2.99 (2 H, t, *J* 7.8 Hz, benzylic CH_2), 2.69 (3 H, s, 10-Me), 1.75-1.69 (2 H, m), 1.52-1.30 (8 H, m), and 0.89 (3 H, t, *J* 6.7 Hz, heptyl CH_3); *m/z* 396 (M^+, 81%) and 311 (100).

1-*Heptyl*-3-*methoxy*-2-*methyl*-9H-*carbazole* (**383**).- A mixture of carazostatin (**375**) (11.2 mg, 0.038 mmol) and potassium carbonate (106 mg, 0.76 mmol) in acetone (10 ml) and methyl iodide (1 ml) was refluxed for 24 h. The solvent was evaporated and the residue partitioned between ether and water. The aqueous phase was extracted with ether and the combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give the *title*

compound (**383**) (11.5 mg, 98%), m.p. 94-95°C (Found: M^+, 309.2093. $C_{21}H_{27}NO$ requires M, 309.2093); $\nu_{max}(CHCl_3)$ 3 476, 1 490, 1 450, 1 426, and 1 306 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.99 (1 H, d, *J* 8.3 Hz), 7.79 (1 H, br, NH), 7.42-7.35 (3 H, m), 7.18 (1 H, t, *J* 7.8 Hz), 3.95 (3 H, s, OMe), 2.89 (2 H, t, *J* 7.9 Hz, benzylic CH_2), 2.35 (3 H, s, 2-Me), 1.65-1.59 (2 H, m), 1.49-1.25 (8 H, m), and 0.89 (3 H, t, *J* 6.8 Hz, heptyl CH_3); *m/z* 309 (M^+, 100%), 294 (14), 224 (52), 210 (31), 194 (16), and 180 (31).

1-*Heptyl*-3-*methoxy*-2,9-*dimethyl*-9H-*carbazole* (**384**).- A solution of carazostatin (**375**) (19.8 mg, 0.067 mmol) in dry dimethylformamide (5 ml) was added dropwise to a suspension of sodium hydride (80%, 10 mg, 0.34 mmol) in dry dimethylformamide (5 ml) at 0°C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 5 mins. Methyl iodide (2 ml) was added and the mixture stirred overnight. The reaction mixture was poured into brine and extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:2)] to give the *title compound* (**384**) (11 mg, 51%), m.p. 58-60°C (Found: M^+, 323.2249. $C_{22}H_{29}NO$ requires M, 323.2249); $\nu_{max}(CHCl_3)$ 1 458, 1 410, and 1 110 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.99 (1 H, d, *J* 7.7 Hz), 7.41-7.37 (3 H, m), 7.16 (1 H, t, *J* 7.2 Hz), 4.05 (3 H, s), 3.94 (3 H, s), 3.12 (2 H, m, benzylic CH_2), 2.37 (3 H, s, 2-Me), 1.65 (2 H, m), 1.51-1.25 (8 H, m), and 0.90 (3 H, t, *J* 6.7 Hz, heptyl CH_3); *m/z* 323 (M^+, 100%), 308 (11), 238 (55), 224 (17), and 194 (16).

3-*Acetoxy*-1-*heptyl*-2-*methyl*-9H-*carbazole* (**385**).- A solution of carazostatin (**375**) (11.0 mg, 0.037 mmol) in acetic anhydride (0.5 ml) and pyridine (2 ml) was stirred at room temperature for 12 h. The mixture was diluted with water and extracted with ether. The combined ether extracts were washed with saturated aqueous copper (II) sulphate solution, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**385**) (12.3 mg, 98%), m.p. 97-99°C (Found: M^+, 337.2042. $C_{22}H_{27}NO_2$ requires M, 337.2042); $\nu_{max}(CHCl_3)$ 3 476, 1 752, and 1 222 cm^{-1}; δ(250 MHz;

$CDCl_3$) 7.94 (1 H, d, *J* 8.0 Hz), 7.90 (1 H, br, NH), 7.56 (1 H, s, 4-H), 7.41-7.37 (2 H, m), 7.18 (1 H, t, *J* 8 Hz), 2.86 (2 H, t, *J* 8 Hz, benzylic CH_2), 2.39 (3 H, s, 2-Me), 2.25 (3 H, s, CH_3CO), 1.68-1.62 (2 H, m), 1.49-1.25 (8 H, m), and 0.89 (3 H, t, *J* 6.7 Hz, heptyl CH_3); *m/z* 337 (M^+, 20%), 295 (100), and 210 (57).

