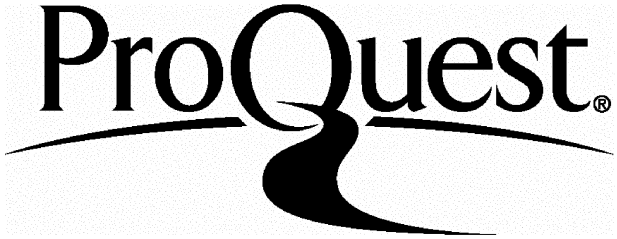
A NOVEL APPROACH TO STEGANONE ANALOGUES *VIA* METAL-MEDIATED CYCLISATIONS

by Adrian Bradley

A thesis presented in partial fulfilment of the requirements for the degree of PhD in the Faculty of Science of the University of London

Christopher Ingold Laboratories, University College London, 1996



Abstract

Transition metal mediated cyclisation reactions are utilised in the synthesis of analogues of the naturally-occurring antileukemic bisbenzocyclooctadiene lignan, steganone.

The first approach involves the metal-mediated [2+2+2] cycloaddition of a rationally designed linear 1,9-diyne with a hindered alkyne. This diyne is formed *via* a convergent synthetic sequence starting from 3,4,5-trimethoxybenzaldehyde and paraconic acid. The cyclisation reaction proceeds diastereospecifically to give the atropisomer relevant to the natural product. The cycloadduct thus formed has been elaborated to give several novel analogues of steganone.

The reaction of this diyne and a model diyne with a chromium carbenoid complex is investigated. This methodology is found to be unsuitable to the formation of this ring system.

A family of macrocycles is postulated, in which one aryl ring present in steganone is replaced with an enediyne moiety. It is suggested these will furnish steganone analogues after Bergman cycloaromatisation. A number of approaches to this class of compound are described. Several advanced linear macrocycle precursors are synthesised, and their metal-mediated cyclisation reactions are investigated.

The final approach to steganone analogues involves cascade carbopalladation of a linear bromoenyne. This bromoenyne is synthesised via a similar synthetic sequence to the diyne previously mentioned. The co-cyclisation of this bromoenyne with trimethylsilylethyne under conditions of palladium catalysis is investigated.

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Acknowledgements

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Contents

Abbreviations

A	Adenine
Ac	Acetyl
AcAc	Acetylacetonate
AIBN	α-Azo *iso*-butyronitrile
aq.	Aqueous
Ar	Aromatic
atm.	Atmospheres
br.	Broad
Bu	Butyl
t-Bu	*tert*-Butyl
cat.	Catalytic
CI	Chemical Ionisation
cm^{-1}	Wavenumbers
C	Cytosine
COD	Cycloocta-1,5-diene
Cp	η^5-Cyclopentadienyl
Cp*	η^5-Pentamethylcyclopentadienyl
Cy	Cyclohexyl
d	Doublet
Δ	Heat
DCM	Dichloromethane

dd	double doublet
ddd	double doublet of doublets
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
dec.	decomposes
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulphoxide
dt	double triplet
E	Unspecified electrophile
EI	Electron impact
eq.	Equivalent
Et	Ethyl
FAB	Fast atom bombardment
FT-IR	Fourier transform infra-red
G	Guanine
h.	hour
hν	Irradiation of unspecified wavelength
IR	Infra-red
J	Coupling constant
L	Unspecified ligand
LDA	Lithium di-*iso*propylamide
lit.	Literature value
M	Molar concentration or Unspecified metal
m	Multiplet or medium

Me	Methyl
min.	minutes
mmHg	Millimetres of mercury
mol %	Molar percentage
m. pt.	Melting point
N	Molal
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Nu	Unspecified nucleophile
P	Unspecified protecting group
p	Para
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
i-Pr	Isopropyl
q	Quartet
R	Unspecified group
s	Singlet or strong
sat.	Saturated
soln.	Solution
T	Thymine
t	Triplet
$t_{1/2}$	Half-life
TBAF	Tetra-*n*-butylammonium fluoride

TBS	*tert*-Butyldimethylsilyl
TEMPO	1,1,5,5-Tetramethyl piperidine *N*-oxide
tert	tertiary
Tf	Trifluoromethanesulphonyl
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*para*-Toluenesulphonyl
w	Weak
X, Y, Z	Unspecified heteroatom substituents

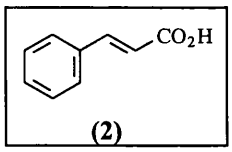
Chapter 1. Introduction

1.0 General Remarks.

The present thesis is concerned with synthetic approaches to unnatural analogues of the antileukemic lignan, steganone **(1)**. Since a key element in the synthetic strategy was that formation of one of the aromatic rings should occur during the synthesis, and not introduced as a pre-formed entity, cycloaromatisation reactions constitute a major part of the work. Accordingly, the introductory review is divided into three sections. The first part (section 1.1) describes previous synthetic approaches to the natural product. The second part (section 1.2) consists of a review of the synthesis of benzenes *via* [2+2+2] cycloaddition reactions of alkynes, which played an important role in one of our approaches to steganone analogues. The third part (section 1.3) consists of a review of the (*Z*)-3-ene-1,5-diynes (enediynes), the Bergman cyclisation reaction they undergo, the naturally occurring compounds containing this element and the synthetic potential of this reaction.

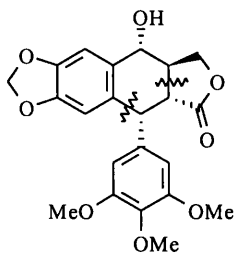
1.1 Lignans: Definitions.

The lignans are a naturally-occurring group of phenolic plant derivatives, characterised by their dimeric relationship to cinnamic acid **(2)** or its biogenetic congeners. They are structurally related to lignin, a three-dimensional polymer whose function is to give rigidity to plant skeletons. They constitute a broad and chemically diverse class of

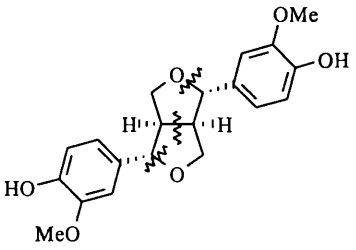


(2)

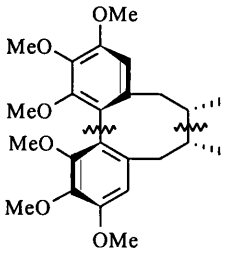
naturally occurring compounds, and some representative structures are shown (scheme **1**); the dashed lines serve to illustrate the underlying cinnamic acid motifs.



Podophyllotoxin **(3)**



(+)-Pinoresinol



(+)-Deoxyschizandrin

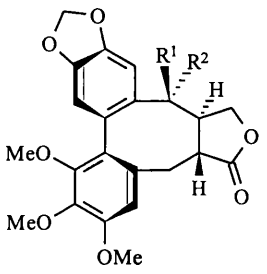
Scheme 1 Representative Structures of Some Lignan Natural Products.

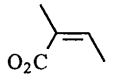
The differences in oxidation level of the cinnamic acid carboxy terminus, the degree of oxygenation of the aryl ring and the points of fusion of the two cinnamate residues account for the structural variation seen in this class of natural products.

The lignans display a wide range of biological activities, and in a number of cases exhibit clinical usefulness. Podophyllotoxin **(3)** and related compounds, in particular, have been used in folk medicines for the treatment of a number of ailments.[1] One medical text over a thousand years old relates to the preparation from the roots of wild Chevril (containing several lignans, including deoxypodophyllotoxin) of a salve for the treatment of cancer.

1.2 Lignans Isolated From *Steganotaenia Araliciae* Hochst.

In 1973, a number of lignans were isolated from the wood and bark of an Ethiopian shrub, *Steganotaenia Araliciae* Hochst.[2] These lignans were structurally characterised, and found to fall into a previously unknown class, the bisbenzocyclooctadiene lignan lactones (scheme **2**).

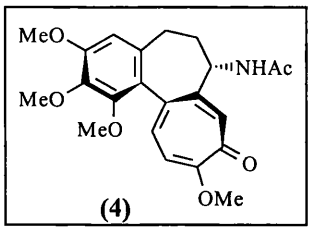


Lignan	R^1	R^2
Steganacin	OAc	H
Steganangin		H
Steganol	OH	H
Episteganol	H	OH
Steganone (1)	O	O

Scheme 2 Lignans Isolated from *Steganotaenia Araliciae* Hochst.

This class of compounds was noteworthy because of the bisbenzocyclooctadiene ring which had only been observed in one other (small) group of lignans at the time,[3] and also because of the atropisomerism arising from the biaryl axis, although this was not discovered in the initial structural elucidation. The discovery excited considerable interest, not only because of the unique structural features inherent in these lignans, but also because of the significant biological activity of the compounds; all isolated lignans showed activity against P-388 leukaemia in mice, and cytotoxicity against a KB cell culture *in vitro* at concentrations of 10^{-1}-10^{-3} μg/mL.

1.3 Mode of Biological Action



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The bisbenzocyclooctadiene lignans isolated from *Steganotaenia Araliciae* Hochst have been shown[4] to belong to the category of cytotoxins known as spindle poisons. These substances exhibit their action by

inhibiting the polymerisation of tubulin (a dimeric protein) into microtubules, thus preventing spindle formation and cell division.[5] The *Steganotaenia* lignans have been shown to bind to dimeric tubulin at the same specific site which is known to be the binding site of one of the first known spindle toxins, colchicine **(4)**. This is known as the colchicine site, and has been shown to be the binding site of a number of these toxins,[6] including podophyllotoxin **(3)**. It is interesting to note the underlying structural similarity between colchicine **(4)**, podophyllotoxin **(3)** and the *Steganotaenia* lignans (Scheme **2**), all of which posses non-coplanar aryl rings.

1.4 Previous Synthetic Approaches to Steganone.

Although the initial stereochemical assignments, based on correlation with the structure of podophyllotoxin **(3)** were incorrect, and the atropisomerism arising from the asymmetric biaryl axis was not uncovered, the structural novelty, biological activity and synthetic challenge presented by these lignans almost immediately attracted the attention of synthetic chemists.

While all of the lignans isolated from *Steganotaenia Araliciae* Hochst have been the subject of synthetic studies, we shall concentrate in this survey on the ketone steganone **(1)**, which is the focus of this study, and has so far attracted the majority of synthetic attention, principally because the other lignans are readily derived from it.[7]

The published syntheses of steganone can be subdivided into three conceptual classes, based on the strategic approach taken. The three main retrosynthetic strategies are, briefly;

i) Installation of the biaryl axis by means of non-phenolic oxidative coupling;

ii) Installation of the biaryl axis by means of an Ullman or similar organometallic coupling reaction;

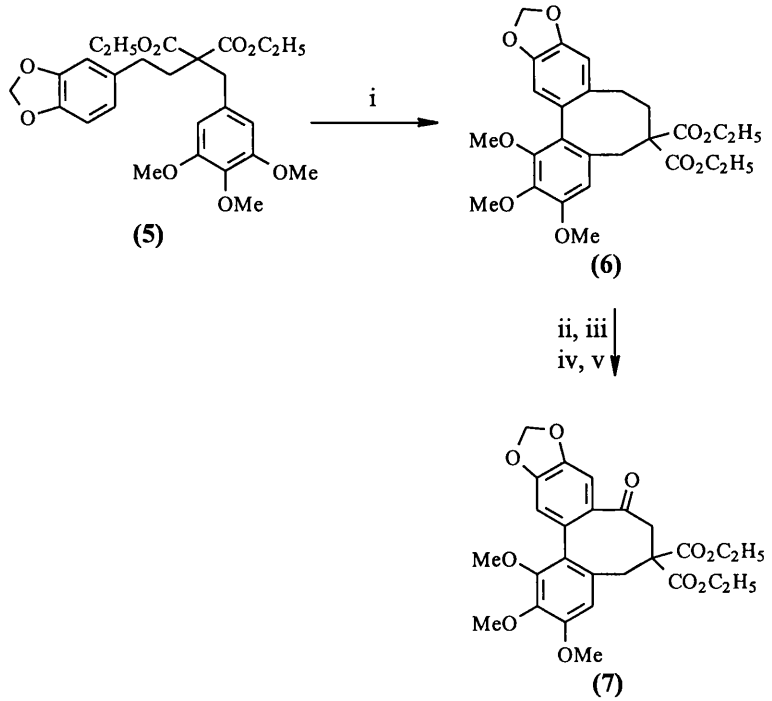
iii). Installation of the biaryl axis by other means.

We shall now examine some of the milestones in the synthesis of steganone, based on these classifications.

1.4.1 Syntheses of Steganone Employing Non-Phenolic Oxidative Couplings

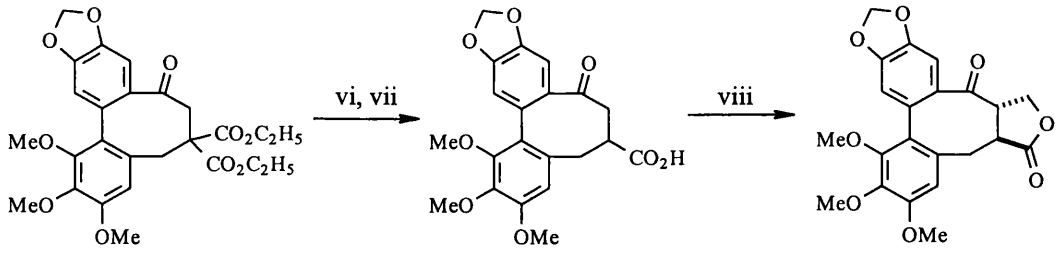
1.4.1.1. The Kende Synthesis of Steganone

The first successful synthesis of steganone was published by Kende and co-workers.[8] The approach adopted by this group was to couple both aromatic portions of steganone onto diethyl malonate to give **(5)**, and then to form the eight membered ring compound **(6)** by non phenolic oxidative coupling (Scheme **3**).



Scheme 3 Reagents and Conditions; i) VOF_3, $(CF_3CO)_2O$, CH_2Cl_2, 1 h., 45 %; ii) *N*-Bromosuccinimide, CCl_4, reflux, 2 h.; iii) AgO_2CCF_3, DMSO, 25 °C; iv) Et_3N/H_2O work up; v) CrO_3-Pyridine, CH_2Cl_2, 60 % from **(6)**.

Initial studies aimed at conducting the key non-phenolic oxidative biaryl coupling in the presence of any oxygen functionality in the benzylic position were completely unsuccessful, requiring the late three stage bromination/hydroxylation/oxidation protocol (scheme **3**), giving **(7)**. Saponification of this material, followed by thermal decarboxylation gave oxo-acid **(8)**; condensation with basic aqueous formaldehyde yielded the racemic natural product in 10 % overall yield from homopiperonal alcohol (Scheme **4**).

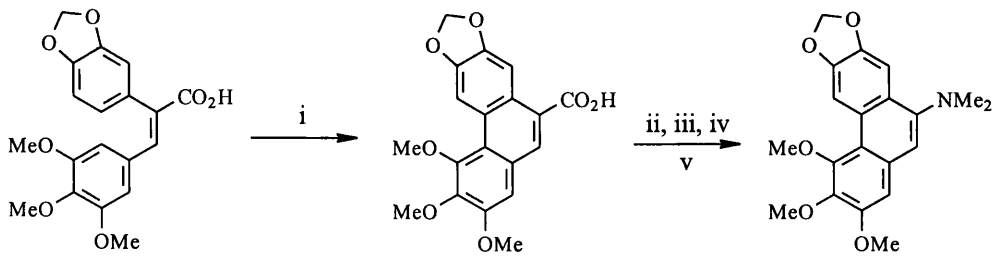


(7) **(8)** **(1)**

Scheme 4 Reagents and Conditions; vi) KOH (aq., 2.7 M), EtOH, reflux, 6 h. vii) Neat, 200 °C, 95 % over 2 steps; viii) 37 % aq. formaldehyde, KOH (aq., 0.4 M), 1 h., 77 %.

1.4.1.2 The Krow Synthesis of Steganone

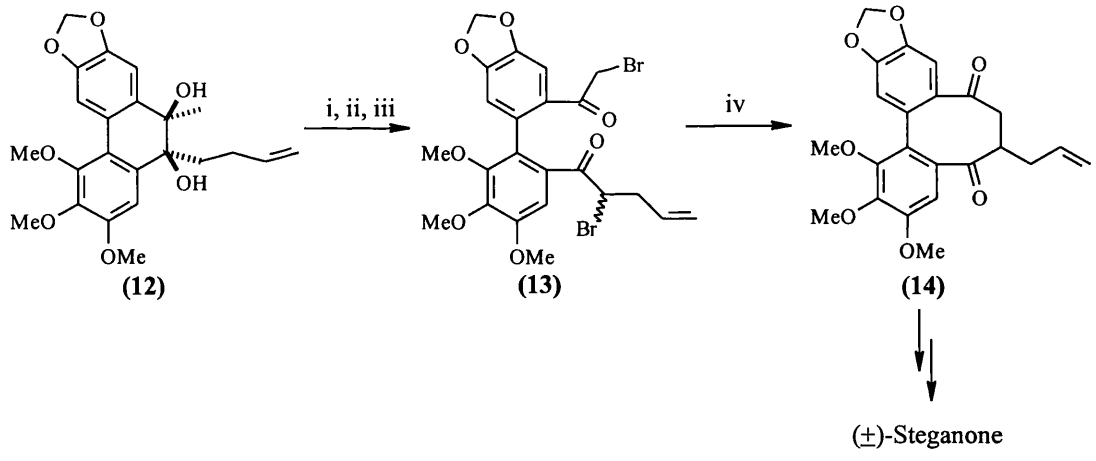
Krow's route to steganone,[9] in common with that of Raphael,[10] relies upon a double ring expansion of a phenanthrene intermediate with dimethyl but-2-ynedioate. The aryl-aryl axis was formed by photochemical ring closure of stilbene **(9)** giving 9-carboxyphenanthrene **(10)** in good yield (Scheme **5**). **(10)** was converted to enamine **(11)** by a modified Curtius rearrangement. From this point on, the synthesis closely resembles the (chronologically earlier) synthesis of Raphael (p. 20).



Scheme 5 Reagents and Conditions; i) hν, I_2, benzene, 20 h., 81 %; ii) NaOMe, MeOH then $(COCl)_2$, benzene, reflux 2 h.; iii) Trimethylsilyl azide, benzene, reflux 24 h.; iv) $LiAlH_4$, THF, reflux 1 h.; v) Trimethyl phosphate, reflux 2 h., 80 % from acid **(10)**.

1.4.1.3 The Ghera Synthesis of Steganone

The approach of Ghera[11] (Scheme **6**) involves oxidative cleavage of diol **(12)** and α bromination to give dibromide **(13)**. Reductive cyclisation of this compound with a zinc/silver couple installed the eight membered ring in 57 % yield as a rapidly interconverting mixture of atropisomers.

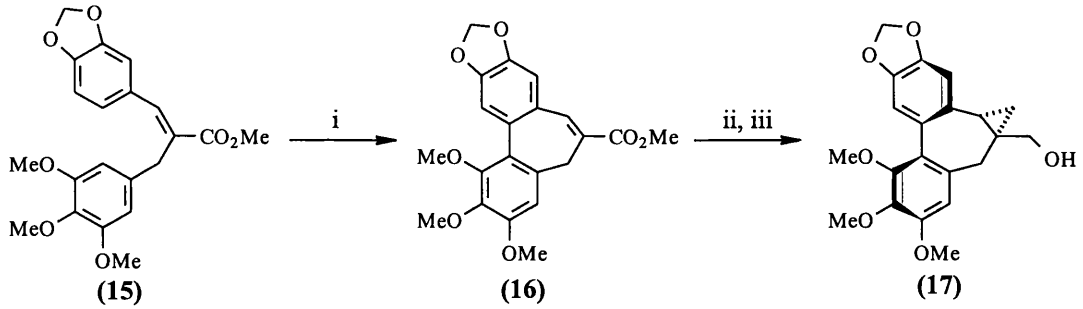


Scheme 6 Reagents and Conditions; i) $Pb(OAc)_4$, 91 %; ii) *n*-BuLi, -78 °C, THF then Me_3SiCl; iii) *N*-Bromosuccinimide, 79 % over 2 steps; iv) Zn/Ag, 57 %.

Elaboration of the key bisbenzocyclooctadiene intermediate **(14)** to (±)-steganone was achieved in ten further steps.

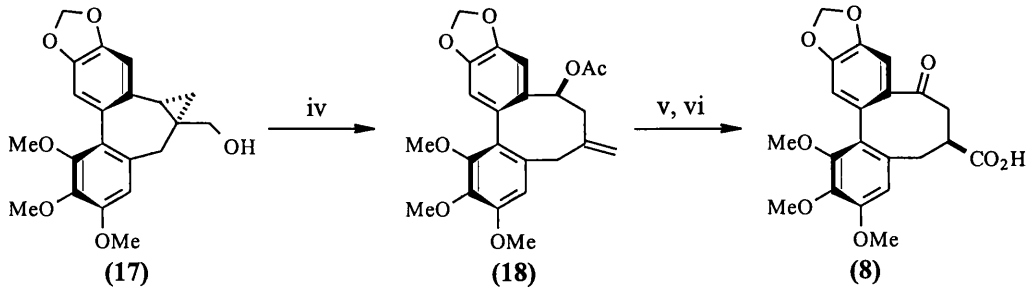
1.4.1.4 The Magnus Synthesis of Steganone

The Magnus group used as their key reaction the non-phenolic oxidative coupling of biaryl **(15)** to bisbenzocycloheptatriene **(16)** using thallium(III) trifluoroacetate as the oxidant (Scheme **7**). The coupling is remarkable in that the yield is approximately twice that of similar couplings used in steganone syntheses.[12]



Scheme 7 Reagents and conditions; i) $Tl(O_2CCF_3)_3$, CF_3CO_2H, -18 °C, 81 %; ii) $LiAlH_4$, 71 %; iii) CH_2I_2, Zn/Cu, 74 %.

Reduction of **(16)**, and Simmons-Smith cyclopropanation of the allylic alcohol gave **(17)** as a single diastereomer. The eight-membered ring of the natural product was then installed by treatment of **(17)** with acid to give exocyclic alkene **(18)** (Scheme **8**). Hydroboration, saponification and oxidation then follow on to the familiar oxo-acid **(8)**.

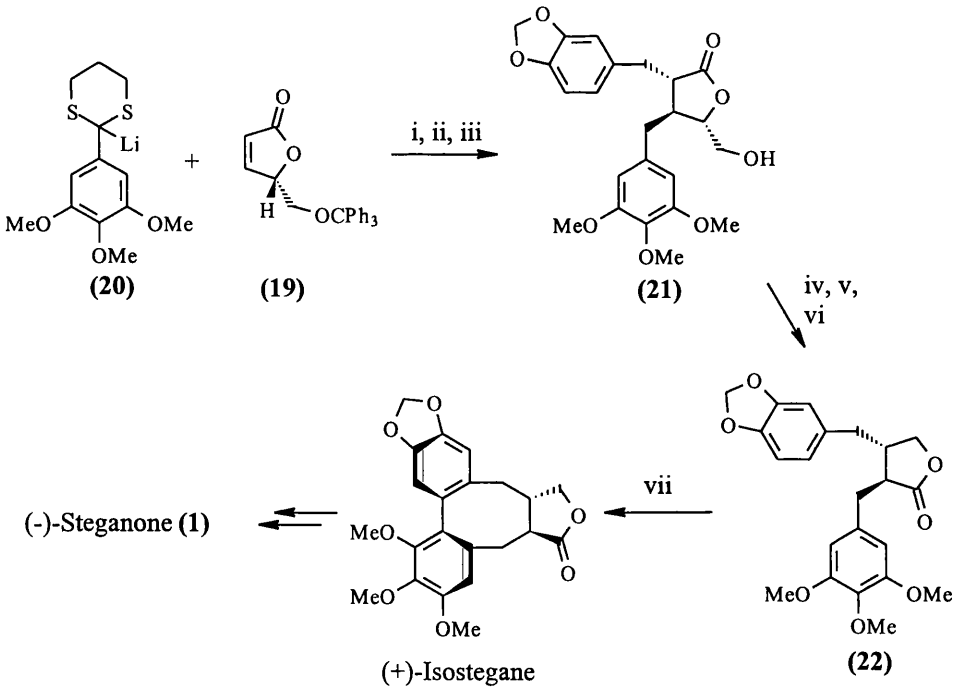


Scheme 8 Reagents and Conditions; iv) AcOH, AcONa, $HClO_4$, 45 °C, 3 h., 97 %; v) BH_3, THF, 0 °C, then H_2O_2/NaOH, 80 %; vi) Jones' oxidation, 80 %.

The synthesis provided oxo-acid **(8)** in 24 % yield from piperonal, and neatly circumvents the inability experienced by earlier workers to carry out non-phenolic oxidative couplings in the presence of benzylic oxygen functionality.

1.4.1.5 The Koga Synthesis of Steganone

Koga[13] took a similar approach to that of Kende[8] (p. 15) in that he also employed non-phenolic oxidative coupling to install the biaryl axis and the eight-membered ring, with subsequent introduction of benzylic oxygen functionality. In this instance, however, the approach makes use of a chiral butenolide **(19)** and is therefore intrinsically asymmetric in nature.



Scheme 9 Reagents and conditions; i) THF, -78 °C, 2.5 h.; then piperonyl bromide -78 °C, then ambient temp., 9.5 h. ii) HCl wash iii) Raney Ni, EtOH, reflux, 12 h., 9 % over 3 steps, based on consumed **(19)**; iv) $LiAlH_4$, THF, 1h., 97 %; v) $NaIO_4$, *t*-BuOH, 50 min., 85 %; vi) CrO_3/Pyridine, CH_2Cl_2, 80 min., 95 %; vii) VOF_3, CF_3CO_2H, CH_2Cl_2, -40 °C, 64 %.

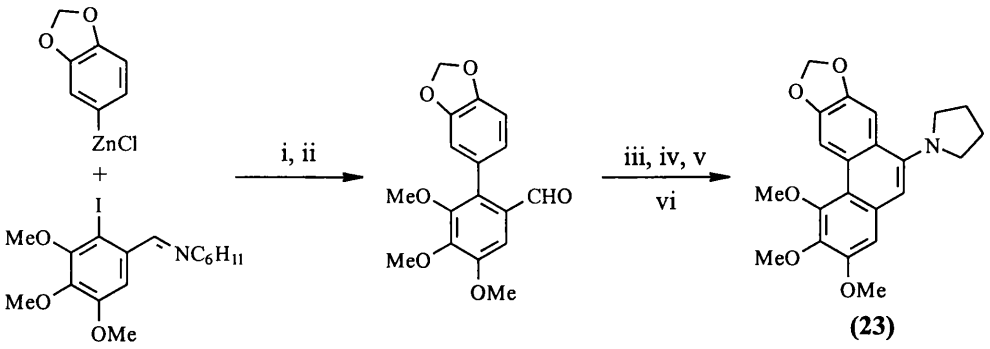
Thus, 1,4 addition of the dithiane anion **(20)** to the trityl butenolide **(19)**, and subsequent trapping of the resultant anion with piperonyl bromide proceeded with essentially complete stereocontrol, although in rather poor chemical yield. Replacement of the trityl group by benzyl ether protection resulted in reduced optical purity, although it did improve the yield. Mild acid deprotection and Raney nickel desulphurisation of the adduct thus formed gave alcohol **(21)**. This was converted in three steps to the natural product (+)-deoxypodohrizon **(22)**. Non-phenolic oxidative coupling proceeded in better yield than that achieved by Kende, to give (+)-isostegane. Further manipulations of the benzylic position were then used to provide all the *Steganotaenia* lignans, including steganone **(1)**.

At this stage, comparison of the optical rotation of the synthetic lignans (derived from butenolides of certain absolute stereochemistry) with those of natural samples revealed them to be equal in magnitude but opposite in sign. This led to a revision of Kupchan's[2] original stereochemical assignment.

1.4.2 Syntheses of Steganone Employing Organometallic Biaryl Couplings

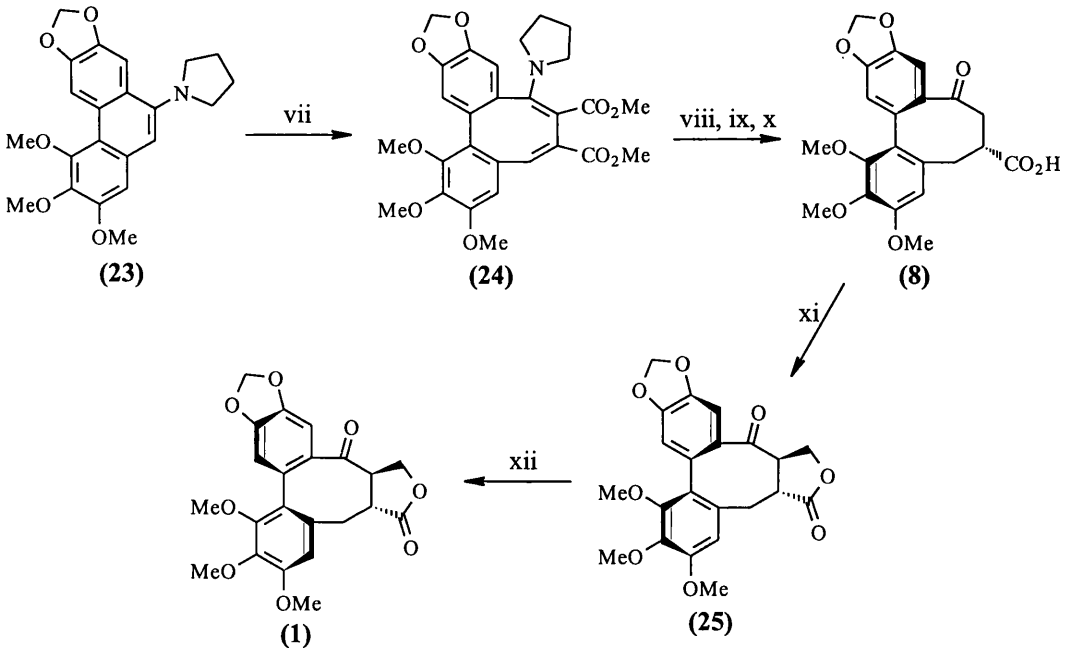
1.4.2.1 The Raphael Synthesis of Steganone

The route of Raphael *et al* used the substituted 9-(pyrrolidin-1-yl) phenanthrene **(23)** as the key intermediate. It was originally[14,7] formed by photocyclisation of an enamine precursor, but this was found to be effective only for small-scale work, and in subsequent[10] work was replaced by an alternative route (Scheme **10**).



Scheme 10 Reagents and Conditions i) $Ni(AcAc)_2$, PPh_3, THF, -20 °C, 4 h.; ii) Aq. HCl, reflux, 1.5 h., 82 % over 2 steps; iii) 2-trimethylsilyl-1,3-dithiane, *n*-BuLi, THF, 21 h., 92 %; iv) $HgCl_2$, HCl, MeOH, reflux, 10 min., 82 %; v) pyrrolidine, reflux, 10 h., 96 %; vi) $POCl_3$, $CHCl_3$, reflux, 5 h., 94 %.

A double ring expansion of phenanthrene **(23)** with dimethyl but-2-ynedioate gave the bisbenzocyclooctatetraene intermediate **(24)** in excellent (89 %) yield (Scheme **11**). This was converted to familiar oxo-acid **(8)**, and this was resolved to give it in its enantiomerically pure form. Base catalysed condensation with formaldehyde, and subsequent Jones' oxidation led to (+)-isosteganone **(25)**, the unnatural atropisomer, which was found to thermally interconvert to (-)-steganone upon heating.



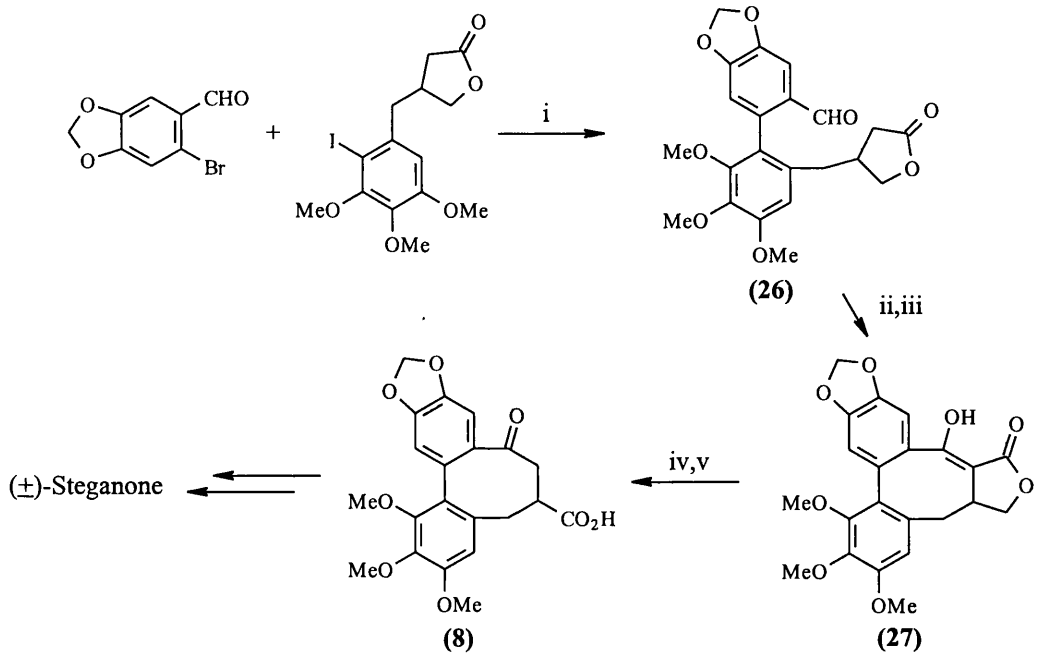
Scheme 11 Reagents and Conditions vii) Dimethyl but-2-ynedioate, 1,4-dioxan, reflux 24 h., 89 %; viii) HCl, MeOH, reflux, 3h., 93 %; ix) H_2, Raney Ni, methyl acetate, 1 atm., 2.5 h, 94 %; x) LiOH, H_2O, 12 h., 95 %; xi) KOH, HCHO, H_2O, then Jones' oxidation, 83 % (based on consumed **(8)**); xii) Xylene, reflux, 1 h, 92 %.

The Raphael synthesis of (-)-steganone **(1)** is noteworthy for a number of reasons. It is highly efficient, giving an overall yield of 10.3 % from 3,4,5-trimethoxybenzyl alcohol, even after resolution. The recognition of the inherent biaryl chirality of the molecule also represented a significant advance in the study of bisbenzocyclooctadiene lignan lactones.

1.4.2.2 The Brown Synthesis of Steganone

The synthetic approach taken by Brown was to form the biaryl axis by means of an Ullman reaction at an early stage (Scheme **12**).[15] This gave the biaryl **(26)** in 59 % yield. An intramoleculer aldol condensation was then used to form the eight-

membered ring as a mixture of diastereomers, which on subsequent oxidation was reported to give enol **(27)**.



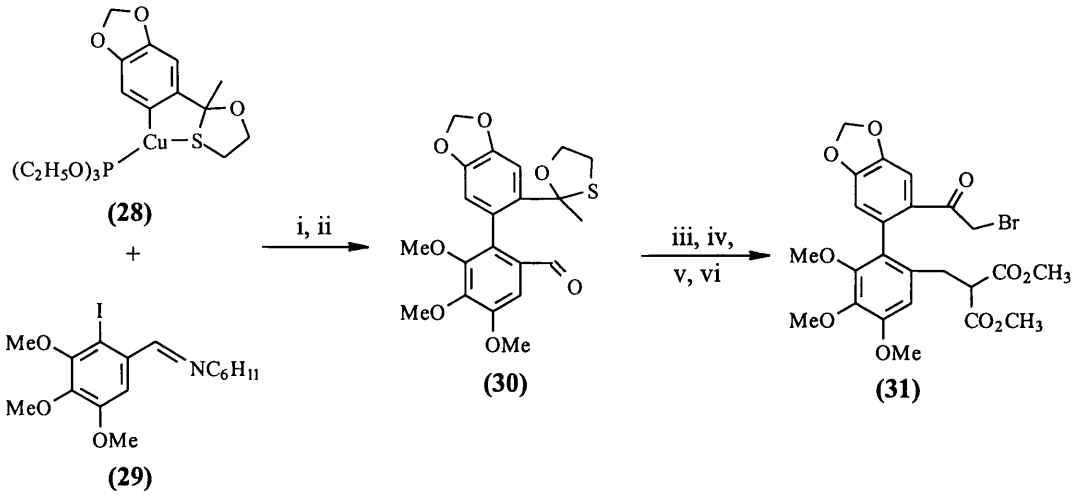
Scheme 12 Reagents and Conditions; i) Cu, Δ, 59 %; ii) LiHMDS, THF, 100 %; iii) Jones' oxidation, 52 %; iv) $Ba(OH)_2$, 80 %; v) Jones' oxidation.

Treatment with base led to decarboxylation, and subsequent oxidation gave the familiar γ-keto-acid **(8)**, which was converted to racemic steganone by Raphael's method[7] in 7 % overall yield from 3,4,5-trimethoxybenzaldehyde.

1.4.2.3 The Ziegler Synthesis of Steganone

The elegant methodology developed by Ziegler and his group[16] for conducting aryl-aryl couplings by a ambient temperature variant of the Ullman reaction was appropriately illustrated by application to the syntheses of several members of the *Steganotaenia* lignans. The system made use of an organocopper reagent **(28)**, stabilised by an intramolecular oxathiolane ligand, which also served as a masked

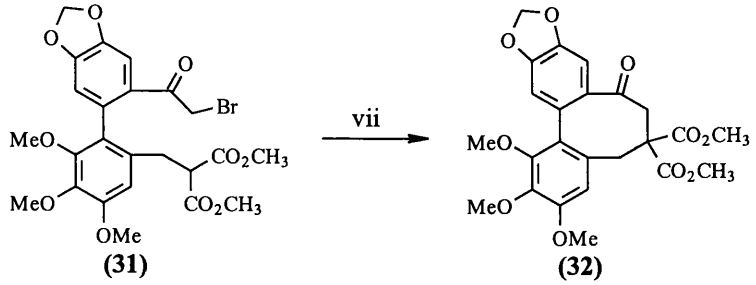
ketone group. This reacted smoothly with iodide **(29)** to give, after acidic hydrolysis of the imine, the biaryl **(30)** (scheme **13**).



Scheme 13 Reagents and Conditions i) THF, 20 h.; ii) 15 % aq. AcOH, 12 h., 82 % over 2 steps; iii) Dimethyl malonate, piperidine, benzene, reflux, 10 h., 78 %; iv) MeI, acetone, reflux 12 h., 91 %; v) Raney Ni, H_2, 1 atm., EtOH, 95 %; vi) $C_6H_5NHBr.Br_2$, CF_3CO_2H, CH_2Cl_2, 3.5 h., 85 %.

Knoevenagel condensation of **(30)** with dimethyl malonate, oxathiolane removal, hydrogenation and bromination of the methyl ketone afforded cyclisation precursor **(31)**.

Cyclisation conditions were chosen carefully, as the molecule contains both methylene and methine acidic protons. Thermodynamic control was ensured by use of a system of *t*-BuOK in *t*-BuOH/THF. Dropwise addition of the bromide **(31)** to the basic solution furnished **(32)**, the dimethyl analogue of Kende's intermediate **(7)** (scheme **14**).

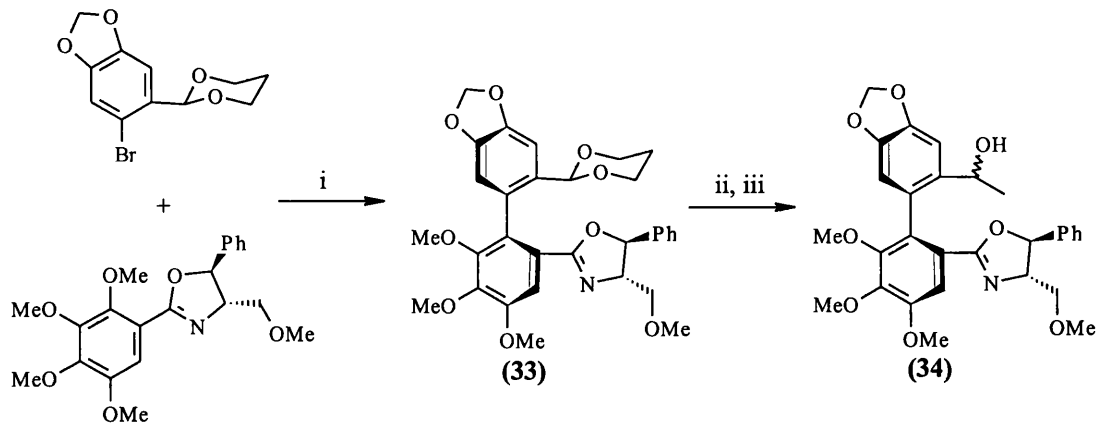


Scheme 14 Reagents and Conditions; vii) *t*-BuOK, *t*-BuOH, THF, addition of **(31)** over 45 min., stir for 45 min., 73 %.

The conversion of **(32)** into racemic steganone was then accomplished following the methodology employed by Kende[8] and Raphael.[7]

1.4.2.4 The Meyers Synthesis of Steganone

The approach adopted by the Meyers group[17] also formed the biaryl axis at a very early stage in his synthesis, but was conceptually novel in that it introduced it in an asymmetric fashion by application of a chiral auxiliary (scheme **15**).

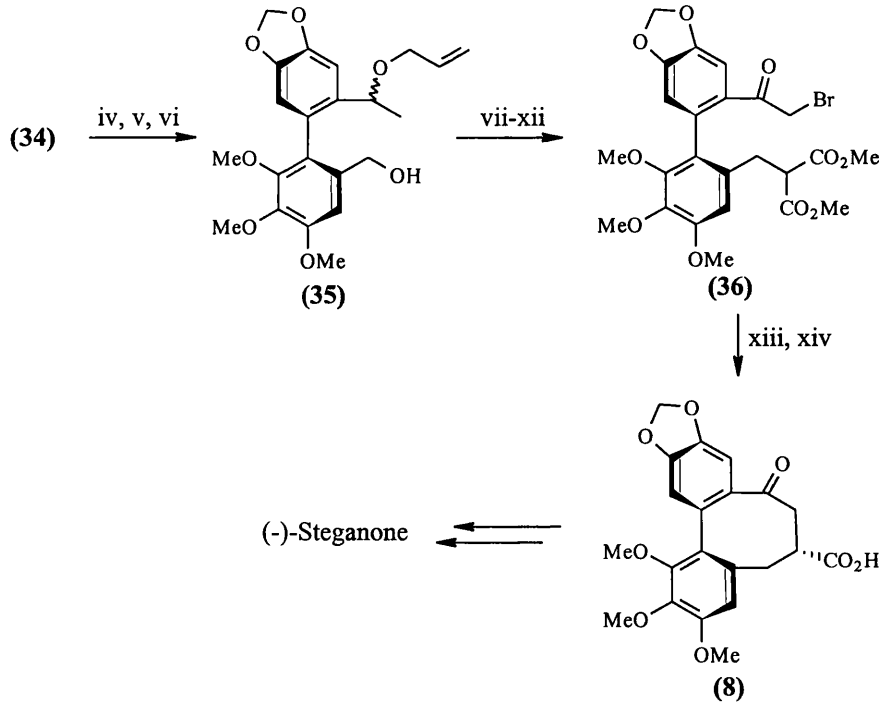


Scheme 15 Reagents and Conditions; i) Mg, 1,2-dibromoethane, reflux, 65 % (9 % of other diastereomer); ii) 3 M HCl, THF, -5 °C; iii) MeMgBr, -78 °C (91 % over 2 steps).

The key coupling reaction formed the biaryl **(33)** in 74 % overall yield, in a ratio of 7:1 in favour of the desired diastereomer. Deprotection of this biaryl intermediate

under acidic conditions was found to bring about rapid racemisation, due to the introduction of an extra sp^2 substituent on the aromatic ring facilitating aryl-aryl bond rotation. Fortunately, this could be minimised by conducting the reaction and work-up at low temperature, and using the aldehyde immediately in the next step. Following this protocol, it proved possible to isolate alcohol **(34)** as a 1:1 mixture of diastereomers at the alcohol centre.

The alcohol functionality was protected as its allyl ether, and the chiral auxiliary cleaved using bisulphite followed by lithium aluminium hydride reduction (scheme **16**) to give alcohol **(35)**.



Scheme 16 Reagents and Conditions iv) Allyl iodide, NaH, THF, 85 %; v) HSO_4^-, THF; vi) $LiAlH_4$, THF, 0 °C; vii) *N*-Bromosuccinimide, PPh_3; viii) NaOMe, $(MeO_2C)_2CH_2$, MeOH, 61 % over four steps; ix) $(Ph_3P)_3RhCl$, $HgCl_2$-HgO, 83 %; x) Pyridinium Dichromate, CH_2Cl_2; xi) CF_3CO_2H, CH_2Cl_2; xii) C_5H_6N, Br_2 xiii) KO^{t}Bu, THF, 54 % over 5 steps; KOH, H_2O, 30 %.

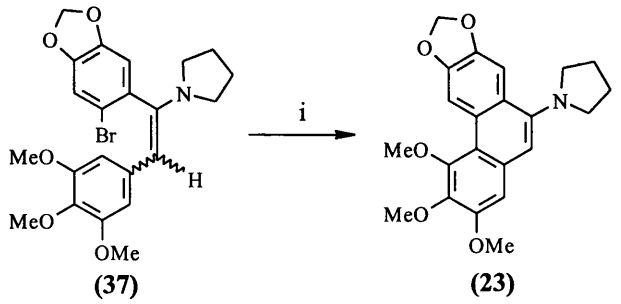
The benzylic alcohol was converted to a bromide, and this was subsequently displaced with dimethyl malonate anion to install a malonate activating group. Removal of the

secondary alcohol protecting group, oxidation and bromination alpha to the ketone gave cyclisation precursor **(36)**. The cyclisation reaction proceeded with overall formation of the bisbenzocyclooctadiene ring in 54 % yield over the five preceding steps. Saponification with decarboxylation went in disappointingly low yield to give γ-keto-acid **(8)**, which was obtained as a 1:1 mixture of atropisomers. Fortunately, it proved possible to separate the two, and thermal interconversion of the undesired isomer allowed 90 % of the appropriate diastereomer to be obtained. The synthesis, from this point on, followed along the lines of all other syntheses passing through γ-keto-acid **(8)**. Comparison of the optical rotation of the synthetic steganone thus produced with an authentic sample indicated that 10-12 % racemisation had occurred. The authors state that this racemisation probably occurred during the bromination stage (step xii, scheme **16**), which undoubtedly passes through the enol form, introducing a benzylic sp^2 centre.

1.4.3 Syntheses of Steganone Employing Other Biaryl Couplings

1.4.3.1 The Narasimhan Formal Synthesis of Steganone

Narasimhan and Aiden's[18] approach to steganone, like that of Raphael[7] (p. 20) and Krow[9] (p.16) involves double ring-expansion of a phenanthrene intermediate. Narasimhan, however, employs a radical-mediated intramolecular arylation to form the aryl-aryl bond (scheme **17**).



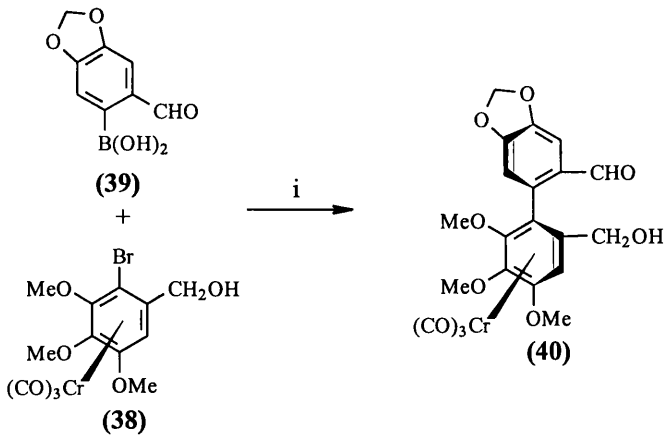
(37) (23)

Scheme 17 Reagents and Conditions i) Tri-*n*-butyltin hydride, AIBN, benzene, reflux 2-2.5 h., 66 %.

Cyclisation of bromoenamine **(37)** with tri-*n*-butyltin hydride/AIBN gave phenanthrene **(23)** in good yield. As **(23)** was used as an intermediate in the Raphael[14] synthesis of (±)-steganone, this constituted a formal total synthesis of the natural product.

1.4.3.2 The Uemura Formal Synthesis of Steganone

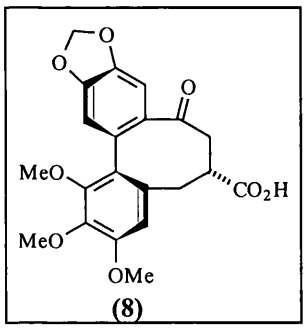
The most recent contribution[19] to steganone synthesis has also culminated in the Meyers[17] intermediate **(36)** (p. 25), and is therefore a formal synthesis of (-)-steganone (Scheme **18**). The synthesis hinges on the Suzuki coupling of the homochiral chromium tricarbonyl-arene complex **(38)** with boronic acid **(39)**.