7.6 Experimental for Chapter 6

Preparation of Methyl 1-*benzyl*-1,4,5,6-*tetrahydrocyclopenta*[b]*pyrrol*-2-*ylacetate*

1-*Benzyl*-1,4,5,6-*tetrahydrocyclopenta*[b]*pyrrole*-2-*carboxylic acid* (**419**).- Aqueous potassium hydroxide solution (5 M, 30 ml) was added to a stirred solution of ethyl 1-benzyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole-2-carboxylate (**418**)[116] (4.04 g, 15.0 mmol) in tetrahydrofuran (30 ml) and methanol (30 ml) and the mixture heated under reflux for 4 h. After cooling to room temperature, the mixture was diluted with water, extracted with ether, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue recrystallised (ether-light petroleum) to give the *title compound* (**419**) (3.24 g, 90%), m.p. 154-156°C (decomp.) (Found: C, 74.45; H, 6.2; N, 6.0. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.3; N, 5.8%); ν_{max}(Nujol) 1 640 cm^{-1}; δ[250 MHz; $CDCl_3$ + $(CD_3)_2SO$] 7.27-7.23 (3 H, m), 7.08 (2 H, d, *J* 8 Hz), 6.78 (1 H, s, 3-H), 5.51 (2 H, s, benzylic CH_2), 2.64-2.55 (4 H, m), and 2.39-2.33 (2 H, m); *m/z* 241 (M^+, 19%), 197 (23), and 91 (100).

1-*Benzyl*-1,2,3,4-*tetrahydrocyclopenta*[b]*pyrrole* (**414**).- The acid (**419**) (2.74 g, 11.35 mmol) was heated under nitrogen until it melted and evolution of carbon dioxide ceased. After cooling to room temperature, the residue was chromatographed [ether-light petroleum (1:5)] to give the *title compound* (**414**) (2.22 g, 99%) as a pale yellow oil, (Found: M^+, 197.1204. $C_{14}H_{15}N$ requires *M*, 197.1204); ν_{max}(film) 2 940, 2 852, 1 494, 1 452, 1 352, 1 272, 734, and 696 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.32-7.23 (3 H, m), 7.10 (2 H, d, *J* 8 Hz), 6.57 (1 H, d, *J* 2.6 Hz, 2-H), 5.95 (1 H, d, *J* 2.6 Hz, 3-H), 4.94 (2 H, s, benzylic CH_2), 2.66-2.60 (2 H, m), 2.54-2.49 (2 H, m), and 2.43-2.34 (2 H, m); *m/z* 197 (M^+, 54%) and 91 (100).

1,2,3,4-*Tetrahydrocyclopenta*[b]*pyrrole* (**408**).- A solution of the 1-benzylpyrrole (**414**) (1.01 g, 5.12 mmol) in dry ether (30 ml) was added to

liquid ammonia (90 ml) at -78°C. Sodium (706 mg, 30.72 mmol) was added in small portions to the stirred mixture. The mixture was allowed to warm to room temperature. After the ammonia had evaporated, methanol (10 ml) was added cautiously, followed by water, and the mixture extracted with ether. The combined ether extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give the *title compound* (**408**) (468 mg, 85%) as a pale orange oil, (Found: M^+, 107.0735. C_7H_9N requires M, 107.0735); ν_{max}(film) 3 376, 2 948, 2 900, 2 856, and 712 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.84 (1 H, br, NH), 6.68 (1 H, t, *J* 2.5 Hz, 2-H), 6.00 (1 H, t, *J* 2.3 Hz, 3-H), 2.71-2.59 (4 H, m), and 2.48-2.39 (2 H, m); *m/z* 107 (M^+, 58%) and 106 (100).

Ethyl 1,4,5,6-*tetrahydrocyclopenta*[b]*pyrrol*-2-*ylglyoxalate* (**423**).- A solution of pyridine (31 mg, 0.40 mmol) in dry dichloromethane (2 ml) was added dropwise to a stirred solution of ethyl oxalyl chloride (50 mg, 0.36 mmol) in dry dichloromethane (2 ml) at -78°C under nitrogen. A solution of the pyrrole (**408**) (35.5 mg, 0.33 mmol) in dry dichloromethane (2 ml) was added dropwise and the resulting solution stirred at -78°C for 10 h and then left in the freezer overnight. The solution was washed with dilute hydrochloric acid, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:1)] to give the *title compound* (**423**) (37 mg, 54%), m.p. 111-113°C (Found: C, 63.7; H, 6.3; N, 6.8. $C_{11}H_{13}NO_3$ requires C, 63.8; H, 6.3; N, 6.8%); ν_{max}($CHCl_3$) 3 436, 3 264, 1 728, and 1 620 cm^{-1}; δ(250 MHz; $CDCl_3$) 9.49 (1 H, br, NH), 7.11 (1 H, s, 3-H), 4.39 (2 H, q, *J* 7.1 Hz, ester CH_2), 2.76 (2 H, t, *J* 7.2 Hz), 2.64 (2 H, t, *J* 6.9 Hz), 2.51(2 H, quintet, *J* 7 Hz, $CH_2CH_2CH_2$), and 1.41 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 207 (M^+, 23%) and 134 (100).

Ethyl 1-*benzyl*-1,4,5,6-*dihydrocyclopenta*[b]*pyrrol*-2-*ylglyoxalate* (**424**).- A solution of pyridine (260 mg, 3.29 mmol) in dry dichloromethane (6 ml) was added dropwise to a stirred solution of ethyl oxalyl chloride (412 mg, 3.02 mmol) in dry dichloromethane (6 ml) at -78°C under nitrogen. A solution of the pyrrole (**414**) (541 mg, 2.74 mmol) in dry dichloromethane (6 ml) was added dropwise and the solution allowed to warm slowly to room

temperature. After stirring for 48 h, the solution was washed with dilute hydrochloric acid, water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give the *title compound* (**424**) (734 mg, 90%), m.p. 63-64°C (Found: C, 72.5; H, 6.4; N, 4.7. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%); ν_{max}(Nujol) 1 720 and 1 624 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.29-7.25 (3 H, m), 7.15 (2 H, m), 7.04 (1 H, s, 3-H), 5.54 (2 H, s, benzylic CH_2), 4.35 (2 H, q, *J* 7.1 Hz, ester CH_2), 2.67-2.61 (4 H, m), 2.46-2.35 (2 H, m), and 1.38 (3 H, t, *J* 7.1 Hz, ester CH_3); *m/z* 297 (M^+, 15%), 224 (100), 196 (9), and 91 (71).

1-*Benzyl*-1,4,5,6-*tetrahydrocyclopenta*[b]*pyrrol*-2-*ylglyoxalic acid* (**427**).- To a solution of the ester (**424**) (4.38 g, 14.73 mmol) in tetrahydrofuran (90 ml) and methanol (10 ml) was added aqueous potassium hydroxide solution (2 M, 75 ml) dropwise with stirring. The mixture was stirred for 1 h, diluted with water, extracted with ether, and this extract discarded. The aqueous phase was acidified and extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue recrystallised (ethyl acetate-light petroleum) to give the *title compound* (**427**) (3.85 g, 97%), m.p. 133-136°C (Found: C, 71.2; H, 5.6; N, 5.2. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6; N, 5.2%); ν_{max}(Nujol) 3 284, 1 754, and 1 608 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.91 (1 H, s, 3-H), 7.31-7.26 (3 H, m), 7.07-7.03 (2 H, m), 5.54 (2 H, s, benzylic CH_2), 2.69 (4 H, t, *J* 6.9 Hz), and 2.45 (2 H, quintet, *J* 7 Hz, $CH_2CH_2CH_2$); *m/z* 269 (M^+, 29%), 224 (87), 196 (13), and 91 (100).

Methyl 1-*benzyl*-1,4,5,6-*tetrahydrocyclopenta*[b]*pyrrol*-2-*ylacetate* (**393**).- A mixture of the keto-acid (**427**) (1.58 g, 5.87 mmol), powdered potassium hydroxide (2.14 g, 38.14 mmol), and hydrazine monohydrate (0.57 ml, 11.73 mmol) in ethanol (5 ml) was heated under nitrogen in an oil bath at 80°C for 1 h and then at 150°C for 1 h. After cooling to room temperature, the mixture was diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue dissolved in dry ether (10 ml). Ethereal diazomethane was added until evolution of nitrogen

ceased. The solvent was evaporated and the residue chromatographed [ether-light petroleum (1:4)] to give the *title compound* (**393**) (1.49 g, 94%) as a yellow oil (Found: C, 75.5; H, 7.0; N, 5.2. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%); ν_{max}(film) 1 738 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.30-7.25 (3 H, m), 6.98 (2 H, d, *J* 7.3 Hz), 5.90 (1 H, s, 3-H), 5.01 (2 H, s, benzylic CH_2), 3.56 (3 H, s, CO_2Me), 3.49 (2 H, s, CH_2CO_2Me), 2.64 (2 H, t, *J* 6.8 Hz), 2.54 (2 H, t, *J* 6.7 Hz), and 2.41-2.31 (2 H, m, $CH_2CH_2CH_2$); *m/z* 269 (M^+, 31%), 210 (88), and 91 (100).