Scheme 18 Reagents and Conditions i) $Pd(PPh_3)_4$ (0.05 eq.), aq. Na_2CO_3, MeOH, Reflux 1 h., 67 %.

The biaryl **(40)** was formed in good yield, and was converted in a further 7 steps into **(35)**, bringing the sequence into convergence with that of Meyers.

1.4.4 Overview of Published Synthetic Routes to Steganone



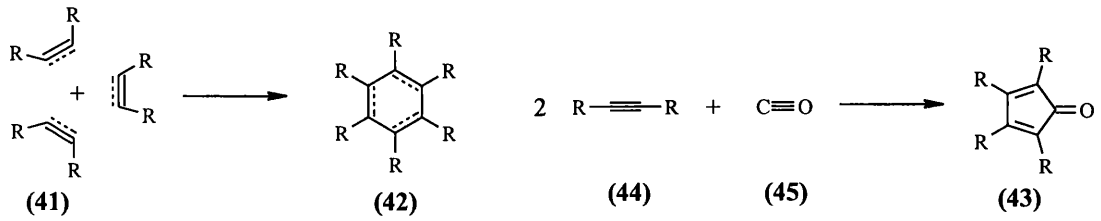
(8)

The synthesis of steganone and its related lignans has attracted the attention of a number of research groups over the past 20 years, and has resulted in some creative and highly efficient routes. However, a number of surprising facts emerge; eleven of the twelve synthetic approaches (including the formal syntheses) pass through oxo-acid **(8)**. This is a surprising pattern in the light of the fact that the subsequent conversion to the natural product proceeds in extremely variable yield, often as low as 11 %.[17] Apart from the routes of Uemura[19] and Narasimhan,[18] all the routes invoke modified Ullman or non-phenolic oxidative biaryl couplings. Clearly there was scope for further contributions.

1.5 [2+2+2] Cycloaddition Reactions

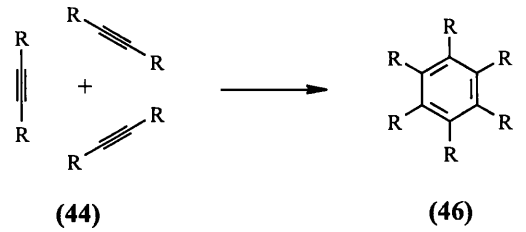
[2+2+2] Cycloadditon reactions can generally be defined as those in which three reacting components, each with 2 π electrons **(41)**, combine to form a single cyclic product **(42)** (scheme **19**). In the course of such a reaction, three new σ bonds are formed. The designation [2+2+2] refers to the number of π electrons contributed by each reacting component, rather than the number of atoms: the formation of a cyclopentadienone **(43)** from two molecules of alkyne **(44)** and one of carbon

monoxide **(45)** would therefore belong to this classification. However, as the construction of six membered aromatic rings was to be our primary interest, it is these reactions which shall receive the majority of our attention.



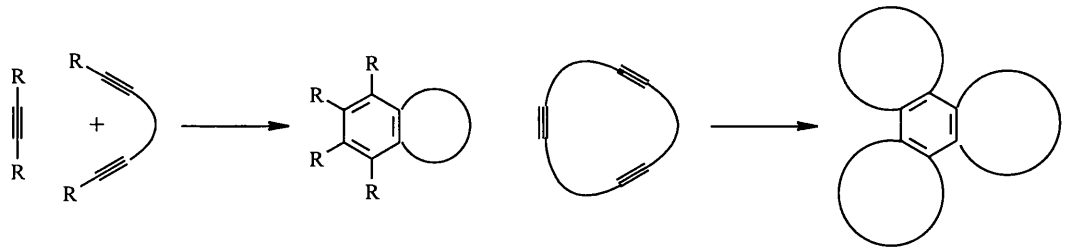
Scheme 19 Prototypical [2+2+2] Cycloadditions.

A reaction which has received increasing interest from synthetic chemists over recent years is the [2+2+2] cyclotrimerisation of alkynes **(44)** to give arenes **(46)**. The appeal of such an approach is immediately apparent when one considers the potential of forming three new carbon-carbon bonds in a single step (scheme **20**), as well as the fact that a very concise route to highly substituted arenes then results.



Scheme 20 Generalised [2+2+2] Cycloaddition of Alkynes.

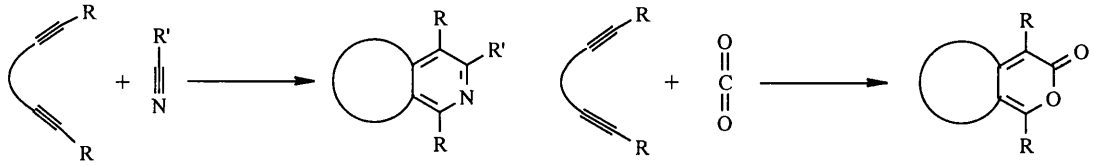
Partially **(47)** or completely **(48)** intramolecular variants are even more appealing, allowing not only rapid construction of bi- and polycyclic systems **(49)** and **(50)** (Scheme **21**) but also leading to improved regiocontrol.



(47) (49) (48) (50)

Scheme 21 Generalised Intramolecular [2+2+2] Cycloadditions.

When one considers the possibility of synthesising heteroaromatic compounds such as pyridines **(51)** and pyrones **(52)** from compounds containing carbon-heteroatom π-bonds, the scope of the reaction becomes even broader (scheme **22**).



(51) (52)

Scheme 22 Heteroaromatic Compounds *via* [2+2+2] Cycloadditions.

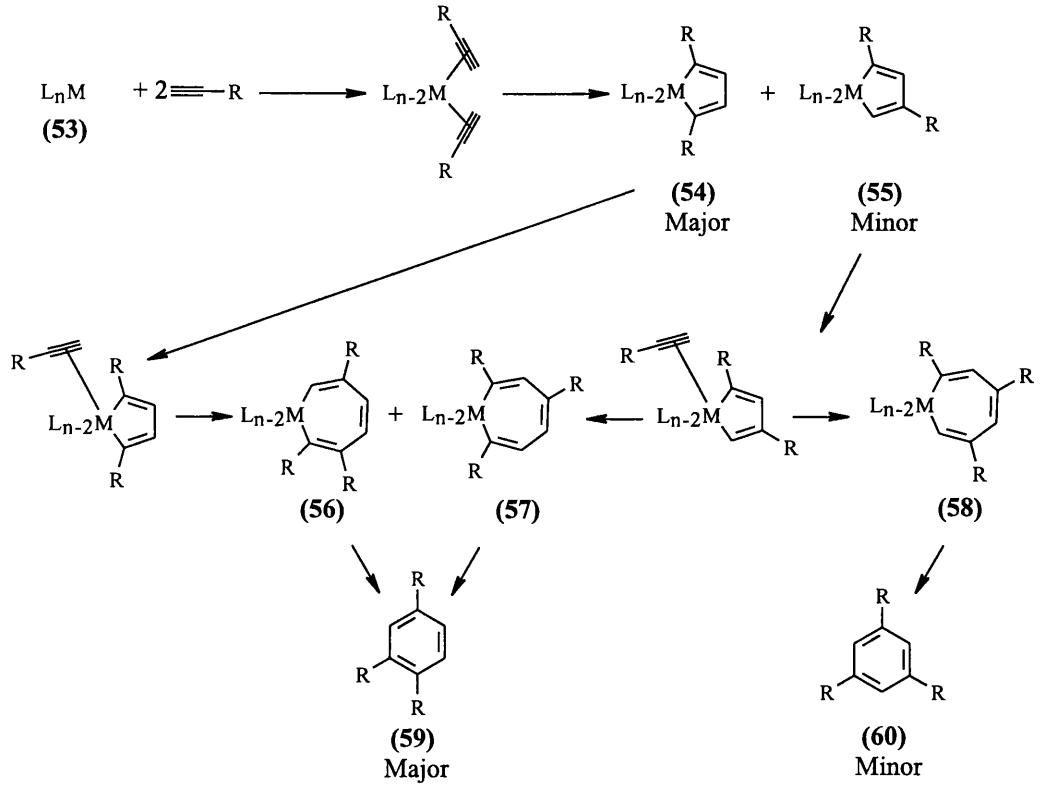
The cyclotrimerisation of acetylene to benzene is a highly exothermic process,[20] calculated to be -594 $kJmol^{-1}$. The reaction has been known for over 100 years;[21] the thermal reaction, however, requires high temperatures (400 °C)[22] and gives a large number of side products, including higher oligomers of acetylene. Kinetic and entropic factors are presumably responsible for the rarity of thermal [2+2+2] cycloadditions, and the fact that the transformation was not added to the organic chemists' synthetic repertoire until relatively recently.

1.5.1 Metal Catalysed [2+2+2] Cycloadditions

In 1949 Reppe demonstrated that acetylene, in the presence of a nickel(0) catalyst, underwent trimerisation to give benzene in 80 % yield.[23] Monoalkylacetylenes gave 1,3,5- or 1,2,4- trialkyl benzenes, depending on the reaction conditions, and the exact spatial and electronic requirements of the catalyst. A variety of other functional groups were tolerated; however, internal acetylenes were not cyclised. Since that time, a large number of transition metal compounds have been found to catalyse the trimerisation of acetylenes,[24] although until recently they were of interest mainly from a mechanistic and organometallic, rather than a preparative point of view.

1.5.1.1 Chemo- and Regio- selectivity

As discovered by Reppe, the use of terminal acetylenes gives rise to questions of regio- and chemoselectivity, which can be rationalised by mechanistic considerations. The diversity of organometallic compounds which are known to catalyse [2+2+2] cycloadditions of acetylenes mean that a variety of pathways are involved, each characteristic of the metal present in the system. The most common mechanism involves sequential exchange of two ligands of a transition metal complex **(53)** with substrate terminal alkynes. Oxidative coupling leads to metallacyclopentadienes **(54)** and **(55)**. Co-ordination of these species to a third alkyne is then followed by insertion to give metallocycloheptatrienes **(56)**, **(57)** and **(58)** and subsequent reductive elimination then gives the product 1,2,4- **(59)** and 1,3,5- **(60)** substituted arenes (scheme **23**).



Scheme 23 Mechanism of [2+2+2] Cycloaddition of Alkynes.

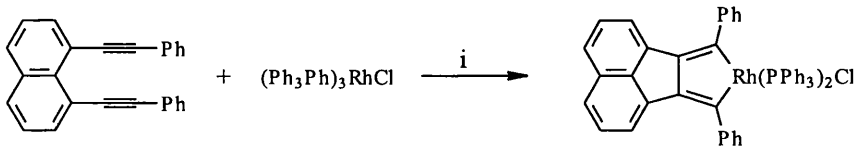
Considerations of regioselectivity arise at two distinct steps in the overall pathway viz., the formation of the metallocyclopentadienes **(54)** and **(55)**, and the orientation of insertion of the third alkyne, leading to **(56)**, **(57)** and **(58)**. A preference for formation of metallacyclopentadiene **(54)** has been noted and rationalised on molecular orbital grounds;[25] this inevitably leads to formation of 1,2,4-trisubstituted arenes **(59)** (or alkynes with larger substituents in the 1,2,4- positions, in the case of non-terminal alkynes), regardless of the orientation of the final alkyne insertion.

In some cases,[26,27] Diels-Alder addition of the third alkyne to metallacyclopentadienes **(54)** and **(55)**, followed by elimination of the metal with concomitant aromatisation has been proposed to be the mechanism involved.

Although several systems have been developed to allow the selective preparation of 1,3,5- or 1,2,4- trisubstituted arenes from alkynes, such reactions are of limited value in more synthetically useful cross-couplings as questions of chemo- as well as regio-selectivity arise. One popular strategy which circumvents these problems is to incorporate two or more of the reacting components in the same molecule, making the reaction either partially or wholly intramolecular. Some of these strategies will subsequently be discussed.

1.5.1.2 Rhodium Mediated [2+2+2] Cycloadditions

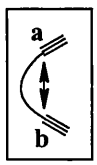
Metallacyclopentadiene complexes of rhodium and iridium were first isolated in the late 1960's,[28] and were shown to be intermediates in the cyclotrimerisation of alkynes by rhodium and iridium catalysts. Müller found that stirring 1,8-bis[phenylethynyl]naphthalene **(61)** with tris(triphenylphosphine)rhodium(I) chloride in benzene gave a green solution of the rhodacycle **(62)** (scheme **24**).[29]



(61) **(62)**

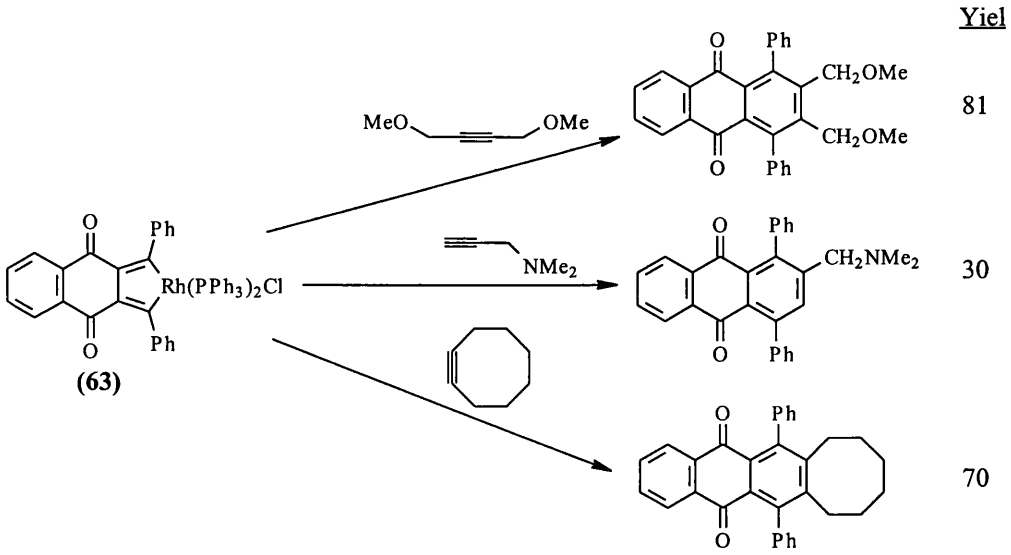
Scheme 24 Reagents and Conditions i) PhH, 24 h., 88 %.

The scope of rhodacycle formation was found to be broad; most 1,5- or 1,6- diyne systems would react with tris(triphenylphosphine)rhodium(I) chloride to give similar products. A study of the scope of the reaction led to the general conclusion that in cases where the distance between alkyne atoms **a** and **b** was not greater than 3.4 Å, formation of the rhodium complex should prove possible,



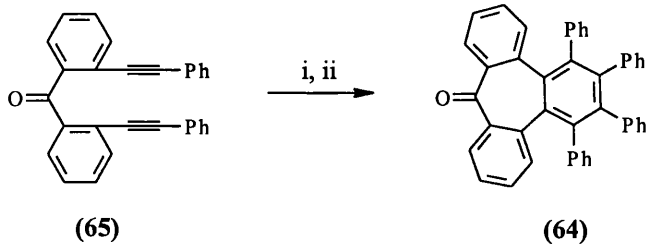
but the reaction was particularly suitable for the preparation of metallacycles from bis ynones.[30]

The isolated metallacycles could then be reacted with a variety of alkynes to give arenes. Some representative examples[30] are shown (scheme **25**).



Scheme 25 Reagents and Conditions; rhodium complex **(63)**, alkyne, xylene, reflux, yield as shown.

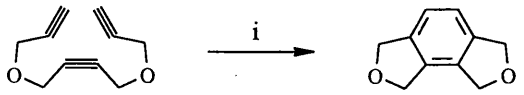
The reaction has been used[31] to prepare seven-membered ring compounds such as tropolone **(64)** from 1,8- diynes **(65)**, although in rather poor yield (scheme **26**).



Scheme 26 Reagents and Conditions; i) $(Ph_3P)_3RhCl$, PhH, 24 h; ii) Diphenylacetylene, xylene, reflux, 7 h., 20 % over 2 steps.

The attractiveness of using such a reaction which is stoichiometric in rhodium is, of course, severely curtailed by the extreme expense of this metal. Grigg[32] introduced a catalytic modification of this reaction, using 0.5 - 2 mol % of

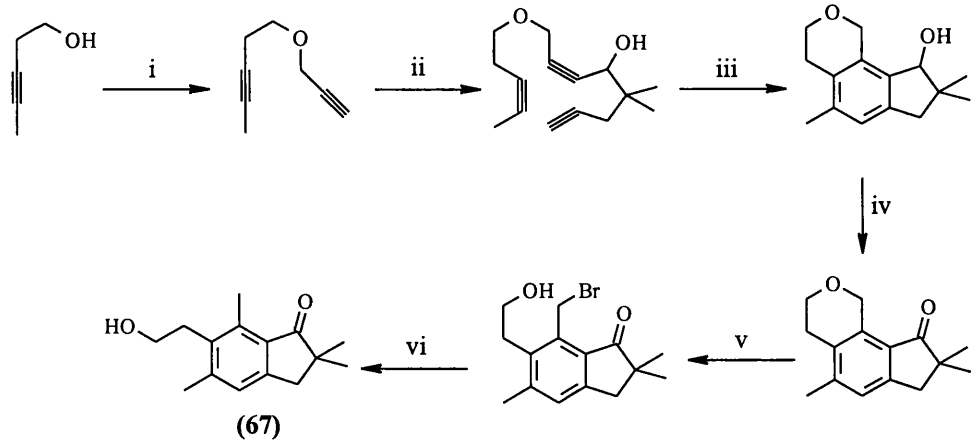
tris(triphenylphosphine)rhodium(I) chloride to catalyse the reaction of 1,6-heptadiynes with terminal alkynes in ethanol. The reaction showed good tolerance of functional groups, and was used to synthesise both spiro-compound and polycyclic systems such as **(66)** in good yield (scheme **27**).



(66)

Scheme27 Reagents and Conditions i) $(Ph_3P)_3RhCl$ (2 mol %), EtOH, 25 °C, 2 h., 75 %.

Grigg has accounted[33] for the chemo- and regioselectivities he observed in these reactions. The methodology has been utilised[34] in a concise, stereospecific synthesis of several illudalanes, including Pterosin Z **(67)** (scheme **28**).

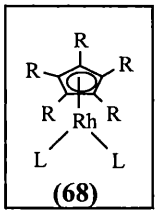


(67)

Scheme 28 Reagents and Conditions i) NaOH, propargyl bromide, THF, 60 °C, 66 %; ii) *n*-BuLi, THF, -78 °C, 1 h. then 2,2 dimethyl-4-pentynal, THF -78 °C, 1 h., 76 %; iii) $(Ph_3P)_3RhCl$, EtOH, 12 h., 82 %; iv) PCC, DCM, 1 h, 85 %; v) BBr_3, DCM, -25 °C, 62 %; vi) Tri-*n*-butyltin hydride, AIBN, PhH, reflux, 2 h., 83 %.

This synthesis provides an elegant example of the use of a tethered [2+2+2] cycloaddition in the construction of a highly substituted aromatic nucleus in a regiospecific fashion.

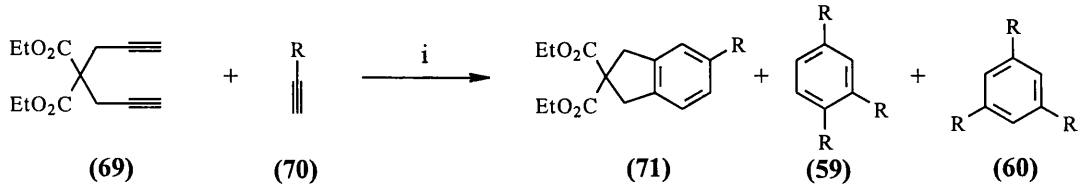
A series of kinetic studies[35] served to highlight a number of key factors in the cyclotrimerisation of dimethylacetylene dicarboxylate. The trimerisations were conducted with a related series of rhodium η^5-cyclopentadienyl catalysts **(68)**, and the rate of trimerisation was measured. The rate was found to increase as the π acceptor strength of the η^5-cyclopentadienyl ligand increased, although this trend was reversed in the trimerisation of hex-3-yne. The nature of the ligand L was also found to affect the rate, implying that L remains bound to the catalyst throughout the catalytic cycle.



(68)

1.5.1.3 Nickel Based [2+2+2] Cycloaddition Reactions

Since the original discovery of the trimerisation of acetylene by nickel(0) species was made by Reppe,[23] nickel based trimerisation has become a fruitful method for the production of benzenes.[36] The co-cyclisation of α,ω-diynes with mono-acetylenes has received less attention. A catalytic system formed by the addition of *n*-butyllithium to tetrakis(triphenylphosphine)nickel(II) chloride[37] has been used to effect the cyclisation of the malonate diyne **(69)** with alkynols **(70)** to form indanes **(71)** in poor to good yield (scheme **29**). Considerable amounts of trimers **(59)** and **(60)** of the monoacetylene were also formed.

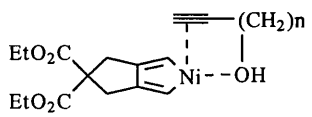


(69) **(70)** **(71)** **(59)** **(60)**

R=$(CH_2)_nOH$

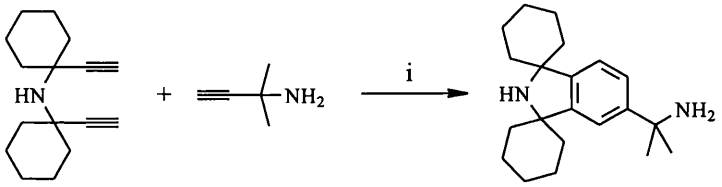
Scheme 29 Reagents and Conditions; i) $NiCl_2(PPh_3)_4$/BuLi, THF, 10-20 h., 0-78 %.

Co-ordination of the oxygen atom of the alkynol **(70)** to the nickel atom was inferred to be of considerable importance in promoting the reaction since variation of



(72)

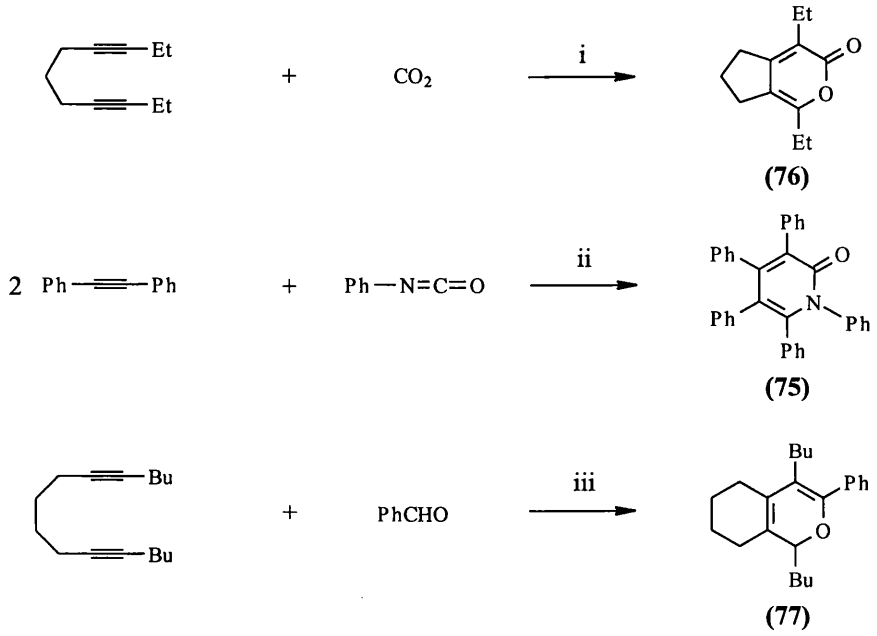
the length of the alkyl chain had a pronounced effect on the yield of indane **(71)**. An intermediate of the type **(72)** was postulated. Similar co-ordination effects may also be operating in the bis(cyclooctadienyl) nickel(0) catalysed co-cyclisation of alkynyl amine **(73)** with diyne **(74)** (scheme **30**).



(74) **(73)**

Scheme 30 Reagents and Conditions i) $Ni(COD)_2$, $P(Oi\text{-}Pr)_3$, THF, reflux, 20 h.

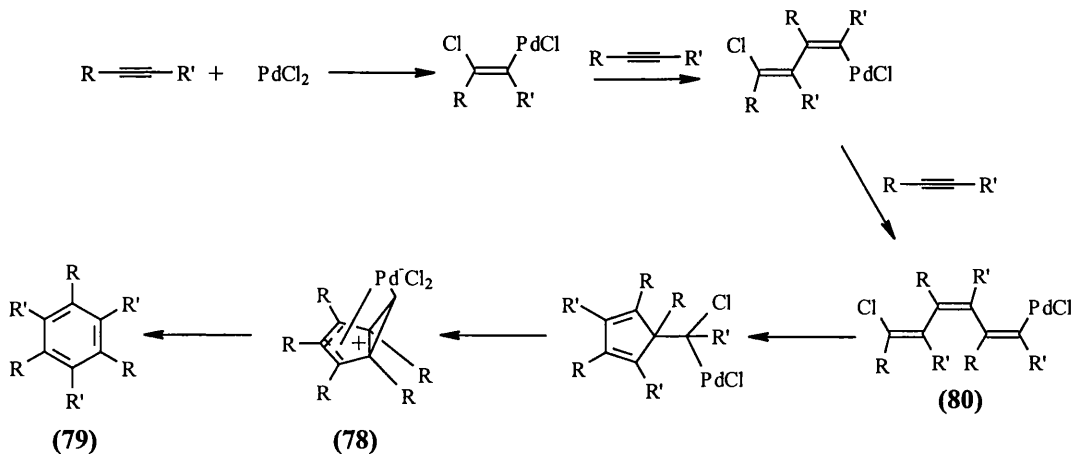
Nickel based catalysts have found more extensive use in the synthesis of heteroaromatic systems. Thus, pyridones **(75)**,[38] pyrones **(76)**[39] and bicyclic α pyrans **(77)**[40] have all been synthesised using similar the bis(cyclooctadienyl) nickel(0)/trialkylphosphine catalyst systems (scheme **31**).



Scheme 31 Reagents and Conditions i) $Ni(COD)_2$, PCy_3, THF, 25 °C, 50 $kgcm^{-2}$, 20 h., 88 %; ii) $Ni(COD)_2$, PCy_3, Toluene, 25 °C, 24 h., 84 %; iii) $Ni(COD)_2$, PCy_3, THF, 120 °C, 5 h., 78 %.

1.5.1.4 Palladium Catalysed [2+2+2] Cycloaddition Reactions

Cyclotrimerisation of alkynes is promoted by palladium(II) chloride, or more commonly, its bis(benzonitrile) complex. It proceeds *via* a mechanism which is different from those previously discussed inasmuch as metallacycles are not believed to be involved. Instead, linear oligomerisation, 5-*exo* cyclisation and formation of the bicyclo [3.1.0] hexane **(78)** are believed[41] to precede ultimate arene **(79)** formation (scheme **32**).



Scheme 32 Mechanism of the Cyclotrimerisation of Alkynes by Palladium(II) Chloride.

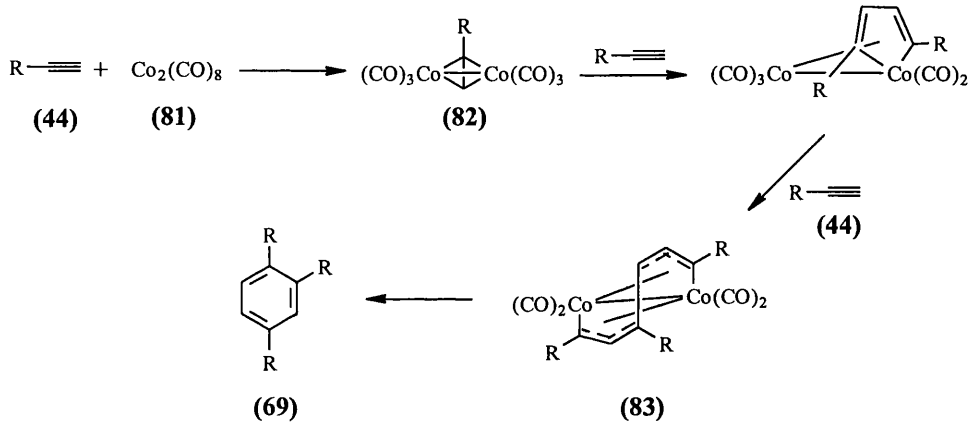
This unique mechanism leads to a regioselectivity which is different from that previously seen; head-to-tail coupling of the alkyne units occurs to give triene **(80)**, in which the bulkier substituents bear a 1,3 relationship to minimise steric congestion. This is ultimately reflected in the orientation of the substituents in the final product **(79)**, with a marked preference for the 1,3,5 substitution pattern.

A soluble catalyst generated by mixing chlorotrimethylsilane with palladium supported on carbon in a suitable solvent gives high yields of hexasubstituted benzenes from internal alkynes.[42] Although the method gives mixtures of regioisomers with unsymmetrical alkynes, it is so simple experimentally as to be the method of choice for the preparation of simple hexasubstituted benzenes. The precise nature and mechanism of the catalyst system are not known.

The applications of this class of reaction have thus far been limited to the preparation of hexasubstituted benzenes; no intramolecular versions have been reported.

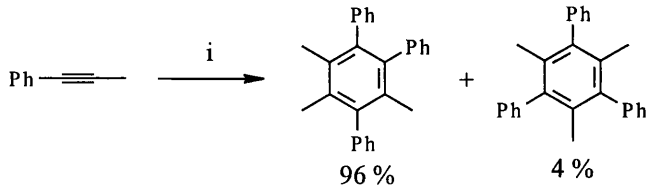
1.5.1.5 Cobalt Catalysed [2+2+2] Cycloaddition Reactions

Dicobalt octacarbonyl **(81)** or systems derived form it are able to catalyse the cyclotrimerisation of alkynes **(44)** through the intermediacy of the well-known complex **(82)**, and by addition of subsequent molecules of alkyne, to the so-called "flyover" complex **(83)** (scheme **33**). Support for this mechanism comes from the isolation and subsequent determination of the X-ray crystal structure of intermediates such as **(83)**.[43]



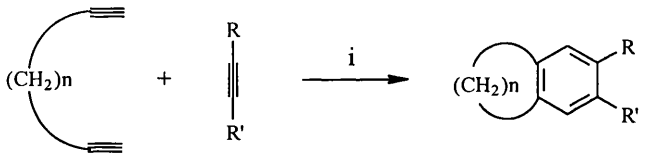
Scheme 33 Mechanism of the Dicobalt Octacarbonyl Catalysed Cyclotrimerisation of Alkynes.

Dinuclear cobalt carbonyl catalysts show high selectivity for the formation of 1,2,4-trisubstituted arenes **(59)** from terminal alkynes, and this tendency is also mirrored for the case of internal acetylenes (scheme **34**).[44]



Scheme 34 Reagents and Conditions i) $Co_2(CO)_6$•PhC≡CH, dioxane, reflux, 1 h., 90 %.

The most extensively studied[45,46] cobalt-based system, and that with the broadest scope for partially intramolecular cycloadditions, is undoubtedly that based on cobalt cyclopentadiene complexes **(84)**, where L is any one of a number of labile ligands (e.g., phosphines, ethene), but most commonly carbon monoxide (L=C≡O). This catalyst was found to catalyse the co-cyclisation of α,ω-diynes **(85)** with mono- or bi-functional alkynes **(44)** to give annulated benzenes **(86)** in moderate to good yield (scheme **35**). A related catalyst system,[47] η^5-cyclopentadienyl bisethene cobalt **(84**, R=C_2H_4**)** has been found to be even more reactive in this class of reactions, inducing cyclisation at temperatures as low as -78 °C.



(85) n=2, 3 ,4, 5 **(44)** **(86)**

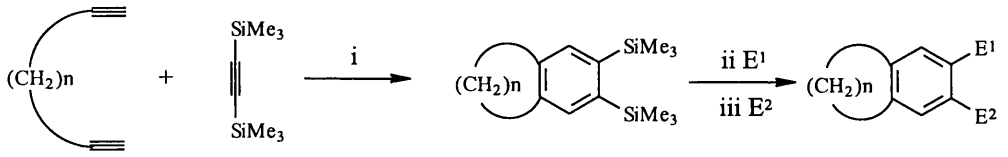
Scheme 35 Reagents and Conditions i) $CpCo(CO)_2$, THF, 30-95 %.

The reaction worked best with diynes **(85)** in which n=3, giving indans, and n=4, giving tetralins, but it was also capable of furnishing benzocyclobutenes in moderate yield.[48, 49] The yields of benzocycloheptenes **(86,** n=5**)**, however, were very low.

The reaction showed very good functional group tolerance toward alkyne **(44)** substituents; R/R'=H, alkyl, aryl, vinyl, CO_2R'', CH_2OH, CH_2OR'', COR'', C=NOR'', NR_2'', SR'' and $Si(CH_3)_3$ all react well under the stated conditions. Alkyl halides, reactive vinyl and aryl halides, and nitro groups all lead to rapid catalyst decomposition, presumably due to facile oxidative addition processes. The major

problem with the reaction was the limited chemoselectivity exhibited by the catalyst; considerable amounts of side-products were formed, especially by the cyclotrimerisation of the alkyne **(44)**.

Vollhardt's[45] solution to this difficulty was to employ a bulky mono-alkyne, too hindered to undergo trimerisation, yet sufficiently reactive to form the third partner in a [2+2+2] cycloaddition in conjunction with a suitable diyne. Bis(trimethylsilyl)ethyne **(87)** was chosen as being particularly suitable;[50] it is incapable of self-trimerisation and it gives excellent yields of arenes **(88)** in conjunction with a variety of diynes **(85)** (scheme **36**).

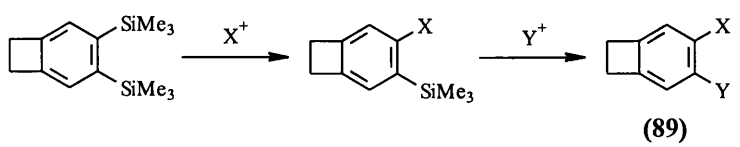


(85) **(87)** **(88)**

n=2, 3 ,4, 5

Scheme 36 Reagents and Conditions i) $CpCo(CO)_2$, Bis(trimethylsilyl)ethyne **(87)** as solvent, reflux, slow addition of **(85)**.

Use of bis(trimethylsilyl)ethyne **(87)** has one other important advantage. The trimethylsilylarenes **(88)** produced undergo facile *ipso* substitution reactions[51] with electrophiles (E^1 and E^2 in scheme **36**). Selective introduction of two different aryl substituents is thus possible, the first *ipso* substitution taking place about 40 times as fast as the second. This was exploited[50] to give a variety of *ortho-* substituted benzocyclobutenes **(89)** by sequential reaction with two electrophiles (scheme **37**).

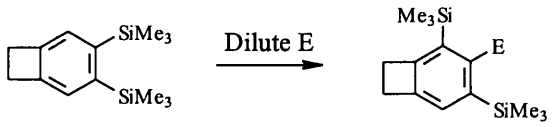


(89)

X	Y
H	H
D	D
Br	Br
Br	I
Br	Ac
I	I

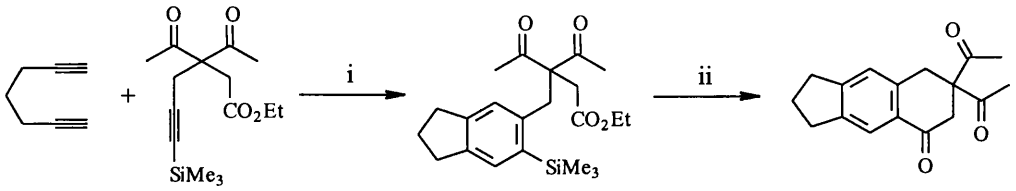
Scheme 37 The Synthesis of Substituted Benzocyclobutenes **(89)**.

Treatment of the bis(trimethylsilyl)arenes **(88)** with dilute solutions of electrophiles lead to substitution only after 1,2-silyl migration thereby giving *meta*-bis(trimethylsilyl)arenes and further enhancing the scope of the reaction (scheme **38**).



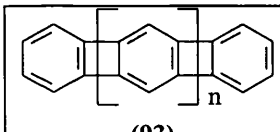
Scheme 38 Rearrangement / Substitution of *o*-bis(trimethylsilyl)benzocyclobutene.

Electrophilic *ipso*- substitution can also be used to effect carbon-carbon bond formation, *via* a silyl mediated Friedel-Crafts reaction[52] (scheme **39**). Cycloaddition of 1,6-heptadiyne **(90)** with silyl acetylene **(91)**, followed by Lewis-acid induced intramolecular Friedel-Crafts acylation gave tricycle **(92)**.



(90) **(91)** **(92)**

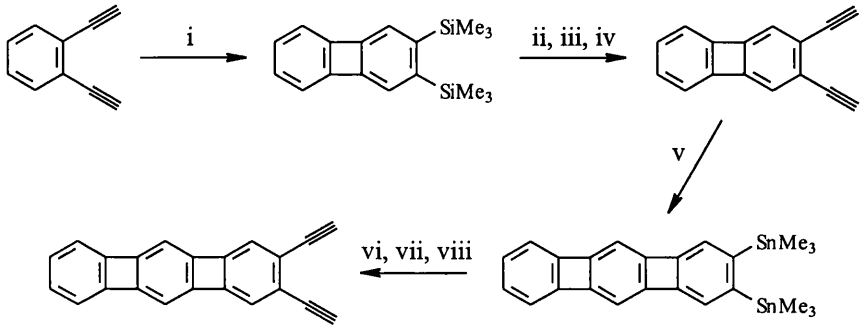
Scheme 39 Reagents and Conditions i) $CpCo(CO)_2$, THF, reflux; ii) BF_3, 70 % over 2 steps.



(93)

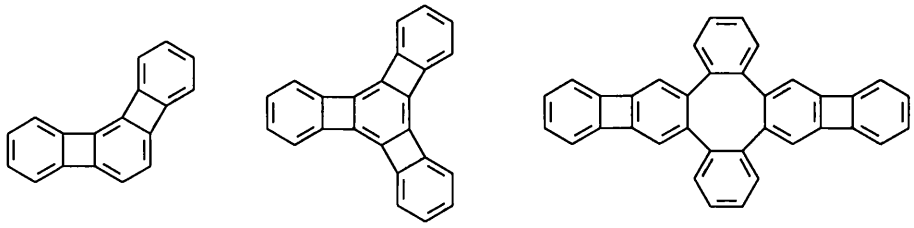
Vollhardt has employed this methodology to synthesise a number of molecules of theoretical interest, most notably the

multiphenylenes **(93)**. These materials are predicted[53] to have potential as novel materials with conductive behaviour. An iterative approach to these substances makes use of the facile exchange of the trimethylsilyl- group for halogen, and the subsequent palladium catalysed alkynylation of the aryl halides (scheme **40**).



Scheme 40 Reagents and Conditions i) Bis (trimethylsilyl)ethyne **(87)**, $CpCo(CO)_2$ **(84)**, Δ, hν, 10 h., 96 %; ii) ICl, CCl_4, 0-20 °C, 1h, 63 %; iii) Trimethylsilylethyne, piperidine, $PdCl_2(PhCN)_2$, CuI, 20-85 °C, 2 h., 75 %; iv) KOH, MeOH, Et_2O, 10 min, 100 %; v) Bis (trimethylstannyl)ethyne, $CpCo(CO)_2$ **(84)**, xylenes, Δ, hν,3.5 h, 20 %; vi) I_2, $CHCl_3$, 1 h., 80 %; vii) Trimethylsilylethyne, triethylamine, cat. $PdCl_2(PhCN)_2$, 23 °C, 20 h., 75 %; viii) KOH, MeOH, 1 h., 95 %.

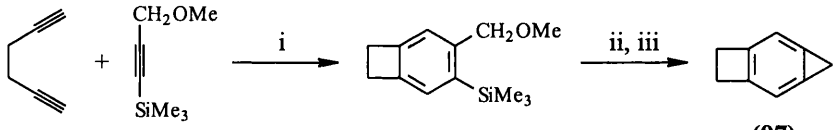
Bis(trimethylstannyl)ethyne is employed as the cyclisation partner in the later stages of the iterative procedure, primarily because of its greater lability in electrophilic substitution reactions.[51] The cobalt catalysed [2+2+2] cycloadditon protocol has also been employed in the preparation of the related compounds terphenylene[54] **(94)** and tris(benzocyclobutadieno)benzene[55] **(95)** (scheme **41**). The latter molecule is of interest, as spectral studies indicate that it has a non-delocalised central cyclohexatriene ring. More complex π-systems, containing four, six and eight membered rings **(96)** have also been made,[56] using cobalt catalysed [2+2+2] alkyne cycloadditions as part of a scheme requiring nickel-, cobalt- and palladium catalysed reactions.



(94) (95) (96)

Scheme 41 Phenylenes of Theoretical Interest.

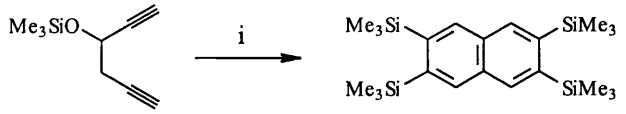
The intriguing molecule **(97)**, dubbed "rocketene" has also been synthesised using a [2+2+2] cycloaddition reaction catalysed by cobalt,[57] in a very concise (albeit low yielding) synthetic sequence (scheme **42**).



(97)

Scheme 42 Reagents and Conditions i) $CpCo(CO)_2$, *n*-octane, reflux, 55 %; ii) Br_2, CCl_4, 65 %; iii) *n*-BuLi, THF, -70 °C, then reflux, 30 min., 5 %.

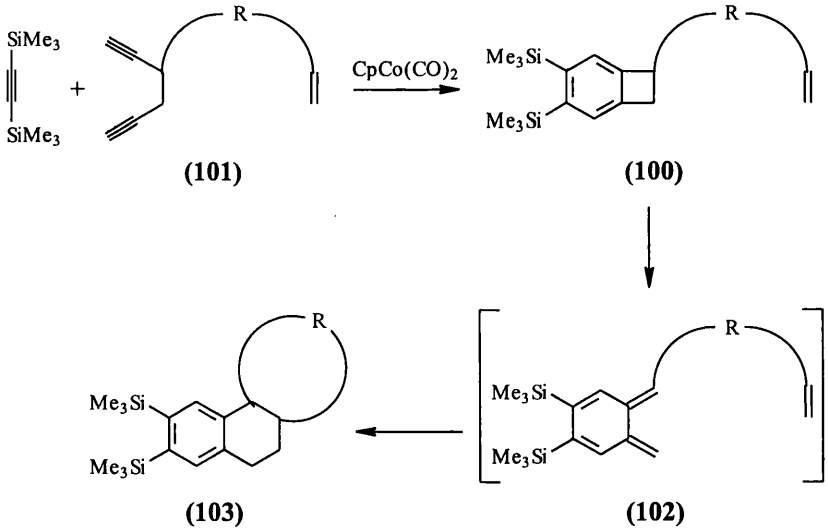
It was found[58] that exposure of hexa-1,5-diyn-3-ol ether derivatives**(98)** to the standard cycloaddition conditions gave the unexpected product **(99)** (scheme **43**). This was suggested to have arisen from ring opening of the initially formed cyclobutene derivative to give an *o*-xylylene, which was subsequently trapped by Diels-Alder cycloaddition to a second molecule of bis(trimethylsilyl)ethyne. Loss of trimethylsilanol, either during reaction or chromatography, with concomitant rearomatisation, ultimately yielded 2,3,6,7-tetrakistrimethylsilyl naphthalene **(99)**.



(98) (99)

Scheme 43 Reagents and Conditions i) Bis(trimethylsilyl)ethyne **(87)**, $CpCo(CO)_2$ **(84)**, reflux, several days, 30 %.

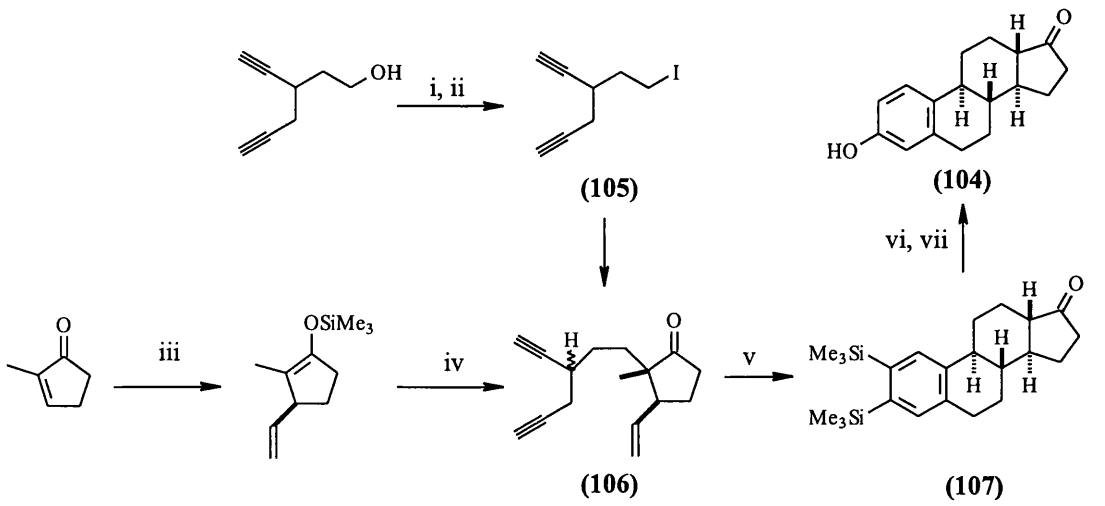
This discovery was incorporated[59] into a cascade sequence leading to polycycle construction (scheme **44**). Initial formation of benzocyclobutene **(100)** from an enediyne **(101)** occurred with subsequent ring opening to give an *ortho-* xylylene **(102)**, which is highly reactive in [4+2] Diels-Alder cycloadditions and can react with a tethered dieneophile to furnish the final tricycle **(103)**.



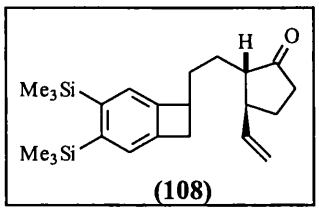
(101) (100) (103) (102)

Scheme 44 Construction of Polycycles by Tandem [2+2+2] / [4+2] Cycloaddition Reactions.

This tandem approach has been incorporated[60] into a remarkably concise synthesis of (±)-estrone **(104)**, the key step being the D→ABCD ring system transformation (scheme **45**).



Scheme 45 Reagents and Conditions i) Tosyl chloride, pyridine, 0 °C, 13 h, 99 %; ii) NaI, acetone, 45 °C, 30 h., 96 %; iii) Vinyl magnesium bromide, CuI, -40 °C, then -60 °C, TMSCl, HMPA, Et_3N, warm to ambient temperature over 2 h., 89 %; iv) $NaNH_2$, NH_3/THF, reflux, 30 min., then add **(105)**, -45 °C, 64 %; v)$CpCo(CO)_2$ **(84)**, Bis(trimethylsilyl)ethyne **(87)**, slow addition of **(106)**, reflux, 35 h., 71 %; vi) CF_3CO_2H, CCl_4, -30 °C, 20 h., 100 %; vii) $Pb(OAc)_4$, CF_3CO_2H, -30 °C to -5 °C over 30 min., 88 %.

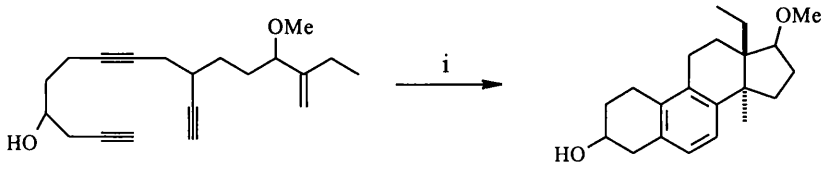


Although the enediyne **(106)** was formed as a 2:1 mixture of diastereomers, this proved to be unimportant, as thermal conrotatory outward ring-opening of the cyclobutene gave the same intermediate xylylene from either diastereomer.

Enediyne **(106)** gave the estrone precursor **(107)** in 18 % yield, together with its benzocyclobutene precursor **(108)** in 61 % yield; fortunately, this was found to thermally convert into the desired tetracycle **(107)** in 98 % yield, giving a 71 % overall yield from **(106)**. The reaction gave essentially a single diastereomer; the excellent stereocontrol was thought to be due to a chair-like *exo* transition state in the Diels-Alder cycloaddition.

Regioselective protodesilylation and subsequent oxidation gave (±)-estrone **(104)** in 21 % overall yield from 2-methylcyclopentenone.

An even more spectacular example of steroid synthesis has been reported.[61] Treatment of the acyclic **(109)** with $CpCo(CO)_2$ in refluxing decane gave the B-ring aromatic steroid analogue **(110)** with assembly of all four rings in one step (scheme **46**).