Preparation and Diels-Alder Reactions of 1-*Benzyl*-5-*methyl*-1,2,3,4-*tetrahydrocyclopenta*[d]*pyrano*[4,3-b]*pyrrol*-7(1H)-*one*

Methyl 3-*acetyl*-1-*benzyl*-1,4,5,6-*tetrahydrocyclopenta*[b]*pyrrol*-2-*ylacetate* (**428**).- A solution of acetyl chloride (64 mg, 0.81 mmol) and titanium (IV) chloride (0.27 ml, 2.43 mmol) in dry dichloromethane (3 ml) was stirred under nitrogen at 0°C for 10 min. A solution of the ester (**393**) (109 mg, 0.40 mmol) in dry dichloromethane (2 ml) was added dropwise. The mixture was allowed to warm to room temperature, stirred for 24 h, poured into water, and extracted with dichloromethane. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-light petroleum (4:1)] to give the *title compound* (**428**) (71 mg, 56%), m.p. 118-119°C (Found: C, 73.1; H, 6.8; N, 4.5. $C_{19}H_{21}NO_3$ requires C, 73.3; H, 6.8; N, 4.5%); ν_{max}(Nujol) 1 724 and 1 644 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.32-7.26 (3 H, m), 7.01 (2 H, d, *J* 7 Hz), 5.00 (2 H, s, benzylic CH_2), 4.04 (2 H, s, CH_2CO_2Me), 3.62 (3 H, s, CO_2Me), 2.87 (2 H, m), 2.56 (2 H, m), 2.41 (2 H, m), and 2.37 (3 H, s, CH_3CO); *m/z* 311 (M^+, 22%), 279 (48), 252 (30), 188 (30), and 91 (100).

3-*Acetyl*-1-*benzyl*-1,4,5,6-*tetrahydrocyclopenta*[b]*pyrrol*-2-*ylacetic acid* (**429**).- To a solution of the ester (**428**) (193 mg, 0.62 mmol) in tetrahydrofuran (5 ml) and methanol (1 ml) was added aqueous potassium hydroxide solution (2 M, 4 ml) dropwise with stirring. The mixture was stirred at room temperature for 2 h. The mixture was diluted with water,

extracted with ether, and this extract discarded. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The combined extracts were washed with water, brine, and dried ($MgSO_4$). The solvent was evaporated and the residue recrystallised (ethyl acetate-light petroleum) to give the *title compound* (**429**) (183 mg, 99%), m.p. 170-172°C (decomp.) (Found: M^+, 297.1365. $C_{18}H_{19}NO_3$ requires M, 297.1365); ν_{max}(Nujol) 1 710 and 1 642 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.38-7.27 (3 H, m), 7.01 (2 H, dd, *J* 7.5, 1.5 Hz), 5.15 (2 H, s, benzylic CH_2), 3.77 (2 H, s, CH_2CO_2H), 2.90-2.84 (2 H, m), 2.62-2.55 (2 H, m), 2.50 (3 H, s, CH_3CO), and 2.49-2.39 (2 H, m); *m/z* 297 (M^+, 4%), 279 (8), 253 (53), and 91 (100).

1-*Benzyl*-5-*methyl*-1,2,3,4-*tetrahydrocyclopenta*[d]*pyrano*[4,3-b]-*pyrrol*-7(1H)-*one* (**430**).- To a solution of the acid (**429**) (154 mg, 0.52 mmol) and triethylamine (0.22 ml, 1.55 mmol) in dry tetrahydrofuran (10 ml) at 0°C under nitrogen was added isobutyl chloroformate (106 mg, 0.78 mmol) in dry tetrahydrofuran (5 ml) dropwise with stirring. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into brine and extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), evaporated, and the residue chromatographed [ether-methanol (19:1)] to give the *title compound* (**430**) (133 mg, 92%), m.p. 158-161°C (Found: C, 77.1; H, 6.05; N, 4.95. $C_{18}H_{17}NO_2$ requires C, 77.4; H, 6.1; N, 5.0%); ν_{max}(Nujol) 1 684, 1 642, 1 614, and 1 574 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.33-7.27 (3 H, m), 7.14 (2 H, d, *J* 9 Hz), 5.49 (1 H, s, 8-H), 4.82 (2 H, s, benzylic CH_2), 2.77-2.71 (2 H, m), 2.58-2.55 (2 H, m), 2.52-2.44 (2 H, m), and 2.44 (3 H, s, 5-Me); *m/z* 279 (M^+, 91%), 188 (100), and 91 (45).

Dimethyl 1-*benzyl*-5-*methyl*-1,2,3,4-*tetrahydrocyclopenta*[b]*indole*-6,7-*dicarboxylate* (**431**).- A mixture of the pyranopyrrolone (**430**) (55 mg, 0.20 mmol) and dimethyl acetylenedicarboxylate (56 mg, 0.39 mmol) in chlorobenzene (10 ml) was refluxed under nitrogen for 4 h. The solvent was evaporated and the residue chromatographed [ether-light petroleum (2:1)] to give the *title compound* (**431**) (66 mg, 89%), m.p. 182-184°C (Found: C, 72.9; H, 6.1; N, 3.7. $C_{23}H_{23}NO_4$ requires C, 73.2; H, 6.1; N, 3.7%);

ν_{max}(Nujol) 1 718 and 1 250 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.78 (1 H, s, 8-H), 7.29-7.26 (3 H, m), 7.03-7.00 (2 H, m), 5.27 (2 H, s, benzylic CH_2), 3.94 (3 H, s, CO_2Me), 3.85 (3 H, s, CO_2Me), 3.04 (2 H, t, *J* 7 Hz), 2.74 (2 H, t, *J* 7 Hz), 2.55 (3 H, s, 5-Me), and 2.55-2.45 (2 H, m); *m/z* 377 (M^+, 66%), 346 (21), and 91 (100).

1-*Benzyl*-5-*methyl*-1,2,3,4-*tetrahydrocyclopenta*[b]*indole* (**432**).- A mixture of the pyranopyrrolone (**430**) (43 mg, 0.15 mmol) and phenyl vinyl sulphoxide (117 mg, 0.77 mmol) in chlorobenzene (1 ml) was refluxed under nitrogen for 24 h. The solvent was evaporated and the residue chromatographed [dichloromethane-light petroleum (1:5)] to give the *title compound* (**432**) (19 mg, 47%), m.p. 71-73°C (Found: M^+, 261.1517. $C_{19}H_{19}N$ requires *M*, 261.1517); ν_{max}($CHCl_3$) 1 450, 1 426, 1 350, and 696 cm^{-1}; δ(250 MHz; $CDCl_3$) 7.31-7.17 (3 H, m), 7.09 (2 H, d, *J* 8 Hz), 7.04-6.92 (2 H, m), 6.82 (1 H, d, *J* 7 Hz), 5.20 (2 H, s, benzylic CH_2), 3.05 (2 H, t, *J* 6.9 Hz), 2.75 (2 H, t, *J* 6.9 Hz), 2.59 (3 H, s, 5-Me), and 2.51 (2 H, quintet, *J* 6.9 Hz, $CH_2CH_2CH_2$); *m/z* 261 (M^+, 100%), 218 (12), 170 (31), and 91 (55).

Tetrahydrofuran studies

Diethyl 1-*methylcyclohexene*-4,5-*dicarboxylate* (**433**).- A mixture of isoprene (50.0 ml, 0.5 mol) and diethyl fumarate (20.0 ml, 0.12 mol) in toluene (100 ml) was refluxed for 72 h. The solvent was evaporated and the residue distilled to give the *title compound* (**433**) (28.36 g, 97%), b.p. 150°C at 4 mm Hg (Found: C, 64.8; H, 8.5. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%); ν_{max}(film) 1 738, 1 444, 1 312, 1 254, 1 182, and 1 038 cm^{-1}; δ(250 MHz; $CDCl_3$) 5.38 (1 H, br, vinylic CH), 4.19-4.09 (4 H, m, ester CH_2), 2.92-2.72 (2 H, m, $CHCO_2Et$), 2.42-2.08 (4 H, m, allylic CH_2), 1.67 (3 H, s, 1-Me), and 1.27-1.22 (6 H, m, ester CH_3); *m/z* 240 (M^+, 1%), 195 (18), 166 (32), and 93 (100).