(109) **(110)**

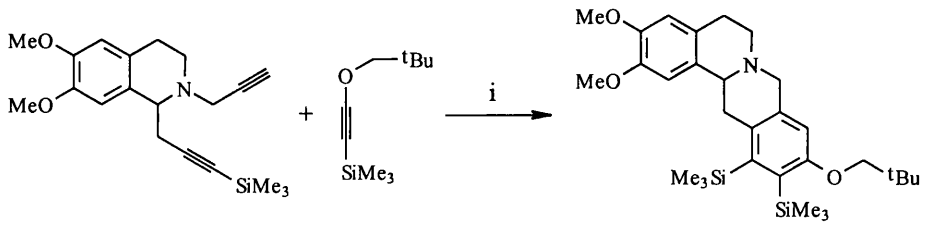
Scheme 46 Reagents and Conditions i) $CpCo(CO)_2$,decane, reflux, 20 h.; hν for 1 h; 92 %.

Other groups have employed similar "Tandem principle" reactions in the synthesis of the basic skeletons of the kaurane[62] **(111)** and stemodan[63] **(112)** groups of natural products (scheme **47**).

(111) **(112)**

Scheme 47 Frameworks of the Kaurane **(111)** and Stemodan **(112)** Groups of Natural Products.

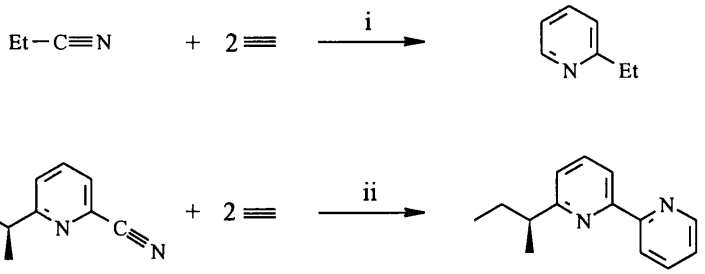
Near-total regiocontrol is exhibited in the synthesis of the protoberberine precursor **(113)**,[64] involving the co-cyclisation of an unsymmetrical alkyne **(114)** with diyne **(115)** (scheme **48**). The regiospecificity of the reaction, which leads to the most sterically crowded isomer, is believed to be electronic in origin.



(115) (114) (113)

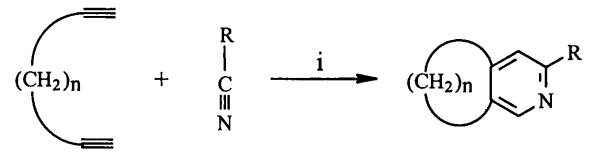
Scheme 48 Reagents and Conditions i) $CpCo(CO)_2$ **(84)**, xylene, reflux, hν, 8 h., 61 %.

Cobalt catalysed co-cyclisation of alkynes and nitriles is a powerful general route to pyridines.[65] The same catalysts that are active in acetylene trimerisation are also active in pyridine formation. Good control of chemoselectivity is possible in the synthesis of 2-substitutes pyridines (scheme **49**).



Scheme 49 Reagents and Conditions i) CpCo(COD), 120 °C, 15 bar, 2h., 96 %; ii) CpCo(COD), toluene, 120 °C, 13 atm., 20 h., 83 %.

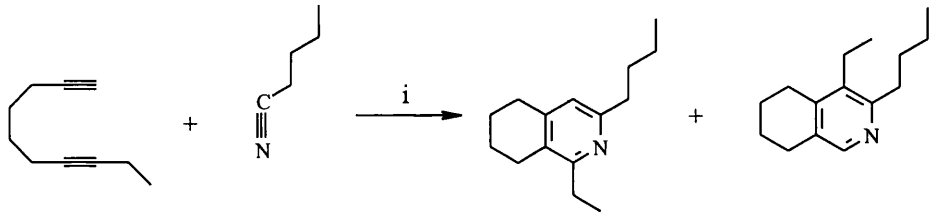
Similarly, in the reaction of symmetrical acetylenes, excellent yields of pentasubstituted pyridines can be obtained. In the reaction of unsymmetrical alkynes, however, product mixtures arise, rendering the method essentially useless in preparative terms. As in the case of alkyne trimerisation, this can be circumvented by employing α,ω-diynes **(85)**,[66] giving bicyclic pyridines **(116)** (scheme **50**); again, the reaction is tolerant of a variety of nitrile substituents; electron deficient nitriles, however, fail to give satisfactory yields.



(85) (116)

Scheme 50 Reagents and Conditions i) $CpCo(CO)_2$ **(84)**, hv, Δ, ; n=3-5, R=alkyl, aryl, CH_2OCH_3, $CH_2CO_2C_2H_5$.

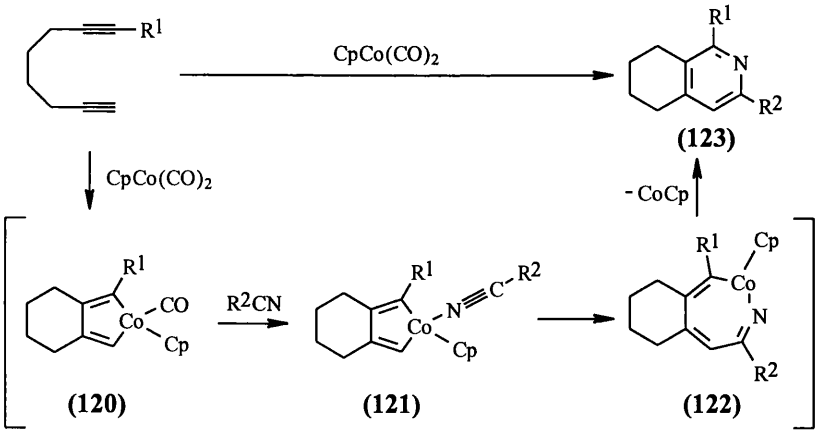
Unsymmetrical diynes react with nitriles to give predominantly the less sterically crowded pyridine. Thus[66] pentanitrile **(117)** reacts with 1,7-decadiyne **(118)** to give predominantly **(119)** (scheme **51**).



(118) (117) **(119)** 73 % 4 %

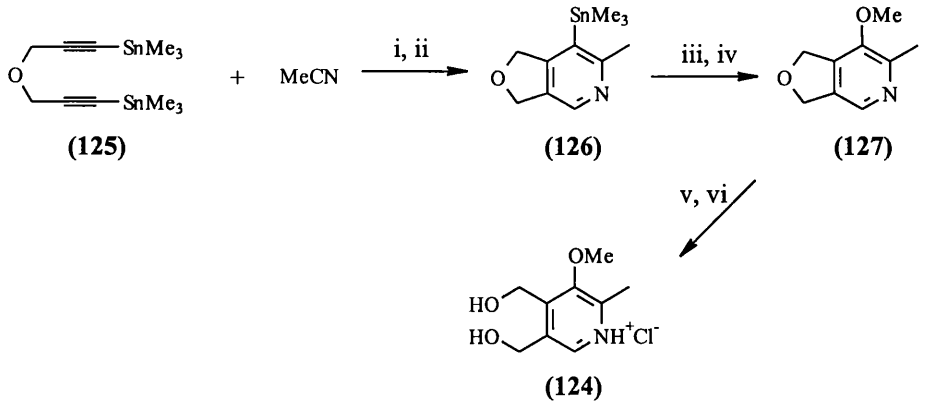
Scheme 51 Reagents and Conditions i) $CpCo(CO)_2$ **(84)**, xylene, reflux, hv, 117 h., 77 % total yield.

The selectivity in favour of this regioisomer is believed to arise form the capacity of the nitrogen atom of the nitrile to act as a ligand for cobalt (III) of the metallacycle **(120)** through its lone pair,[67] giving **(121)**. Insertion into the less-hindered cobalt-carbon bond, placing nitrogen next to cobalt, gives aza-metallacycle **(122)**, and ultimately the observed major product **(123)** (scheme **52**).



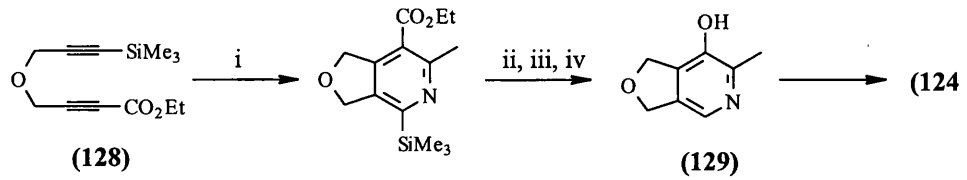
Scheme 52 Mechanism Postulated for the Observed Regiochemistry in the Formation of Annulated Pyridines.

This strategy was employed in the rapid, regioselective construction of vitamin B6 **(124)** (scheme **53**). Cyclisation of bis(trimethylstannyl)diyne **(125)** with acetonitrile, followed by regioselective protodesilylation upon silica gel chromatography gave trimethylstannyl pyridine **(126)** in 45 % yield; this moderate yield was attributed to the instability of **(125)**. Iodination, and subsequent introduction of the methoxy substituent by nucleophilic substitution gave **(127)**; hydrolysis of the ether ring, followed by ion exchange gave the natural product **(124)**.



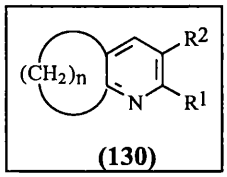
Scheme 53 Reagents and Conditions i) $CpCo(CO)_2$ **(84)**, CH_3CN, xylene, reflux, hν, 48 h.; ii) chromatography (silica gel), 44 % over 2 steps; iii) I_2, $CHCl_3$, 18 h, 99 %; iv) NaOMe, CuI, 2,4,6-collidine, reflux, 16 h., 36 %; v) 48 % aq. HBr, Δ, 2 h.; vi) AgCl, H_2O, reflux, 20 min., 68 %.

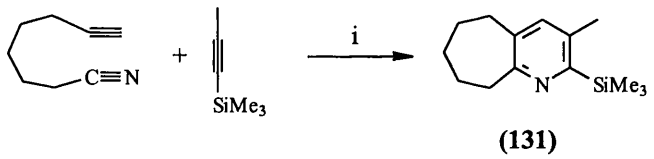
A similar synthetic approach to the same natural product[68] involving co-cyclisation of diyne **(128)** with acetonitrile. Desilylation, Curtius rearrangement, and treatment with nitrous acid gave alcohol **(129)**, which had previously been converted to **(124)** (scheme **54**).



Scheme 54 Reagents and Conditions i) $CpCo(CO)_2$ **(84)**, MeCN, sealed tube, 145 °C, 2 h., 79 %; ii) CsF, EtOH, 87 h., 68 %; iii) KOH, EtOH, 5 h., then HCl., 65 %; iv) Diphenoxyphosphoryl azide, ^tBuOH, Et_3N, 24 h., 68 %; v) HCl, $NaNO_2$, 90 °C, 1 h., 22 %.

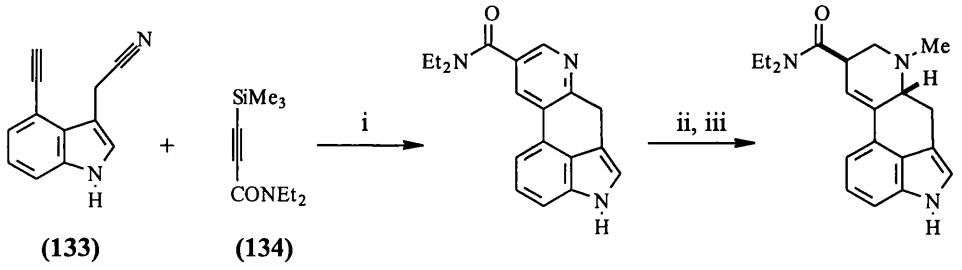
A complementary strategy[69] involves the co-cyclisation of ω-alkynyl nitriles with acetylenes to give the regioisomeric annulated pyridines **(130)**. A rare example of the formation of a fused cycloheptene ring system **(131)** belongs to this class of reaction (scheme **55**).





Scheme 55 Reagents and Conditions i) $CpCo(CO)_2$ **(84)**, xylene, reflux, hν, 4-8 h., 66 %.

A rapid assembly of the powerful psychotropic agent (±)-LSD **(132)** has been reported.[70] Cyclisation of 1,7-alkynenitrile **(133)** with a suitably substituted alkyne **(134)** installed the D and C rings present in the lysergides, albeit in low yield. Two further steps served to convert this material into the hallucinogen (scheme **56**).



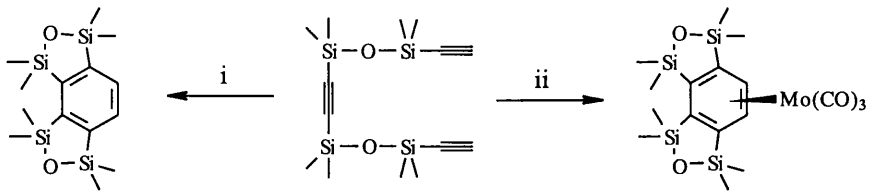
(133) (134) (132)

Scheme 56 Reagents and Conditions i) $CpCo(CO)_2$ **(84)**, THF, high dilution, 65 °C, hν, 12 h., 13 %; ii) $CF_3SO_3CH_3$, THF, 0 °C, 32 %; iii) $NaBH_4$, CH_3CN, 45 %.

1.5.1.6 [2+2+2] Cycloaddition Reactions Catalysed by Other Metals

Ziegler-Natta catalysts promote cyclotrimerisations of alkynes, but often lack chemo- and regio-selectivity;[24] formation of polymers and higher oligomers also competes. Cage compounds have been prepared[71] from triynes in up to 50 % yield with catalysts of this type.

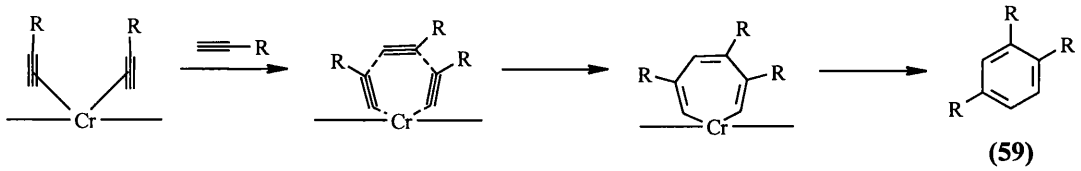
Chromium- and molybdenum- hexacarbonyl[72] serve to cyclotrimerise silyl-triyne **(135)** (scheme **57**). Molybdenum hexacarbonyl furnishes the arene as the metal-tricarbonyl complex **(136)**; chromium hexacarbonyl gives the free arene **(137)**. Attempted cyclisation of a similar macrocyclic triyne system gave only low yields of the arene.



(137) (135) (136)

Scheme 57 Reagents and Conditions i) $Cr(CO)_6$, octane, 140 °C, 22 %; ii) $Mo(CO)_6$, octane, 140 °C, 16 %.

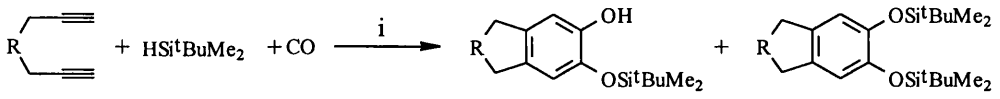
A heterogeneous chromium catalyst[73] consisting of potassium dichromate supported on silica/alumina trimerises alkynes in good yield with moderate selectivity for 1,2,4-trisubstituted arenes(**59**). The reaction is thought to proceed *via* a unique concerted mechanism at the surface of the catalyst (scheme **58**).



(59)

Scheme 58 Cyclotrimetisation of Alkynes at Chromium Catalyst Surface.

An interesting synthetic approach to catechols involving the co-cyclisation of a 1,6-diyne **(138)** with two molecules of carbon monoxide using a ruthenium catalyst has been reported (scheme **59**).[74]



(138) **(139)**

Scheme 59 Reagents and Conditions i) $Ru_3(CO)_{12}$, PCy_3, 50 atm., 140 °C, 20 h., 40-71 % total yield.

By judicious choice of solvent and use of a large excess of silane, total selectivity for the bis-silylated catechol **(139)** could be achieved. Good functional group tolerance was observed for diyne **(138)**, with R=CH_2, O, NTs, $(MeO_2C)_2C$ all reacting in moderate to good yield. Unfortunately, larger annulated rings could not be formed.

The mercury catalyst $[Hg\{Co(CO)_4\}_2]$ catalyses a variety of partially intramolecular [2+2+2] cycloadditions of alkynes, although it rarely exhibits useful chemoselectivity.

Cyclotrimerisation of symmetrical alkynes has been reported[75] using titanium (III) chloride in the presence of a Grignard reagent and cyclooctatetraene. The mechanism

and the active catalytic species are not known, but several of the isolated organometallic complexes were shown not to be catalytically active.

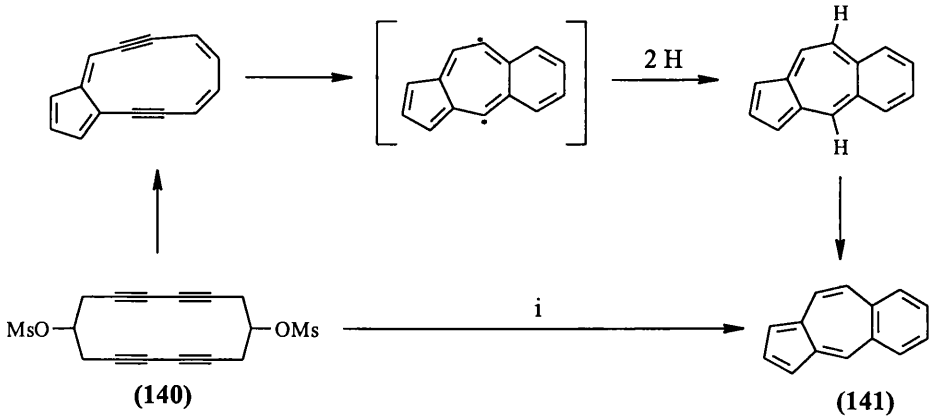
1.5.2 Overview of [2+2+2] Cycloadditions

As is evident from the preceding chapter, metal-mediated [2+2+2] cyclotrimerisation of alkynes is a common reaction which has been developed into a powerful synthetic technique, and has been used as the key step in the synthesis of a number of complex molecules of biological and theoretical interest. However, considering the number of natural product targets featuring an aromatic ring, and the scope this class of reaction offers for the mild, selective introduction of this feature in a functionalised manner, it is perhaps surprising that it has not found wider applicability.

1.6 The Enediynes

1.6.1 The Thermal Cycloaromatisation of Enediynes and Related Compounds

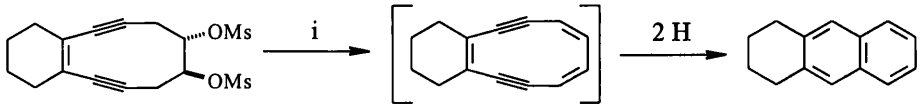
As part of their investigations of annulene chemistry, Mayer and Sondheimer[76] discovered the transformation of mesylate **(140)** into tricycle **(141)**. Although the authors originally proposed a polar mechanism, it is now thought[77] that the reaction proceeds through the diradical species shown (scheme **60**).



(140) (141)

Scheme 60 Reagents and Conditions i) KOH, MeOH, DMSO, Δ.

Five years later, Masamune[78] and co-workers attempted to prepare annulene **(142)**, and instead isolated naphthalene **(143)** (scheme **61**).



(142) (143)

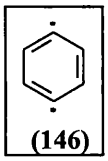
Scheme 61 Reagents and Conditions i) NaOMe

In his seminal publication,[79] Bergman found a rationale for these curious cycloaromatisations. He observed that deuterium-labelled (*Z*)-1,5-hexadiyn-3-ene **(144)**, exhibited scrambling upon gas-phase pyrolysis (scheme **62**) to give the acetylene-labelled isomer **(145)**.

(144) (145)

Scheme 62 Thermal Rearrangement of (*Z*)-1,5-hexadiyn-3-ene.

No other labelling pattern of **(144)** was observed. This led Bergman to propose the 1,4 diyl radical **(146)** as the intermediate in this rearrangement; further support for this hypothesis came from the observation that heating **(144)** in a hydrocarbon solvent gave significant amounts of benzene while heating in carbon tetrachloride lead to the formation of 1,4 dichlorobenzene, both these reactions being typical of free radical intermediates.

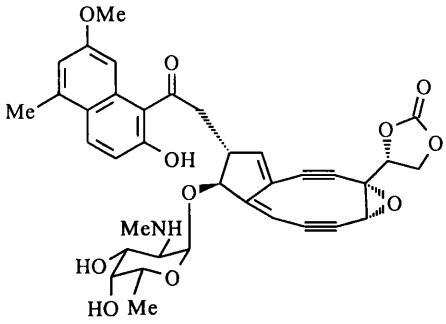


(146)

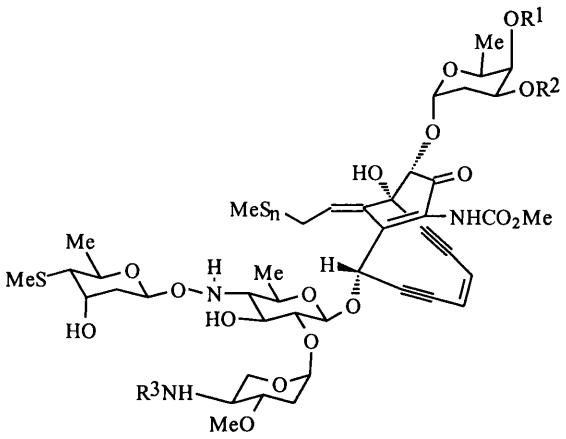
1.6.2 The Naturally Occurring Enediynes

Bergman's discovery attracted considerable interest from theoretical and physical chemists. However, the discovery of a class of naturally occurring antibiotics with an unparalleled potency and an unprecedented mode of action lead to an exponential increase in the amount of research interest in the enediyne class of compounds.

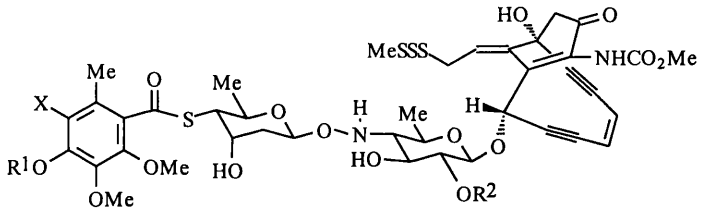
Neocarzinostatin, a natural product isolated[80] in 1965, was found to have potent anti-tumour and antibiotic activity. It was found to consist of a protein tightly complexed to a non-protein chromophore; moreover, most of the biological activity was found to reside in the non-protein component. Seto[81] proposed the structure **(147)** for the neocarzinostatin chromophore, the non-protein component of neocariznostatin containing an enediyne element resembling the systems already seen in this section. The discovery two years later of the calicheamicins[82] **(e.g. 148)** and the esperamicins[83] **(e.g. 149)**, containing a contiguous yne-ene-yne (or 'enediyne') system fuelled considerable interest in the chemistry of these compounds.



(147)



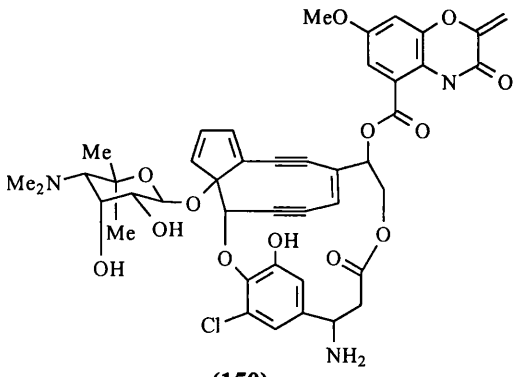
(148)



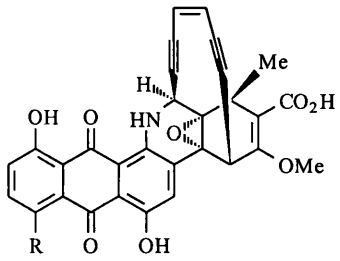
(149)

Scheme 63 Structures of Some of the Enediyne Antibiotics.

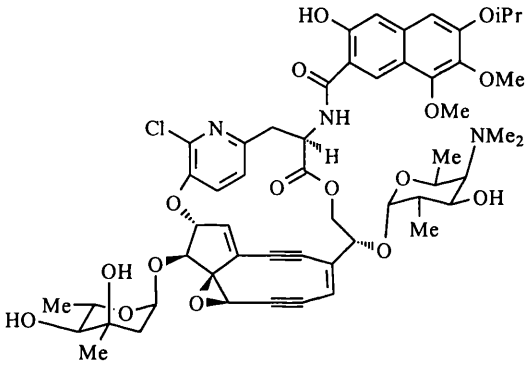
Three other naturally occurring classes of enediyne antibiotics have also been isolated viz., the kedarcidin chromophore **(150)**, the dynemicins **(151)** and the C-1027 chromophore **(152)** (scheme **64**).



(150)



(151)



(152)

Scheme 64 Enediyne Antibiotics.

1.6.2.1 The Mode of Action of the Enediyne Anti-cancer Antibiotics.

The enediyne class of natural products, together with the closely related neocarzinostatin chromphore, constitute some of the most potent anti-bacterial and anti-tumour agents known.[84] The profound biological activity exhibited is due to their ability to cleave DNA irreversibly. DNA cleavage generally proceeds in four stages:

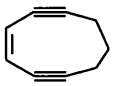
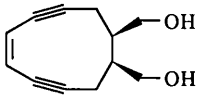
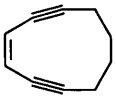
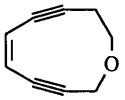
1. Recognition of and binding to a specific site of DNA.

2. Activation of enediyne moiety by structural modification of the molecule.

3. Bergman cycloaromatisation of the activated enediyne producing a reactive 1,4 aryl diradical.

4. Abstraction of two hydrogen atoms from the target DNA, leading to single and double-strand cuts, genetic damage and cell death.

The activation step (step 2) generally proceeds *via* a conformational change in the enediyne macrocycle, leading to an increase in strain energy. The relief of this strain energy in going from the enediyne to the cyclised aromatic system then provides the driving force for the system to undergo Bergman cycloaromatisation. Comparison of the half-lives ($t_{1/2}$) of simple model cyclic enediynes (scheme **65**) indicates that the distance between the remote alkyne carbons (c-d distance) gives a guide to stability, but the situation is considerably more complex in the case of bicyclic systems, and systems of higher complexity.[85]

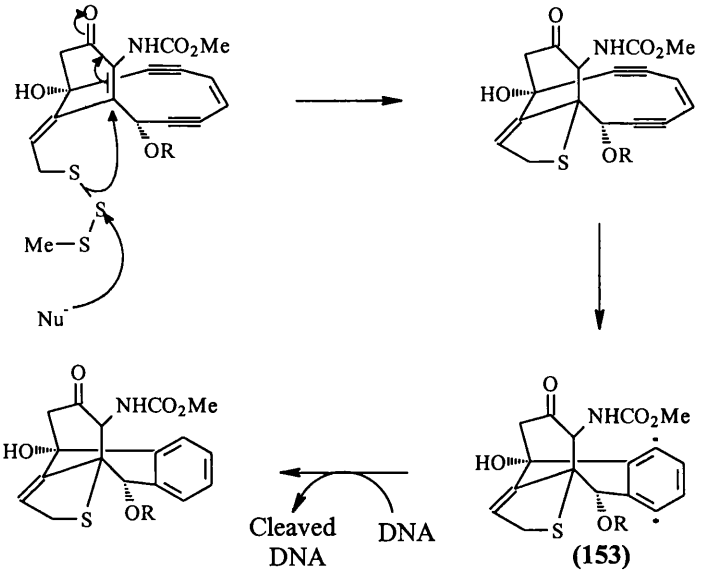
Structure	c-d distance [Å]	$T_{1/2}$ (h.)
	2.84	Unknown Compound
	3.20	11.8
	3.25	18
	3.40	52

Scheme 65 Stabilities of Enediyne Macrocycles.

1.6.2.2 The Mode of Action of the Calicheamicins and Esperamicins

The first enediynes to have their structures unambiguously assigned, the calicheamicins **(148)** and esperamicins **(149)**, have been the most extensively studied.

The mode of triggering of the Bergman cyclisation for one member of this class, calicheamicin γ_1^I is perhaps best understood. Nucleophilic cleavage of the trisulphide group of the DNA-bound molecule generates an allylic thiolate, which then undergoes intramolecular Michael addition to the enone moiety. This induces a structural change in the enediyne macrocyclic ring, triggering Bergman cyclisation to give diradical **(153)**. This abstracts two hydrogen atoms from the bound DNA, leading to cleavage and ultimate cell death (scheme **66**).

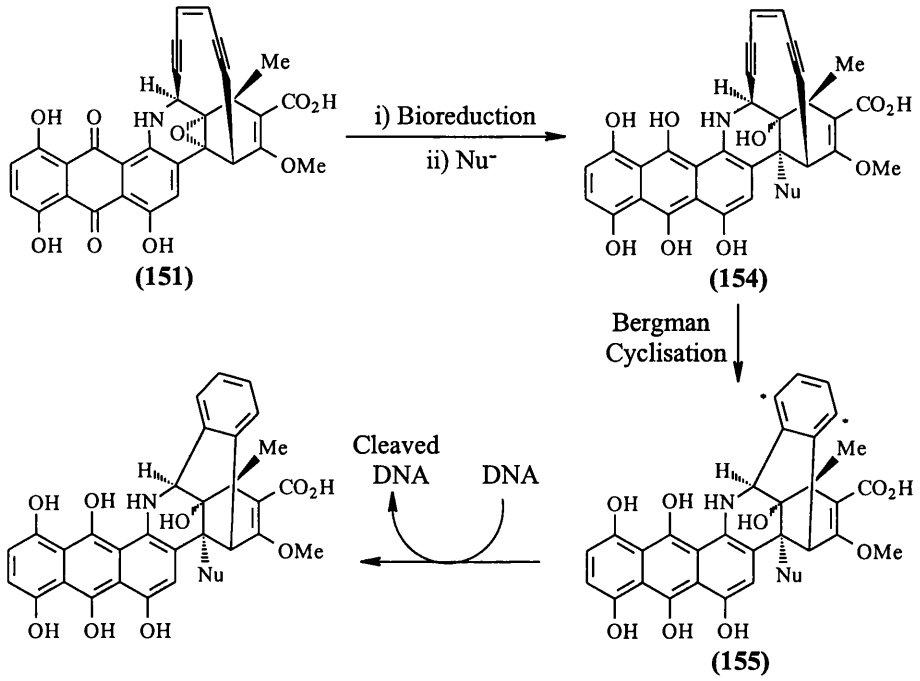


Scheme 66 Mechanism of Activation and Bergman Cyclisation of Calicheamicin γ_1^I.

While the bicyclic enediyne core of the calicheamicins and esperamicins is responsible for causing the damage to DNA, it is the oligosaccharide portion of these molecules which is responsible for their recognition and subsequent binding and hence for their sequence specificity for their targets. The aryltetrasaccharide of calicheamicin γ_1^I binds tightly into the minor groove DNA,[86] showing high specificity for sequences such as 5'-TCCT-3' and 5-TTTT-3'. Esperamicins show a lower sequence specificity; there is, however, a marked preference for T > C > A > G.

1.6.2.3 The Mode of Action of the Dynemicins

Dynemicin A **(151,** R=OH) and the closely related deoxydynemicin A **(151,** R=H) are the only enediyne natural products combining the structural features of the anthraquinone chromophore of the anthracycline antibiotics with a ten-membered enediyne ring thus far discovered.[87] The anthraquinone ring system is known to be capable of association with DNA through intercalation and this is thought to be the manner in which dynemicin binds to DNA in order to effect its cleavage.[88] Nucleophilic ring opening of the epoxide ring, after bio-reduction of the paraquinone ring system, induces a conformational change in the ten membered enediyne ring (scheme **67**). Since the c-d distance in **(154)** is reduced to 3.54 Å, compared to 4.17 Å in **(151)** and strain energy is considerably increased, Bergman cyclisation then occurs, giving diradical **(155)**. This cleaves DNA in the same way as the calicheamicin and esperamicin diradical species.

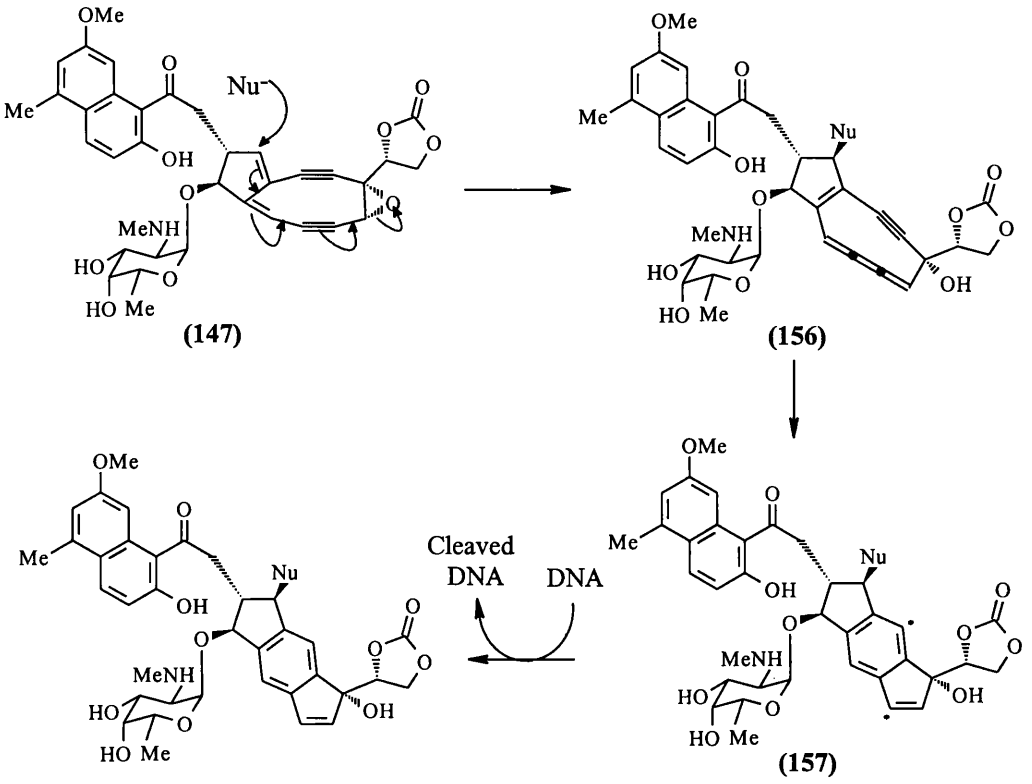


Scheme 67 Mechanism of Activation and Bergman Cyclisation of Dynemicin.

1.6.2.4 The Mode of Action of Neocarzinostatin Chromophore

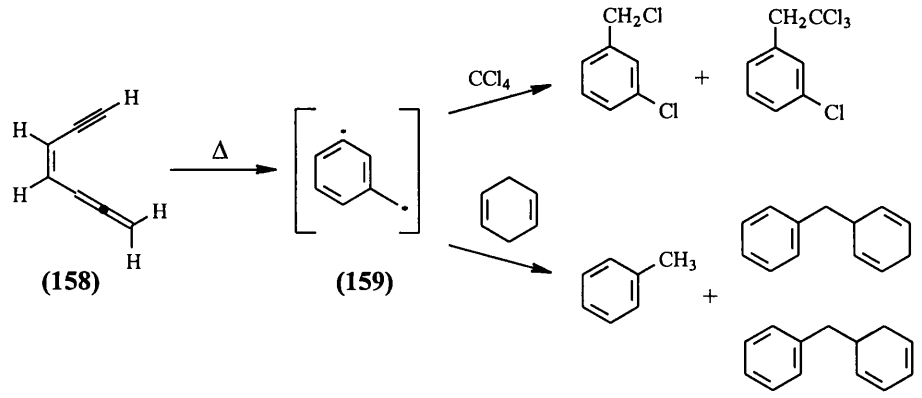
Neocarzinostatin chromophore **(147)** has a mode of action which is different, although closely related, to the other enediyne antibiotics. Its isolation as a non-covalently bound complex to a protein is thought to protect the neocarzinostatin chromophore from degradation[89] prior to its delivery to target DNA.

Myers[90] proposed that DNA cleavage occurs *via* a chemical cascade commencing with nucleophilic attack at C-12 (scheme **68**), with epoxide ring opening and formation of the cumulene **(156)**.



Scheme 68 Mechanism of Activation and Cycloaromatisation of Neocarzinostatin Chromophore.

Supporting evidence[91] for this mechanism was provided by the identification of cumulene **(156)** in a low temperature NMR experiment during the reaction of neocarzinostatin chromophore with methyl thioglycolate (Nu=$CH_3O_2CCH_2S$). The generation of diradical species **(157)** from cumulene **(156)** highlighted a new electrocyclisation reaction, that of eneyne-allenes. Myers[92] synthesised the parent of this class of compounds, *cis*-1,2,4-heptatrien-6-yne **(158)**, and demonstrated its thermal cyclisation to the α,3 dehydrotoluene diradical **(159)**, which underwent a number of characteristic radical reactions (scheme **69**).



Scheme 69 Generation and Reactions of α,3 dehydrotoluene diradical **(159)**.

This generation of diradical species from enyne-allenes has been christened the Myers cyclisation. It is interesting to note that although the Bergman cyclisation of (*Z*)-1,5-hexadiyn-3-ene **(144)** to give 1,4 diyl radical **(146)** is endothermic,[79] the cyclisation of (*Z*)-1,2,4-heptatien-6-yne **(158)** gives a radical **(159)** with full benzylic stabilisation, lying approximately 63 kJmol^{-1} below **(158)** in energy.

1.6.2.5 The Mode of Action of the Chromoprotein Enediyne Antibiotics

The most recent class of enediyne antibiotics to come to light are those consisting of a DNA cleaving enediyne chromophore, tightly complexed to a protein, which serves to stabilise the chromophore until delivery to its target. These have been given the collective name "chromoproteins".

Kedarcidin was first isolated[93] in 1991, and its potent *in vivo* anti-tumour activity was observed. The elucidation of the structure of the component responsible for DNA cleavage, the kedarcidin chromophore **(150)** was elucidated the following year.[94] It features a strained nine-membered enediyne ring, which is prevented from aromatising by the locking allylic epoxide group. Activation is believed to occur by

nucleophilic addition to this feature, causing opening of the epoxide ring; the change in ring geometry facilitates the Bergman cyclisation, and cycloaromatisation then occurs. Double hydrogen abstraction from the target DNA, causing predominantly single strand cuts follows.

C-1027 was isolated[93] as a 1:1 complex of a 110-amino acid residue peptide tightly complexed to a non-protein component. The non-protein component was subsequently shown[95] to be C-1027 chromophore **(152)**. C-1027 chromophore **(152)** has thus far proved to be unique amongst enediyne antibiotics, in that it contains no mechanism for triggering cycloaromatisation. Instead, the chromophore is stabilised by its complexation to the protein component. This is demonstrated by the observation[96] that C-1027 can be stored for extended periods without losing its antibiotic properties, whereas isolated C-1027 chromophore **(152)** decomposes rapidly ($t_{1/2}$=10 h. at room temperature).

Several other natural products awaiting full structural elucidation are believed to be members of the class of chromoproteins. Maduropeptin[97] consists of a water soluble, acidic carrier protein, tightly complexed to a nine-membered enediyne bicycle, similar to that of C-1027 chromophore **(152)** and kedarcidin chromophore **(150)**. It exhibits potent *in vivo* anti-tumour activity. The methanol adduct and the cycloaromatisation product of the non-protein component of maduropeptin have been characterised; the exact structure of the enediyne remains elusive. Actinoxanthin[98] and auromycin (macromycin)[99] are also believed to belong to this group; their modes of action and structures have yet to be established.

1.6.3 Synthesis of the Enediyne Antibiotics

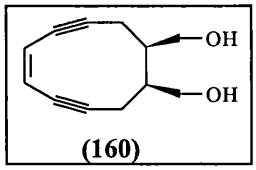
The structural complexity, exceptional biological activity and unprecedented mode of action of the enediyne antibiotics have proved an excellent opportunity for synthetic chemists to demonstrate their creativity and ingenuity. It is beyond the scope of this review to describe all of the contributions which have been made in this field. It will suffice to draw the attention of the interested reader to the landmarks in this field; Nicolaou's[100] and Danishefsky's[101] syntheses of calicheamicin γ_1^I , Myers'[102] and Danishefsky's[101] syntheses of (+)-dynemicin A **(151** R=OH**)**. Significant advances towards the synthesis of other enediynes, and neocarzinostatin chromophore **(147)** have been made, and these have been the subject of a recent review.[84]

1.6.4 Enediyne Model Systems

Despite their profound biological activity, the enediyne anti-tumour antibiotics seem unlikely candidates for use as therapeutic agents, due to problems of toxicity. An exception is esperamicin A_1, which is currently in phase II clinical trials. Various enediyne-antibody conjugates also offer potential.[86]

The mode of action of the natural enediynes has served as an inspiration to chemists searching for potential drug leads. They have sought to incorporate an enediyne system, together with a rationally designed triggering system in a simple molecular structure.[103] Design and study of such enediyne prodrugs also gives insight into the mode of action of the natural enediynes.

The first system of this kind to be investigated[104] was the ten membered enediyne diol **(160)**. It was found to cyclise thermally



(160)

in the presence of 1,4-cyclohexadiene, and was found to cleave DNA *in vitro*. Whilst it is clearly unsuitable as a drug, as it is already activated, and lacks selectivity and binding potential, it served to prove the point that a simple enediyne available in very few steps could cause DNA cuts. Investigation[105] of a series of similar designed enediynes served to highlight the importance of electronic factors in the rate of cyclisation of enediynes; **(161)** has a half-life of 18 h., while **(162)** has a half-life of 4.5 h. (scheme **70**).

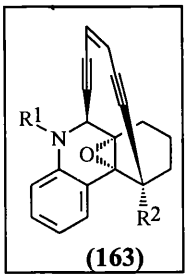
(161) $t_{1/2}$=18 h. (37 °C)

(162) $t_{1/2}$=4.5 h. (37 °

Scheme 70 Half-Lives of Simple Enediyne Macrocycles.

The same investigators found that substitution at the vinylic position had an even more pronounced effect on the rate of Bergman cycloaromatisation of simple cyclic enediynes.

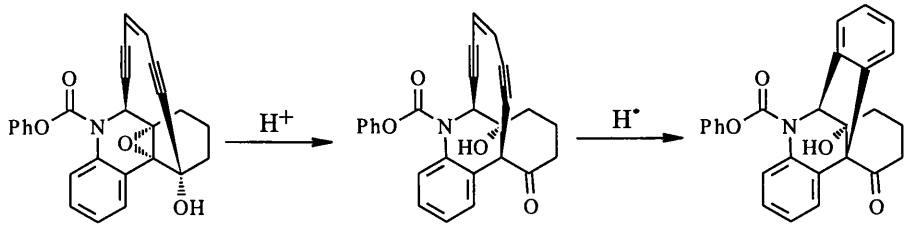
Somewhat more sophisticated systems incorporating novel triggering devices have also been described. These work on one of two basic principles; the strained enediyne contains a "locking" element, preventing Bergman cyclisation (in analogy with the calicheamicins, esperamicins and dynemicins), or introducing some functional element to complete the enediyne system.



(163)

Examples of the first class of synthetic enediynes include the library of modified dynemicin analogues synthesised by Nicolaou,[85] based on the simplified core structure **(163)**. Several interesting triggering modes were disclosed by the study of compounds of this class. For

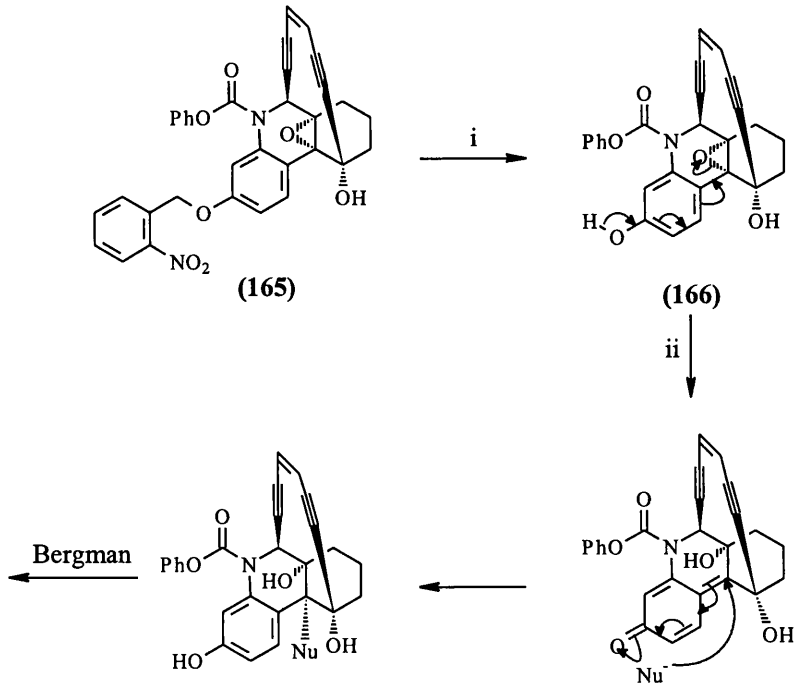
example the simplest member,[106] the hydroxy-compound **(164)** underwent a pinacol-type rearrangement under acidic conditions, thereby decreasing the c-d distance and triggering a Bergman cyclisation (scheme **71**).



(164)

Scheme 71 Pinacol-Type Rearrangement Induced Bergman Cyclisation of Dynemicin Analogue **(164)**.

A number of "second generation" model systems based on structure **(163)**, containing acid-, base-, and photolytic-triggering devices show ability to cleave DNA. **(165)**, for example, was designed[107] to undergo photolytic cleavage to **(166)**, which is very susceptible to epoxide opening (scheme **72**).

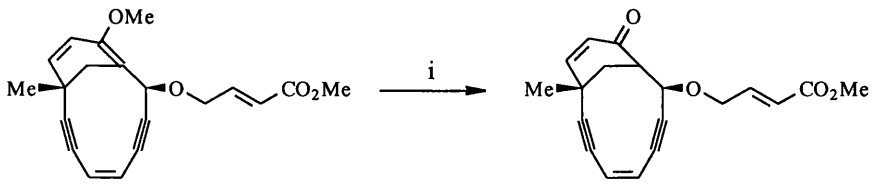


(165) **(166)**

Scheme 72 Reagents and Conditions i) hv, THF, H_2O, 0 °C, 40 min. ii) NuH, THF phosphate buffer, (pH 8.0), 25 °C, 1.5 h.

The Nicolaou group have also extensively investigated a variety of calicheamicin/esperamicin analogues equipped with a range of tethers and triggers. One such designed calicheamicin[108] is equipped with a thioacetate trigger as opposed to the trisulphide present in the natural compounds. This molecule, calicheamicin θ_1^I, is currently the most potent anti-cancer agent known.

Semmelhack conceived a novel way to remove the bridgehead double bond from a bicyclic enediyne moitey.[109] Hydrolysis of an enol ether **(167)** gives ketone **(168)**, with the blocking group removed. The greater activity of the latter toward Bergman cyclisation is evidenced by the difference in half-lives of these molecules (scheme **73**).

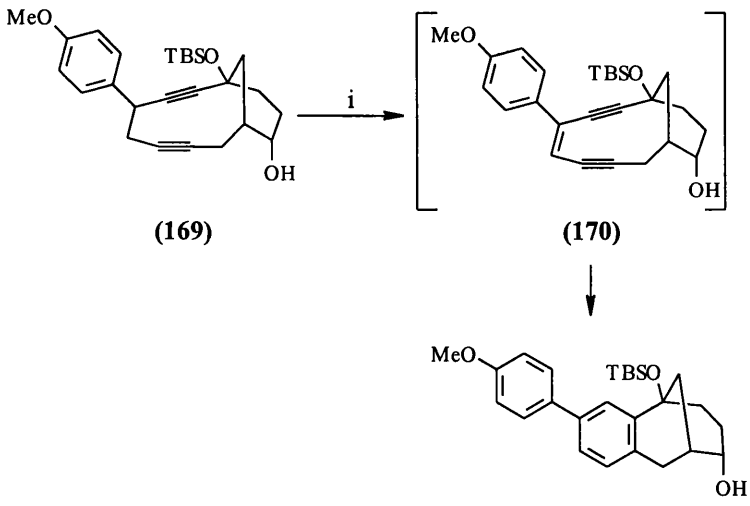


(167)
$t_{1/2}$=12 h. at 37 °C

(168)
$t_{1/2}$<60 min. at 37 °C

Scheme 73 Reagents and Conditions i) KCl-HCl buffer (pH 2)/THF/EtOH.