4,5- *Di*(2-*hydroxyisopropyl*)-1-*methylcyclohexene* (**434**).- Methyl iodide (10.3 ml, 166 mmol) in dry ether (50 ml) was added dropwise to a stirred suspension of magnesium turnings (4.04 g, 166 mmol) in dry ether (50 ml) under nitrogen. The ester (**433**) (6.65 g, 27.67 mmol) in dry ether (100 ml) was added dropwise and the mixture refluxed for 24 h. After cooling, the reaction was quenched with saturated ammonium chloride solution. The mixture was extracted with ether and the combined extracts dried ($MgSO_4$). The solvent was evaporated and the residue recrystallised (light petroleum) to give the *title compound* (**434**) (2.57 g, 44%), m.p. 102-104°C (Found: C, 73.5; H, 11.6. $C_{13}H_{24}O_2$ requires C, 73.5; H, 11.4%); ν_{max}(Nujol) 3 240 cm^{-1}; δ(250 MHz; $CDCl_3$) 5.47 (1 H, brs, vinylic CH), 3.39 (2 H, s, OH), 2.11-1.85 (6 H, m, allylic CH_2 + $CHCMe_2$), 1.70 (3 H, s, 1-Me), 1.27 (6 H, s, Me_2COH), and 1.11 (6 H, s, Me_2COH); *m/z* 179 (16%), 136 (44), 121 (47), 107 (16), 93 (100), 79 (21), 59 (98), and 43 (93).

1,1,3,3,5-*Pentamethyl*-3a,4,7,7a-*tetrahydrophthalan* (**435**).- A mixture of the diol (**434**) (1.05 g, 4.95 mmol) and *p*-toluenesulphonic acid (47 mg, 0.25 mmol) was heated to 150°C at 1 mm Hg in a Kugelrohr apparatus. The distillate was chromatographed [ether-light petroleum (1:10)] to give the *title compound* (**435**) (740 mg, 77%), b.p. 90°C at 1.5 mm Hg (Found: MH^+, 195.1749. $C_{13}H_{22}O$ requires *M*H, 195.1749); ν_{max}(film) 1 442, 1 364, 1 272, 1 186, and 946 cm^{-1}; δ(250 MHz; $CDCl_3$) 4.42 (1 H, br, vinylic CH), 2.10-1.76 (6 H, m), 1.71 (3 H, s, 5-Me), 1.27 (6 H, s), 1.05 (3 H, s), and 1.01 (3 H, s); *m/z* (CI, NH_3) 195 (MH^+, 100%) and 177 (44).

2,2,5,5-*Tetramethyl*-4-(2-*oxopropyl*)*tetrahydrofuran*-3-*ylacetic acid* (436).- The cyclohexene (**437**) (204 mg, 1.05 mmol) was dissolved in dry dichloromethane (10 ml). Ozone was bubbled through the solution at -78°C until it became blue. Excess ozone was blown out with oxygen and then nitrogen. The solution was warmed to room temperature and evaporated under reduced pressure. The residue was treated with formic acid (1 ml) and hydrogen peroxide (30%, 0.5 ml). The mixture was stirred at room temperature for 15 minutes and then at 100°C for 30 minutes. After cooling, water was added and the mixture extracted with ethyl acetate. The combined extracts were washed

with brine and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed [ether-methanol (95:5)] to give a gummy solid which was triturated with light petroleum to give the *title compound* (**436**) (108 mg, 42%), m.p. 127-129°C (Found: C, 64.3; H, 9.45. $C_{13}H_{22}O_4$ requires C, 64.4; H, 9.15%); ν_{max}(Nujol) 3 200-2 400 (br), 1 730, 1 294, 1 214, and 1 158 cm^{-1}; δ(250 MHz; $CDCl_3$) 2.75-2.64 (1 H, m), 2.56-2.43 (3 H, m), 2.40-2.34 (1 H, m), 2.29-2.17 (1 H, m), 2.14 (3 H, s, CH_3CO), 1.24 (3 H, s), 1.22 (3 H, s), 1.10 (3 H, s), and 1.07 (3 H, s); *m/z* 243 (MH^+, 2%), 227 (91), 209 (15), 169 (41), 127 (31), and 43 (100).

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