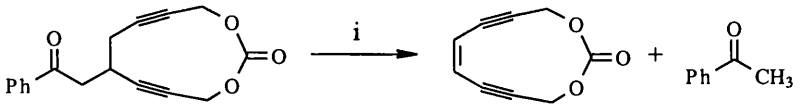
An example of the second mode of operation is the generation of a reactive enediyne by oxidation of prodrug **(169)**. This was acheived[110] chemically by DDQ, to give active enediyne **(170)**, cyclising at room temperature (scheme **74**). **(169)** proved cytotoxic in vitro against rat embryo fibroblast cells, suggesting oxidative activation may occur in biological systems.



(169) (170)

Scheme 74 Reagents and Conditions i) DDQ, PhH, ambient temperature, 2-3 h.

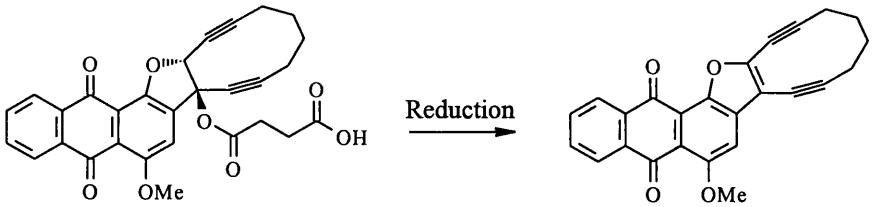
A Norrish type II reaction was employed[111] to complete the enediyne system of **(171)** (scheme **75**). This kind of photochemically triggered enediyne has therapeutic potential in the treatment of cancers which are accessible by light.



(171)

Scheme 75 Reagents and Conditions i) PhH, hv, 87%.

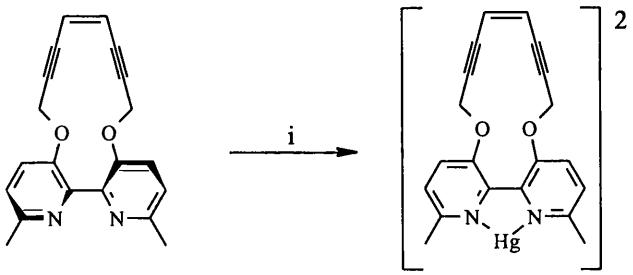
Another method of introducing the olefinic bond into a diyne prodrug to give a strained enediyne system was conceived by Myers (scheme **76**). Reduction of the anthraquinone derived **(172)** occurs rapidly with a flavin-based enzymatic system to give enediyne **(173)**. The enediyne **(173)** cyclises slowly at 37 °C ($t_{1/2}$=48 h.), perhaps due to the annulated aromatic system.



(172) (173)

Scheme 76 Reductive Activation of Myers' Enediyne Precursor **(172)**.

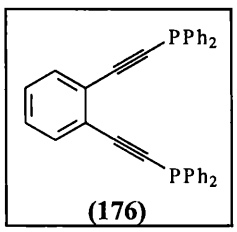
Several systems have been designed in which macrocyclic enediynes undergo conformational change upon co-ordination to metal ions. Bipyridyl system[112,113] **(174)** exists in the eclipsed conformation in the absence of metal ions; upon co-ordination to mercury(II), it becomes forced into a planar conformation **(175)** (scheme 77), reducing the c-d distance and the strain energy in the ground state. This is evidenced by differential scanning calorimetry since **(175)** decomposes at 145 °C, some 100 °C lower than the uncomplexed compound **(174).**



(174) (175)

Scheme 77 Reagents and Conditions i) $Hg(O_2CCF_3)_2$, acetonitrile, 5 h., 59 %.

Co-ordination of 1,2-bis(diphenylphosphinoethynyl)benzene **(176)** to palladium(II) or platinum(II) accelerated its cycloaromatisation by a factor of 30,000; co-ordination to mercury(II) had an inhibitory effect.[114]

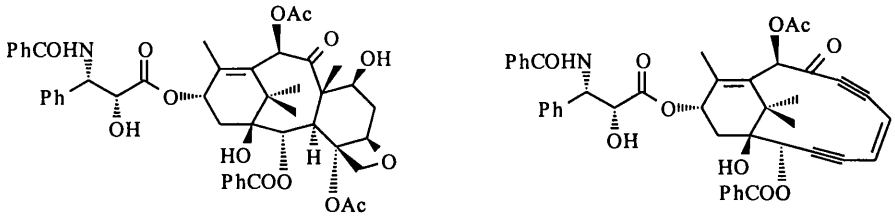


(176)

1.6.5 Natural Compound Analogues Featuring Enediyne Moieties

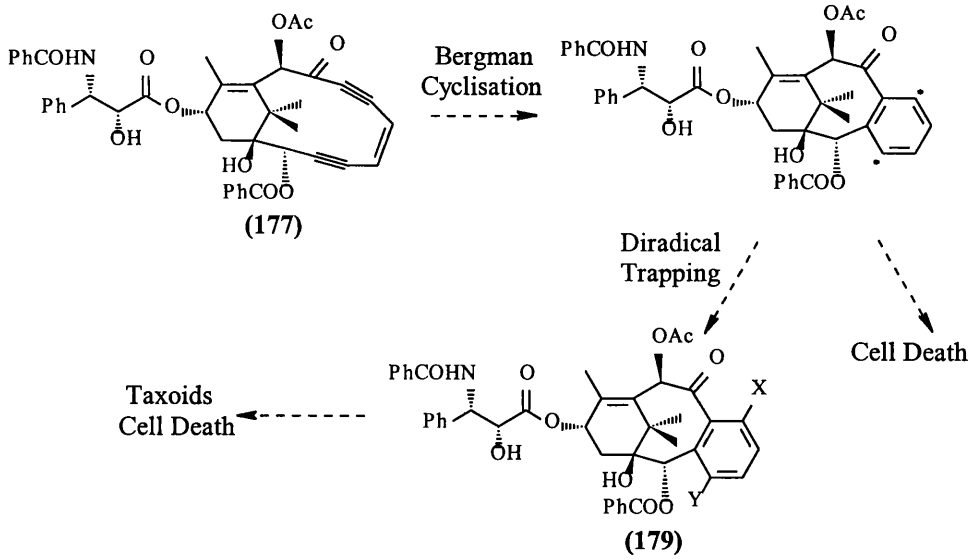
A number of workers have attempted to combine the reactivity of the enediyne anti-cancer antibiotics within the molecular frameworks of other classes of naturally occurring compounds. The aim of such projects is twofold. Controlled Bergman cyclisation may provide a facile, regiospecific entry into complex, polysubstituted aromatic systems; and the enediynes themselves may combine the biological activities of both the enediyne group and the natural compound upon which it was based.

This was the concept behind Fallis's synthesis[115] of his hybrid taxol/enediyne molecules, the "taxamycins", **(177)**. He hoped to obtain rapid access to C-ring aromatic analogues of taxol **(178)**, a compound[116] with potent anti-cancer activity (scheme **78**).



Scheme 78 Structures of Taxol **(178)** and a Prototype Taxamycin **(177)**.

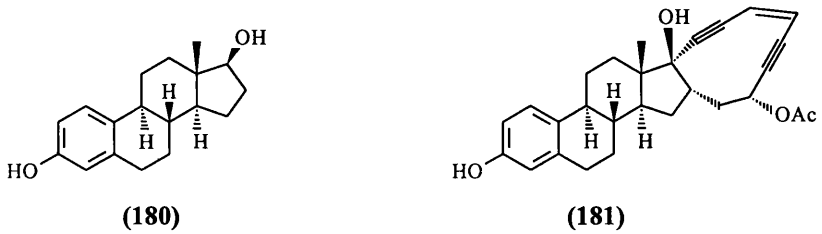
In vitro Bergman cyclisation of **(177)** might cause DNA cleavage, in addition giving taxol analogues (taxoids, **(179)**) upon cyclisation. It is hoped that these compounds will have a twofold mode of biological activity (scheme **79**).



Scheme 79 Proposed Mode of Cyclisation and Biological Activity of the Taxamycins **(177)**.

Unfortunately, the taxamycin synthesised,[117] **(177)**, dubbed taxamycin-12 because of the twelve-membered enediyne ring, underwent cycloaromatisation in very poor (5 %) yield under standard conditions (1,4 cyclohexadiene, benzene, reflux). This was deemed to be due to the large c-d distance (estimated to be ≈3.8 Å) in **(177)**. Ten-membered analogues are hoped to cyclise more efficiently.

A related strategy, specifically targeting mammary cancers, was that of Wang and De Clercq.[118] Such cancers are known to be particularly rich in estrogen **(180)** receptors; the researchers designed and synthesised an estrogen analogue **(181)** (scheme **80**), in the hope that it would undergo cycloaromatisation and cause DNA cleavage and cell death in these cells.



Scheme 80 Estrogen **(180)** and a Designed Estramycin **(181)**.

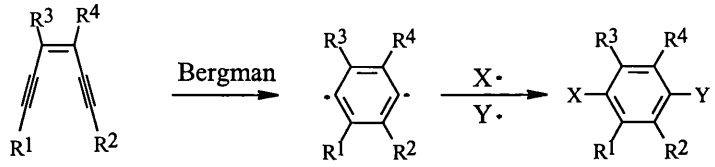
The ten-membered ring estramycin **(181)** was shown to undergo cycloaromatisation at a useful rate ($t_{1/2}$=108 min. at 25 °C.).

Although neither the estramycin **(181)** nor the taxamycin **(177)** thus far synthesised offer useful biological activity, they do highlight the potential for more sophisticated designed enediynes, based on known classes of natural products, binding to specific targets. It is worth noting that neither **(177)** nor **(181)** are equipped with triggering devices, as found in the natural enediynes.

Nicolaou has attached his dynemicin A model system **(163)** to various species capable of intercalating and binding to DNA, such as the calicheamicin sugar moity,[119] an anthraquinone unit and a distamycin unit.[85]

1.6.6 Synthetic Applications of Enediyne Systems

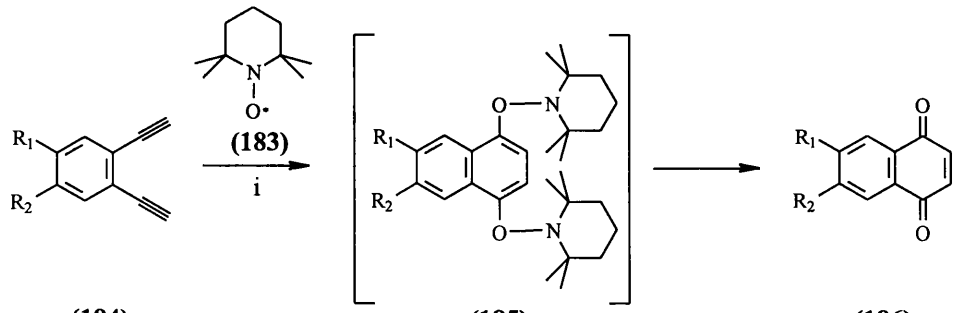
A number of researchers[84] have sought to harness the regiospecific formation of the 1,4 aromatic diradical produced by Bergman cyclisation through the use of a suitable radical trap which can then allow for the construction of a hexasubstituted aromatic nucleus **(182)** (scheme **81**).



(182)

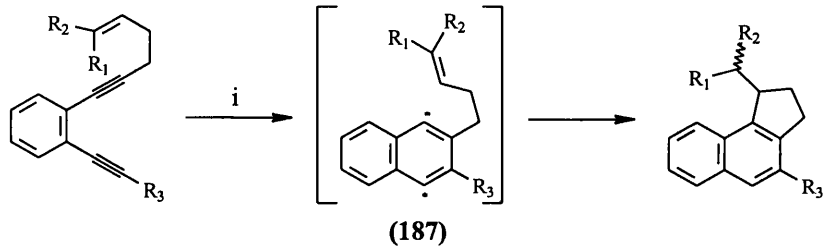
Scheme 81 Cyclisation and Trapping of an Enediyne.

The well-known radical trap TEMPO **(183)** has been used[120] to trap the radical intermediates in the cyclisation of arylenediynes **(184)** to give adducts **(185)**, which spontaneously undergo further reaction to naphthoquinones **(186)** (scheme **82**).



Scheme 82 Reagents and Conditions i) TEMPO **(183)**, PhCl, 150-160 °C, 47-73 %.

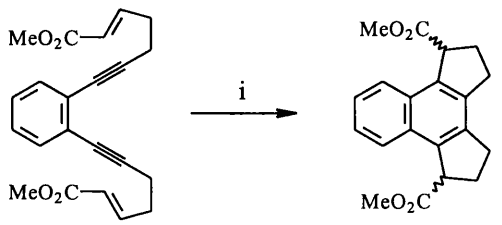
Intramolecular trapping of the diradical species by 5-*exo*-trig cyclisation with an alkene has been shown to proceed in good yield[121] (scheme **83**). Mechanistic studies[122] have shown the intermediacy of a distinct 1,4 diradical arene species **(187)**.



Scheme 83 Reagents and Conditions i) 1,4 cyclohexadiene, PhCl, 190 °C, 70-90 %.

6-*exo* examples required higher temperatures, and were complicated by the formation of side products.

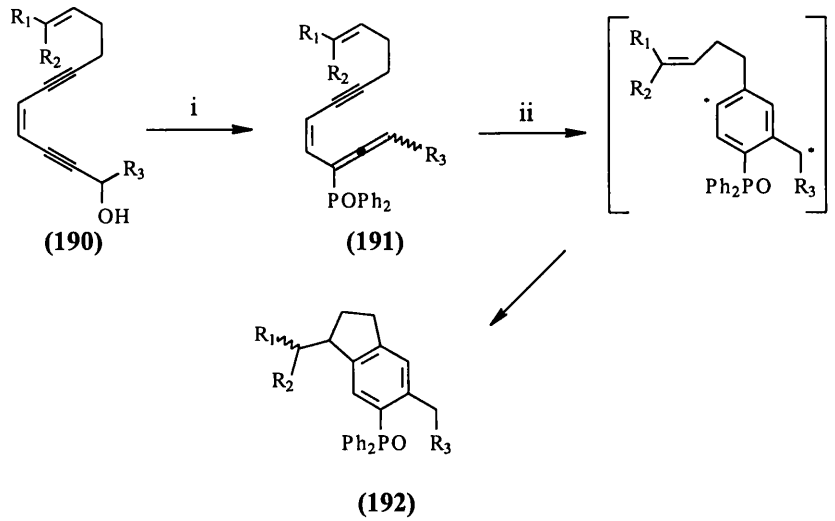
Thermolysis of **(188)**, bearing two radical acceptors, underwent a tandem radical cyclisation subsequent to Bergman cyclisation (scheme **84**) to give tetracylic products **(189)** in excellent yield.[123]



(188) (189)

Scheme 84 Reagents and Conditions i) 1,4-cyclohexadiene, PhCl, 230 °C, 99 %, 1:1 mixture of diastereomers.

Myers-type cyclisation has also been used[124] as the initiating step in a radical cyclisation process. Treatment of enediynes **(190)** with PPh_2Cl and base at -78 °C led smoothly to formation of enyne-allenes **(191)**; this was reacted *in situ* with 1,4-cyclohexadiene at 37 °C to give indenes **(192)** (scheme **85**).

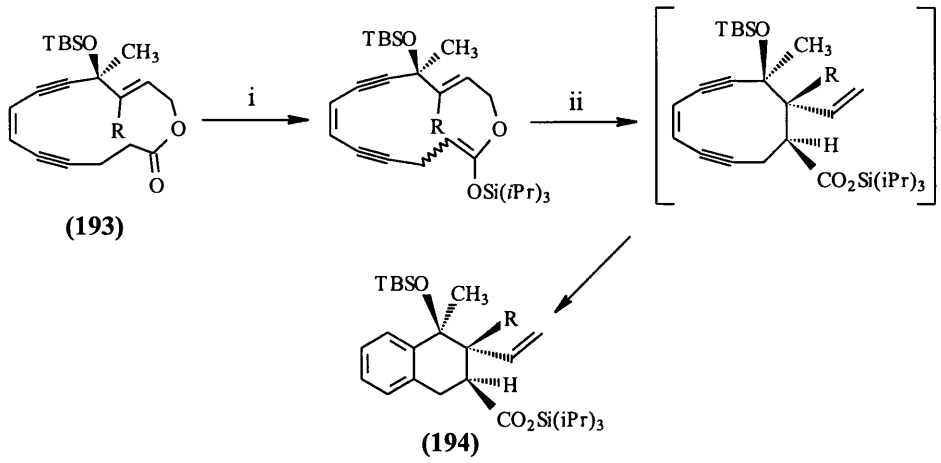


(190) (191) (192)

Scheme 85 Reagents and Conditions i) PPh_2Cl, NEt_3, CH_2Cl_2, -78 °C → 0 °C ii) 1,4-cyclohexadiene, PhH, 37 °C, 12 h., 50-70 %.

Another strategy attempts to employ a Bergman cyclisation triggered by a preceding reaction, generally involving a structural rearrangement. Magriotis and Kim[125] used an Ireland-Claisen rearrangement to bring about a ring contraction of enediynes **(193)**,

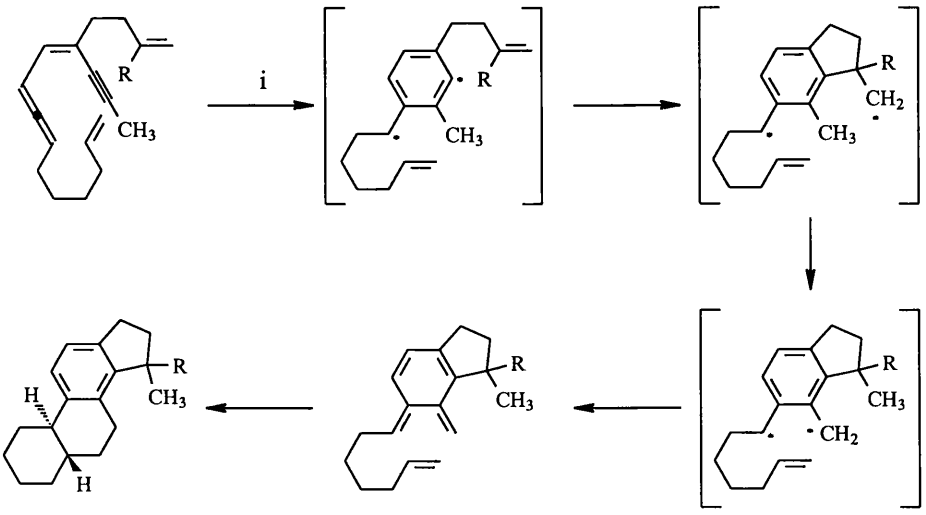
thus triggering a Bergman cyclisation. This leads to the stereocontrolled formation of tetrahydronaphthalenes **(194)** (scheme **86**).



(193) **(194)**

Scheme 86 Reagents and Conditions i) $LiN(SiMe_3)_2$, $(iPr)_3SiOTf$, THF, -78 °C, 80-85 %; ii) 1,4-cyclohexadiene, PhH, 140 °C, 5 h., 50 %.

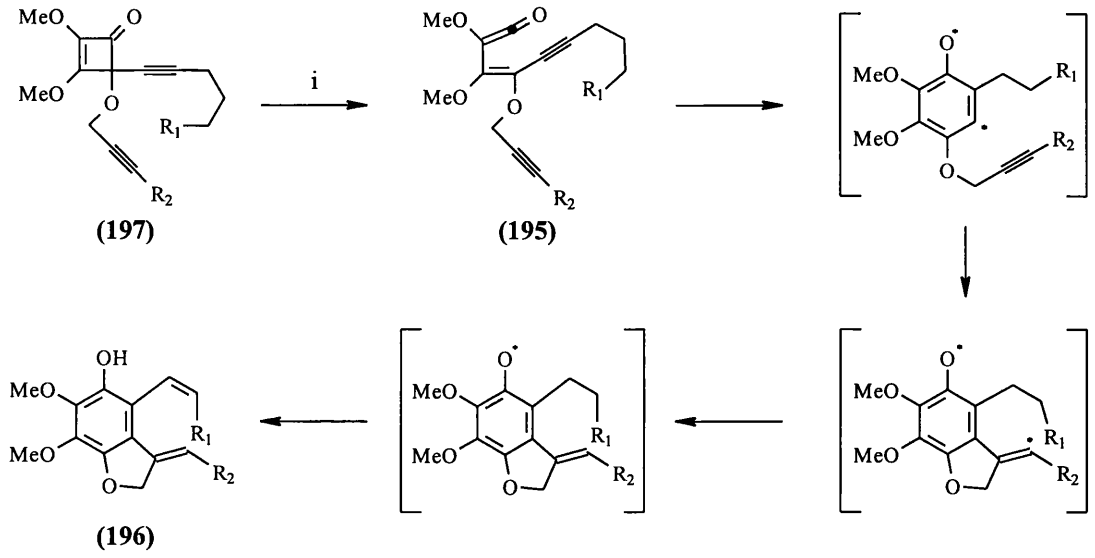
More complex radical cascades commencing with cycloaromatisations have been reported. The spectacular example by Wang[126] features Myers cycloaromatisation, radical cyclisation, 1,5 hydrogen transfer and Diels-Alder cycloadditon (scheme **87**).



Scheme 87 Reagents and Conditions i) PhH, Δ, 50 % (R=H), 13 % (R=Me).

Employing a cyclisation of enyne-ketenes **(195)** related to the Myers cyclisation, Moore *et al* were able[127] to construct highly congested benzofurans **(196)**. The enyne-

ketenes **(195)** themselves were generated by the ring-opening of 4-alkynyl-4-propargyloxy cyclobutenones **(197)** (scheme **88**).



Scheme 88 Reagents and Conditions i) *p*-xylene, Δ, 49-75 %.

1.6.7 The Enediynes-Overview

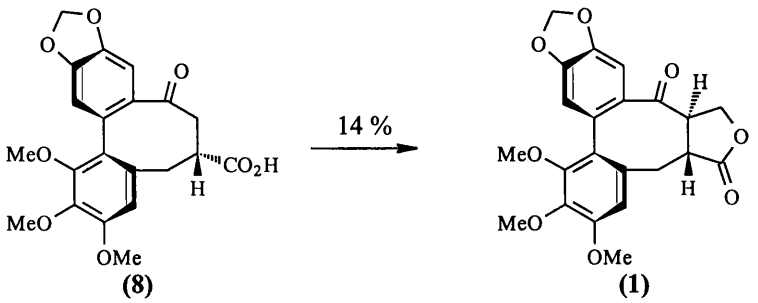
The profound biological activity of the naturally occurring enediynes, combined with their highly unusual mode of action, has provided an inspiration for a huge number of chemists. Many have directed their efforts toward total synthesis. A significant number, pursuing biologically active leads, have sought to ape nature with rationally designed enediynes incorporating novel triggering mechanisms and DNA binding devices. A smaller, but still significant number, have sought to harness the potential of the enediynes, and the Bergman cycloaromatisation they undergo, to initiate chemical cascades and utilise them in the construction of complex molecular frameworks. This diversity of appeal of the enediynes ensures that this will be an area of organic chemistry that continues to attract creative contributions for a long while to come.

Chapter 2. Results and Discussion

2.1 Previous Work in the Group

An ongoing programme of research in our laboratories has been that directed towards the assembly of complex natural product frameworks employing novel synthetic methodologies. A particularly attractive target has been the bisbenzocyclooctadiene lignan lactone steganone **(1)**. It combines a broad spectrum of biological activity[2] with structural features presenting a significant synthetic challenge.

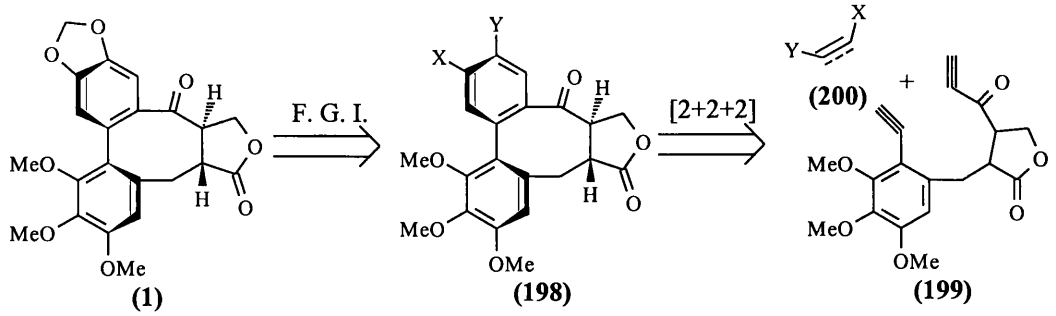
This natural product has also attracted the attention of other groups, being the subject of twelve total/formal syntheses. Despite the range of approaches employed, ten of these have passed through the intermediate **(8)**, despite the yield for the conversion to the actual natural product being variable and in some instances rather poor (scheme **89**).



Scheme 89 Conversion of Keto-Acid **(8)** to Steganone **(1)**.

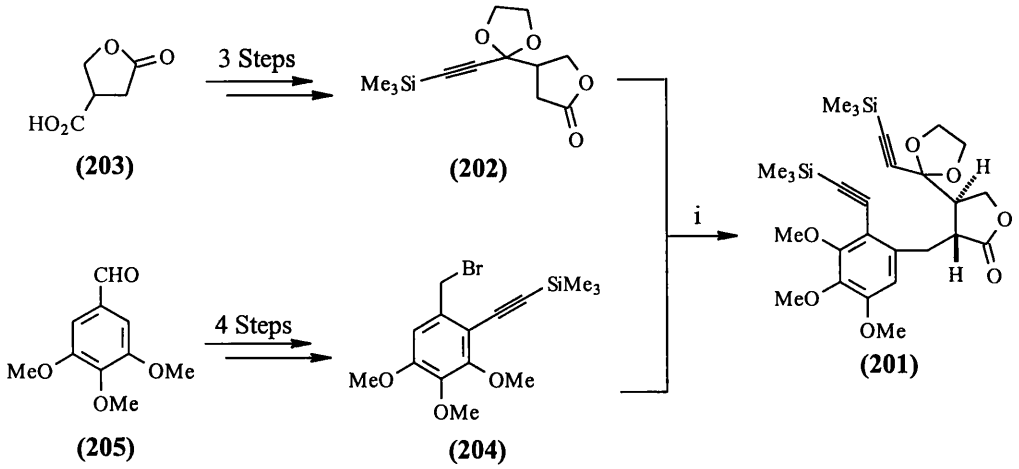
Additionally, all but two of the twelve syntheses relied on non-phenolic oxidative coupling or Ullman type coupling methodologies to install the biaryl axis. Clearly there was scope for an alternative route.

The retrosynthetic analysis of Motherwell and Ujjainwalla[128] was based on the disconnection of biaryl **(198)**, *via* a [2+2+2] cycloaddition, to the diyne **(199)** and a suitable third 2π-component **(200)** (scheme **90**).



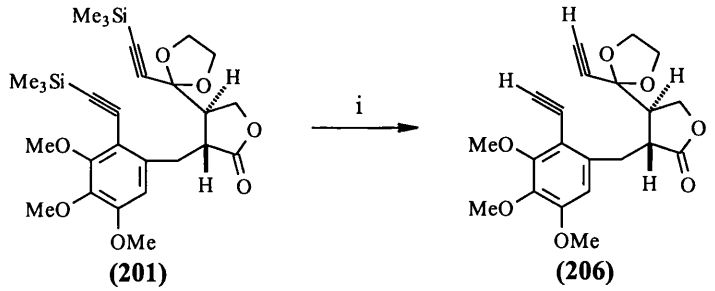
Scheme 90 Motherwell and Ujjainwalla's Retrosynthesis of Steganone **(1)**.

A highly convergent route to diyne **(199)** *via* the protected intermediate **(201)** was developed (scheme **91**). Anionic coupling of lactone fragment **(202)** (available in 3 steps from paraconic acid **(203)**) and benzylic bromide **(204)** (available in 4 steps from 3,4,5-trimethoxybenzaldehyde **(205)**) gave protected diyne **(201)** in excellent yield.



Scheme 91 Reagents and Conditions i) **(202)**, LDA, THF, -78 °C, 1 h.;addition of **(204)**, -78 °C to -35 °C, 1 h., then 20 °C, 12 h., 80 %.

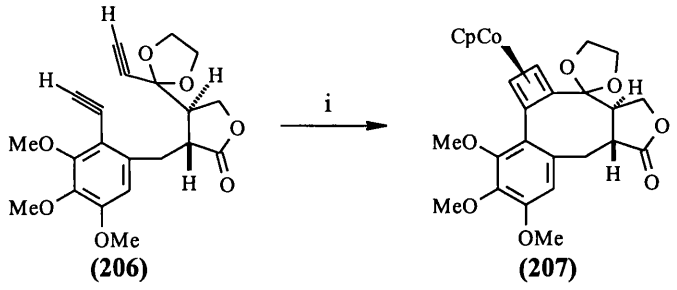
Global desilylation of **(201)** with K_2CO_3 in methanol then gave the cycloaddition precursor **(206)** (scheme **92**).



(201) **(206)**

Scheme 92 Reagents and Conditions i) K_2CO_3, MeOH, 24 h., 96 %.

With **(206)** in hand, Motherwell and Ujjainwalla embarked upon a series of studies directed towards the co-cyclisation of **(206)** with a variety of 2π-addends. Initial studies, using the conditions of Vollhardt[129] (catalytic η^5-cyclopentadienyl cobalt dicarbonyl **(84)**, bis(trimethylsilyl)ethyne **(87)** as 2π-addend, photochemical activation) gave none of the expected [2+2+2] cycloaddition product, but instead gave the cobalt-cyclobutadiene complex **(207)** together with recovered starting material (scheme **93**).

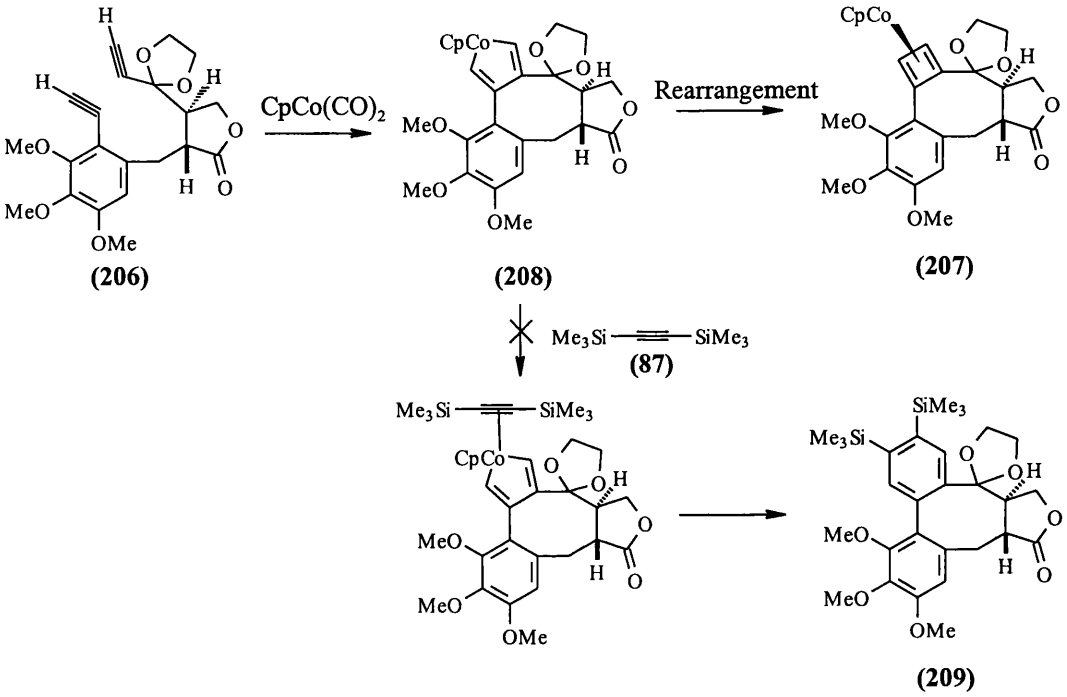


(206) **(207)**

Scheme 93 Reagents and Conditions i) Bis(trimethylsilyl)ethyne **(87)**, reflux, addition of **(206)** and $CpCo(CO)_2$ **(84)** in THF over 9 h., hν (300 W. tungsten lamp), 47 % (40 % recovered **(206)**).

The structure of **(207)** was confirmed by X-ray crystallography. Its formation was attributed to reductive elimination of the metallacyclopentadiene species **(208)**, rather

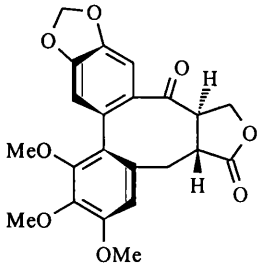
than the desired co-ordination to bis(trimethylsilyl)ethyne **(87)** and subsequent biaryl **(209)** formation (scheme **94**).



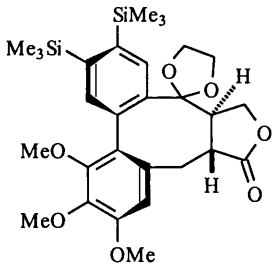
Scheme 94 Mechanism of the Formation of Cobalt-Cyclobutadiene Complex **(207)**.

A series of careful optimisation studies were undertaken; under conditions of lower temperature (~50 °C), and using synchronous addition of separate solutions of diyne **(206)** and catalyst **(84)**, it proved possible to isolate the desired biaryl **(209)** in 14 % yield, along with 56 % of the cyclobutadiene complex **(207)**.

Fortunately, nOe studies conducted upon the biaryl **(209)** concluded that the biaryl axis had been installed as the correct atropisomer, obviating the need for thermal interconversion at a later stage in the synthesis (scheme **95**).



(1)



(209)

Scheme 95 Structures of Natural Steganone **(1)** and the [2+2+2] Cycloadduct **(209)**.

Attempts were made to improve on the yield of **(209)** observed by varying the catalyst and also using a variety of 2π addends. None of these conditions led to the formation of congeners of **(209)**, and only mixtures of **(207)** and starting material were isolated. Despite its shortcomings, the synthesis provides a highly flexible, convergent route to the bisbenzocyclooctadiene lignan lactones, furnishing **(209)** in a completely diastereoselective fashion in remarkably few steps. It also has an in-built potential to become enantioselective, as paraconic acid **(203)** can been resolved into its enantiomers by a known procedure.[130] The scope for analogue synthesis is also appealing; the convergency of the approach obviates the necessity to repeat the whole synthetic route in order to change only one element of the molecule.

The synthesis is also remarkable in establishing the eight-membered ring, the biaryl axis and the upper aryl ring in one step. Very few examples of the synthesis of medium-sized carbocyclic rings using [2+2+2] cycloaddition reactions are known in the literature and those that are invariably proceed in exceptionally poor yield.[48]

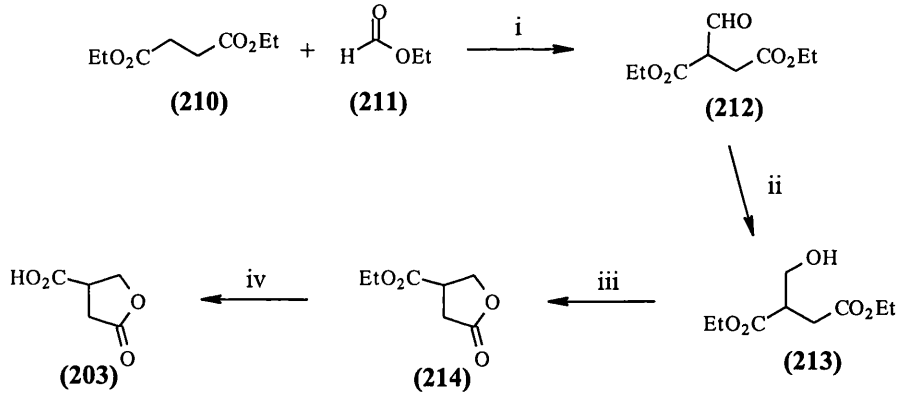
It was decided, as one part of the ongoing research project, to follow on from the work of Ujjainwalla and Motherwell,[128] by attempting to improve the yield of the cycloaddition step and also to synthesise a range of analogues using the existing

methodology. With these objectives in mind, we commenced work on the synthesis of paraconic acid **(203)**.

2.2 Cobalt Mediated [2+2+2] Cycloaddition Studies Directed Towards the Synthesis of Steganone Analogues

2.2.1 Synthesis of Paraconic Acid (203)

Paraconic acid **(203)** was available *via* a well-established literature[130] route (scheme **96**).



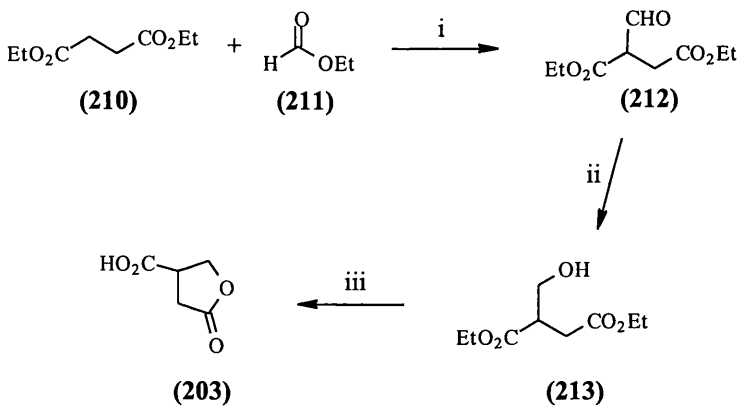
Scheme 96 Reagents and Conditions i) Na, Et_2O, 18 h., 70 %; ii) H_2, 150 atm., Raney Ni, EtOH, 70 °C, 24 h., 90 %; iii) 1 mmHg, 80 °C, 92 %; iv) 6 M NaOH, EtOH, reflux, 1 h., 87 %.

The Claisen condensation of diethyl succinate **(210)** and ethyl formate **(211)** was initiated, in the literature report, by warming the reaction vessel. As the reaction is exothermic, and the heat evolved is considerable when conducted on a large scale (ca. 0.5 mol), it was considered safer to trigger the reaction by addition of 1 mol % of ethanol. Under these conditions, the reaction proceeded smoothly, and after 18 h. afforded a thick orange suspension of the sodium salt of **(212)**. After acidification, **(212)** was isolated in 60 % yield.

The literature procedure then described high pressure (150 atm.) hydrogenation of **(212)** over Raney nickel catalyst. Ujjainwalla[128] investigated the possibility of using lower pressures and other catalysts, but no reduction was observed, even in the presence of acid to facilitate keto-enol equilibration. He was ultimately obliged to use the literature conditions, which proved inconvenient as the apparatus available was only suitable for batches of 10 g., necessitating repeated runs.

As the alcohol **(213)** would be required in large quantities, a new method of effecting the reduction was therefore sought. Fortunately, a simple sodium borohydride reduction took place in under 1 h. at 0 °C, allowing the alcohol **(213)** to be isolated in 40 % yield. Although this yield was lower than the published procedure, the extreme experimental simplicity, amenability to large scale work and rapidity made it the method of choice for a conversion that was to be repeated a large number of times.

In the original report, the authors described a two-step conversion of alcohol **(213)** into paraconic acid **(203)**, proceeding *via* thermal lactonisation under reduced pressure to give ethyl paraconate **(214)**, followed by saponification (scheme **96**). It was found that one of these steps was superfluous, however, as direct saponification of the bis ester **(213)**, followed by passage through a column of Amberlite®-IR120 acid ion-exchange resin effected direct conversion to paraconic acid **(203)**. It was necessary to acidify the solution in this way, as paraconic acid is extremely water-soluble, thereby preventing conventional work-up. The modified route to paraconic acid is summarised in scheme **97**, and allowed quantities in excess of 20 g. to be prepared in three days from diethyl succinate **(210)**.



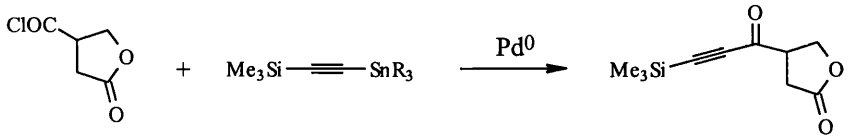
(210) (211) (212) (203) (213)

Scheme 97 Reagents and Conditions i) Na, Et_2O, EtOH (1 mol %), 18 h., 60 %; ii) $NaBH_4$, MeOH, 0 °C, 1 h., 40 %; iii) 6 M NaOH, reflux, 1 h., then passage through Amberlite®-IR120 ion exchange resin, 58 %.

2.2.2 Elaboration of Lactone Fragment (202)

With substantial quantities of paraconic acid **(203)** in hand, we were in a position to undertake the synthesis of the lactone fragment **(202)** of the [2+2+2] cycloaddition precursor **(206)**.

Following our group's established method,[128] based on that of Logue and Teng,[131] we sought to install the acetylenic moiety of **(202)** by a palladium catalysed coupling of acid chloride **(215)** with an alkynyl stannane **(216)** (scheme **98**).

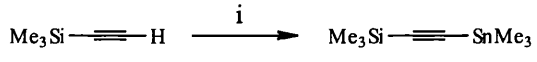


(215) (216) (218)

Scheme 98 Palladium Catalysed Coupling of Acid Chloride **(215)** and Alkynylstannane **(216)**.

It was found that use of [(trimethylsilyl)ethynyl]trimethylstannane **(216**, R=Me), offered considerable advantages over the tri-*n*-butyl- species **(216**, R= *n*-Bu)

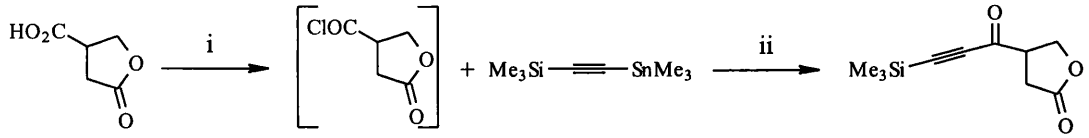
employed by Logue and Teng. Yields were substantially higher, and the work-up was considerably simplified thanks to the water-soluble nature of the tin by-product. [(Trimethylsilyl)ethynyl]trimethylstannane **(216**, R=Me**)** was prepared by treatment of trimethylsilylethyne **(217)** with *n*-butyllithium in THF, and quenching of the trimethylsilylacetylide anion with trimethyltin chloride (scheme **99**). This procedure enabled **(216**, R=Me**)** to be isolated in 76 % yield.



(217) **(216)**

Scheme 99 Reagents and Conditions i) THF, 0 °C, addition of *n*-BuLi in hexanes over 30 min., stir 30 min.; addition of trimethyltin chloride, 0 °C to 20 °C, 12 h., 76 %.

Paraconic acid **(203)** was converted to the corresponding acid chloride by treatment with oxalyl chloride in DCM with a catalytic quantity of DMF. The acid chloride was used without purification in the next step and underwent bis(triphenylphosphine)palladium(II) chloride catalysed coupling in good yield with **(216**, R=Me**)**, providing ynone **(218)** (scheme **100**) in good yield.

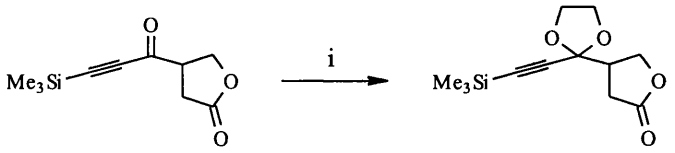


(203) **(215)** **(216**, R=Me**)** **(218)**

Scheme 100 Reagents and Conditions i) $(COCl)_2$, DCM, cat. DMF., 1 h.; ii) 1,2 Dichloroethane, $Pd(PPh_3)_2Cl_2$, 50 °C, 16 h., 67 % over 2 steps.

The rather unstable ynone **(218)** was immediately protected as its ketal. Ketalisation was achieved by refluxing **(218)** in benzene with ethylene glycol and a catalytic amount of pyridinium *p*-toluenesulfonate with azeotropic removal of water (scheme

101). This milder acid catalyst was selected in favour of the more normal *para*-toluenesulphonic acid to avoid protodesilylation of the alkyne.



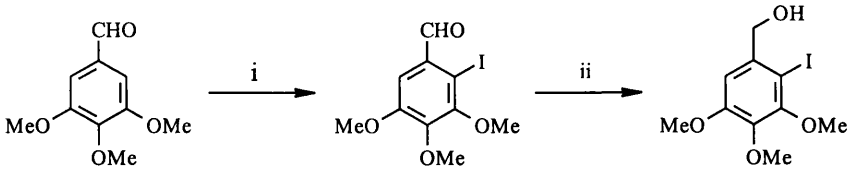
(218) **(202)**

Scheme 101 Reagents and Conditions i) Ethylene glycol, pyridinium *p*-toluenesulfonate, PhH, reflux, azeotropic removal of water, 12 h., 87 %.

With the fully-protected lactone fragment **(202)** in hand, we were ready to embark upon the synthesis of the benzylic bromide **(204)**.

2.2.3 Synthesis of Benzylic Bromide (204)

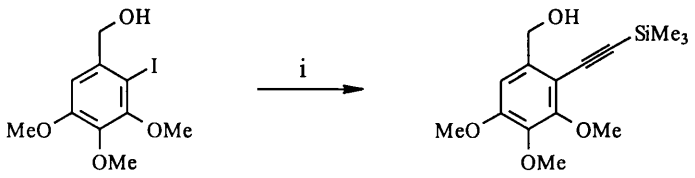
Electrophilic iodination of 3,4,5-trimethoxybenzaldehyde **(205)** according to the method of Raphael,[132] and borohydride reduction of the resultant iodobenzaldehyde **(219)** proceeded in excellent yield, giving 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)** (scheme **102**).



(205) **(219)** **(220)**

Scheme 102 Reagents and Conditions i) $Ag(O_2CCF_3)$, DCM, addition of I_2 over 3 h., stir 12 h., 96 %; ii) $NaBH_4$, MeOH, -5 °C, 30 min., 88 %.

The iodobenzyl alcohol **(220)** was coupled with trimethylsilylethyne **(217)** by means of a Stephans-Castro coupling under the mild conditions of Hahihara (scheme **103**).[133]

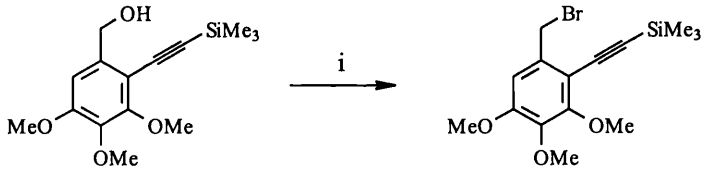


(220) **(221)**

Scheme 103 Reagents and Conditions i) Trimethylsilylethyne **(217)**, $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, 50 °C, 2 h., 74 %.

Initially research on this coupling reaction was conducted[128] using protected versions of **(220)**, as it was assumed that a free benzylic alcohol would adversely affect the reaction. In the event, this precaution was unwarranted, as **(220)** underwent the coupling to give the alkyne **(221)** in good yield. The same compound has previously been synthesised by other workers *via* a similar route.[134]

A suitable leaving group was then introduced in the benzylic position using a triphenylphosphine/carbon tetrabromide methodology[135] to give bromide **(204)** in good yield (scheme **104**).



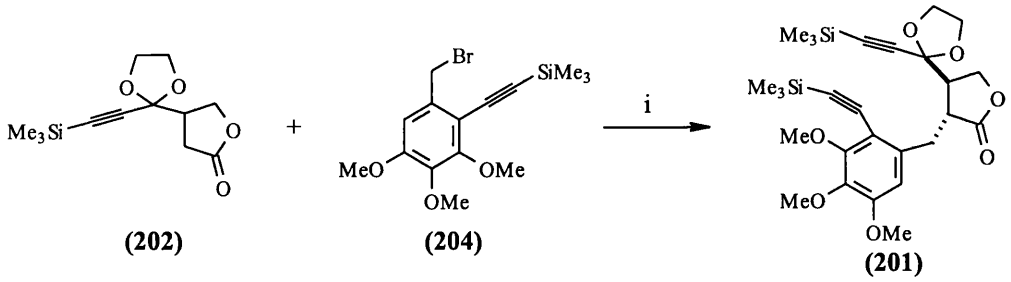
(221) **(204)**

Scheme 104 Reagents and Conditions i) CBr_4, PPh_3, Et_2O, 24 h., 72 %.

2.2.4 Coupling of Lactone Fragment (202) and Benzyl Bromide (204)

The coupling of the lactone fragment **(202)** and the benzylic bromide **(204)** was achieved by deprotonation of **(202)** with lithium diisopropylamide in THF at -78 °C, and subsequent addition of a solution of bromide **(204)** in THF at -35 °C. These conditions were found[128] to be optimal for the coupling reaction, and meant that 72 %

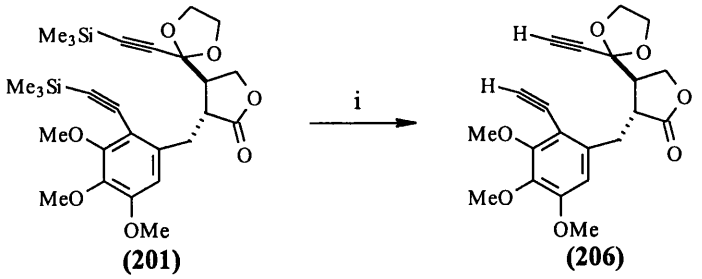
of the desired product **(201)** could be isolated, as a single diastereoisomer. No trace of the *cis* isomer, or of any di-alkylated product could be detected (scheme **105**).



(202) **(204)** **(201)**

Scheme 105 Reagents and Conditions i) **(202)**, THF, LDA, -78 °C, 1 h.; then warm to -35 °C, add **(204)**, stir 1 h., warm to ambient temp, stir 12 h., 72 %.

Deprotection of both alkyne functionalities was then achieved by stirring **(201)** with potassium carbonate in methanol (scheme **106**).



(201) **(206)**

Scheme 106 Reagents and Conditions i) K_2CO_3, MeOH, 15 h., 88 %.

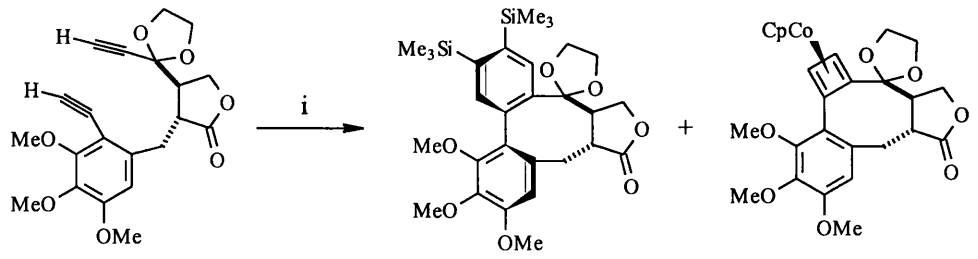
Using this route, it proved possible to prepare the cycloaddition precursor **(206)** in quantities of up to 2.6 g. The stage was therefore set to embark upon initial cycloaddition studies.

2.2.5 Cobalt-Based Cycloaddition Studies

2.2.5.1 Optimisation Studies Employing the η^5-cyclopentadienyl Cobalt dicarbonyl/bis(trimethylsilyl)ethyne system

Using the partially-optimised conditions previously employed within the group, we sought to effect the cycloaddition of **(199)** with bis(trimethylsilyl)ethyne **(87)**. This involved motorised syringe pump addition of two separate solutions of **(199)** and catalyst **(84)** to a stirred solution of a further quantity of catalyst in a 2:1 mixture of bis(trimethylsilyl)ethyne to THF. Addition of this further amount of catalyst was necessary because of the formation of the catalytically inactive **(207)**. Irradiation was conducted with a 300 W. tungsten lamp, and no other source of heating was used. In our hands, this procedure led to variable yields (0-10 %) of biaryl **(209)**. Isolation also proved problematic, as a number of unidentifiable side-products, of similar polarity to **(209)** were formed.

Fortunately, by the simple expedient of changing from THF to acetonitrile as co-solvent, the reaction gave a higher, reproducible yield (19 %) on a 100 mg scale. Formation of a complex product mixture was also avoided, as only cobalt-cyclobutadiene complex **(207)** and biaryl **(209)** were formed. These were easily separable by chromatography on silica (scheme**107**).

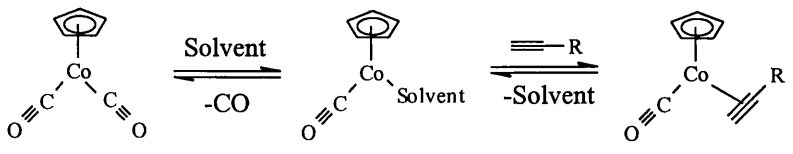


(206) (209) (207)

Scheme 107 Reagents and Conditions i) Addition of **(206)** and η^5-cyclopentadienyl cobalt carbonyl **(84)** over 9 h. to a solution of **(84)** in bis(trimethylsilyl)ethyne **(87)**/acetonitrile, reflux 8 h., 19 % **(209)**, 35 % **(207)**.

There are a number of possible reasons for this improved yield and reproducibility. It was noted that when acetonitrile was used as co-solvent, the solvent mixture was seen to gently reflux because of the heat emitted by the 300 W. tungsten lamp. It was thus held at a constant temperature (the boiling point). This was not the case with the higher-boiling THF, which did not reflux under these conditions. Considerable temperature fluctuation must occur in this case, perhaps accounting for yield variation.

The second factor which may explain this observation is the differing abilities of THF and acetonitrile to act as ligands for cobalt. Displacement of a carbonyl ligand by a solvent molecule to form a weakly-bound complex **(222)** conceivably assists in the co-ordination of cobalt to alkynes (scheme **108**).



(222)

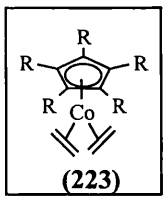
Scheme 108 Solvent-Assisted Alkyne Co-ordination of Cobalt Catalyst **(84)**.

Acetonitrile, because of its π-acceptor character, may well be a superior ligand to THF for cobalt. It could therefore be postulated either that acetonitrile facilitates carbon monoxide displacement more efficiently than THF, or that because of its linearity and smaller steric bulk, subsequent alkyne complexation is easier.

Although the reaction gave reproducible yields of **(209)** on a 100 mg. scale, when an attempt was made to reproduce the reaction on a larger scale (1 g), to our dismay, no desired biaryl **(209)** could be isolated, and the cobalt-cyclobutadiene complex **(207)** was the only product. The reason for this scale-up anomaly is not clearly understood; it may be that the lower surface-area-to-volume ratio of the larger reaction vessel employed adversely affects the photochemical activation process. We were thus obliged to resort to repeated runs of the reaction on a smaller scale.

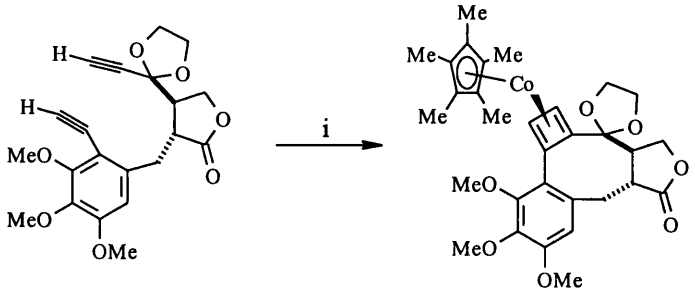
2.2.5.2 Use of Alternative Cobalt-Based Catalyst Systems

In an effort to improve the yield of the [2+2+2] cycloaddition process, we decided to investigate η^5-cyclopentadienyl cobalt bis(ethene) catalysts of the general formula **(223)**. Catalysts of this type have been shown to be active at temperatures some 100 °C lower than the carbonyl analogues, because of the much greater lability of the ethene ligands. Several attempts were made to prepare η^5-cyclopentadienyl-cobalt bis(ethene) **(223**, R=H) by the literature route [47], but the "red-brown needles" described in the original paper were never isolated. A red-brown solid was isolated, but unfortunately this exhibited no catalytic activity.



(223)

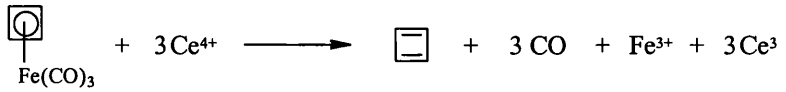
We were kindly supplied with a sample of η^5-pentamethylcyclopentadienyl cobalt bis(ethene) **(223**, R=Me), which is more stable than η^5-cyclopentadienyl-cobalt bis(ethene) **(223**, R=H). This catalyst did indeed undergo reaction with diyne **(199)** at ambient temperature, without the need for photochemical activation; the only product to be isolated, however, was the metallacyclobutadiene complex **(224)** in 22 % yield as yellow crystals (scheme **109**).



(206) **(224)**

Scheme 109 Reagents and Conditions i) Addition of solutions of **(206)** and $Cp^*Co(C_2H_4)_2$ **(223**, R=Me) in THF over 8 h. to a solution of $Cp^*Co(C_2H_4)_2$ **(223**, R=Me) in bis(trimethylsilyl)ethyne **(87)**/THF, stir 8 h. thereafter, 22 %.

It seems unfortunate that whilst cyclobutadiene complexes such as **(207)** and **(224)** can be formed, sometimes in good yield, they cannot be put to synthetic use. It is possible, for instance, to liberate free cyclobutadienes **(225)** from iron tricarbonyl **(226)** complexes by oxidative decomposition (scheme **110**).



(226) **(225)**

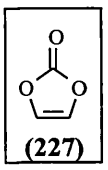
Scheme 110 Oxidative Liberation of Cyclobutadiene **(225)** From Cyclobutadiene-Iron Tricarbonyl Complex **(226)**.

Cyclobutadienes undergo rapid Diels-Alder reactions, and this could conceivably be put to good use as trapping the free cyclobutadiene derived from **(224)** or **(207)** with a

variety of dieneophiles would give rise to interesting steganone analogues via their Dewar benzene derivatives. Unfortunately, it proved impossible to liberate the free cyclobutadiene with a range of single electron oxidants. This has been attributed to the presence of the extremely electron-rich trimethoxyaryl ring, which undergoes facile oxidation to the radical cation in preference to oxidation of the metal centre. This facile oxidation of the trimethoxyaryl ring is evidenced by the synthetic approaches to steganone relying upon non-phenolic oxidative couplings (p. 15).

2.2.5.3 Application of Other Cycloadducts

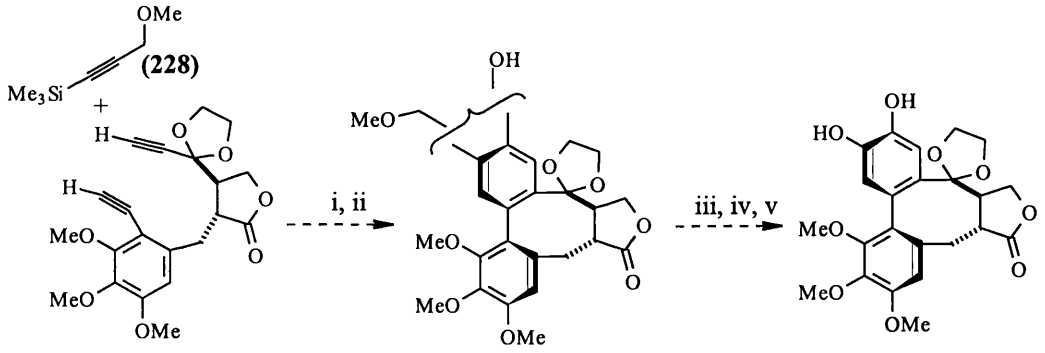
In the original study, Ujjainwalla[128] investigated the possibility of employing alternative 2π-addends in the cobalt-based cycloaddition of diyne **(206)**. The reasons for this were twofold; to improve upon the observed yield, and to introduce different functionality into the upper aryl ring. To this end, he conducted the reaction using i) acetonitrile and ii) vinylene carbonate **(227)** as 2π-addends. The latter was particularly appealing, as it was hoped cycloaddition would introduce the oxygen functionality appropriate to the natural product.


(227)

Unfortunately, in both cases the only products were the cyclobutadiene complex **(207)** and starting diyne **(206)**. These observations are perhaps not wholly surprising in the light of Vollhardt's[46] observation that in a given cycloaddition, bis(trimethylsilyl)ethyne **(87)** is the best co-cyclisation partner when combined with a given diyne. Co-cyclisations with alkenes, in particular, are considerably more demanding than those with alkynes; generally, the alkene component has to be intramolecular for reasonable yields of diene complexes to be obtained.

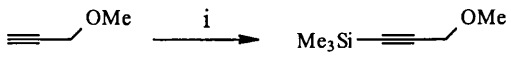
Despite the lack of success of these earlier attempts, we resolved to employ a less bulky alkyne. It was felt that the extremely hindered nature of bis(trimethylsilyl)ethyne **(87)** was preventing co-ordination to the metallacyclopentadiene **(208)**, and this was leading to the alternative product **(207)** (scheme **94**).

The alkyne **(228)** was chosen as a suitable candidate as a cyclisation partner, not only because of its less hindered nature, but also because of the potential to convert a cycloadduct into a suitable phenol by means of a Dakin reaction (scheme **111**).[136]



Scheme 111 Reagents and Conditions i) $CpCo(CO)_2$, hν ii) Conversion of $SiMe_3$ to OH iii) Deprotection of OMe iv) Oxidation to aldehyde v) Dakin reaction.

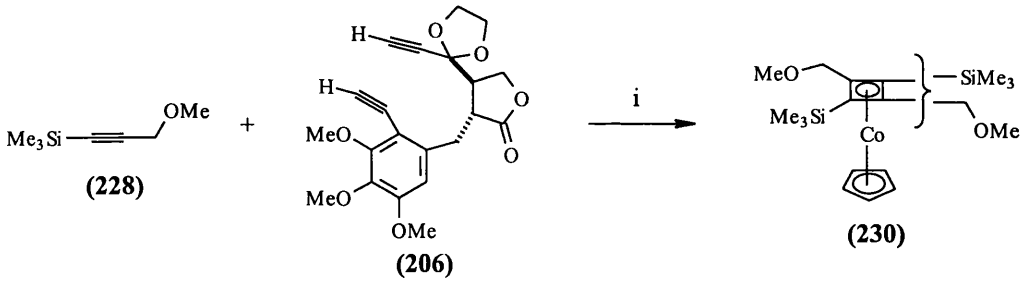
Alkyne **(228)** was readily synthesised from propargyl methyl ether **(229)** by deprotonation at low temperature and quenching with trimethylchlorosilane (scheme **112**).



(229) **(228)**

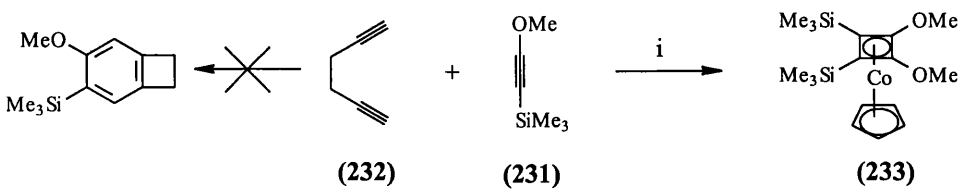
Scheme 112 Reagents and Conditions i) THF, *n*-BuLi, -78 °C 15 min., then Me_3SiCl, -78 °C, 1 h., warm to 20 °C, 1 h., 67 %.

Using our standard cycloaddition conditions (alkyne **(228)** as solvent, THF co-solvent, syringe pump addition of **(206)** and catalyst **(84)**, irradiation), we attempted the co-cyclisation of diyne **(206)** and alkyne **(228)**. The only product isolable from the reaction mixture was the cyclobutadiene complex **(230)** as red crystals, identified from its ^{1}H NMR spectrum, although the regiochemistry could not be assigned on this basis (scheme **113**).



Scheme 113 Reagents and Conditions i) Addition of solutions of **(206)** and η^5-cyclopentadienyl cobalt dicarbonyl **(84)** in THF over 9 h. to a solution of η^5-cyclopentadienyl cobalt dicarbonyl **(84)** in alkyne **(228)**/THF, hv, stir 9 h., 9 % (based on starting catalyst).

Vollhardt[60] has experienced a similar outcome in his attempt to co-cyclise trimethylsilyl(methoxy)ethyne **(231)** with 1,5-hexadiyne **(232)** with η^5-cyclopentadienyl cobalt dicarbonyl **(84)**. Instead of the [2+2+2] cycloadduct, he isolated cyclobutadiene complex **(233)** in quantitative yield (based on starting **(84)**) (scheme **114**).



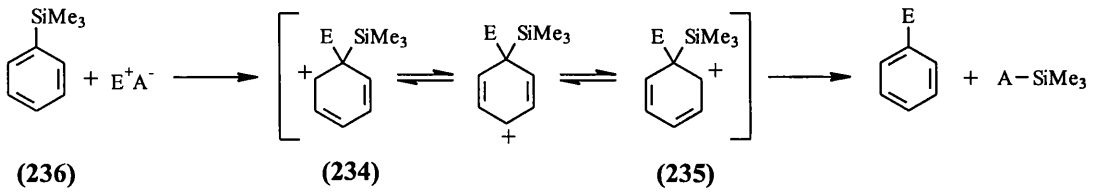
Scheme 114 Reagents and Conditions i) $CpCo(CO)_2$ **(84)**, octane, reflux, 30 h., 99 % (based on $CpCo(CO)_2$).

The failure of these attempts serve to illustrate the finely balanced nature of the reaction. Bis(trimethylsilyl)ethyne **(87)** is the ideal cycloaddition partner in [2+2+2] cycloadditions of diynes; it is sufficiently reactive to give good yields of arenes, but is too hindered to undergo self-trimerisation or formation of cyclobutadiene complexes. In contrast, alkyne **(228)** is less hindered, and is evidently capable of undergoing such reactions resulting in the formation of catalytically inactive species such as **(230)**.

2.2.5.4 Synthesis of Steganone Analogues

Frustrated by our attempts to improve upon the yield of the cobalt-based [2+2+2] cycloaddition reaction, we turned our attention to the elaboration of biaryl **(209)**. Part of the appeal of using bis(trimethylsilyl)ethyne **(87)** as a cyclisation partner is the potential it allows for regioselective functionalisation of the resultant bis(trimethylsilyl)arenes by means of electrophilic substitution.

Electrophilic substitution of silyl arenes is believed[51] to proceed *via* a mechanism similar to the closely analogous electrophilic substitution of hydrogen (scheme **115**). Trimethylsilyl arenes are particularly susceptible to electrophilic substitution due to the ability of silicon to stabilise β-carbocations, lowering the energy of Wheland intermediates such as **(234)** and**(235)**.

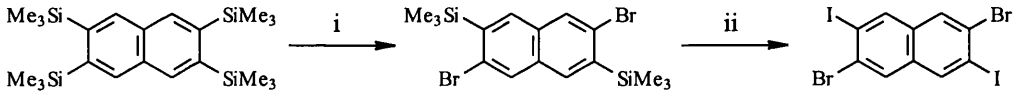


(236) **(234)** **(235)**

Scheme 115 Electrophilic Substitution of Trimethylsilylbenzene **(236)**.

The Ph-Si bond is much more susceptible to cleavage by electrophiles than the Ph-H bond. The former is cleaved faster than the latter, for instance, by a factor of 10^4 in aqueous sulphuric acid at 25 °C.[137]

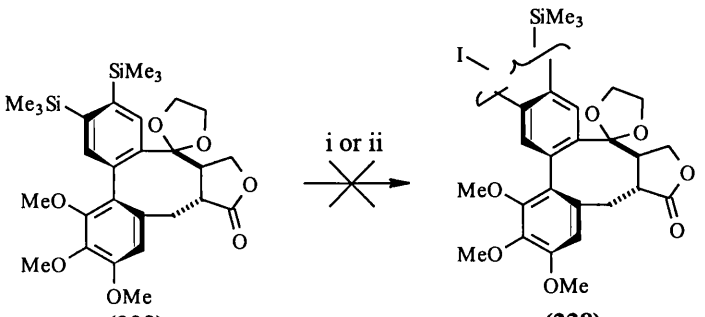
Substitution by a wide variety of electrophiles is possible, permitting synthetically useful transformations. Substitutions by hydrogen (and isotopes), halogens, pseudohalogens, sulphur trioxide, carbocations and metals are all documented.[51] Moreover, in the case of 1,2 bis(trimethylsilyl)arenes, the first trimethylsilyl group is found to be approximately 40 times more reactive towards electrophilic substitution than the second.[50] This characteristic has been exploited[58] in the regiospecific synthesis of the dibromodiiodo naphthalene **(237)** (scheme **116**).



(237)

Scheme 116 Reagents and Conditions i) Br_2, Pyridine, CCl_4, 89 %; ii) ICl, CCl_4, 88 %.

This literature precedent gave us good grounds for anticipating that we would be able to achieve regioselective functionalisation of the upper aryl ring of biaryl **(209)**. Our initial study was to attempt direct iodination of **(209)** with iodine monochloride (ICl) in carbon tetrachloride (scheme **117**).



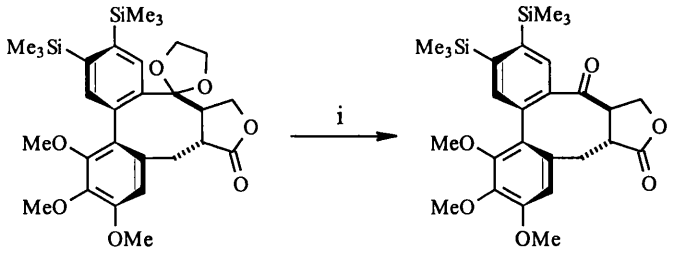
(209) **(238)**

Scheme 117 Reagents and Conditions i) ICl, CCl_4, reflux, 24 h., recover 84 % of **(209)** ii) $Ag(O_2CCF_3)$, DCM, addition of I_2 in CH_2Cl_2 over 3 h. stir 5 h., recover 71 % of **(209)**.

These conditions failed to give any yield of iodinated product **(238)**, with only starting biaryl **(209)** being recovered. A similar outcome was observed when iodination was attempted using silver(I) trifluoroacetate and iodine in DCM (conditions ii, scheme **117**).

The failure of these attempts is perhaps attributable to the deactivated nature of the upper aryl ring in which the acetal group is electron-withdrawing. Moreover, the potentially activating trimethoxyaryl substituent cannot achieve co-planarity and thus cannot exert any activating effect.

At this stage, it was decided to hydrolyse ketal **(209)** to the ketone, which is the functional group present in steganone. This was smoothly accomplished by stirring the acetal in formic acid at ambient temperature over 24 h. (scheme **118**) giving ketone **(239)**.

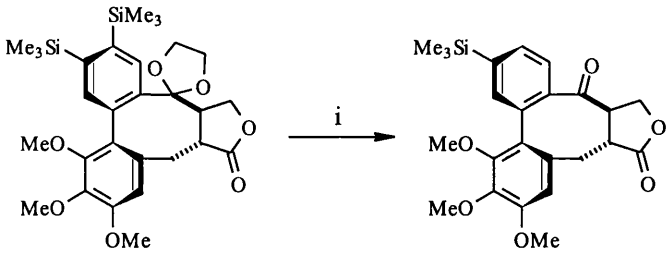


(209) **(239)**

Scheme 118 Reagents and Conditions i) HCO_2H, 20 °C, 24 h., 54 %.

Although the yield of this apparently trivial step is only moderate, it should be borne in mind that reactions on biaryl **(209)** were typically performed on 7-10 mg. of material, because of the low yield and scale-up problems in the preceding [2+2+2] cycloaddition step.

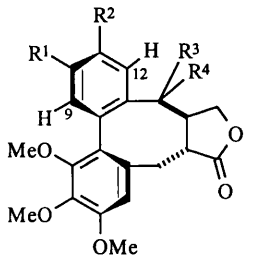
Under these mildly acidic conditions, no protodesilylation was observed. However protodesilylation has been found to be effected by trifluoroacetic acid at ambient temperature.[138] Gratifyingly, changing to this stronger acid medium induced selective protodesilylation at the -11 position, presumably after ketal hydrolysis, to give **(240)** in good yield (scheme **119**).



(209) **(240)**

Scheme 119 Reagents and Conditions i) CF_3CO_2H, 20 °C, 12 h., 73 %.

The regiospecificity of the protodesilylation step was confirmed on examination of the ^1H NMR spectrum of biaryl ketone **(240)**. The ortho- ketone moiety in **(240)** is seen to exert a deshielding effect on the H-12 proton. Indeed, this effect is re-inforced on consideration of the chemical shifts observed for aryl protons in a series of related bisbenzocyclooctadienes (table **1**).



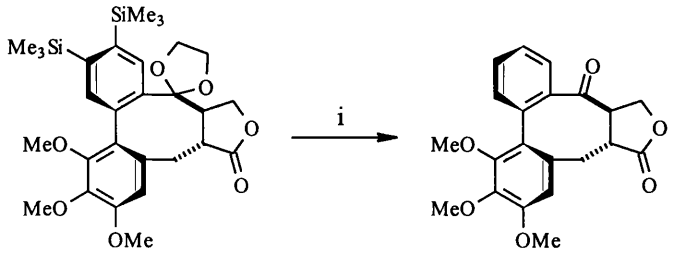
Scheme 120 Structure of Bisbenzocyclooctadienes in table **1**.

Compound	R^1	R^2	R^3	R^4	$\delta_{H\text{-}12}$ (ppm)	$\delta_{H\text{-}9}$ (ppm)
Steganone[a]	$-OCH_2O-$		=O		7.53	6.63
(209)[b]	Me_3Si	Me_3Si	$-OCH_2CH_2O-$		7.84	7.33
(239)[b]	Me_3Si	Me_3Si	=O		8.29	7.46

(240)[b]	Me_3Si	H	=O	8.31	7.57
(241)[b]	H	H	=O	8.03	7.21

Table 1 Chemical Shifts of Bisbenzocyclooctadiene Aryl Protons.
Notes: a)270 MHz[17] b)400 MHz

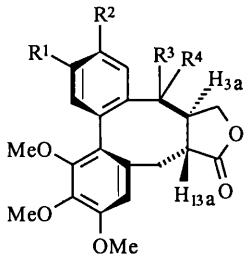
Use of harsher acidic conditions (scheme **121**) effected protodesilylation at both positions, giving the nor(methylenedioxy)steganone **(241)**.

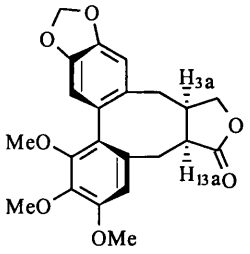


(209) **(241)**

Scheme 121 Reagents and Conditions i) CF_3CO_2H, reflux, 12 h., 51 %.

We were initially concerned that the use of such acidic conditions would result in the loss of stereochemical integrity of the γ-lactone junction *via* enolisation of the ketone. These concerns subsequently proved groundless. The coupling constants observed in the ^1H NMR spectrum between the H-3a and H-13a were all large (~13 Hz) in the case of the bisbenzocyclooactadienes prepared. This was indicative of a *trans* fused system (table **2**, scheme **122**). These values are also consistent with that observed for steganone **(1)**, upon which the original stereochemical assignment was made. The value of the same coupling constant observed for picrostegane **(242)**, a naturally-occurring lignan with a (Z)-fused γ-lactone ring, is included for comparison.[139]





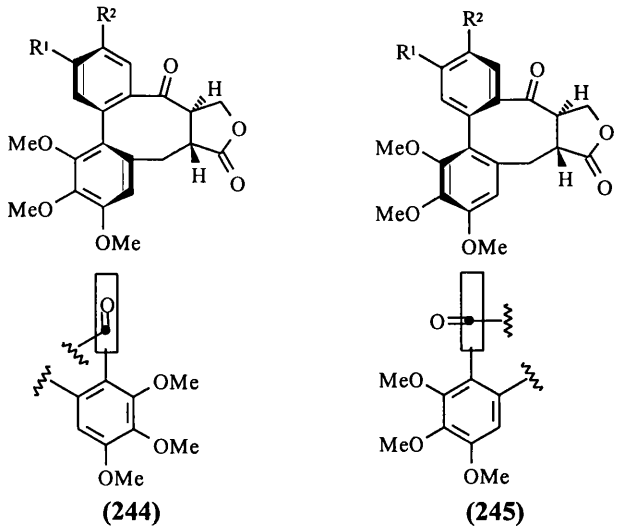
(242)

Scheme 122 General Structure of Bisbenzocyclooctadienes and picrostegane **(242)** in table **2.**

Compound	R^1	R^2	R^3, R^4	$J_{H3a-H13a}$ (Hz)
Steganone	$-OCH_2O-$		=O	13.0
(209)	$SiMe_3$	$SiMe_3$	$-OCH_2CH_2O-$	13.4
(239)	$SiMe_3$	$SiMe_3$	=O	12.6
(240)	$SiMe_3$	H	=O	13.9
(241)	H	H	=O	13.0
Picrostegane				8.0

Table 2 Coupling Constants of Bisbenzocyclooctadienes.

Ujjainwalla established that the original cycloadduct **(209)** possessed the atropisomerism relevant to natural (-)-steganone **(1)** with the aid of a carefully-designed series of nOe experiments. Further confirmation of this fact was provided by spectroscopic studies on the deprotected bisbenzocyclooctadienes. Infra-red spectroscopy was particularly useful in this regard. Kende has observed that while natural steganone exhibited a ketone C=O stretch at 1667 cm^{-1} (lowered due to conjugation with the aryl ring), isosteganone **(243)** exhibits a ketone carbonyl stretch at 1707 cm^{-1}.[140] The ketone group is perpendicular to the aryl ring in the latter compound, and cannot conjugate to it (scheme **123**). The values for (-)-steganone, isosteganone and the synthetic bisbenzocyclooctadienes are listed in table **3**. The values for the synthetic substances can be seen to correlate closely with those of steganone **(1)**.



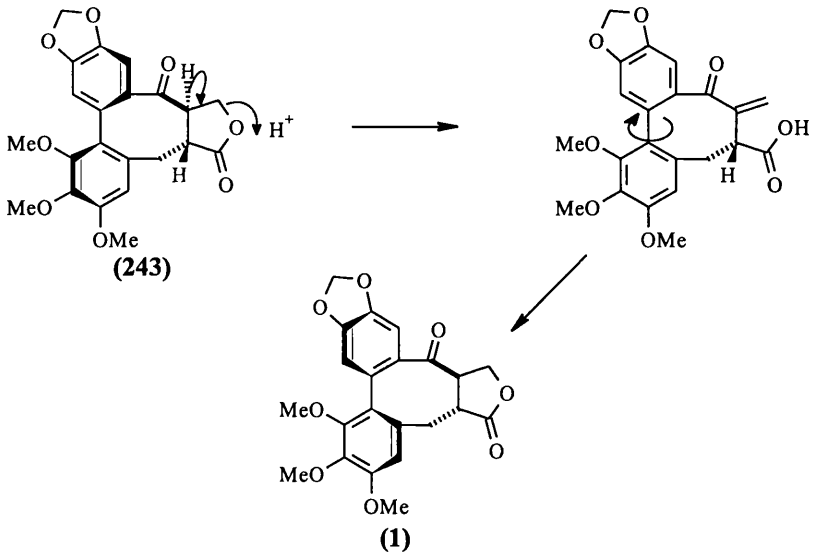
Scheme 123 Structures of Lignans **(244)** and *Iso*-lignans **(245)** in table **3**.

Compound	Structure **(Scheme 123)**	R_1	R_2	υ_{max} (cm^{-1})
Steganone	**(244)**	$-OCH_2O-$		1667
Isosteganone	**(245)**	$-OCH_2O-$		1707
(239)	**(244)**	Me_3Si	Me_3Si	1674
(240)	**(244)**	Me_3Si	H	1673
(241)	**(244)**	H	H	1674

Table 3 Ketone Carbonyl Stretching Frequencies of Lignans and Isolignans.

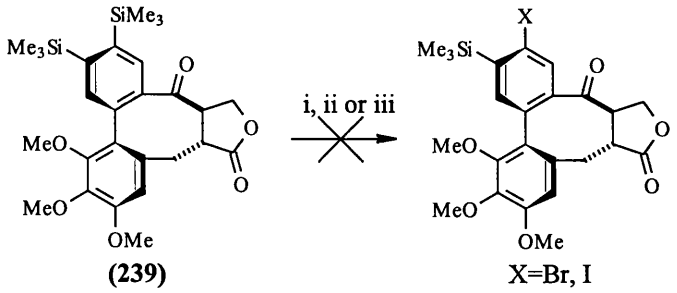
Further supporting evidence for the coplanarity of the ketone group and the upper aryl ring is provided by the downfield shift of the aryl proton *ortho-* to the carbonyl group (table **1**). Again, this is observed in steganone **(1)** but not in isosteganone **(243)**.[140] Raphael[7] has reported the facile conversion of (+)-isosteganone **(243)** to (-)-steganone **(1)** after heating at reflux for 1 h. in xylene. The isomerisation is believed to proceed via β-elimination, rotation and relactonisation (scheme **124**). Our desilylation conditions typically involved heating overnight at reflux in trifluoroacetic acid, as in the case of **(241)**. We were therefore further convinced of our isolation of the

thermodynamic product under the reaction conditions, with a stereochemistry corresponding to natural steganone **(1)**.



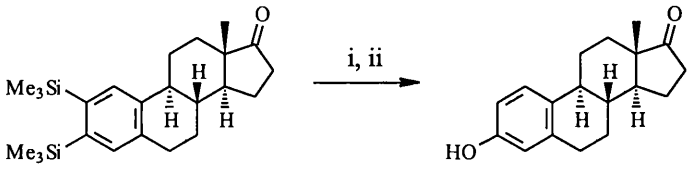
Scheme 124 Mechanism of the Acid catalysed Isomerisation of Isosteganone **(243)** to Steganone **(1)**.

Disappointingly, introduction of halide functionality into the upper ring by *ipso*-substitution remained elusive using **(239)** as a substrate. Both Vollhardt's iodine monochloride protocol,[143] and the technology of Wilbur[141] *et al* involving *in situ* generation of halogen monochlorides led either to decomposition or to recovery of starting material **(239)** (scheme **125**).



Scheme 125 Reagents and Conditions i) ICl, CCl_4, reflux, 12 h., decomposition; ii) *N*-chlorosuccinimide, NaBr, HOAc, ambient temperature, 12 h. recover 67 % **(239)**; iii) *N*-chlorosuccinimide, NaI, HOAc, 60 °C, 20 h., recover 73 % **(239)**.

Particularly appealing was the conversion of the trimethylsilyl groups present in biaryl **(209)** into oxygen functionality, as found in the naturally occurring lignans. Vollhardt[60] achieved this conversion by treatment of bis(trimethylsilyl) arene **(246)** first with trifluoroacetic acid to effect protodesilylation, and then with tetrakis lead(IV) trifluoroacetate to install the phenolic group of (±)-estrone **(104)** (scheme **126**).



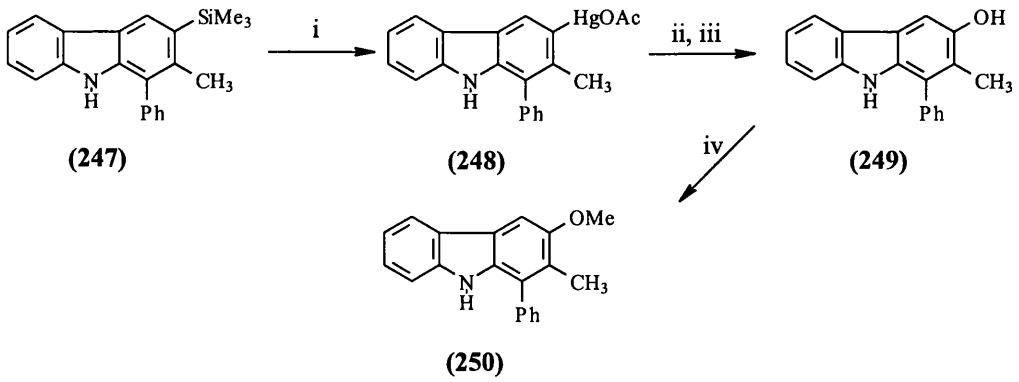
(246) **(104)**

Scheme 126 Reagents and Conditions i) CF_3CO_2H, CCl_4, 10 min., 100 %; ii) CF_3CO_2H, $Pb(OAc)_4$, -30 °C, 30 min, then aq. HCl, 97 %.

Ujjainwalla attempted to introduce hydroxyl functionality into biaryl **(209)** by this means, but unfortunately only succeeded in decomposing the starting material, and was unable to isolate any phenolic product.[142] Possibly the γ-lactone is in equilibrium with the γ-hydroxy-acid under the acidic conditions, and the free alcohol might then be vulnerable to oxidation and decarboxylation, especially since it is now clear the acetal would be cleaved under these conditions, meaning that a β-keto acid system would then exist.

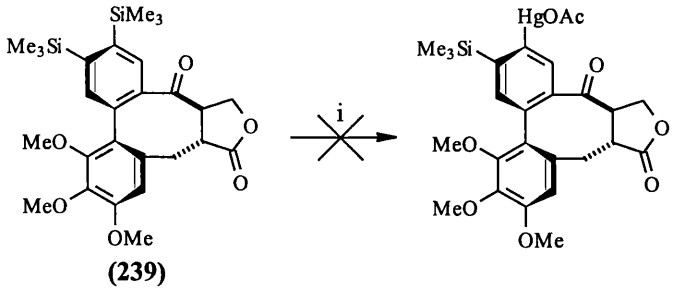
Moody[143] has also observed rapid decomposition of silyl arene **(247)** upon exposure to these conditions. This prompted him to develop alternative methodology based on a three-step mercuriodesilylation/hydroboration/oxidation procedure (scheme **127**). Employing a known[144] transmetallation of aryl silanes with mercury(II) acetate in acetic acid, crude aryl mercury **(248)** was isolated. Hydroboration and oxidation with

alkaline hydrogen peroxide[145] gave carbazole **(249)**, an important intermediate *en route* to the alkaloid hyellazole **(250)**.



Scheme 127 Reagents and Conditions i) $Hg(OAc)_2$, HOAc, 3 min.; ii) BH_3:THF, THF, 40 min.; iii) H_2O_2 (30 % aq. soln.), NaOH (2 M aq soln.), 2 min., 41 % over 3 steps; iv) MeI, K_2CO_3, acetone, reflux, 4 h., 92 %.

We attempted to apply Moody's methodology to introducing the hydroxyl functionality into the upper ring of biaryl **(239)**, knowing its greater reactivity toward electrophiles over ketal **(209)**. However, even after refluxing **(239)** in acetic acid overnight, there was no evidence of transmetallation and only **(239)** was recovered unchanged (scheme **128**).

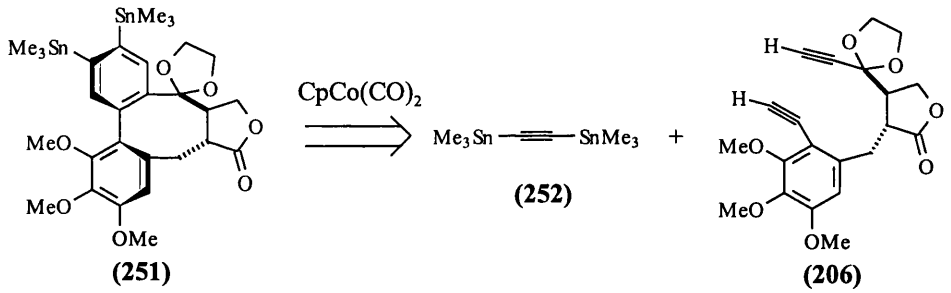


Scheme 128 Reagents and Conditions i) $Hg(OAc)_2$, AcOH, reflux, overnight, recover **(239)** 95 %.

Although a method of converting the bistrimethylsilylarene **(239)** into the natural product remains elusive, the studies thus far undertaken illustrate the potential for sequential, regiospecific electrophilic substitution of each silicon. The range of

steganone analogues accessible by this route could no doubt be considerably increased if the efficiency and scale of the cycloaddition reaction (scheme **107**) could be improved thereby giving access to larger quantities of **(209)**; and if the trimethylsilyl groups could be made more reactive toward electrophiles.

Conceivably, greater reactivity could be achieved by use of a trimethylstannyl arene such as **(251)**. These are known to be much more reactive toward electrophiles than the corresponding silyl arenes.[51] Such a stannyl arene could be formed by the cobaltcatalysed co-cyclisation of bis(trimethylstannyl)ethyne **(252)** with **(206)** (scheme **129**).



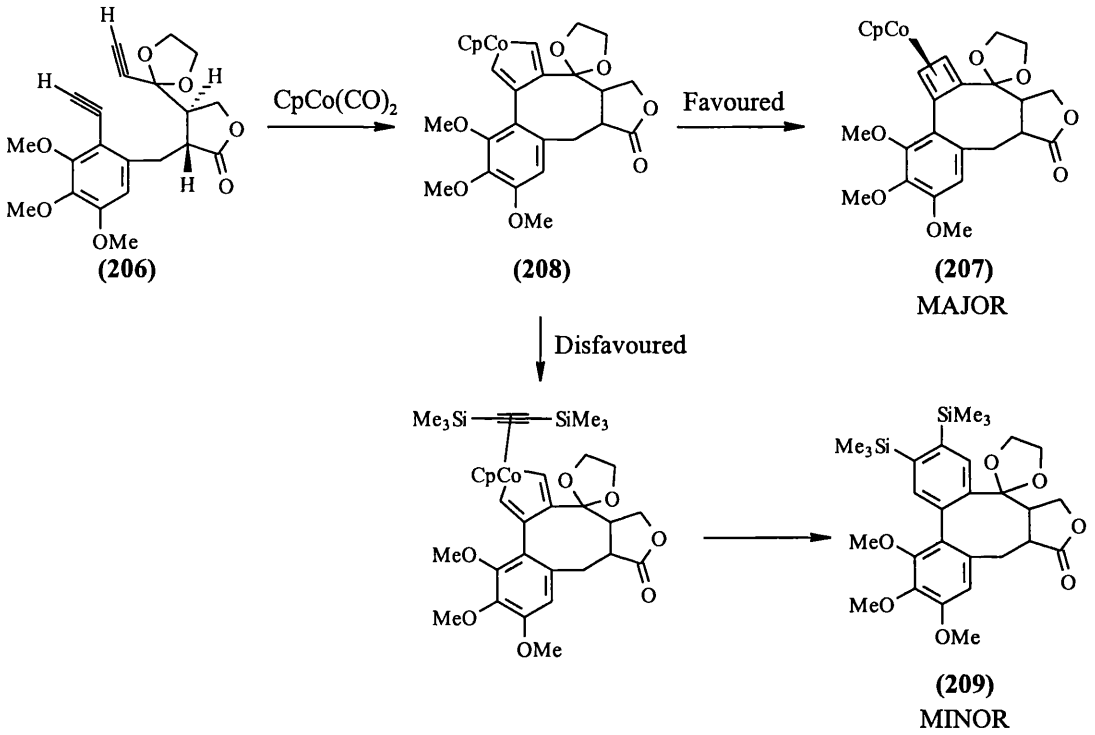
(251) **(252)** **(206)**

Scheme 129 Retrosynthesis of Bis(trimethylstannyl)arene **(251)**.

The appeal of such a synthetic scheme has, however, to be tempered by the realisation that substitution of bis(trimethylsilyl)ethyne **(87)** with the more sterically demanding tin analogue **(252)** would in all probability decrease the yield of the cycloaddition reaction still further. Moreover, in the light of Vollhardt's observation that bis(trimethylstannyl)arenes undergo instantaneous protodestannylation on neutral alumina,[146] it seems unlikely that a species such as **(251)** could be isolated from the reaction mixture.

2.3 Tethered [2+2+2] Cycloaddition Approaches to Steganone Analogues

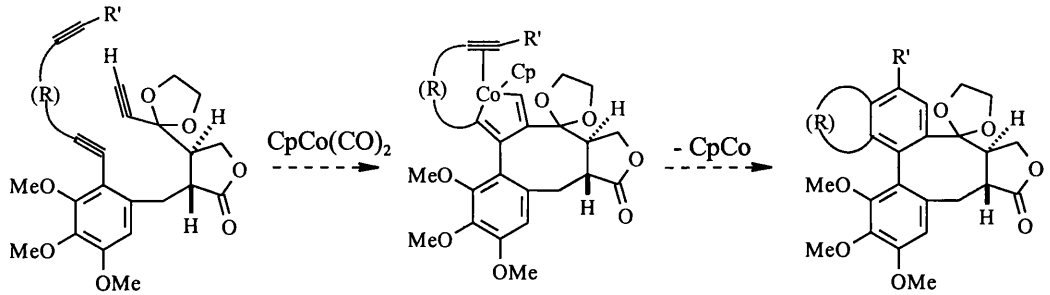
Consideration of the co-cyclisation of diyne **(206)** with bis(trimethylsilyl)ethyne **(87)** led us to postulate that, the rearrangement of the cobaltacyclopentadiene intermediate **(208)**, to the cobalt cyclobutadiene complex **(207)** was preferable to co-ordination of a molecule of bis(trimethylsilyl)ethyne **(87)** and subsequent arene formation (scheme **130**).



Scheme 130 Mechanism of the Cobaltcatalysed Co-cyclisation of **(206)** and Bis(trimethylsilyl)ethyne **(87)**.

Accordingly, we surmised that we might be able to favour the desired [2+2+2] pathway by tethering the third alkynyl component to diyne **(206)**, thus making the entire reaction intramolecular. Such a reaction would be intrinsically more favourable on entropic grounds (scheme **131**), but might also conceivably lead to the generation

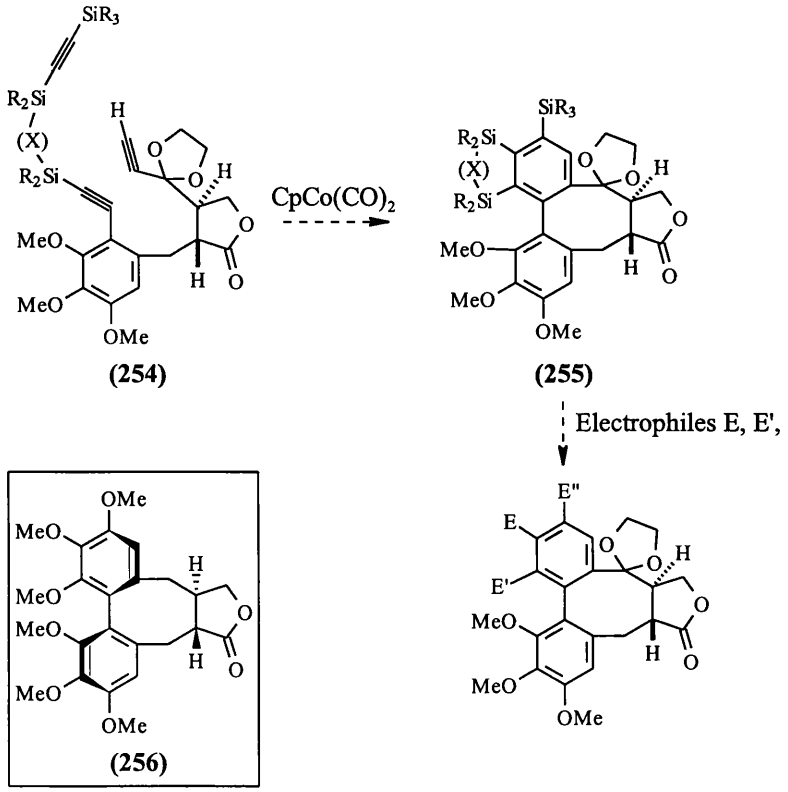
of one or more entirely different metallacyclopentadiene intermediates prior to the insertion of the third alkyne component.



(253)

Scheme 131 Cobalt catalysed Cycloaddition of Tethered Triyne **(253)**.

We were attracted to silicon-containing tethered systems such as **(254)**, because silyl alkynes are good substrates for [2+2+2] cycloadditions. Furthermore, the cyclised products **(255)** would provide a novel entry to trifunctionalised upper ring lignans (scheme **132**) of relevance to natural products such as (+)-steganolide A **(256)**.

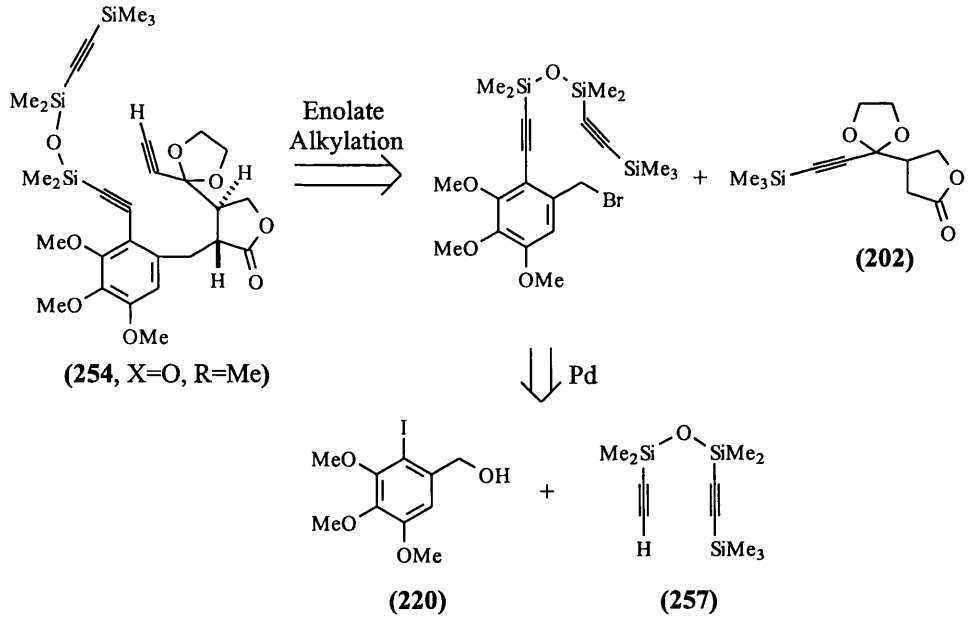


(254) **(255)** **(256)**

Scheme 132 Synthesis of Lignan Analogues *via* Cyclisation of **(254)**.

2.3.1. Tethers Incorporating a Disiloxane Moiety

The simple tethered triyne **(254**, X=O, R=Me**)**, with a three-atom tethering chain, which gives rise to a kinetically favourable fused five-membered ring system **(255**, X=O, R=Me**)** was selected for initial study. We disconnected **(254**, X=O, R=Me**)** in a logical fashion to the lactone **(202)** and a suitable bromide with the tether affixed; this in turn was to be constructed from aryl iodide **(220)** and a suitable diyne **(257)** (scheme **133**).

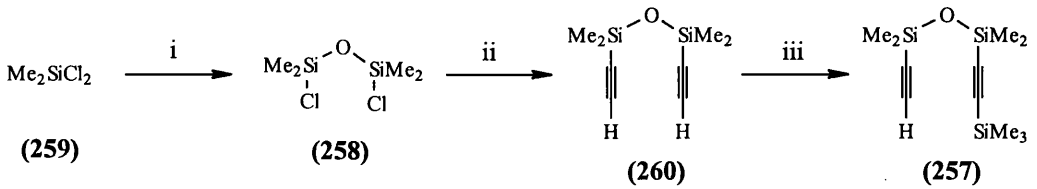


Scheme 133 Retrosynthesis of Triyne **(254**, X=O, R=Me**)**.

2.3.1.1 Synthesis of the Disiloxane Tether

A three-step synthetic route to silylated diyne **(257)** was employed (scheme **134**). 1,3-dichlorotetramethyldisiloxane **(258)** was synthesised from dichlorodimethyl silane **(259)** according to the method of Elliott and Breed.[147] Double ethynylation was then effected with ethynyl magnesium bromide in THF, giving **(260)** in good yield. **(260)**

was monosilylated by low-temperature deprotonation in THF, followed by trapping with chlorotrimethylsilane to furnish the desired compound **(257)** as a colourless oil.

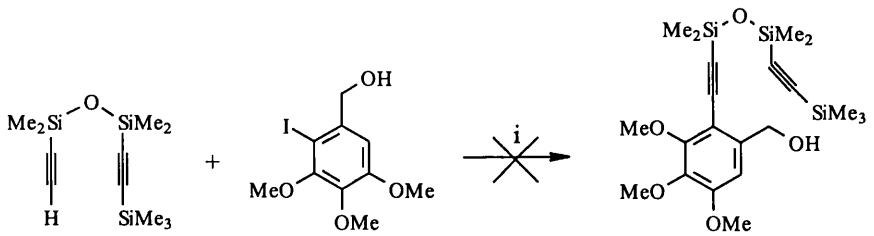


(259) (258) (260) (257)

Scheme 134 Reagents and Conditions i) Addition EtOH over 30 min., ambient temperature, 30 min., then $FeCl_3$, reflux, 4 h., 24 %; ii) Addition **(258)** to HC≡CMgBr in THF over 1 h., 0 °C; stir 1 h., then ambient temperature 5 h., 66 %; iii) *n*-BuLi, THF, -78 °C, 1 h., then Me_3SiCl, stir 1 h.; warm to ambient temperature, stir 1 h., 51 %.

2.3.1.2 Attempted Coupling of the Disiloxane Tether With Aryl Iodide (220)

Unfortunately, all attempts to effect a palladium-mediated coupling of diyne **(257)** with 2-iodo-3,4,5-trimethoxy benzyl alcohol **(220)** resulted in complex mixtures of products, none of which could be isolated in a pure form (scheme **135**).



(257) (220)

Scheme 135 Reagents and Conditions i) Ambient temperature, CuI, 12 h., refer to table 4.

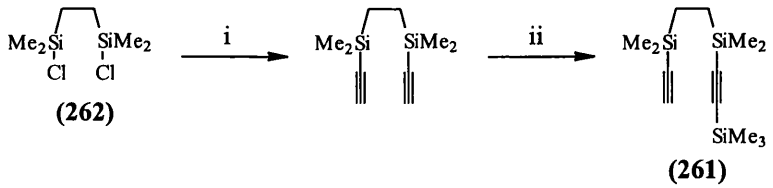
Solvent	Catalyst	Result
Et_2NH	$PdCl_2(PPh_3)_2$	Complex Mixture
Et_3N	$PdCl_2(PPh_3)_2$	Recover 32 % **(220)**
Et_2NH	$Pd(PPh_3)_4$	Complex Mixture
Benzene/ *n*-$BuNH_2$	$Pd(PPh_3)_4$	Complex Mixture

Table 4 Conditions and Results Corresponding to Scheme **135**.

The reasons for this failure are not clearly understood. One possible reason is the differing electronic character of trimethylsilyl ethyne **(217)** which undergoes coupling in good yield, and diyne **(257)** which does not. The presence of the additional alkyne moiety could also conceivably led to side-reactions, accounting for the observed plurality of products.

2.3.2 Tethers Featuring a 1,2-Disilylethyl Moiety

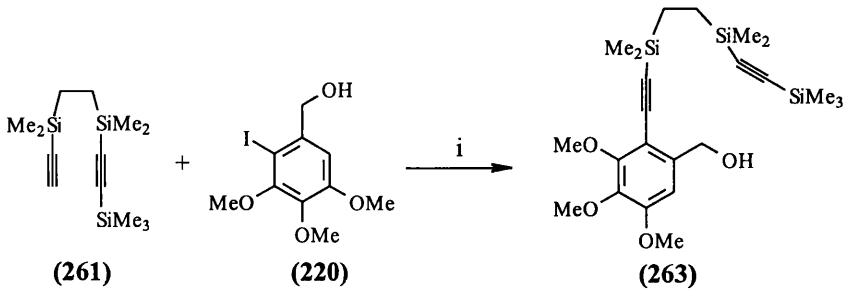
The second tether to be investigated was one in which the linking group was an alkyl chain. The appropriate diyne **(261)** was synthesised in two steps from commercially available 1,2-bis(dimethylchlorosilyl)ethane **(262)**. Ethynylation was again effected with ethynyl magnesium bromide in THF, and one alkyne terminus was selectively silylated by low-temperature deprotonation and quenching with chlorotrimethylsilane to give **(261)** (scheme **136**).



Scheme 136 Reagents and Conditions i) Addition of **(262)** to HC≡CMgBr in THF over 30 min., 0 °C, stirred 30 min., then ambient temperature, overnight, 42 %; ii) *n*-BuLi, THF, -78 °C, 30 min., addition of Me_3SiCl, 10 min., 50 %.

2.3.2.1 Coupling of Tether (261) with Aryl Iodide (220)

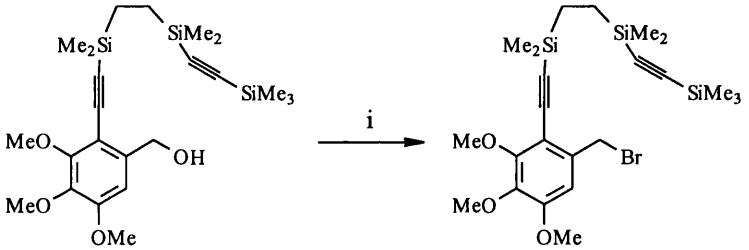
In contrast with diyne **(257)**, **(261)** did undergo coupling with aryl iodide **(220)** although in rather poor yield (scheme **137**).



(261) (220) (263)

Scheme 137 Reagents and Conditions i) $PdCl_2(PPh_3)_2$, CuI, Et_2NH, 50 °C, 2 h., 18 %.

The alcohol **(263)** was then smoothly converted to the corresponding bromide **(264)** by treatment with carbon tetrabromide and triphenylphosphine in ether (scheme **138**).

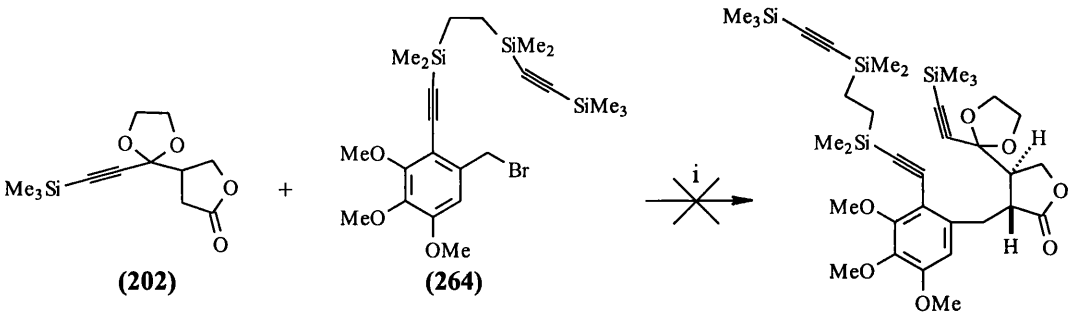


(263) (264)

Scheme 138 Reagents and Conditions i) CBr_4, PPh_3, Et_2O, 24 h., 64 %.

2.3.2.2 Attempted Coupling of Diyne (264) With Lactone (202)

Initial studies aimed at coupling bromide **(264)** with the lactone **(202)** were unsuccessful under the previously employed conditions (scheme **139**). Unfortunately, sufficient quantities of **(264)** were not available for an extended study, mainly due to the poor yield of the palladium catalysed coupling reaction. It remains a target for future work within the group to optimise the coupling of **(261)** and **(220)**, and hence obtain sufficient bromide **(264)** for alkylation with the lactone enolate **(202)**.

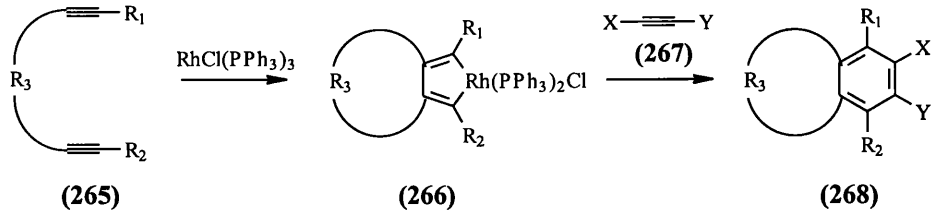


Scheme 139 Reagents and Conditions i) **(202)**, *i*-Pr_2NLi, THF, -78 °C, 1 h., then **(264)**, -78 °C, 1 h., ambient temperature, 12 h., recover 35 % **(264)**.

2.4 Rhodium-Based Approaches to Steganone

As we have seen, cobalt is not the only transition metal capable of mediating [2+2+2] cycloaddition reactions (p. 29). Ujjainwalla,[128] aware of this possibility, investigated the use of nickel- and niobium-based catalysts in an attempt to effect the cyclisation of **(206)**. These attempts, however, did not meet with success.

One approach did still seem worthy of investigation. Müller[30] developed a stepwise reaction in which diynes **(265)** are reacted with rhodium compounds (typically Wilkinson's catalyst) to form rhodacycles **(266)**. These were further reacted with a variety of alkynes **(267)** to generate arenes **(268)** (scheme **140**).



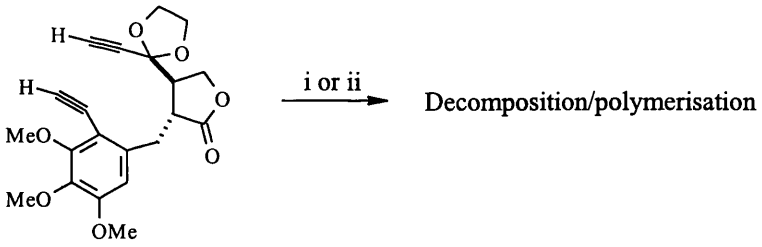
Scheme 140 Rhodium-Mediated [2+2+2] Co-cyclisation of Diyne **(265)** with Alkyne **(267)**.

Although Vollhardt[46] has highlighted the drawbacks of this technology in terms of the stoichiometric catalyst required and the limited substrate applicability, it was felt that

a rhodium-based approach had a good chance of success in the case of **(206)** since benzo-fused medium-sized carbocyclic rings have previously been synthesised[31] by this method.

2.4.1 Rhodium-Mediated Cyclisation Studies on Diyne (206)

Our initial studies followed the protocol of Müller. Stirring diyne **(206)** with Wilkinson's catalyst in xylene encouragingly gave an orange/red precipitate, and this solution was heated to reflux, upon which a clear brown solution formed. Analytical tlc at this stage indicated that no free diyne **(206)** remained in solution. After a further hour, butyne-1,4-diol which was known to be effective in this type of cyclisation was added. Upon warming to reflux, a black precipitate was formed, and no evidence of biaryl could be found by tlc or ^{1}H NMR (scheme **141**, conditions i).

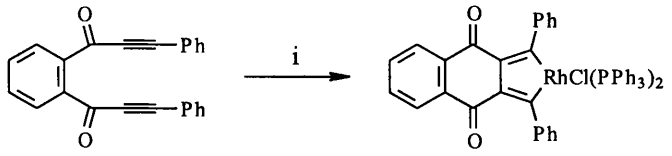


(206)

Scheme 141 Reagents and Conditions i) $RhCl(PPh_3)_3$, xylene, 1 h., then add $HOCH_2C{\equiv}CCH_2OH$, heat to reflux; ii) Addition of **(206)** in xylene to $RhCl(PPh_3)_3$ in xylene over 12 h., then add $HOCH_2CCCH_2OH$, heat to reflux.

This failure was put down to formation of a polymeric metallacycle. Repetition of the reaction under high dilution conditions only resulted in formation of the same black precipitate (scheme **141**, conditions ii). No trace of the desired biaryl could be isolated from the reaction mixture.

We noted however that Müller had discovered alkynones to be particularly suitable substrates for the rhodacyclopentadiene formation reaction, although it is not stated whether electronic or steric factors are responsible.[30] For instance, rhodacycle **(63)** is formed in 98 % yield from diketone diyne **(269)** (scheme **142**).



(269) **(63)**

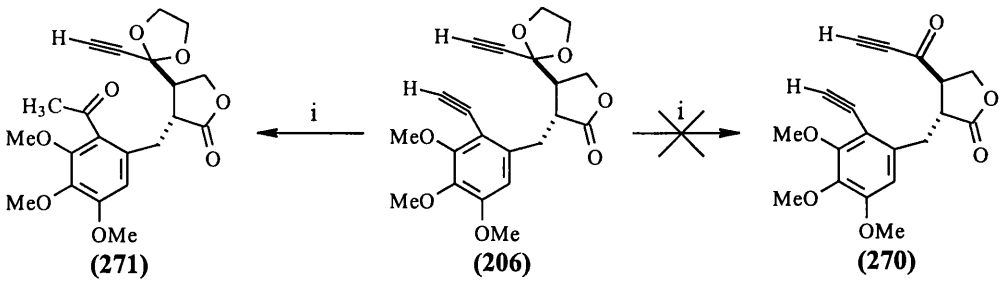
Scheme 142 Reagents and Conditions i)$RhCl(PPh_3)_3$, xylene, reflux, 30 min., 98 %.

With this in mind, we decided to attempt to conduct rhodacycle formation upon the free ketone **(199)**. This was thought to be accessible from **(206)** *via* the same formic acid deketalisation protocol that was used to convert **(209)** to **(239)** (scheme **118**).

2.4.2 Deprotection Studies on Diynes (206) and (201)

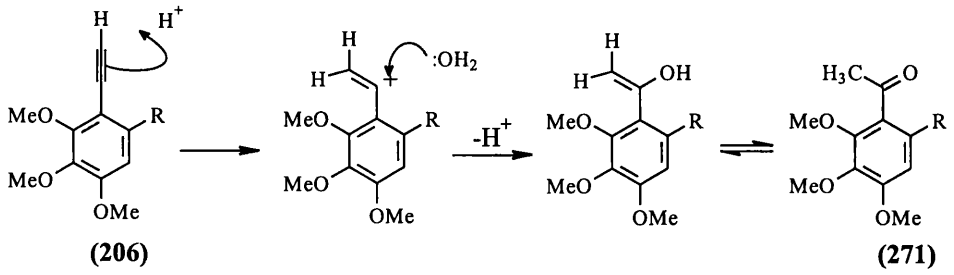
When **(206)** was stirred in formic acid at ambient temperature, it was smoothly converted into a new product, which promisingly showed two carbonyl absorbtions in the infra red spectrum. However, when the ^1H NMR spectrum was recorded, the characteristic ketal multiplet was still present! Moreover, a new singlet corresponding to three protons had appeared at δ_H 2.50, and the alkyne singlet corresponding to the phenyl ethynyl proton had disappeared, indicating that the desired product **(270)** had not been formed.

This evidence corresponded to a structure of type **(271)** (scheme **143**). This was supported by mass spectrometric evidence, showing a strong peak at m/z 404, in accordance with the proposed structure.



Scheme 143 Reagents and Conditions i) HCO_2H, 20 °C, 1 h., 72 % of **(271)**.

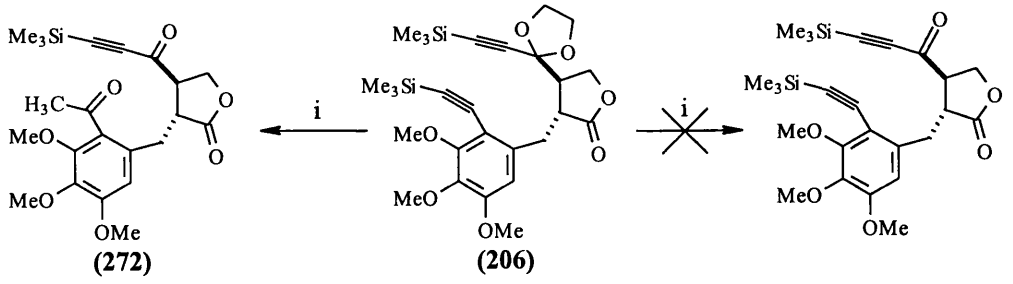
This facile, selective hydrolysis of the trimethoxyphenylethynyl group was presumed to be due to the ready electrophilic addition undergone by compounds of this class. In fact, reactions of this type are common to this functional group (p. 162). The mechanism of this reaction presumably proceeds *via* protonation, subsequent addition of water and enolisation (scheme **144**).



Scheme 144 Mechanism of Aryl Ketone **(271)** Formation.

Attempted hydrolysis of the ketal group in the bis(trimethylsilyl)alkyne **(201)**, led to isolation of a single product, whose ^1H NMR spectrum indicated that, on this occasion, the ketal had disappeared. Disappointingly, however, it also revealed that protodesilylation of the trimethoxyphenyl(trimethylsilyl)ethyne group had occurred,

and the free alkyne had once again undergone hydration to give methyl ketone **(272)** (scheme **145**).



(272) **(206)**

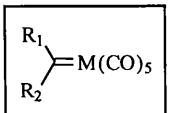
Scheme 145 Reagents and Conditions i) HCO_2H, 20 °C, 18 h. 58 % of **(272)**.

Several other methods of deketalisation were investigated, but in every case facile protodesilylation followed by alkyne hydration was observed. As we were reluctant to devise an entirely new synthetic route specifically directed towards **(270)**, we turned our attention instead towards alternative cyclisation strategies.

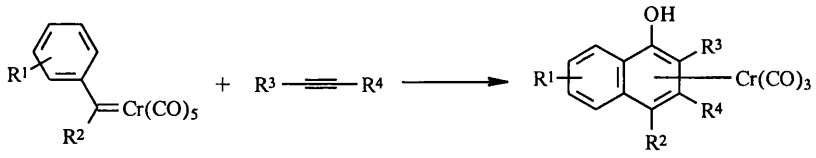
2.5 Strategies Based Upon the Dötz-Type Benzannulation

2.5.1 Background of the Dötz Benzannulation of Metal Carbenoids With α,ω-Diynes

Fischer carbenoid complexes of the type **(273**, M=Cr, W) undergo a variety of synthetically useful reactions. One of the most widely-investigated and best understood is that developed by Karl Heinz Dötz,[148] in which an aryl carbenoid complex **(274)** reacts with an alkyne **(275)** to give substituted naphthols as their chromium tricarbonyl complexes **(276)** (scheme **146**).



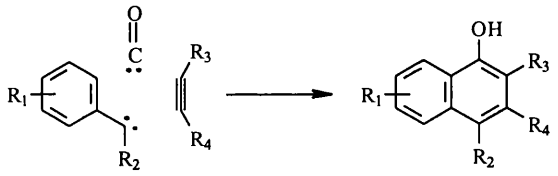
(273)



(274) (275) (276)

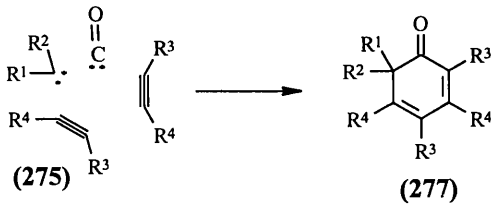
Scheme 146 Reaction of Chromium Carbenoid **(274)** With Alkyne **(275).**

The reaction can be formally visualised as a cycloaddition of the carbenoid carbon and its attached aromatic moiety with the alkyne and one of the carbon monoxide ligands from the metal (scheme **147**). The reaction can also be conducted with vinylic carbenoids to give phenols.



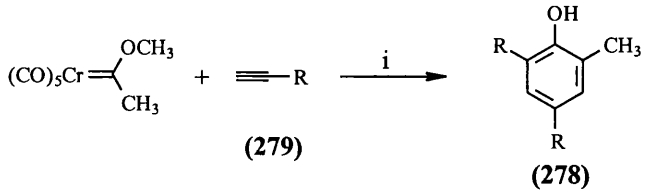
Scheme 147 Schematic Representation of the Dötz Benzannulation.

A related cyclisation which has so far received less synthetic interest is the co-cyclisation of two alkynyl units with a Fischer carbenoid complex. This represents a [2+2+2+2] cycloaddition (electron designation) and a (2+2+1+1) cycloaddition (atom designation) (scheme **148**).



Scheme 148 Schematic Representation of the Reaction of Carbene **(273)** with Alkyne **(275).**

In cases where R^1 or R^2 is a potential leaving group, the product cyclohexadienone **(277)** usually aromatises under the reaction conditions to give a substituted phenol. Completely intermolecular versions give only modest yields of phenols **(278)** (scheme **149**), although the regioselectivity is very good, with the larger alkyne **(279)** substituents being oriented 1,3 to one another in the final product **(278)**.

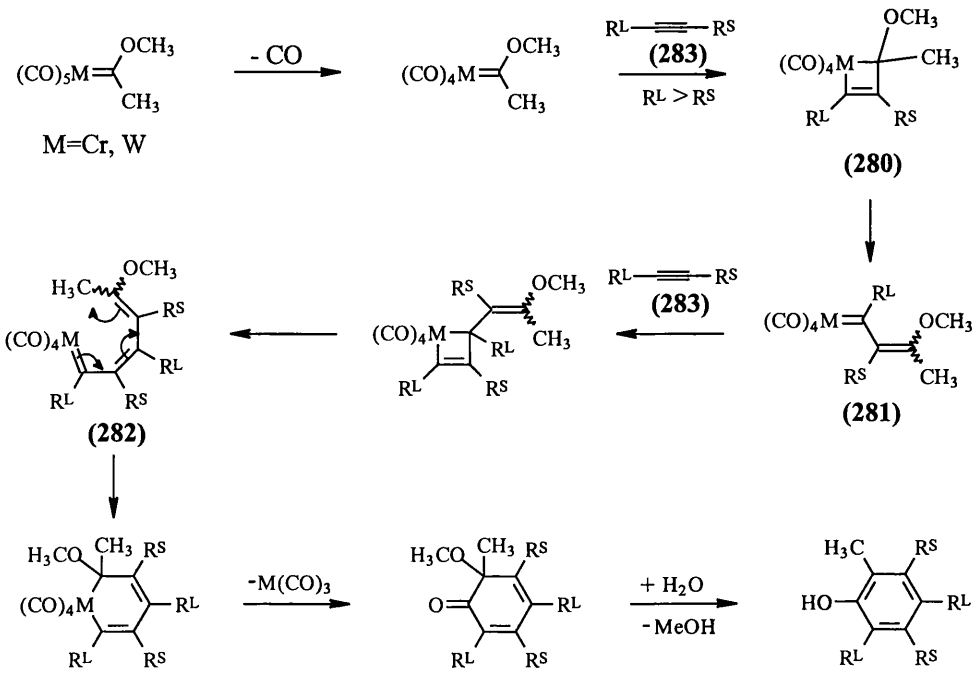


(279) (278)

R	Yield
Me	23 %
nPr	11 %
Ph	29 %

Scheme 149 Reagents and Conditions i) THF, 48 °C, 24 h., yield as shown.

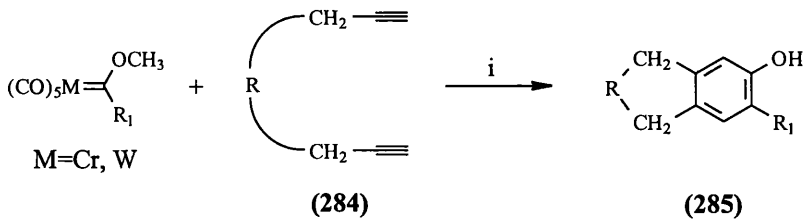
The mechanism is believed[149] to proceed *via* loss of carbon monoxide ligand, formation of metallacyclobutene **(280)** and electrocyclic ring opening to give a vinylic carbenoid complex **(281)**. A second molecule of alkyne then reacts in a similar way, and the intermediate thus formed **(282)** undergoes electrocyclisation, transfer of carbon monoxide and metal elimination (scheme **150**).



Scheme 150 Mechanism of Coupling of Metal Carbenoid **(273)** With Alkyne **(283)**.

Evidence for the proposed mechanism comes from the isolation of side-products such as cyclobutenenones, 1,3-dienes and polyalkenes, and it is the formation of these which results in the poor yields of phenols **(278)**.

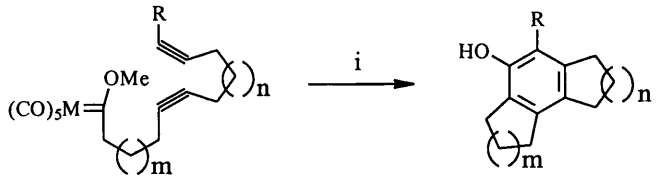
Wulff sought to circumvent these problems by the use of an α,ω-diyne **(284)** to effect intramolecular delivery of the second alkyne component. He was thus able to synthesise a variety of bicyclic products **(285)** in modest to good yield (scheme **151**).



Scheme 151 Reagents and Conditions i) Addition of **(284)** over 48 h., THF, 70 °C, 31-72 %.

A variety of functional groups were tolerated (R=O, $C(CO_2Et)_2$, CH_2), although yields were significantly lower in the case of tetralin formation ($R=CH_2CH_2$) than for the cases of five-membered rings.

Completely intramolecular variants[150] in which the carbenoid complex is incorporated into the same molecule as the diyne **(286)** have allowed formation of polycycles **(287)** (scheme **151**). This methodology has been employed in the synthesis of steroid ring systems.[150]



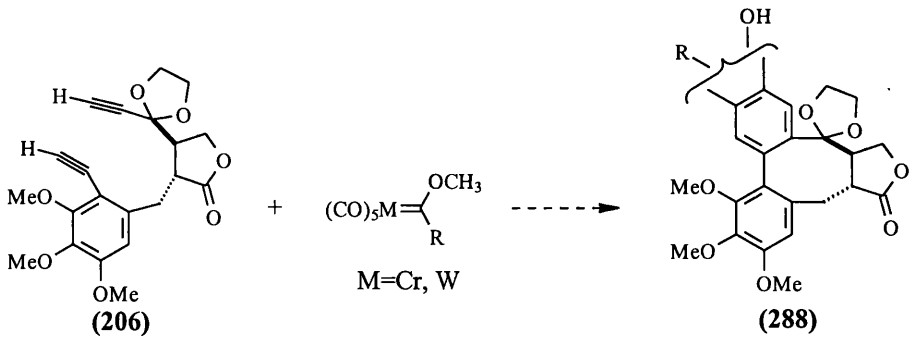
M=Cr, W
(286)

(287)

Scheme 151 Reagents and Conditions i) Addition of **(286)** over 16-24 h., 70 °C (M=Cr), 120 °C, (M=W), solvent, 10-61 %.

2.5.2 The Potential for a Route to Steganone Analogues Employing the Dötz Benzannulation

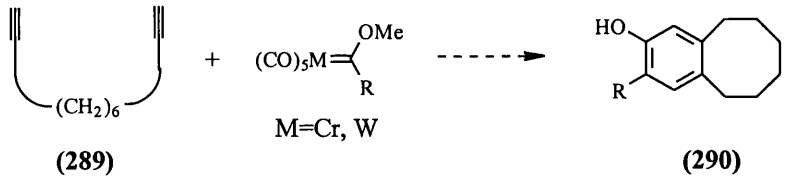
We therefore addressed ourselves to the question of whether it would prove possible to form the biaryl system present in steganone **(1)** by co-cyclisation of diyne **(206)** with a metal carbenoid **(273)** (scheme **152**).



Scheme 152 The Potential for a Route to Steganone Analogues **(288)** *Via* Co-cyclisation of Metal Carbenoids **(273)** with Diyne **(206)**.

2.5.2.1 Dötz Benzannulation Studies on Model Systems

The lack of precedent for the formation of medium-sized benzo-fused rings prompted us to undertake a very simple model study. We decided to attempt the benzannulation of deca-1,9-diyne **(289)** with a metal carbenoid to give a fused benzocyclooctene **(290)** (scheme **153**).

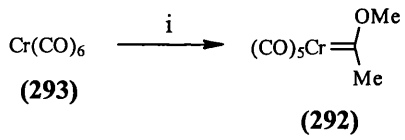


Scheme 153 Envisaged Dötz Benzannulation of Deca-1,9-diyne **(289)**.

It was felt that the cyclisation of this simple diyne would be considerably more challenging than that of diyne **(206)**, as it cannot benefit from any "rigid unit" effects which have been shown[151] to be of considerable importance in the synthesis of medium and large rings. If **(289)** could be made to undergo any degree of cyclisation, optimisation studies could be performed on this readily available material in preference to the rather precious **(206)**.

Fortunately, deca-1,9-diyne **(289)** was available through a reliable literature route. Formation of sodium acetylide in liquid ammonia followed by quenching with 1,6-dibromohexane **(291)** furnished the desired product in 53 % yield after work-up and distillation. With the model diyne **(289)** in hand, we turned our attention to the synthesis of the Fischer carbenoid component.

We elected to employ, in our initial studies, the chromium carbenoid complex **(292)**, which has also been used by Wulff.[149] Wulff describes the preparation of this complex in 60-70 % yield using an unspecified "modification" of the original method of Senoff *et al.*[152] We found that the same compound could be isolated in a virtually pure form by slow addition of methyllithium in hexanes to a stirred solution of chromium hexacarbonyl **(293)** in ether at room temperature. After five minutes the solution was cooled to -10 °C, and the anion formed was quenched with methyl triflate (scheme **154**). After a rapid aqueous wash, complex **(292)** could be isolated in 82 % yield.

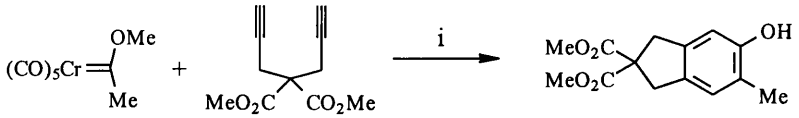


(293) **(292)**

Scheme 154 Reagents and Conditions i) Ether, CH_3Li, 10 min, then -10 °C, $CF_3SO_2CH_3$, 10 min., 82 %.

With carbenoid **(292)** in hand, we decided to repeat a literature co-cyclisation of an α,ω-diyne to ascertain if our **(292)** was suitably active for further studies. We chose 1,4-diyne **(294)** as being a suitable substrate for this purpose, as it possesses ester functionality similar to the lactone group found in diyne **(206)**. The cyclisation of this compound has been reported by Wulff,[149] and indeed in our hands a 48 % yield of

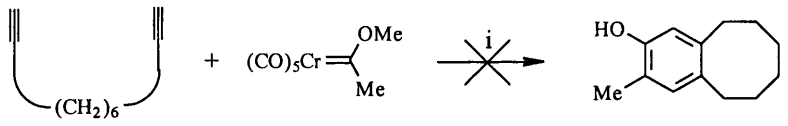
phenol **(295)** was obtained. Slow addition of diyne **(294)**, as in the original report, was found to be unnecessary.



(292) **(294)** **(295)**

Scheme 155 Reagents and Conditions i) THF, 70 °C, 2 h., 48 %.

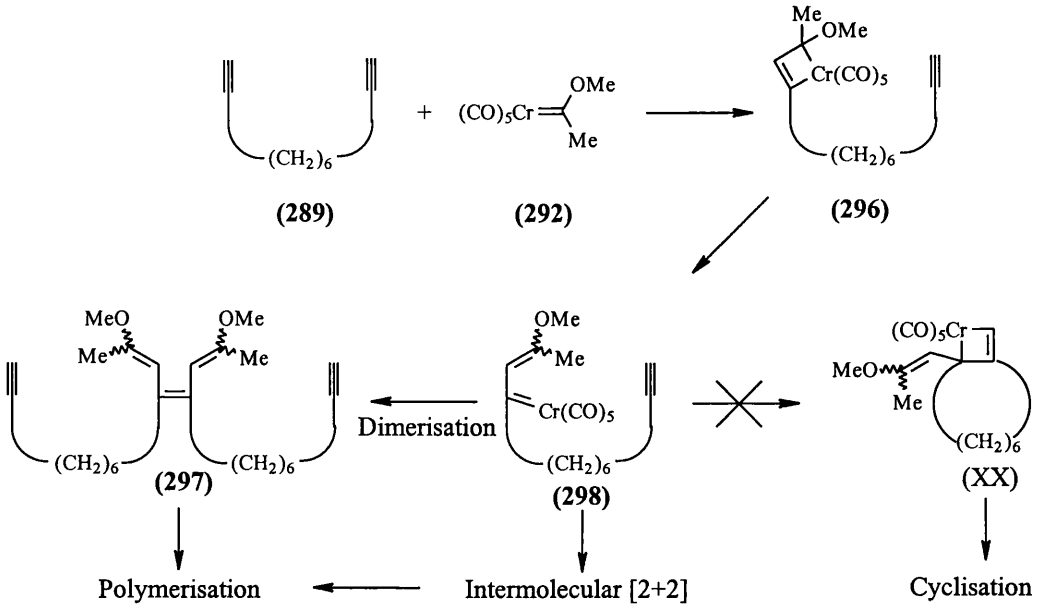
We then turned our attention to the cyclisation of model 1,9-diyne **(289)**. The normal dilution conditions which had proved successful in the case of **(294)** failed in the case of **(289)**. Further experiments, introducing progressively higher dilution regimes, again led only to decomposition/polymerisation of starting material, and in no case was any cyclised product isolated (scheme **156**).



(289) **(292)**

Scheme 156 Reagents and Conditions i) **(292)** in THF, 70 °C, addition of diyne **(289)** in THF over a) 24 h.; b) 48 h.; c) 84 h., decomposition/polymerisation.

These results, although disappointing, are perhaps not too surprising in the light of the complete freedom of rotation of the alkyl chain of deca-1,9-diyne **(289)**. Presumably, initial metallacyclobutene **(296)** formation occurs readily, but other mechanistic pathways can take place in preference to cyclisation. Dimerisation to give **(297)** or intermolecular [2+2] cycloaddition of vinyl carbene **(298)** are both plausible competing pathways eventually leading to polymerisation, for which there is some precedent (scheme **157**).[148]

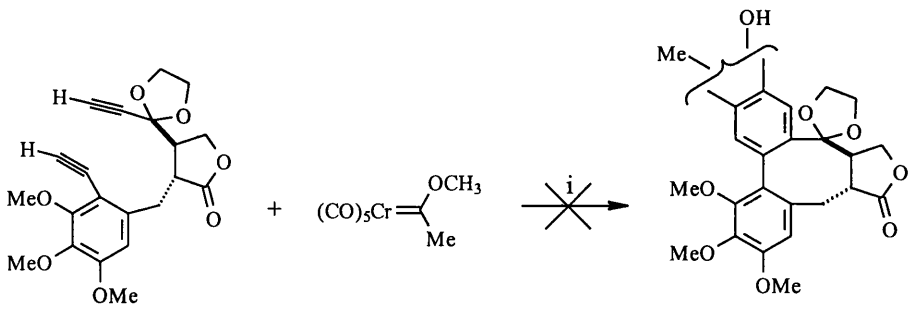


Scheme 157 Proposed Mechanism of Polymerisation of Deca-1,9-diyne **(289)** in the Presence of Chromium Carbenoid **(292)**.

2.5.2.1 Dötz Benzannulation Studies on Diyne (206)

We had greater hopes for the cyclisation of diyne **(206)**, as it was felt the greater number of sp^2 centres and the considerably restricted rotation possible in this system would favour intramolecular reaction of both alkyne moieties, particularly since this effect had already been demonstrated in our cobalt-based cyclisations of **(206)**.

These hopes were not, however, to be realised in practice; under a variety of slow addition regimes, no biaryl product was ever isolated (scheme **158**). Evidently, even in the more favourable case of **(206)**, inter- rather than intra-molecular processes are strongly favoured; the very range of reactions undergone by Fischer carbenoids must also contribute to the lack of success of this approach to the lignan cyclooctadiene biaryl system.

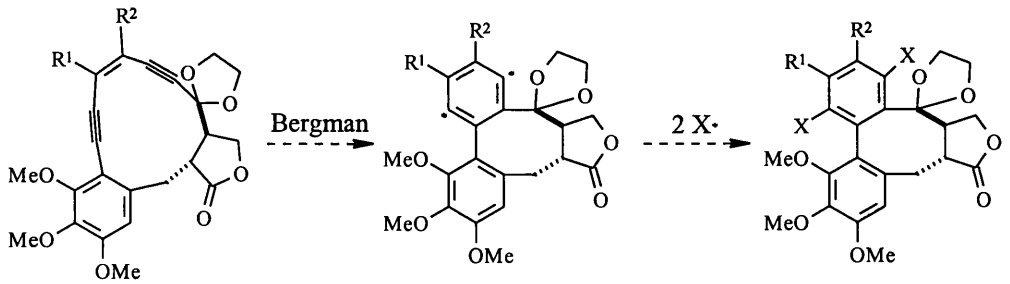


(206) (292)

Scheme 158 Reagents and Conditions i) **(292)** in THF, 70 °C, addition of diyne **(206)** in THF over a) 8 h.; b) 84 h., decomposition/polymerisation.

2.6 Approaches to Steganone Analogues Based on the Bergman Cyclisation

The Bergman cyclisation of molecules containing a contiguous yne-ene-yne system (or "enediynes") to give aromatic 1,4 diradicals has been extensively discussed in the introduction. We contemplated the possibility that a suitably designed enediyne system **(299)** could be induced to undergo Bergman cycloaromatisation to give a diradical **(300)** which, after reaction with a suitable radical trap, would regiospecifically give steganone analogues **(301)** with a variety of interesting functionalities (scheme **159**).



(299) (300) (301)

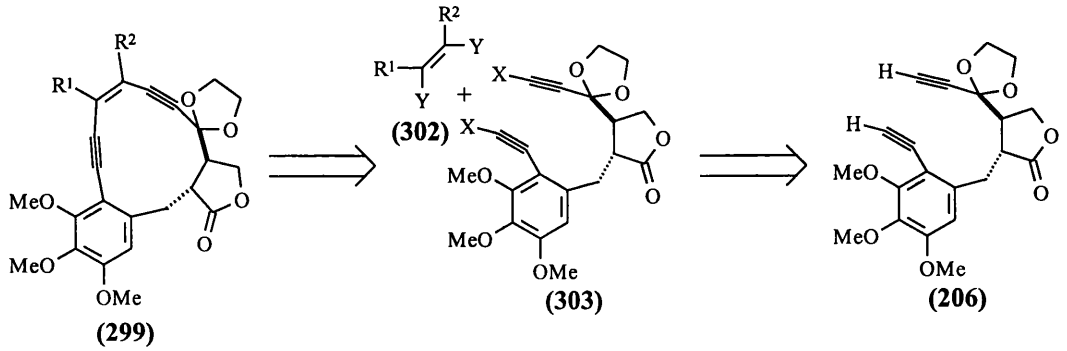
Scheme 159 The Potential for the Synthesis of Steganone Analogues **(301)** Utilising Enediyne Precursor **(299)**.

We were also aware of the pharmacological potential of compounds such as **(299)**, which we have nominated the "stegamicins" (based on analogy with the naturally

occurring calicheamicins, dynemicins and esperamicins). Within the last three years, other groups[117,118] have also sought to replace the aromatic groups present in other classes of natural products (e.g. Taxol, estrogen) with enediyne units in the hope of combining the enediyne's ability to cause DNA damage with the substrate specificity found in the basis natural product.

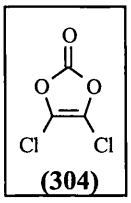
2.6.1 Studies Towards Stegamicins Involving "Capping" Strategies

One can envisage a number of potential disconnections of the prototype stegamicin **(299)**, and we investigated a number of these in the course of our study. Initially, we saw a "capping" strategy (scheme **160**) as being extremely appealing; two bonds are formed in a single step, completing the enediyne element and effecting the macrocyclisation. This could be accomplished by coupling of a suitable alkene unit **(302)** with a diyne **(303)**, which, in turn, could be derived from our readily accessible diyne **(206)**.

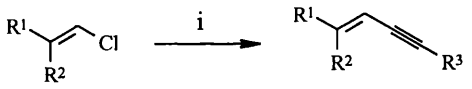


Scheme 160 Retrosynthesis of Stegamycin **(299)** from Diyne **(303)**.

2.6.1.1 Palladium-Mediated Coupling Studies on 4,5-dichloro-1,3-dioxol-2-one (304)


(304)

4,5-dichloro-1,3-dioxol-2-one **(304)** was of immediate appeal as an alkene component. This could potentially react with diyne **(206)** using a palladium catalysed coupling reaction, thereby introducing appropriate oxygen functionality at R^1 and R^2 (scheme **160**). This approach was further reinforced by the fact that Linstrumelle[153] had developed an efficient procedure for the coupling of terminal alkynes with vinyl chlorides **(305)** to form enynes **(306)** (scheme **161**). Furthermore, the methodology had been employed[154] to synthesise (*E*)-enediynes from (*E*)-chloroenynes.



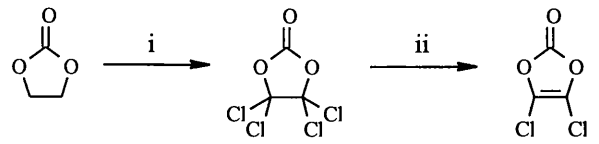
(305) **(306)**

Scheme 161 Reagents and Conditions i) $R^3C{\equiv}CH$, $PdCl_2(PhCN)_2$, piperidine.

Two questions needed to be addressed before such a coupling strategy could be employed in the synthesis of stegamicins, namely; could 4,5-Dichloro-1,3-dioxol-2-one **(304)** be coupled successfully with terminal alkynes by means of a palladium catalysed reaction, and secondly, could such a reaction be used to form an enediyne macrocycle?

4,5-Dichloro-1,3-dioxol-2-one **(304)** was prepared according to the method of Liebig.[155] 1,3-Dioxolan-2-one **(307)** was subjected to exhaustive photochemical chlorination, and yielded 58 % of tetrachloro-1,3-dioxolan-2-one **(308)**. This was treated with a zinc/copper couple prepared by the Le Goff method[156] in diethyl ether

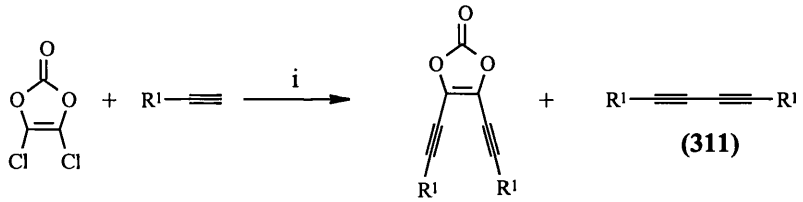
containing a catalytic amount of DMF to give the desired product **(304)** as a colourless, unstable, evil-smelling oil (scheme **162**).



(307) **(308)** **(304)**

Scheme 162 Reagents and Conditions i) Cl_2, hν, CCl_4, reflux, 24 h., 58 %; ii) Zn/Cu, Et_2O, DMF, reflux, 10 h., 76 %.

Initial attempts aimed at assessing the ability of **(304)** to undergo coupling with terminal alkynes closely mirrored the conditions of Linstrumelle.[157] A variety of catalysts (incorporating a copper(I) co-catalyst), solvents and bases were investigated. Either trimethylsilylethyne **(217)** or phenylethyne **(309)** was employed as the alkyne partner. The results are summarised below (scheme **163**, table **5**).



(304) **(310)** **(311)**

Scheme 163 Reagents and Conditions i) Conditions as in table **5**, 24 h, yields as shown in table **5**.

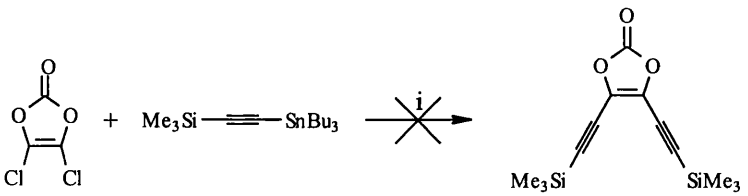
Alkyne (R^1)	Temperature	Base	Catalyst	Solvent	Yield of **(310)**	Yield of **(311)**
Me_3Si	0 °C	*i*-Pr_2EtN	$Pd(PPh_3)_4$, CuI	DMF	0 %	0 %
Me_3Si	0 °C	*i*-Pr_2EtN	$Pd(PPh_3)_4$, CuI	Benzene	0 %	0 %
Ph	20 °C	*i*-Pr_2EtN	$Pd(PPh_3)_4$, CuI	Benzene	12 %	64 %
Ph	0 °C	*i*-Pr_2EtN	$Pd(PPh_3)_4$, CuI	Benzene	0 %	75 %
Ph	20 °C	*i*-Pr_2EtN	$Pd(PPh_3)_4$, CuI	Toluene	0 %	22 %
Ph[a]	20 °C	*i*-Pr_2EtN	$Pd(PPh_3)_4$, CuI	Benzene	0 %	30 %
Ph	20 °C	*i*-Pr_2EtN	$Pd(PPh_3)_2Cl_2$, CuI	Benzene	0 %	0 %
Ph	20 °C	*i*-Pr_2EtN	$Pd(PPh_3)_4$	Benzene	0 %	18 %
Ph	20 °C	Piperidine	$Pd(PPh_3)_4$, CuI	Benzene	0 %	27 %
Ph	20 °C	*n*-butylamine	$Pd(PPh_3)_4$, CuI	Benzene	3 %	32 %

Table 5 Yields of **(310)** and **(311)**.
Notes: Unless otherwise stated, normal dilution conditions were employed and the reactions run for 24 h. a) Addition of **(304)** over 24 h.

Although the desired enediyne **(310,** R^1=Ph**)** was isolated in some cases, it did not prove possible to increase the isolated yield of this product. It seems that the instability of **(304)** under the basic conditions necessary for the Stephens-Castro coupling is largely responsible for the poor yields; this was perceptible from the quick blackening and occasional effervescence of the reaction mixtures. The dimeric products **(311)** are formed by means of a Glaser coupling, the known copper-promoted coupling of terminal alkynes. A similar coupling also takes place even when copper is omitted from the reaction mixture, showing that palladium is also capable of inducing alkyne dimerisation.

Running the reaction at lower temperature failed to improve the yield, as did varying the catalyst, base and solvent. The low yields obtained led to scepticism that **(304)** could be used in a "capping" strategy, in which the complication of macrocyclisation would arise. However, the preparation of a novel and potentially interesting class of enediynes from the extremely unstable dichloride **(304)** should not be overlooked.

The palladium catalysed reactions of stannyl alkynes with vinyl halides do not require addition of an equivalent of base as do the couplings of terminal alkynes with vinyl halides. The former thus proceed under essentially neutral conditions, and it was therefore envisaged that such a coupling would prove more appropriate to couplings involving **(304)**. However, the attempted coupling of **(304)** with trimethylsilyl(tributylstannyl)ethyne **(312)** gave a complex mixture of products, none of which could be identified (scheme **164**).

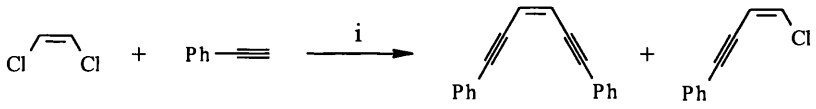


(304) (312)

Scheme 164 Reagents and Conditions i) $Pd(PPh_3)_2Cl_2$, $(CH_2Cl)_2$, 24 h., complex mixture.

2.6.1.2 Capping Studies Employing Alternative (*Z*)-1,2-Dichloroalkenes

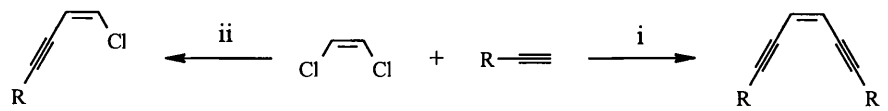
We decided that a more stable 1,2-dichloroalkene could be employed as a coupling component, and in the first instance we opted to employ the simplest member of the class, (*Z*)-1,2-dichloroethene **(313)**. Our initial studies gave a 5:3 mixture of enediyne **(314)** and chloroenyne **(315)** (scheme **165**).



(313) (309) (314) (315)

Scheme 165 Reagents and Conditions i) $C_3H_7NH_2$, CuI, $Pd(PPh_3)_4$, PhH, 24 h., 49 % **(314)**, 30 % **(315)**.

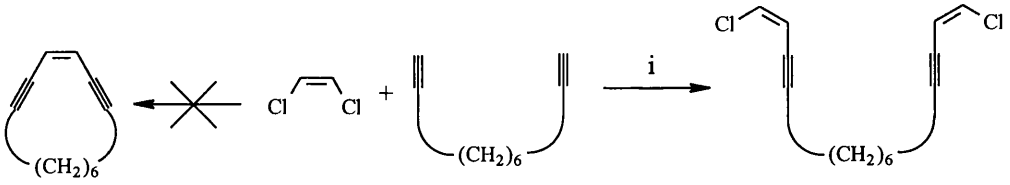
During the course of our study, Linstrumelle[157] reported his own work on a similar coupling reaction, obviating the need for extensive optimisation to obtain chemoselectivity. He discovered that he could obtain exclusively enediyne **(316)** or chloroenyne **(317)** by careful choice of conditions (scheme **166**).



(317) (313) (318) (316)

Scheme 166 Reagents and Conditions i) **(318)** (2.2 equiv.), *n*-$C_4H_9NH_2$, CuI, $Pd(PPh_3)_4$, CuI, 3 h., 50-90 %; ii) **(318)** (0.5 equiv.), *n*-$C_4H_9NH_2$, CuI, $Pd(PPh_3)_4$, CuI, 5 h., 76-93 %.

Initial macrocyclisation studies again employed deca-1,9-diyne **(289)** as a simple model. Lamentably, reaction of **(289)** with **(313)** under a variety of conditions failed to give the desired enediyne macrocycle **(319)**, and instead gave the bis(chloroenyne) **(320)** as the only identifiable product (scheme **167**).



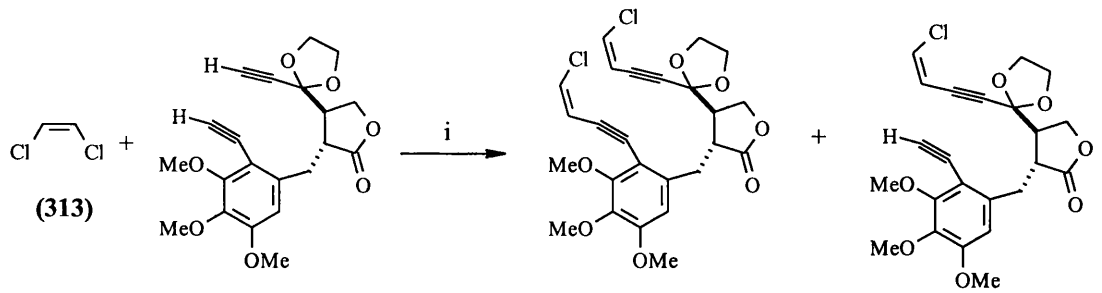
(319) **(313)** **(289)** **(320)**

Scheme 167 Reagents and Conditions i) PhH, slow addition of solutions of **(313)** and **(289)** see table **6.**

Time of Addition	Temperature	Base	Yield of **(320)**
18 h.	20 °C	n-$C_3H_7NH_2$	2 %
18 h.	20 °C	n-$C_4H_9NH_2$	20 %
24 h.	Reflux	n-$C_3H_7NH_2$	0 %
18 h.	50 °C	Et_2NH[a]	21 %
72 h.	Reflux	Et_2NH[a]	0 %

Table 6 Yield of **(320)** Notes: a) Diethylamine as solvent.

Attempts to cyclise diyne **(206)** with (Z)-1,2-dichloroethene **(313)** gave an inseparable mixture of chloroenyne **(321)** and bis(chloroenyne) **(322)** as observed from the ^1H NMR spectrum (scheme **168**).

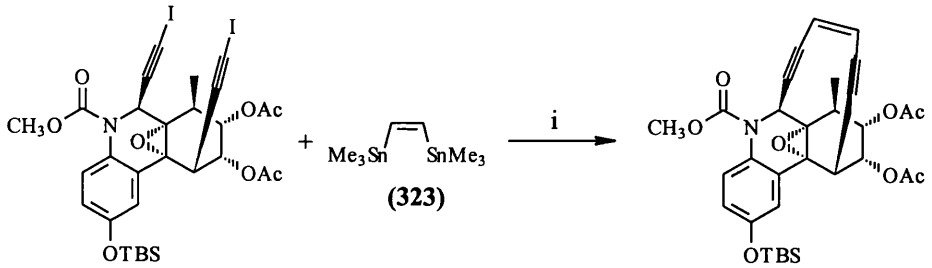


(313) **(206)** **(322)** **(321)**

Scheme 168 Reagents and Conditions i) Addition of **(206)** and **(313)** in PhH over 24 h. to $C_4H_9NH_2$, CuI and $Pd(PPh_3)_4$ in PhH, 20 °C, 6 % combined yield.

2.6.1.3 Alkynyl Iodide/Vinyl Stannane Coupling Approaches to Stegamicins

At this stage report from the laboratories of the Danishefsky group[158] attracted our attention describing the synthesis of dynemicin A **(151)**. The key step was the installation of the enediyne unit by coupling of (*Z*)-distannylethene **(323)** with bis(iodoalkyne) **(324)** under palladium catalysis (scheme **169**).

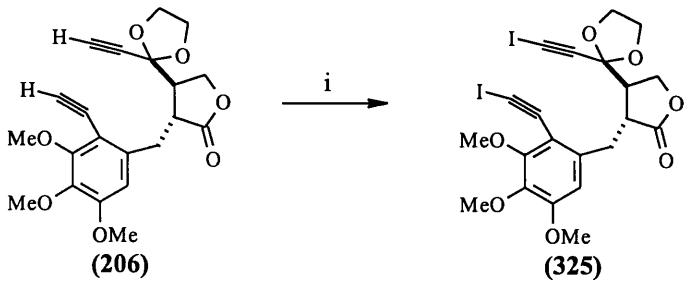


(324) **(323)**

Scheme 169 Reagents and Conditions i) $Pd(PPh_3)_4$, DMF, addition of **(323)** over 1 h., 60 °C, 80 %.

The appeal of Danishefsky's methodology was, of course, irresistible. We postulated that by converting diyne **(206)** into the corresponding bis(iodoalkyne), we could employ a similar cyclisation reaction to obtain stegamicins **(299)**.

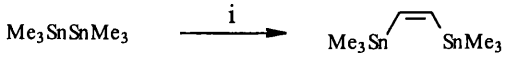
Gratifyingly, diyne **(206)** was converted in good yield to bis(iodoalkyne) **(325)** by treatment with two equivalents of *N*-iodosuccinimide and catalytic silver iodide in THF (scheme **170**).[159]



(206) **(325)**

Scheme 170 Reagents and Conditions i) *N*-iodosuccinimide, $AgNO_3$, THF, 24 h., 66 %.

The literature method[160] of preparing (*Z*)-distannylethene initially proved to be troublesome, but ultimately, it was found that use of rigorously purified 1,4-dioxan together with 5 mol % of catalyst (rather than the 0.05 mol % specified in the original paper) gave rise to a satisfactory yield of **(323)** (scheme **171**).



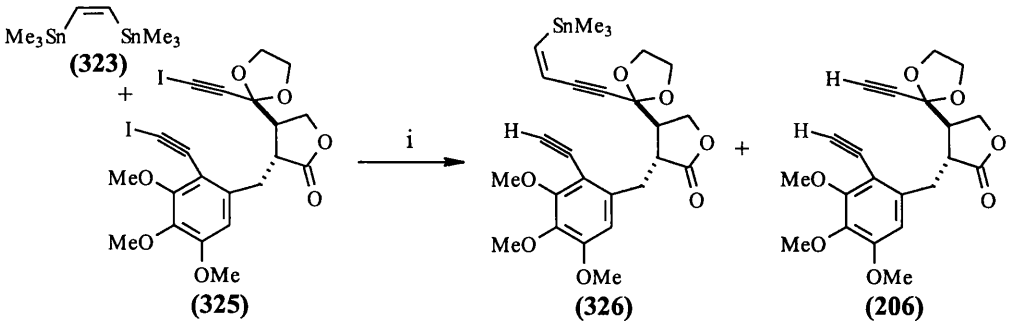
(313)

Scheme 171 Reagents and Conditions i) $Pd(PPh_3)_4$, acetylene, 1,4-dioxan, 60 °C, 3.5 h., 69 %.

With both of the necessary fragments in hand, we set out yet again to forge the same crucial carbon-carbon bonds.

Initially, the reaction conditions reported by Danishefsky were followed closely. We were pleased to observe the formation of a new product by thin layer chromatography, and after work-up, this material was isolated, although in trace amounts, as a colourless gum, along with a small amount of a colourless solid which proved to be the parent deiodinated diyne **(206)**. The colourless gum gratifyingly showed the presence of a new AB quartet corresponding to two vicinal vinyl protons in the ^1H NMR spectrum. This proton spectrum also indicated the presence of a trimethylstannyl group. The appearance of an alkyne proton singlet at δ_H 3.40 corresponding to the arylethynyl proton led us to tentatively assign the structure **(326)**, which was supported by high-resolution mass spectrometry (scheme **172**).

Attempts were made to induce cyclisation by means of higher dilution, or inverse addition regimes, but only diyne **(206)** and **(326)** could be isolated.

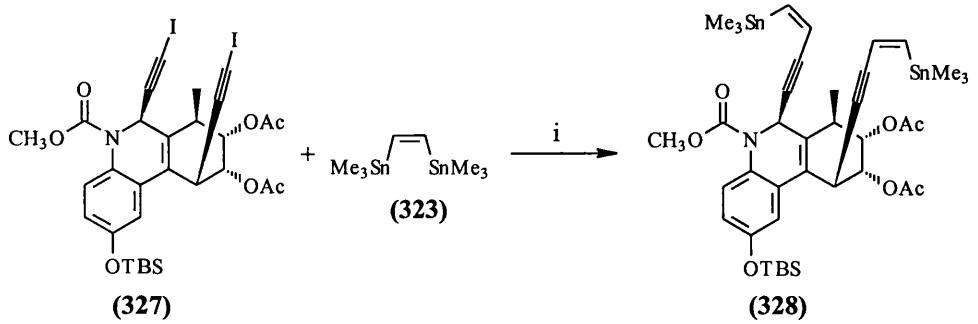


Scheme 172 Reagents and Conditions i) DMF, $Pd(PPh_3)_4$, 60 °C; see table 7.

Conditions	Time of Addition	Yield of **(206)**	Yield of **(326)**
A	1 h.	21 %	6 %
A	12 h.	21 %	0 %
B	1 h.	10 %	0 %

Table 7 Yield of **(326)** and **(206)** Condition A: slow addition of **(323)** to reaction mixture; condition B: slow addition of **(325)** to reaction mixture.

In retrospect, the failure of this capping strategy is not entirely surprising in the light of Danishefsky's observation that while **(324)** undergoes efficient cyclisation (scheme **169**), the alkene analogue **(327)** instead gives bis(stannylenyne) **(328)** (scheme **173**). The authors postulated that this was due to the larger distance between the alkyne termini in **(327)** than in **(324)**. Clearly, in our substrate **(325)** has more freedom to rotate than either **(324)** or **(327)**, and the termini will be a considerable distance from one another in most conformations. This may well explain the fact that enediyne formation could not be detected in our reactions.

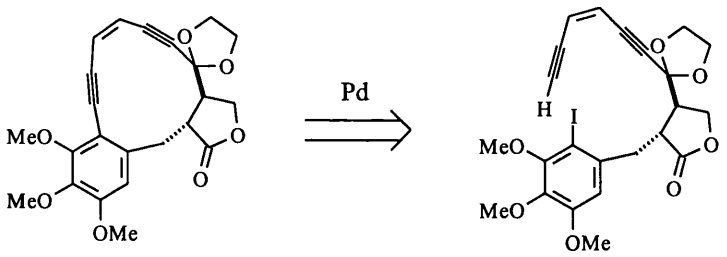


Scheme 173 Reagents and Conditions i) $Pd(PPh_3)_4$, DMF, addition of **(323)** over 1 h., 60 °C.

The failure of these capping strategies can perhaps be ascribed to the competing demands of the intermolecular coupling, for which high concentrations are optimum for a satisfactory rate of reaction, and the subsequent macrocyclisation, for which low concentrations are necessary in order to prevent competing intermolecular reaction.

2.6.2 Approaches to Stegamicins Employing Aryl Iodide/Alkyne Couplings

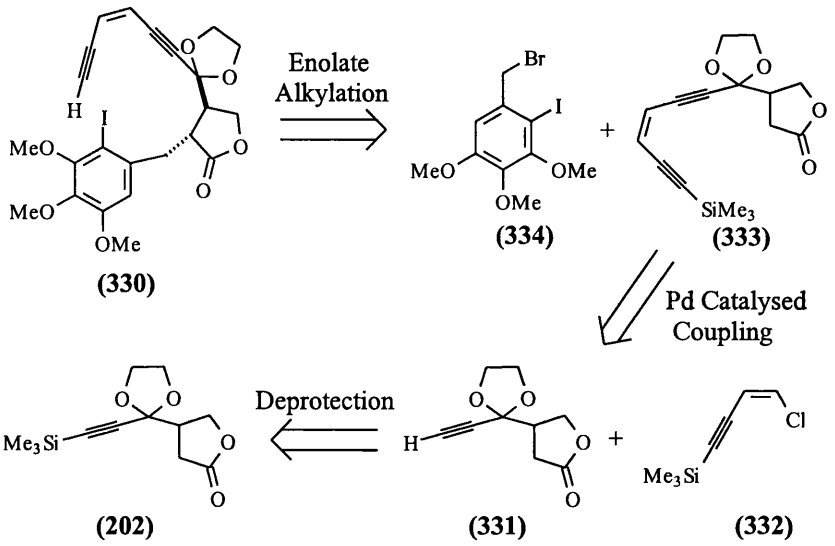
In order to circumvent this difficulty, we decided to investigate a route to stegamicins **(299)** which involved formation of a single bond in the macrocyclic ring closure step. The first disconnection of this type was one in which the macrocyclisation was effected by a palladium catalysed coupling of an aryl iodide with the terminal alkyne of an enediyne unit (scheme **174**).



(329) **(330)**

Scheme 174 Retrosynthesis of Stegamicin **(329)**.

The advantage of such a disconnection lay in the potential to adapt the synthesis of **(206)** to a synthesis of iodo-alkyne **(330)** with minor modifications (scheme **175**).

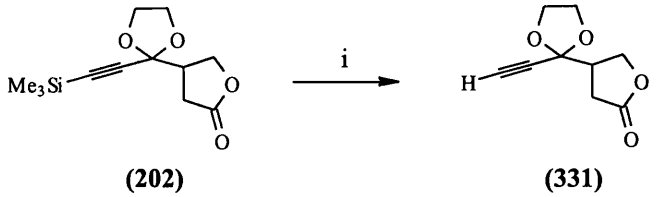


Scheme 175 Retrosynthesis of **(330)**.

Hypothetically, deprotection of our previously used trimethylsilylalkyne **(202)** followed by palladium catalysed coupling of the resultant terminal alkyne **(331)** with chloroenyne **(332)** would give enediyne lactone **(333)**. Formation of the enolate, and alkylation of this with bromide **(334)** was then envisaged to furnish the target cyclisation precursor **(330)**.

2.6.2.1 Synthesis of Enediyne Lactone (333)

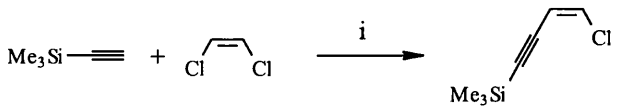
Accordingly, deprotection of **(202)** was effected in good yield using a potassium carbonate/methanol protocol (scheme **176**).



Scheme 176 Reagents and Conditions i) K_2CO_3, MeOH, ambient temperature, 12 h., 70 %.

We hoped to install the enediyne unit by coupling **(331)** with chloroenyne **(332)** using the conditions of Linstrumelle.[157] **(332)** itself has been synthesised by Linstrumelle

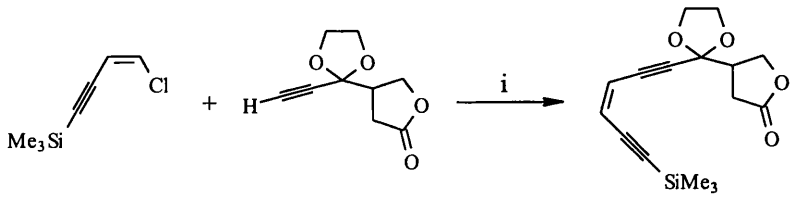
but, in our hands, his conditions gave only low isolated yields. Changing the solvent and prolonging the reaction time enabled several grams of **(332)** to be prepared in good yield (scheme **177**).



(217) **(313)** **(332)**

Scheme 177 Reagents and Conditions i) $Pd(PPh_3)_4$, CuI, *n*-$C_4H_9NH_2$, Et_2O, ambient temperature, 12 h., 62 %.

The coupling of **(332)** and **(331)** was carried out using tetrakis(triphenylphosphine) palladium(0) with copper(I) co-catalyst (scheme **178**). Unfortunately, the yield of enediyne **(333)** could not be improved upon. The mass-balance of the reaction was also very poor, with only **(333)** and recovered **(332)** being isolated, in low yield.

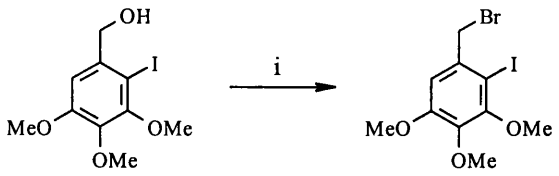


(332) **(331)** **(333)**

Scheme 178 Reagents and Conditions i) $Pd(PPh_3)_4$, CuI, *n*-$C_4H_9NH_2$, PhH, ambient temperature, 5 h., 37 %.

2.6.2.2 Synthesis of Iodobenzyl Bromide (334)

With **(333)** in hand, we focused on preparing the iodo-bromide **(334)**. This was very easily prepared from 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)** by means of a carbon tetrabromide/triphenylphosphine protocol (scheme **179**). The product was obtained as colourless needles in 48 % yield, but was extremely thermally unstable.

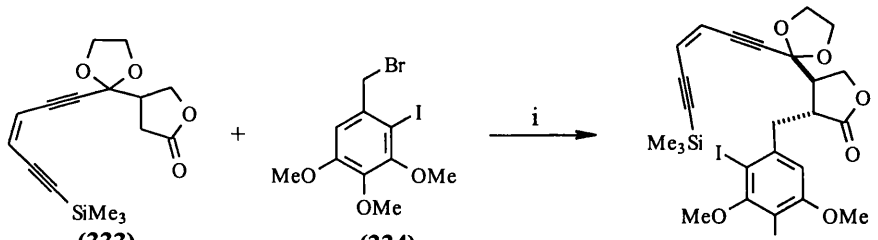


(220) (334)

Scheme 179 Reagents and Conditions i) CBr_4, PPh_3, Et_2O, ambient temperature, 18 h., 48 %.

2.6.2.3 Coupling of Iodobenzyl Bromide (334) with Enediyne Lactone (333)

In initial coupling studies, conditions were chosen to be identical to the coupling of **(202)** with **(204)** (scheme **105**). Thus, deprotonation of the lactone in THF with LDA at -78 °C, and quenching the enolate anion with the electrophile **(334)** at -35 °C. Under these conditions, however, extensive decomposition was seen to occur in the deprotonation step, and no coupled product could be isolated. This problem was overcome by effecting the deprotonation at a lower temperature (scheme **180**).

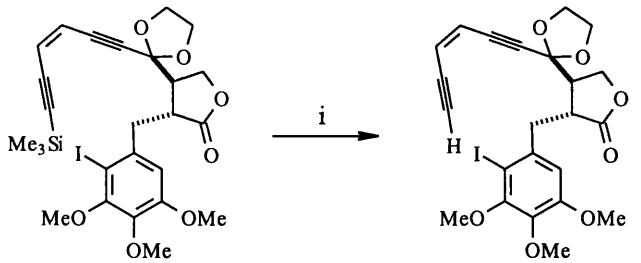


(333) (334) (335)

Scheme 180 Reagents and Conditions i) **(333)**, THF, -100 °C, LDA, 30 min., addition to **(334)** in THF at -100 °C, stir 1 h., then ambient temperature, 12 h., 12 % **(335)**, 54 % recovered starting material **(334)**.

The poor yield of the coupled product is probably due to the fragility of the enediyne unit under the basic conditions necessary for deprotonation. Deprotection of **(335)** was effected with tetra-*n*-butylammonium fluoride (scheme **181**) which was chosen in favour of the previously employed potassium carbonate/methanol protocol because of the shorter reaction time. The product **(330)** was very unstable with substantial

decomposition occurring after 1 h. at ambient temperature. Low yields were obtained using the original deprotection methodology.

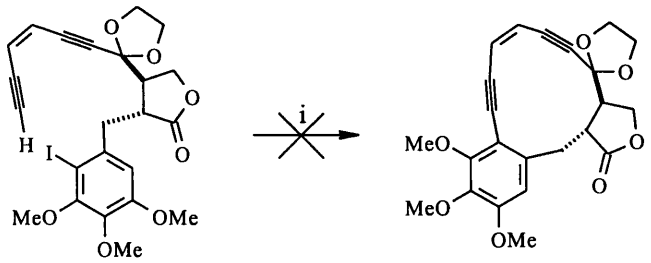


(335) (330)

Scheme 181 Reagents and Conditions i) (n-$C_4H_9)_4NF$, THF, ambient temperature, 1 h., 52 %.

2.6.2.4 Attempted Macrocyclisation of Iodoaryl Enediyne (330)

The instability of **(330)** necessitated its rapid use in the cyclisation step. High dilution conditions were utilised in this reaction to favour the intramolecular reaction. Although complete consumption of starting material was observed by thin-layer chromatography, no cyclised product could be isolated (scheme **182**).



(330) **(329)**

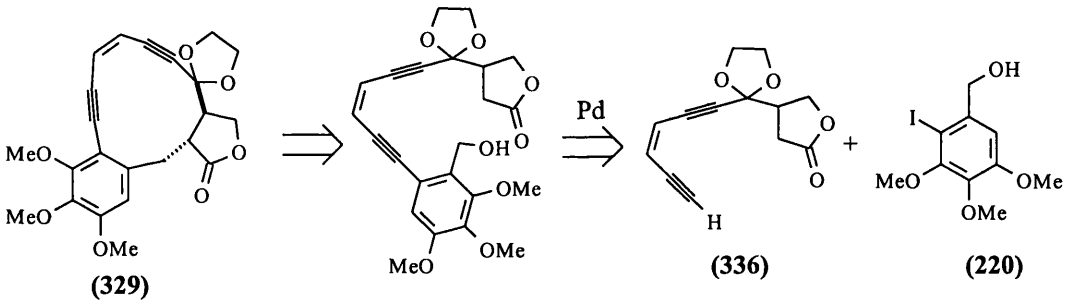
Scheme 182 Reagents and Conditions i) $Pd(PPh_3)_4$, CuI, n-$C_4H_9NH_2$, PhH, addition of **(330)** in PhH over 24 h., decomposition.

The poor yield of the synthetic route to **(330)**, combined with its inherent instability prompted us to abandon this tactic in favour of one avoiding the potentially troublesome palladium catalysed macrocyclisation step. Instead, we decided to

investigate an ionic macrocyclisation approach; such reactions are better investigated and understood, particularly within the enediyne theatre.[161]

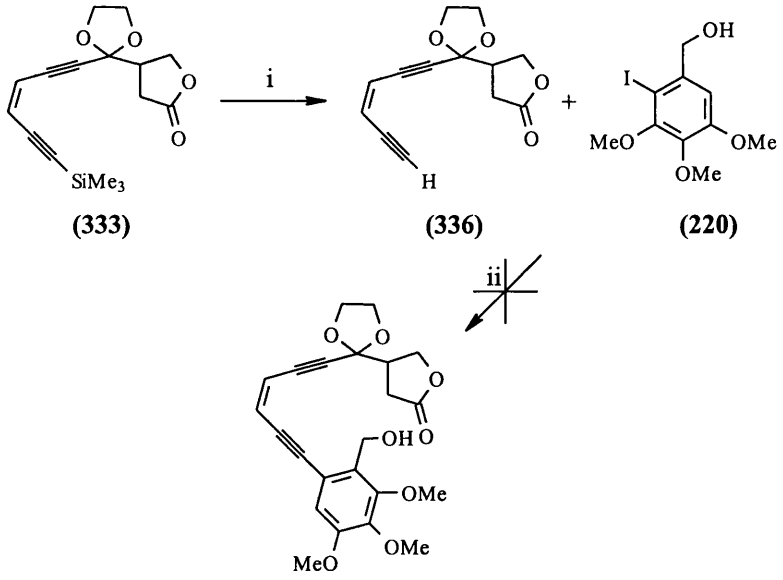
2.6.2.5 Attempted Coupling of Terminal Enediyne (336) with Aryl Iodide (220)

We therefore assessed the feasibility of a scheme similar to the first enediyne macrocyclisation route, but with the key steps reversed (scheme **183**). Thus, palladium catalysed coupling of terminal enediyne **(336)** would precede ionic ring closure, possibly *via* lactone enolate formation.



Scheme 183 Retrosynthesis of Stegamicin **(329)** *via* Palladium Catalysed Coupling of **(336)** and **(220)**.

Deprotection of **(333)** was again accomplished with tetra-*n*-butylammonium fluoride. Interestingly, the terminal enediyne **(336)** also proved to be highly unstable, discolouring upon concentration after chromatography. Unfortunately, all attempts to couple this species with 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)** failed, with thin layer chromatography indicating decomposition of both starting materials (scheme **184**).



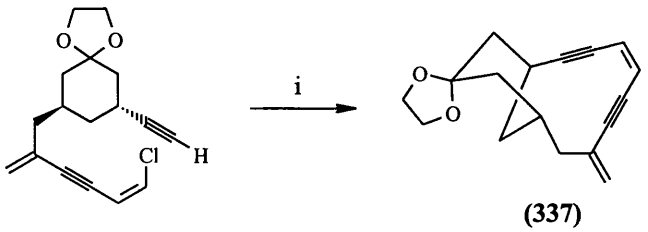
(333) (336) (220)

Scheme 184 Reagents and Conditions i) (n-$C_4H_9)_4NF$, THF, ambient temperature, 1 h., 45 %; ii) $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, 55 °C, decomposition.

The failure of these two routes to the stegamicins is probably due at least in part to the inherent reactivity of the terminal enediyne moiety, and the unsuitability of this unit for participation in palladium catalysed couplings. Consequently, we decided to investigate the possibility of an approach to stegamicins in which the formation of intermediate terminal enediyne units such as those present in **(336)** and **(330)** could be avoided.

2.6.3 Approaches to Stegamicins Involving Macrocyclisation with Concomitant Enediyne Formation

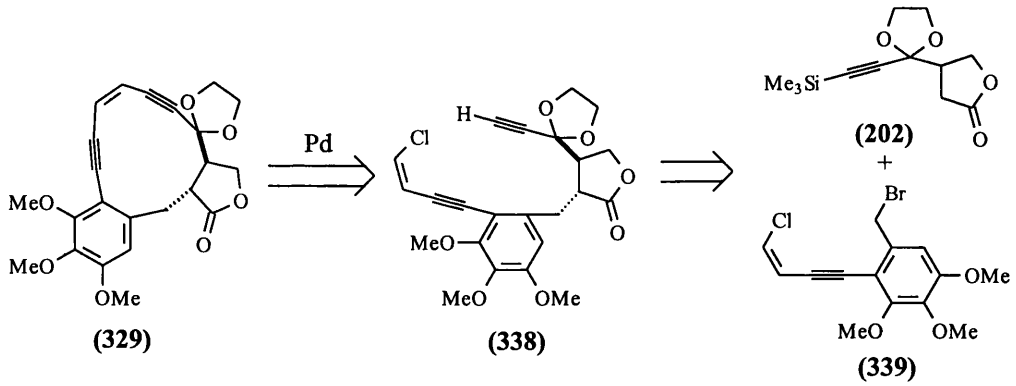
Schinzer[162] has effected macrocyclic ring closure together with enediyne formation in the synthesis of the calicheamicin model system **(337)** by means of a palladium catalysed coupling (scheme **185**).



Scheme 185 Reagents and Conditions i) $Pd(PPh_3)_4$, CuI, *n*-$C_4H_9NH_2$, 24 %.

Such a ring closure would be highly attractive in a synthesis of stegamicins, as it would conveniently circumvent the problems associated with the instability of the terminal enediyne-lactone units.

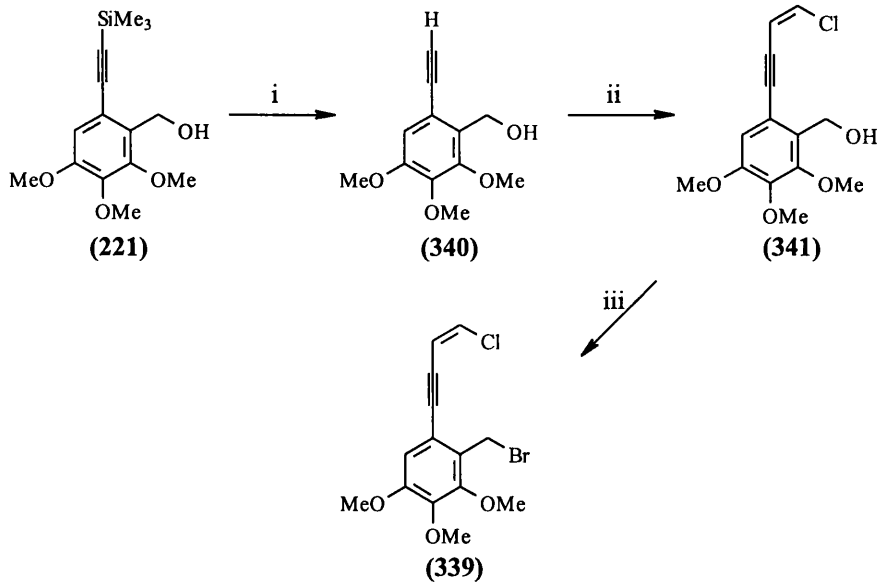
Initially, we decided to assess the ring-closure potential of chloroenyne **(338)**. This could, in turn, be derived from a suitable benzylic bromide **(339)**, and the lactone fragment **(202)**, which we already had in hand (scheme **186**).



Scheme 186 Retrosynthesis of Stegamicin **(329)** from Chloroenyne **(338)**.

2.6.3.1 Synthesis of Aryl Chloroenyne Portion (339)

(339) was synthesised from **(221)** in a three-step sequence (scheme **187**).



(221) (340) (341) (339)

Scheme 187 Reagents and Conditions i) K_2CO_3, MeOH, ambient temperature, 12 h., 88 %; ii) (*Z*)-1,2-dichloroethene, $Pd(PPh_3)_4$, CuI, *n*-$C_4H_9NH_2$, PhH, ambient temperature, 3 h., 52 %; iii) CBr_4, PPh_3, Et_2O, 24 h., 68 %.

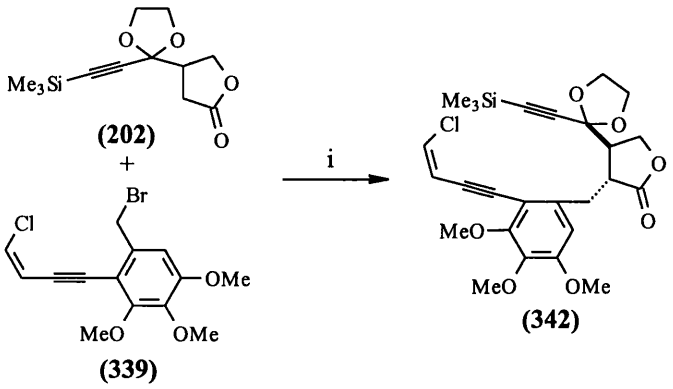
The terminal alkyne **(340)** proved considerably less stable than its trimethylsilyl precursor **(221)**, and upon storage decomposed to give a blue polymer. This may be due to the ready addition of electrophiles to such systems, as evidenced by the hydrolysis of diyne **(206)**. Any trace of acid could well induce polymerisation.

Use of several equivalents of (*Z*)-1,2-dichloroethene **(313)** ensured that chloroenyne **(341)** was the predominating product, and the alternative enediyne product was not observed. The benzylic alcohol was converted to a suitable nucleofuge by the method previously employed for similar conversions, viz; the carbon tetrabromide / triphenylphosphine protocol thereby providing **(339)** in good yield.

2.6.3.2 Coupling of Lactone (202) with benzyl bromide (339)

The coupling of lactone **(202)** with benzyl bromide **(339)** was accomplished by deprotonation of the former with lithium diisopropylamide at -78 °C. Quenching of

this anion with bromide **(339)** gave, after work-up, 45 % of the desired coupled product **(342)** (scheme **188**). Although the stereochemistry of the gamma-lactone ring junction could not be unambiguously ascertained by ^{1}H NMR spectrometry, this technique did indicate that only a single diastereomer was present, and based on very good precedent[142] we were optimistic that this had provided the desired *trans*-isomer.



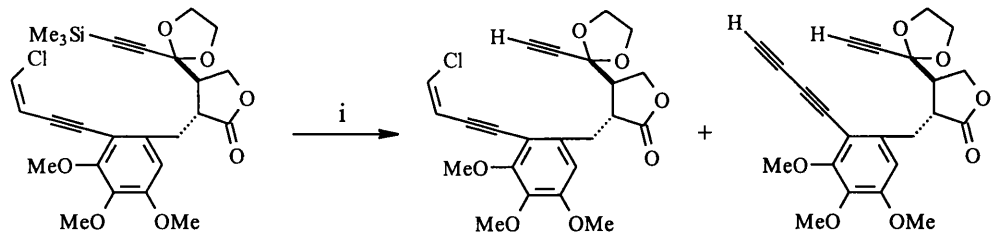
Scheme 188 Reagents and Conditions i) **(202)**, *i*-Pr_2NLi, THF, -78 °C, 30 min, then **(339)**, -78 °C, 1h., ambient temperature, overnight, 45 %.

2.6.3.3 Deprotection of Silyl Chloroenediyne (342)

Treatment of **(342)** with tetra-*n*-butylammonium fluoride in THF led to complete consumption of starting material within ten minutes, and the appearance of a single spot as observed by thin layer chromatography. This was isolated after chromatography as a colourless solid. The ^{1}H NMR spectrum gratifyingly indicated that the singlet corresponding to the trimethylsilyl group in **(342)** was no longer present. We were surprised, however, to observe considerably more signals than would correlate with the expected structure **(343)**. In particular, six singlets corresponding to aromatic methoxy groups, two aromatic singlets and three terminal alkynyl singlets were observed, but only one set of signals corresponding to the vicinal vinyl chloride AB system. These results were especially confusing when

combined with the observation of a strong parent ion in the FAB mass spectrum at m/z 469.1040, corresponding to $C_{23}H_{23}O_7ClNa$, the expected empirical formula for **(343)**.

On repeating the reaction using fewer equivalents of tetra-*n*-butylammonium fluoride a single product was isolated following chromatography on silica. The ^1H NMR spectrum of this product, however, showed that some of the signals had altered in intensity when a comparison was made with the ^1H NMR spectrum obtained from the initial experiment. It was concluded that the "single spot" was not, in fact, a single product, but an inseparable mixture of two similar products. One product appeared to contain two terminal alkyne groups, but no vinylic protons; the other contained signals corresponding to the vinyl AB system, and one terminal alkyne group. This led us to put forward the suggestion that what was isolated was, in fact, an approximately 1:1 mixture of the expected product **(343)** and the triyne **(344)** (scheme **189**).

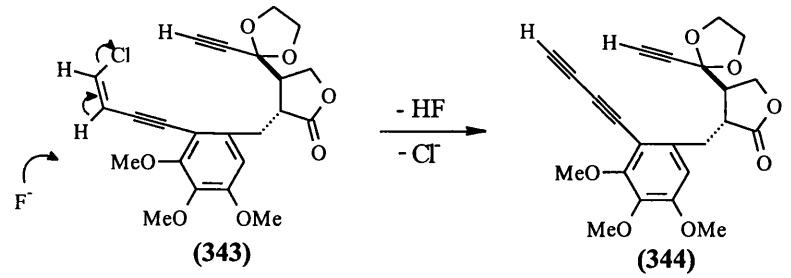


(342) **(343)** **(344)**

Scheme 189 Reagents and Conditions i) $(n\text{-}C_4H_9)_4NF$, THF, ambient temperature, 10 min.

Re-examination of the FAB mass spectrum indeed showed a strong peak at m/z = 410, corresponding to the structure of **(344)**. We were initially surprised by the formation of such a product, but consideration of the side reactions sometimes associated with

the basicity of tetra-*n*-butylammonium fluoride led us to propose a reasonable mechanism for its formation from **(343)** (scheme **190**).



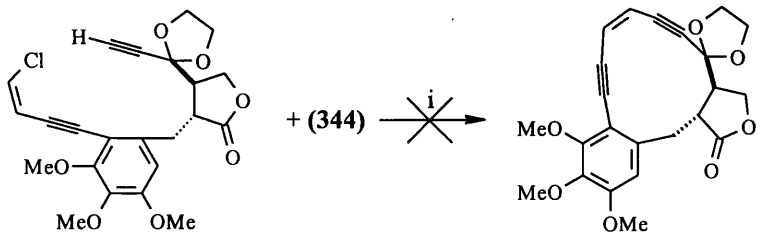
(343) **(344)**

Scheme 190 Proposed Mechanism for the Base-Induced Elimination of **(343)**.

Literature precedent for this proposed scheme was then provided from the work of Kende,[163] who has described the treatment of chloroenynes with tetra-*n*-butylammonium fluoride as a mild method for the preparation of 1,3 diynes.

The constraints of time and limited availability of **(342)** prevented us from investigating alternative non-basic sources of fluoride ion to effect the transformation. However, by using fewer equivalents of tetra-*n*-butylammonium fluoride, we were able to isolate **(342)** contaminated with approximately 20 % of triyne **(344)**, and decided to conduct cyclisation studies upon this mixture.

Frustratingly, using the previously successful conditions employed in the coupling of aryl iodides with terminal alkynes, with high dilution of **(343)**, we failed to isolate any cyclised product (scheme **191**).



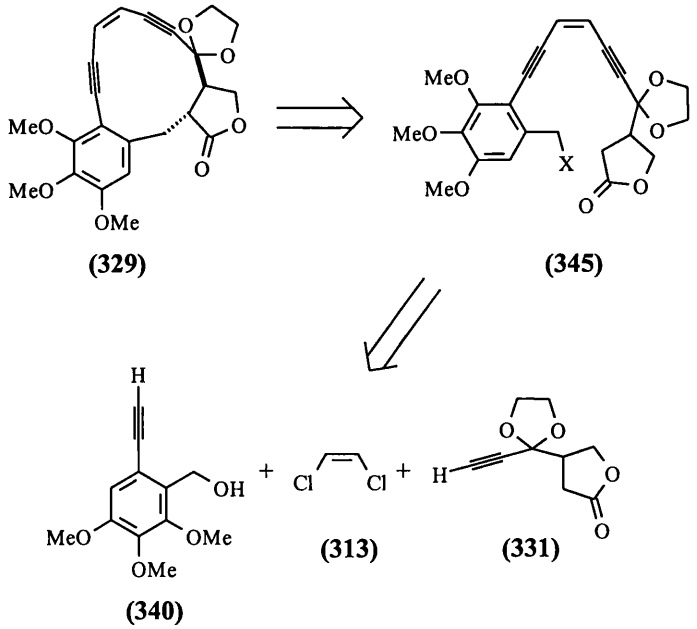
(343) **(329)**

Scheme 191 Reagents and Conditions i) $Pd(PPh_3)_4$, CuI, n-$C_4H_9NH_2$, PhH, ambient temperature, addition of **(343)** over 8 h., decomposition.

This failure to isolate any cyclised product, when combined with the poor yields observed in the synthesis of **(342)** and the competitive elimination side-reaction associated with deprotection prompted us to abandon this synthetic scheme and seek an alternative disconnection.

2.6.4 Synthesis of Stegamicin Precursors by Coupling of Two Alkyne Portions to a Central Alkene Unit

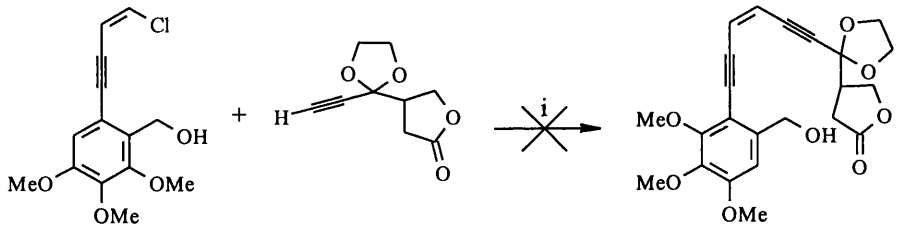
The final synthetic tactic which we decided to employ in our search for a route to the stegamicins involved sequential coupling of both alkyne fragments onto a central bifunctional alkene moiety to form a linear enediyne **(345)**, which could conceivably undergo subsequent cyclisation by means of an ionic ring closure (scheme **192**).



Scheme 192 Retrosynthesis of Stegamicin **(329)** From Alkynes **(340)** and **(331)**.

2.6.4.1 Attempted Coupling of Chloroenyne (341) with Alkyne (331)

The initial attempt to synthesise a linear enediyne of type **(345)** used the coupling of (*Z*)-1,2-dichloroethene with alkyne **(340)**, as in scheme **187**, giving chloroenyne **(341)**. In this instance, we hoped that the free hydroxyl group present in **(341)** would not interfere with the subsequent palladium catalysed coupling reactions since previous experience had shown us that this was generally the case. No coupled product could however be isolated under any of the conditions employed (scheme **193**).



(341) **(331)** **(346)**

Scheme 193 Reagents and Conditions i) 24 h., CuI, ambient temperature, see table **8.**

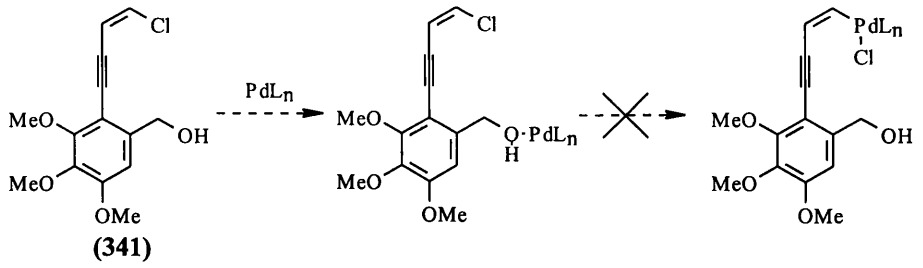
Solvent	Base	Catalyst	Yield of **(346)**	Recovered **(341)**	Recovered **(331)**
Benzene	*n*-$BuNH_2$	$Pd(PPh_3)_4$	0 %	30 %	0 %
Benzene	(*i*-Pr)$_2$EtN	$Pd(PPh_3)_4$	0 %	45 %	45 %
Piperidin	-	$Pd(PhCN)_2Cl_2$	0 %	41 %	0 %

Table 8 Conditions and Yields Observed Corresponding to scheme **193.**

The failure of the initial conditions to give any coupled product **(346)**, when taken with the observation that only chloroenyne **(341)** was recovered was attributed to the instability of lactone **(331)** under the reaction conditions. It was thought that the primary amine employed, *n*-butylamine, might effect nucleophilic attack on the lactone ring. The more hindered base, diisopropylethylamine (Hünig's base), did

indeed result in less decomposition of **(331)** (45 % recovery), but, alas, no enediyne formation was observed. We also assessed the use of an alternative catalyst system, palladium(II) chloride-benzonitrile complex, which has been found to induce rapid coupling of vinyl chlorides with terminal alkynes,[153] but again, recovered chloro-enyne **(341)** was the only product to be isolated.

We were therefore slightly concerned that the free hydroxyl group present in **(341)** was adversely affecting the coupling reaction, possibly by co-ordination of the palladium catalyst to the free hydroxyl group, preventing insertion into the carbon-chlorine bond (scheme **194**). As we have seen, this is not a problem in similar reactions, such as the alkynylation of 2-iodo-3,4,5-trimethoxy benzyl alcohol **(220)** (scheme **103**), since the carbon-halogen bond is much closer to the hydroxyl group than in **(341)**.

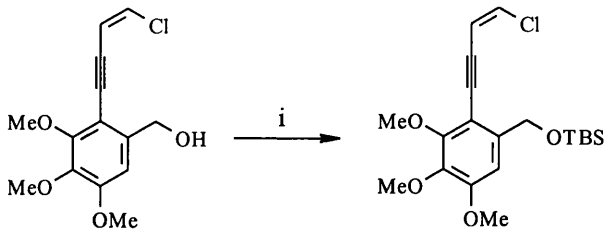


Scheme 194 Palladium Co-ordination to Hydroxyl Group Preventing C-Cl Insertion.

2.6.4.2 Coupling of Protected Chloroenyne (347) with Alkyne(331)

In order to investigate whether such co-ordination effects were at play, we chose to synthesise a hydroxy-protected analogue of **(341)**. We selected the *tert*-butyl dimethyl silyl (TBS) group as being suitable; it shows good stability under a variety of reaction conditions, is easily installed and removed, and its considerable steric bulk would hopefully strongly disfavour co-ordination to palladium.

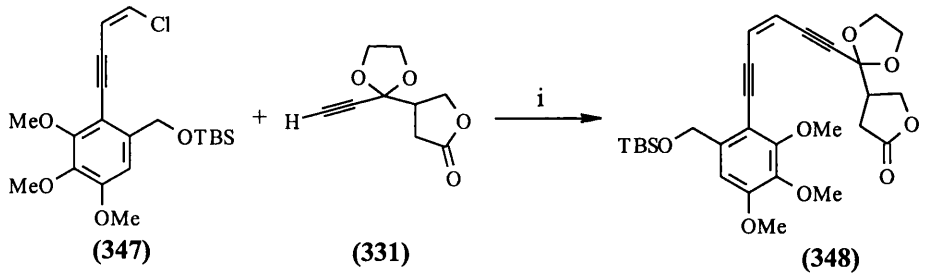
The TBS group was readily introduced by treatment of **(341)** with *tert*-butyldimethylsilyl chloride in DCM, with triethylamine as base and catalytic DMAP (scheme **195**).



(341) **(347)**

Scheme 195 Reagents and Conditions i) TBSCl, DMAP, Et_3N, DCM, 0 °C, 30 min., 91 %.

The coupling of the protected chloroenyne **(347)** with terminal alkyne **(331)** was conducted in the first instance under the same conditions which had failed for the free alcohol **(341)** (scheme **196**). After 5 h., the appearance of a new product by thin layer chromatography was observed and after 24 h., consumption of alkyne **(331)** was complete. After work-up and chromatography on silica, 32 % of a new product was isolated, along with 35 % of recovered chloroenyne **(347)**. Gratifyingly, the new product had a ^1H NMR spectrum consistent with enediyne **(348)**, and this was supported by high resolution mass spectrometry.



(347) **(331)** **(348)**

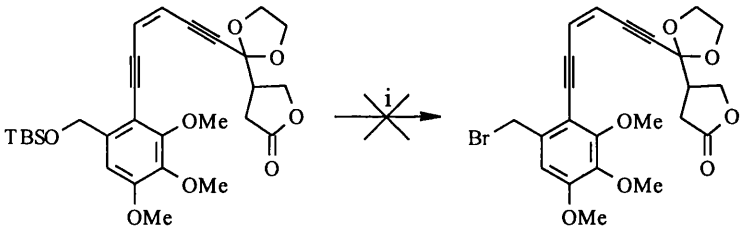
Scheme 196 Reagents and Conditions i) 1 equiv. **(331)**, $Pd(PPh_3)_4$, CuI, *n*-$C_4H_9NH_2$, PhH, 24 h., 35 %; ii) 1.5 equiv. **(331)**, $Pd(PPh_3)_4$, CuI, *n*-$C_4H_9NH_2$, PhH, 24 h., 50 %.

The recovery of 35 % of chloroenyne **(347)** led us to believe that alkyne **(331)** was unstable under the reaction conditions; a repeat run of the reaction using 1.5 equiv. of this compound afforded an improved yield of enediyne **(348)**.

2.6.4.3 Attempted Elaboration of Linear Enediyne (348)

With enediyne **(348)** in hand, we sought to effect the crucial macrocyclisation by a two-step process. We envisaged that conversion of the deprotected hydroxyl group to a suitable leaving group would permit cyclisation to be induced by deprotonation α- to the lactone carbonyl.

It was hoped that we would be able to directly convert the TBS ether present in **(348)** directly into a bromide leaving group by means of treatment with triphenylphosphine dibromide.[164] Under these conditions, however, it did not prove possible to isolate any brominated enediyne **(349)** (scheme **197**).

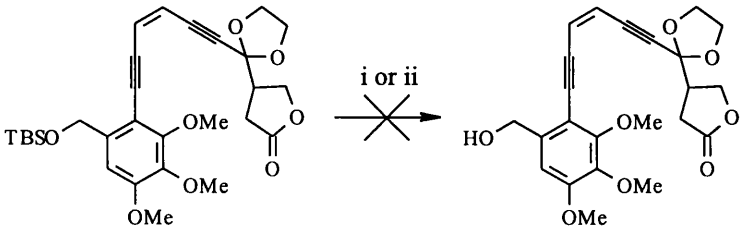


(348) **(349)**

Scheme 197 Reagents and Conditions i) PPh_3Br_2, CH_2Cl_2, ambient temperature, 2 h., 11 % recovered **(348)**.

The failure of the direct conversion of **(348)** to bromide **(349)** prompted us to investigate the two step route of deprotection of the silyl ether to the alcohol **(346)**, with subsequent bromination. Stirring **(348)** with tetra-*n*-butylammonium fluoride in THF led to rapid and complete decomposition of **(348)** at ambient temperature

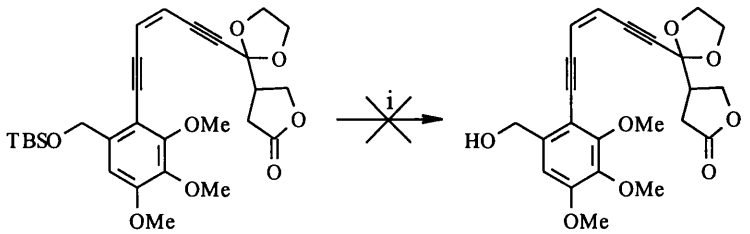
(scheme **198**). The reaction was repeated at -78 °C; however, no reaction was observed at this temperature, and upon warming to 0 °C, decomposition once again occurred.



(348) **(346)**

Scheme 198 Reagents and Conditions i) $(n\text{-}C_4H_9)_4NF$, THF, ambient temperature, 10 min., decomposition; ii) $(n\text{-}C_4H_9)_4NF$, THF, -78 °C, 1 h., then warm to 0 °C, 1 h., decomposition.

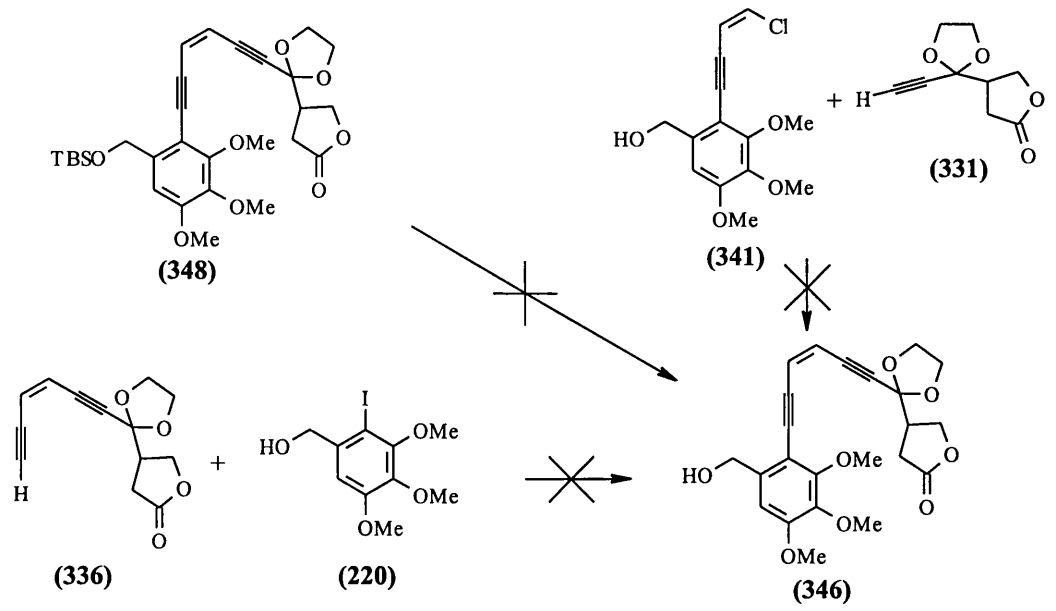
Tetra-*n*-butylammonium fluoride solution in THF is known to be moderately basic, and its basicity has already been shown to promote side-reactions (p. 151). It was felt that a system as sensitive as **(348)** might also be unstable under these reaction conditions. We therefore decided to investigate the alternative deprotection protocol based on buffered HF/pyridine complex, which proceeds under essentially neutral conditions (scheme **199**). To our disappointment, the solution rapidly blackened at 0 °C and thin layer chromatography indicated that only baseline material was present.



(348) **(346)**

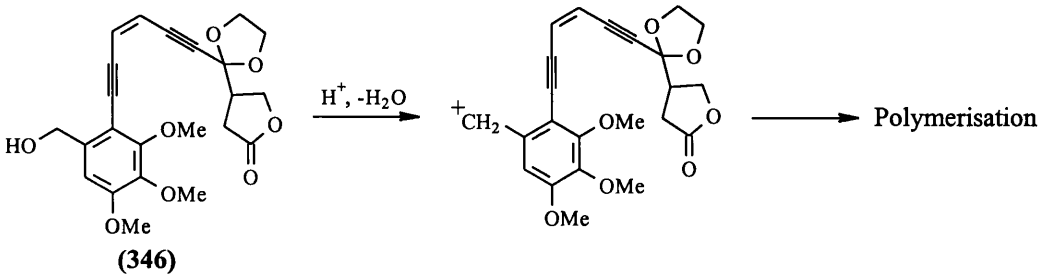
Scheme 199 Reagents and Conditions i) HF/pyridine complex, pyridine, THF, 0 °C, 1 min., decomposition.

A summary of the attempted, but as yet unsuccessful routes to enediyne **(346)** are depicted (scheme **200**).



Scheme 200 Failed Approaches to Enediyne (**346**).

One postulated reason for the failure of these attempts is the inherent instability of (**346**), giving rise to immediate decomposition upon formation. Indeed, formation of a benzylic cation from (**346**), stabilised by virtue of the electron-rich trimethoxyaryl group, can be envisaged. This might undergo a number of fates, including polymerisation (scheme **201**).



Scheme 201 Possible Mechanism for the Decomposition of (**346**).

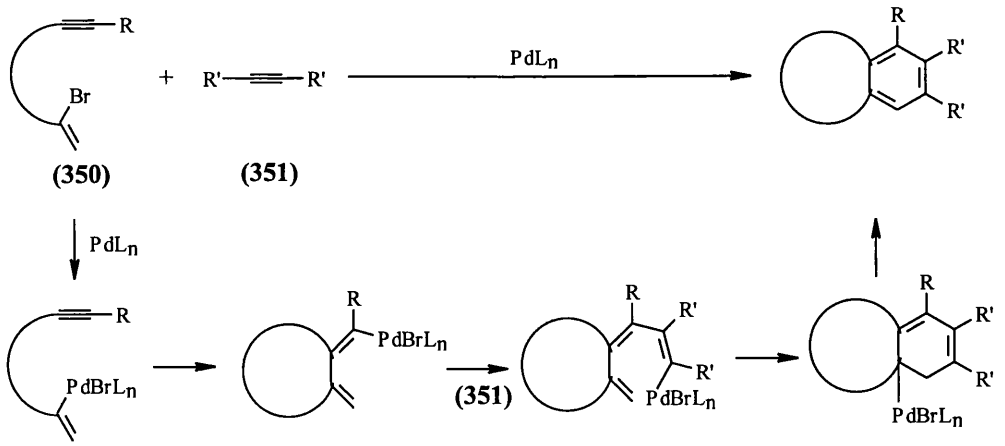
Another possible mode of decomposition of any enediyne system is, of course, the Bergman cyclisation, although this seems unlikely in the light of the high barrier to cyclisation incurred in other simple linear enediynes. (*Z*)-1,5-hexadiyn-3-ene, for instance, undergoes cyclisation only upon exposure to temperatures in excess of

200 °C.[79] However, electronic effects are known to exert a profound influence on the rate of cyclisation of cyclic enediynes,[165, 105] and similar effects may be at play in our example.

2.7 Approaches to Steganone Analogues Using Cascade Carbopalladation

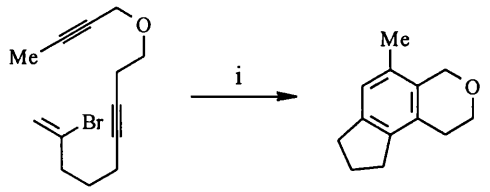
2.7.1 Background: Synthesis of Arenes by Cascade Carbopalladation

A recent application of the Heck reaction has been the formation of aryl rings by inter- and subsequent intra- molecular carbon-carbon bond formation, and final ring closure. Torii and co-workers[166] reported a system which was capable of effecting such a transformation, coupling alkynylvinylbromides **(350)** with alkynes **(351)**. The mechanism is believed to proceed *via* initial carbon-bromine bond insertion by palladium(0) followed by carbon-carbon bond formation and intermolecular coupling with a third alkyne (scheme **202**). Benzannulation is then completed by carbopalladation-dehydropalladation.



Scheme 202 The Mechanism of Palladium catalysed Cascade Carbopalladation.

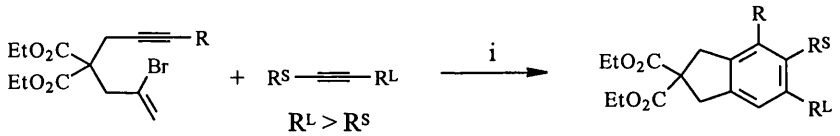
Completely intramolecular versions have subsequently been developed,[167] as in the case of the bromoenediyne **(352)** which was cyclised to give tricycle **(353)** in good yield (scheme **203**).



(352) **(353)**

Scheme 203 Reagents and Conditions i) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, MeCN, 60 °C, 48 h., 67 %.

Negishi[168] has further developed this methodology to provide a regioselective synthesis of fused arenes. Bromoenyne **(354)**, for instance, reacts with a variety of unsymmetrical alkynes **(355)** to give arenes **(356)** with over 90 % regioselectivity (scheme **204**).

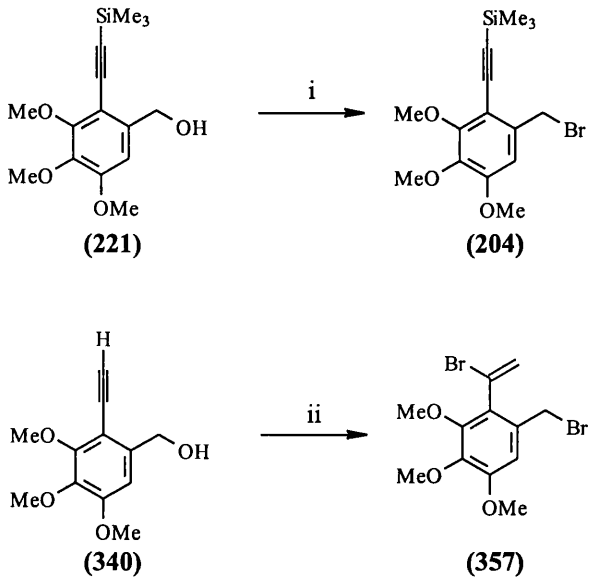


(354) **(355)** **(356)**

Scheme 204 Reagents and Conditions i) $PdCl_2(PPh_3)_2$, *n*-BuLi, NEt_3, DMF, 62-83 %.

2.7.2 Serendipitous Formation of Vinyl Bromide (357)

Our attention was first drawn to such a scheme by our discovery that although treatment of **(221)** with carbon tetrabromide and triphenylphosphine in ether gave good yields of bromide **(204)**, treatment of the terminal alkyne **(340)** under the same conditions gave rise to the unexpected dibromide **(357)** (scheme **205**).

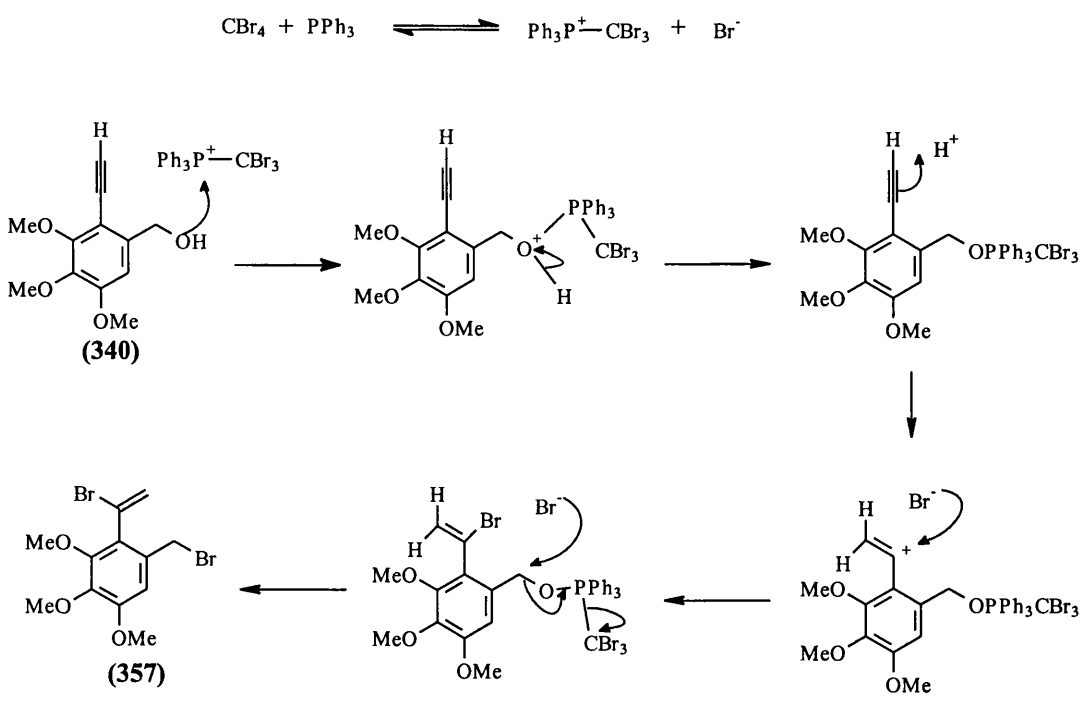


(221) (204)

(340) (357)

Scheme 205 Reagents and Conditions i) CBr_4, PPh_3, Et_2O, ambient temperature, 24 h., 72 %; ii) as i, 41 %.

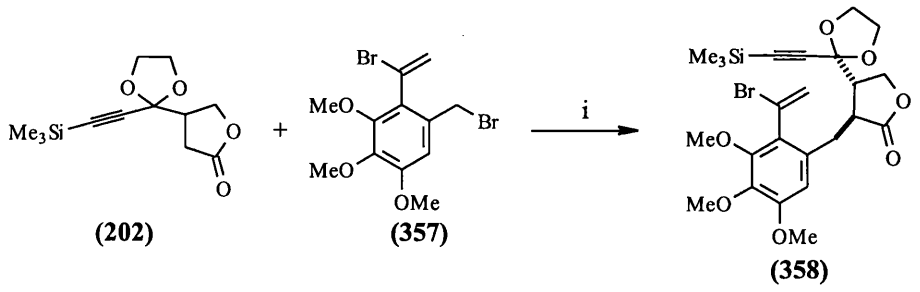
The facile addition of electrophiles to terminal trimethoxyaryl alkynes such as **(340)** has already been observed in this work (p. 121) and indeed, **(340)** is seen to decompose to a blue polymer upon prolonged storage. A possible mechanism for the formation of **(357)** is suggested (scheme **206**).



Scheme 206 Mechanism of the Formation of Dibromide **(357)**.

2.7.3 Coupling of Bromide (357) with Lactone (202)

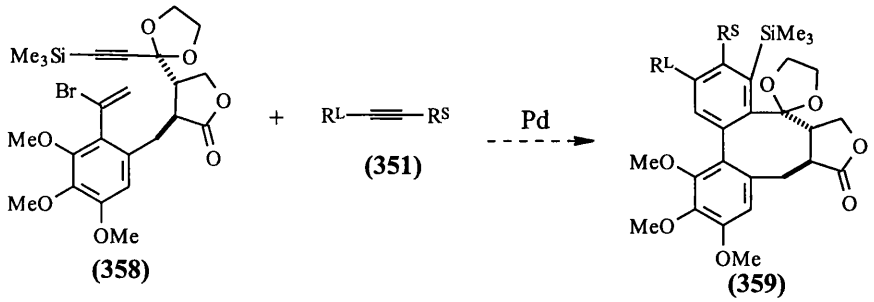
Having unexpectedly synthesised dibromide **(357)**, we decided to try and use this to our advantage by attempting to couple this fragment with lactone **(202)** in the usual way. We were optimistic that the primary benzylic bromide would substitute more readily than the vinylic bromide. To our delight, the coupled product **(358)** was isolated as a single diastereomer in 65 % yield (scheme **207**).



Scheme 207 Reagents and Conditions i) **(202)**, *i*-Pr_2NLi, THF, -78 °C, 1 h., then **(357)**, -78 °C, 1 h., warm to ambient temperature, overnight; 65 % **(358)**, 23 % recovered **(357)**.

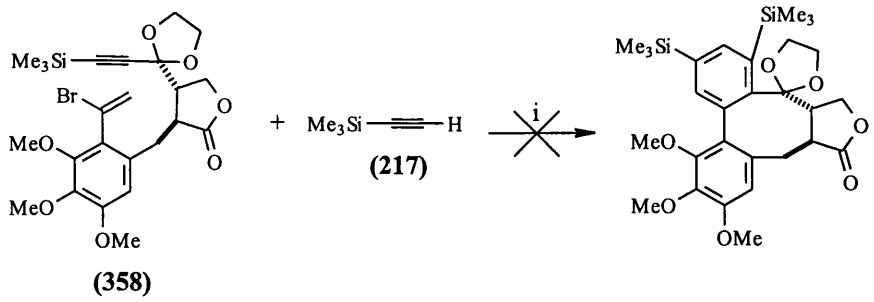
2.7.4 Initial Carbopalladation Studies on (358)

We hoped that a cascade carbopalladation reaction sequence could be employed to furnish steganone analogues **(359)** from the co-cyclisation of **(358)** with an alkyne **(351)** (scheme **208**).



Scheme 208 Synthesis of Steganone Analogues **(359)** by Carbopalladation of bromoenyne **(358)**.

Experiments directed towards effecting this transformation employed trimethylsilylethyne **(217)** as the coupling partner together with Negishi's catalyst,[168] formed by the treatment of bis(triphenylphosphine)palladium(II) chloride with 2 equivalents of *n*-butyllithium. However, in these initial studies no cyclised material could be isolated (scheme **209**).

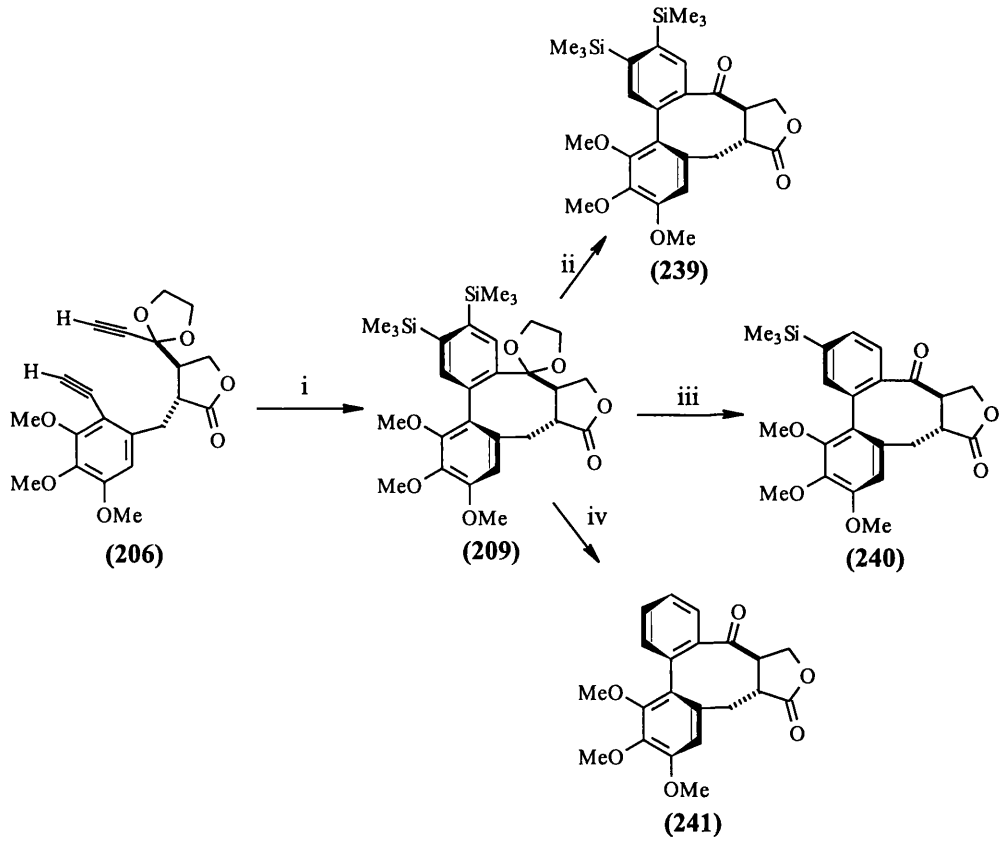


Scheme 209 Reagents and Conditions i) $PdCl_2(PPh_3)_2$/*n*-BuLi, Et_3N, DMF, 100 °C, 2 h., recover 24 % **(358)**.

2.8 Summary, Conclusions and Perspectives

2.8.1 [2+2+2] Cycloaddition Approaches to Steganone Analogues

The cobalt-mediated cycloaddition of a suitable diyne precursor **(206)** with bis(trimethylsilyl)ethyne **(87)** has been used to prepare several novel steganone analogues (scheme **210**). It is highly convergent, and circumvents the problems associated with earlier syntheses of the bisbenzocyclooctadiene lignan lactones. The synthesis is completely diastereoselective, and unusually gives the correct atropisomer. It is also possible to regioselectively functionalise the upper aryl ring by treatment of the cycloadduct **(209)** with electrophiles.

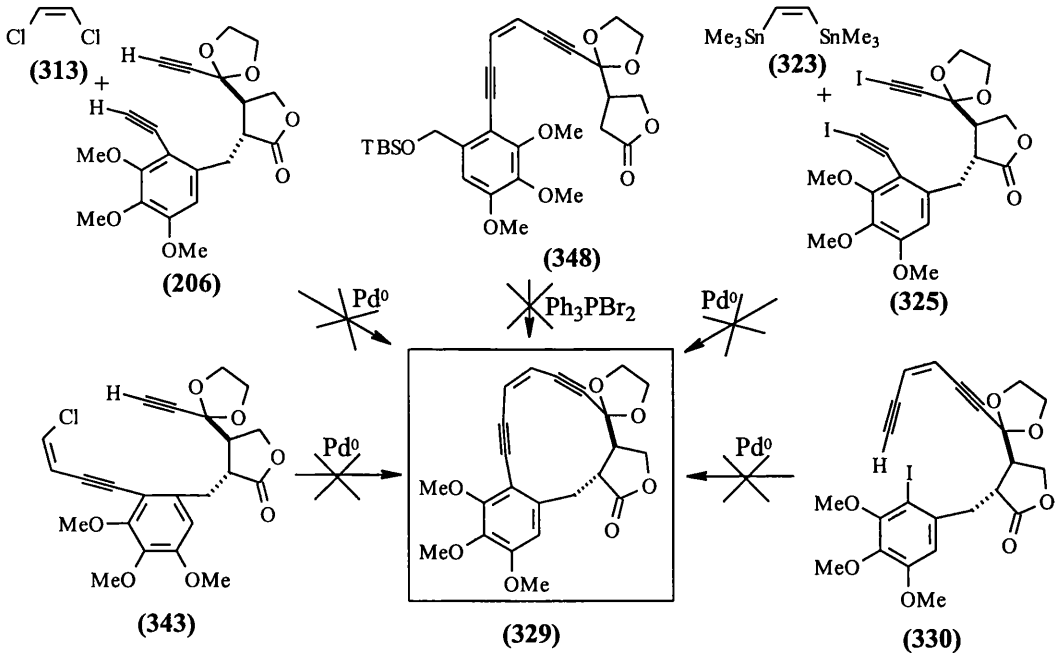


Scheme 210 Reagents and Conditions i) $CpCo(CO)_2$, bis(trimethylsilyl)ethyne **(87)**, MeCN, reflux, addition of **(206)** over 8 h., hν, 19 %; ii) HCO_2H, ambient temperature, 24 h., 54 %; iii) CF_3CO_2H, ambient temperature, 12 h., 73 %; iv) CF_3CO_2H, reflux, 12 h., 41 %.

Unfortunately, it did not prove possible to significantly improve upon the yield of **(209)** in the cycloaddition step through the use of alternative catalysts or monoalkyne cycloadducts. Additionally, the apparently deactivated nature of the bis(trimethylsilyl) aromatic ring present in **(209)** mean that only H^+ has so far been successful in electrophilic *ipso-* substitutions on this substrate.

2.8.2 Approaches to Stegamicins

The synthesis of a series of steganone analogues containing a (*Z*)-hex-3-ene-1,5-diyne (enediyne) unit in place of one of the upper aryl ring ("stegamicins") remains attractive from a synthetic and therapeutic point of view. Several approaches to this interesting class of compounds have been investigated. In every instance, the final macrocyclisation step has proved to be problematic (scheme **211**).



Scheme 211 Approaches to Stegamicin **(329)**.

These studies have highlighted the instability of this particular enediyne unit, and the difficulties associated with palladium catalysed macrocyclisation reactions. The best

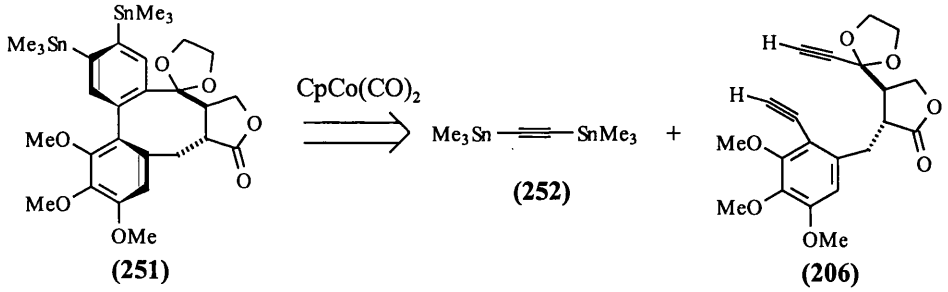
hope for future work rests on systems such as **(348)**, which contains all the structural features present in stegamicin **(329)**.

2.8.3 Other Approaches to Steganone Analogues

Initial approaches to steganone analogues involving cascade carbopalladation and Dötz benzannulation were investigated. Neither of these approaches was however able to furnish the desired biaryl, and further studies are clearly necessary before these methodologies are capable of furnishing medium-sized rings.

2.8.4 Future Work.

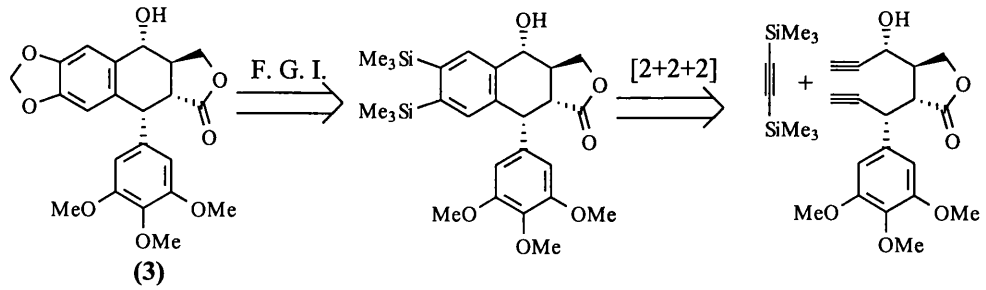
Co-cyclisation of diyne **(206)** with bis(trimethylstannyl)ethyne is predicted to give bis(trimethylstannyl)arene **(251)** (scheme **212**). The trimethylstannyl groups are known to be more labile in electrophilic substitution reactions, and this might be used to enhance the range of analogues available.



(251) **(252)** **(206)**

Scheme 212 Retrosynthesis of bis(trimethystannyl)arene **(251)**

The [2+2+2] cycloaddition methodology could also be used in a synthesis of other lignans, particularly podophyllotoxin **(3)**. In the light of the known ability of 1,5 diynes such as **(360)** to undergo [2+2+2] cycloaddition reactions in good yield, this might well be an attractive route to podophyllotoxin analogues (scheme **213**).



(3)

Scheme 213 Retrosynthesis of podophyllotoxin

Chapter 3 - Experimental

3.1 Experimental Techniques

^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on a Varian VXR 400 at ambient temperature. Spectra were recorded in the solvent specified, with chemical shifts expressed in parts per million (δ) relative to the internal standard. For ^{1}H spectra the residual protic solvent peak was used as the internal standard; for ^{13}C spectra $CDCl_3$ was used. Coupling constants (J) are measured in Hertz (Hz). Mass spectra were recorded by EI or CI (ammonia) on an AutoSpecQ instrument, and by FAB on a VG ZAB SE double focusing instrument. Infrared spectra were recorded on a Perkin Elmer 1600 FT-IR instrument and absorbances are given in wavenumbers (cm^{-1}). Melting points were recorded on an electrothermal apparatus and are uncorrected.

Petrol refers to petroleum ether (b. pt. 40-60 °C) and was distilled prior to use. Ether refers to diethyl ether and was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen immediately prior to use. THF was distilled from sodium benzophenone ketyl under an atmosphere of nitrogen immediately prior to use. Benzene and toluene were distilled from sodium wire under an atmosphere of nitrogen immediately prior to use. Triethylamine, *n*-butylamine, diethylamine, diisopropylamine, diisopropylethylamine and acetonitrile were distilled from calcium hydride under an atmosphere of nitrogen and were stored over 4Å molecular sieves under nitrogen. Dioxan was purified by addition of potassium hydroxide to remove acetaldehyde and subsequent distillation from sodium wire. All other solvents and reagents were used as supplied without further purification.

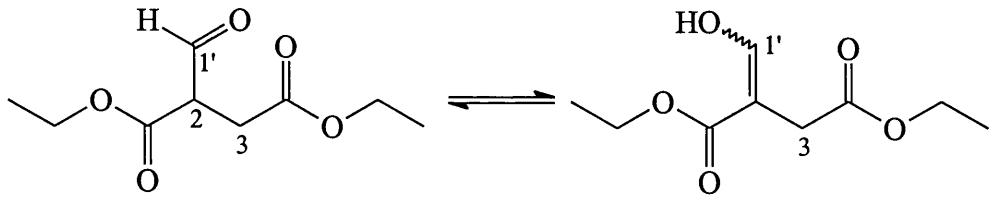
Tetrakis(triphenylphosphine)palladium(0) was made according to the method of Coulson,[169] and was stored under nitrogen or argon at 0 °C.

All reactions were performed under an atmosphere of nitrogen or argon unless otherwise specified. [2+2+2] cycloaddition reactions involving irradiation were conducted with a 400 W tungsten bulb maintaining a distance of 10 cm between the centre of the reaction vessel and the filament of the bulb. Slow addition of solutions was achieved by use of a mechanically driven syringe-pump.

Analytical thin layer chromatography (tlc) was performed on pre-coated glass backed plates (Merck Kieselgel F_{254}) and visualised using long wave (356 nm) or short wave (254 nm) ultraviolet radiation, or with acidified potassium chromate (VII) solution. Preparative chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh).

3.2 Preparation of individual compounds

Preparation of diethyl-2-methanoylbutan-1,4-dioate **(212)**

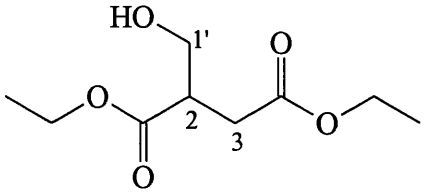


(212a) **(212b)**

Finely divided sodium (16 g, 666 mmol) was added to a solution of diethyl succinate (96 g, 551 mmol) and ethyl formate (62 g, 837 mmol) in ether (1 L). Ethanol (1 mL) was added, and the mixture was stirred at ambient temperature for 18 h. The mixture became extremely viscous, and mechanical stirring was necessary. After this time, water (1 L) was added to the viscous orange mixture, and stirring was continued until dissolution of the suspended solids was observed. The aqueous and organic layers were separated, and the organic layer discarded. The aqueous layer was acidified with 1 M hydrochloric acid, and extracted with ether (3 × 500 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (500 mL) and brine (500 mL), and the solvent was removed under reduced pressure. The residue was distilled (95-96 °C, 0.1 mmHg) (lit.[130] 135-138 °C, 17 mmHg) and **(212)** was collected as a colourless oil (66 g, 60 %); NMR (400 MHz, $CDCl_3$) indicated a 1:1 mixture of keto **(212a)** and enol **(212b)** forms δ_H 9.88 (<1H, s, H-1' of **(212a)**), 7.05 (<1H, d, J=12.6, H-1' of **(212b)**), 4.24 (<2H, q, J=7.1, ethyl CH_2 of **(212a)** or **(212b)**), 4.20 (<2H, q, J=7.0, ethyl CH_2 of **(212a)** or **(212b)**), 4.112 (<2H, q, J=7.1, ethyl CH_2 of **(212a)** or **(212b)**), 4.108 (<2H, q, J=7.1, ethyl CH_2 of **(212a)** or **(212b)**), 3.75 (<1H, t, J=6.1, H-2 of **(212a)**), 3.02

(<2H, s, 2 × h-3 of **(212b)**), 2.91 (<1H, dd, J=17.5, 6.0, H-3 of **(212a)**), 2.83 (<1H, dd, J=17.5, 6.2, H-3 of **(212a)**), 1.23 (13H, 2 × CH_3 of **(212a)**, 2 × CH_3 of **(212b)** and OH of **(212a)**); υ_{max} (NaCl, film) 3400 (w, O-H), 1848 (s, C=O), 1660 (s, C=O), 1382 (m), 1175 (vs), 1090 (s), 1112 (s) cm^{-1}; *m/z* (EI) 203 (MH^+, 0.6 %), 175 (1.6 %), 130 (22.9%), 101 (30.9 %), 83 (42.6 %), 55 (94.5 %), 29 (100 %); Found: C, 53.5; H, 7.04. $C_9H_{14}O_5$ expected C, 53.4; H, 6.9 %.

Preparation of diethyl-2-(hydroxymethyl)butan-1,4-dioate **(213)**

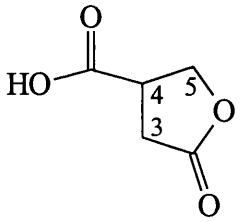


(213)

Sodium borohydride (5.2 g, 138 mmol) was added portion-wise to a stirred solution of **(212)** (70 g, 346 mmol) in methanol (300 mL) at 0 °C over a period of 15 min. The mixture was stirred at this temperature for 1 h. The mixture was allowed to warm to ambient temperature, the solvent was removed under reduced pressure, and 1 M hydrochloric acid (500 mL) was added. The aqueous mixture was extracted with DCM (3 × 200 mL), and the combined organic extracts were washed with sat. $NaHCO_3$ (200 mL) and brine (200 mL), and dried over $MgSO_4$. The solution was filtered, the solvents were removed under reduced pressure, and the residue was distilled (123-125 °C, 0.1 mmHg) (lit.[130] 153-155 °C, 17 mmHg) to yield **(213)** as a pale yellow oil (28 g, 40 %), NMR (400 MHz, $CDCl_3$) δ_H 4.12 (4H, m, 2 × Ethyl CH_2), 3.79 (2H, dt, J=5.8, 1.9, H-1'), 2.98 (1H, m, H-2), 2.71 (1H, dd, J=16.7, 7.1, H-

3), 2.56 (1H, dd, J=16.7, 6.52, H-3), 2.46 (1H, br. s, OH), 1.22 (6H, m, 2 × Me); υ_{max}.3550 (br m, O-H), 2984 (m), 1785 (m, C=0), 1734 (s, C=O), 1375 (m), 1175 (s), 1026 (m) cm^{-1}; *m/z* (EI) 205 (MH^+, 1.2 %), 191 (1.7 %), 159 (63.1 %), 145 (76.4 %), 131 (54.0 %), 113 (88.9 %), 85 (87.6 %), 55 (93.2 %), 29 (100 %); Found: C, 52.34; H, 7.62. $C_9H_{16}O_5$ expected C, 52.9; H, 7.9 %.

Preparation of paraconic acid **(203)**



(203)

A solution of sodium hydroxide (4.4 g, 110 mmol) in water (40 mL) was added over a period of 1 h. to a refluxing solution of **(213)** (6.0 g, 29 mmol) in water (12 mL). Reflux was maintained for an additional 25 min. The solution was allowed to cool to ambient temperature, and was passed through a column of Amberlite® IR-120 ion exchange resin. The column was eluted with distilled water until the washings became neutral. The combined washings were concentrated under reduced pressure, and the residual dark brown oil was purified by bulb-to-bulb distillation (200 °C. oven temperature, 0.1 mmHg) to give paraconic acid **(203)** as a colourless oil, solidifying upon standing to an off-white solid, m. pt. 56-58 °C (lit.[130] 60-63 °C) (2.2 g, 58 %); NMR (400 MHz, $CDCl_3$) δ_H 9.75 (1H, br s, CO_2H), 4.53 (2H, m, H-3), 3.50 (1H, m, H-4), 2.90 (1H, dd, J=18.0, 6.7, H-5), 2.79 (1H, dd, J=18.0, 9.6, H-5); υ_{max} 2998 (br s, O-H), 1776 (br s, C=O), 1387 (m), 1191 (s), 1032 (m), 903 (m), 670 (m) cm^{-1}; *m/z*

(EI) 130 (M^+, 2.7 %), 113 (M^+-OH, 3.5 %), 102 (21.6 %), 86 (24.5 %), 71 (78.9 %), 55 (100 %); Found: C, 45.95; H, 4.52. $C_5H_6O_4$ expected C, 46.1; H, 4.6 %.

Preparation of [(trimethylsilyl)ethynyl]trimethylstannane **(216)**

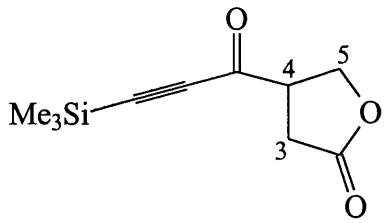
Me_3Si—≡—$SnMe_3$

(216)

A 1.54 M solution *n*-butyllithium in hexanes (33 mL, 50 mmol) was added over 30 min. to a stirred solution of trimethylsilylethyne (4.29 g, 50 mmol) in THF (30 mL) at 0 °C. Stirring was continued at this temperature for a further 30 min. A solution of trimethyl tin chloride (10.00 g, 50 mmol) in THF (5 mL) was then added over a period of 30 min. The solution was allowed to warm to ambient temperature, and stirred overnight. The reaction mixture was poured into ice-water (100 mL) and rapidly extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine at 0 °C., and dried over $MgSO_4$. The solution was filtered, the solvents removed under reduced pressure, and the residual oil purified by bulb-to-bulb distillation (oven temperature 100 °C., 10 mmHg) to give [(trimethylsilyl)ethynyl]trimethylstannane **(216)** as a colourless oil, solidifying to colourless needles upon standing, m. pt. 37-39 °C (lit.[170] 41-44 °C) (10.32 g, 76 %); NMR (400 MHz, $CDCl_3$) δ_H 0.26 (9H, s, $SnMe_3$), 0.15 (9H, s, $SiMe_3$); υ_{max} (NaCl, film) 2981 (s), 2373 (w), 2085 (alkyne, w), 1408 (m), 1249 (s), 842 (s), 699 (s) cm^{-1}; *m/z* (EI) 260 (M^+-H, 1.9 %), 247 (99.4 %), 217 (15.8 %), 185 (17.6 %), 165 (29.6 %), 135 (14.4 %), 115 (14.3 %), 97 (24.09 %), 83 (100 %); Found: C, 37.03; H, 6.85. $C_8H_{18}SiSn$ expected C, 36.8; H, 6.9 %.

Preparation of 4,5-dihydro-4-[[(trimethylsilyl)ethynyl]carbonyl]-2(3*H*)-furanone

(218)

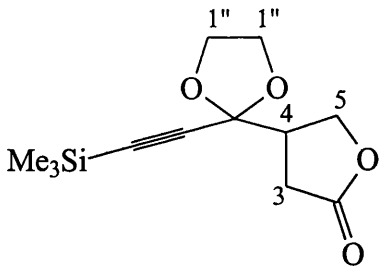


(218)

Oxalyl chloride (3.65 mL, 42 mmol) was added to a stirred suspension of paraconic acid **(203)** (5 g, 38 mmol) in DCM (80 mL). DMF (0.1 mL) was added; effervescence commenced almost at once. When effervescence had subsided, and all the paraconic acid had dissolved (*ca.* 1 h.) the solvent was removed under reduced pressure and the residual solvent removed under high vacuum for 10 min. The residue was dissolved in 1,2-dichloroethane (90 mL), and bis(triphenylphosphine)palladium(II) chloride (0.53 g, 0.75 mmol) was added. A solution of [(trimethylsilyl)ethynyl]trimethylstannane **(216)** (10.00 g, 38 mmol) in 1,2-dichloroethane (5 mL) was added, and the resulting solution was stirred for 16 h. at 50 °C. The black solution was allowed to cool to ambient temperature, and was then filtered through a pad of celite. The solution was poured into water (100 mL), and the aqueous and organic phases were separated. The aqueous phase was extracted with DCM (3 × 100 mL). The combined organic extracts were washed with brine (100 mL) and dried over $MgSO_4$. The solution was filtered and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography

(silica, gradient elution: 20 % ether in petrol to 50 % ether in petrol). **(218)** was collected as colourless needles, m. pt. 38.5-41 °C (5.3 g, 67 %); NMR (400 MHz, $CDCl_3$) δ_H 4.57 (1H, dd, J=5.9, 9.6, H-5), 4.52 (1H, dd, J=8.3, 9.5, H-5), 3.55(1H, m, H-4), 2.97 (1H, dd, J=6.5, 18, H-3), 2.76 (1H, dd, J=9.8, 18.1, H-3), 0.27 (9H, s, $SiMe_3$); υ_{max} (KBr) 2964 (m), 2150 (w, alkyne), 1785 (s, lactone C=O), 1677 (s, ynone C=O), 1472 (m), 1378 (m), 1338 (m), 1258 (s), 1180 (s), 1118 (s), 1005 (m), 844 (s), 766 (m) cm^{-1}; *m/z* (FAB) 228 (M^++Na, 14.1 %), 211 (MH^+, 100 %), 195 (25.0 %), 167 (22.2 %), 137 (37.8 %), 125 (70.7 %); Found M^+ + H 211.0780; $C_{10}H_{15}O_3Si$ requires *M* 211.0790.

Preparation of 4,5-dihydro-4-[2-[(trimethylsilyl)ethynyl]-1,3-dioxolan-2-yl]-2(3*H*)-furanone **(202)**

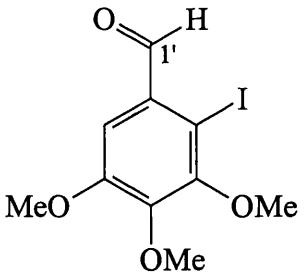


(202)

A solution of **(218)** (5.3 g, 25 mmol), ethane-1,2-diol (27 mL, 500 mmol) and pyridinium *p*-toluenesulphonate (1 g, 4.0 mmol) in benzene (500 mL) was heated at reflux for 12 h. with azeotropic removal of water. The solution was allowed to cool to ambient temperature, and was poured into sat. aq. $NaHCO_3$ (500 mL). The aqueous and organic phases were separated, and the aqueous phase extracted with ether (2 × 100 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The solution was filtered and the solvent removed under reduced pressure.

The residue was purified by flash column chromatography (silica, 50% ether in petrol as eluent) to give the ketal **(202)** as a colourless solid (5.5 g, 87 %); m. pt. 62-65 °C (lit.[128] 61.5-64.5 °C).; NMR (400 MHz, $CDCl_3$) δ_H 4.38 (2H, d, J=6.1, H-5), 4.10 (2H, m, H-1''), 3.99 (2H, m, H-1''), 2.99 (1H, m, H-4), 2.65 (1H, dd, J=17.8, 6.5, H-3), 2.60 (1H, dd, J=17.8, 9.0, H-3), 0.18 (9H, s, $SiMe_3$); υ_{max} 2961 (w), 2989 (w), 1782 (s, C=O), 1250 (m), 1178 (m), 1023 (m), 948 (w), 846 (s), 762 (w) cm^{-1}; *m/z* (FAB) 272 (M^++Na, 18.3 %), 255 (MH^+, 100 %); 239 (20.6 %), 209 (20.0 %), 193 (16.8 %), 169 (72.1 %), 157 (36.8 %), 137 (52.8 %); Found M^+ + H 255.1045; $C_{12}H_{19}O_4Si$ requires *M* 255.1053; Found: C, 56.31; H, 7.24. $C_{12}H_{18}0_4Si$ requires C, 56.7; H, 7.13 %.

Preparation of 2-iodo-3,4,5-trimethoxybenzaldehyde **(219)**

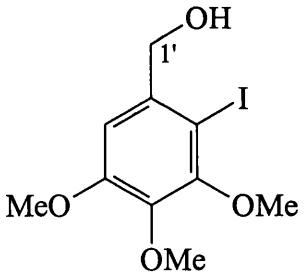


(219)

A solution of iodine (23.7 g, 93 mmol) in DCM (300 mL) was added over a period of 3 h. to a stirred solution of 3,4,5-trimethoxybenzaldehyde (16.7 g, 85 mmol) and silver trifluoroacetate (18.8 g, 85 mmol) in DCM (300 mL). Stirring was continued for 12 h. at ambient temperature. After this time, the solution was filtered, and the residue was washed with DCM (50 mL). The combined filtrate and washings were washed with 1 M aq. $Na_2S_2O_3$ solution (200 mL), sat. aq. $NaHCO_3$ (200 mL) and

brine (200 mL), and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 20 % ether in petrol as eluent) to give **(219)** as yellow crystals m. pt. 63-64 °C (lit.[16] 66-66.5 °C) (26.2 g, 96 %); NMR (400 MHz, $CDCl_3$) δ_H 10.02 (1H, s, H-1'), 7.32 (1H, s, ArH), 3.95 (3H, s, OMe), 3.89 (3H, s, OMe), 3.87 (3H, s, OMe); υ_{max} 2931 (m), 2853 (m), 1686 (s, C=O), 1570 (s), 1473 (s), 1381 (s), 1324 (s), 1161 (s), 1103 (s), 999 (m) cm^{-1}; *m/z* (FAB) 322 (M^+, 100 %), 307 (10.1 %), 165 (8.2 %), 149 (7.0 %); Found: C, 37.44; H, 3.45. $C_{10}H_{11}O_4I$ expected C, 37.3; H, 3.4 %.

Preparation of 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)**

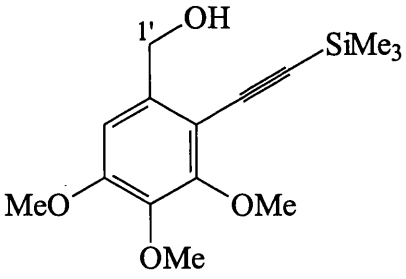


(220)

Sodium borohydride (0.7 g, 18 mmol) was added over a period of 15 min. to a stirred solution of 2-iodo-3,4,5-trimethoxybenzaldehyde **(219)** (5.8 g, 18 mmol) in methanol (50 mL) at -5 °C. Stirring was continued for an additional 15 min. at this temperature. The solution was allowed to warm to ambient temperature, and the solvent was removed under reduced pressure. The residue was acidified with 2 M hydrochloric acid. The aqueous mixture was extracted with ether (3 × 50 mL), and the combined organic extracts were washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL), and

dried over $MgSO_4$. The solution was filtered and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol as eluent) to give **(220)** as colourless needles m. pt. 56-58 °C (lit.[10] 57-58 °C) (5.1 g, 88 %); NMR (400 MHz, $CDCl_3$) δ_H 6.90 (1H, s, ArH), 4.64 (2H, d, J=5.6, H-1'), 3.86 (6H, s, 2 × OMe), 3.84 (3H, s, OMe), 2.08 (1H, br. s, OH); υ_{max} (KBr) 3268 (s, O-H), 2934 (m), 1566 (w), 1479 (s), 1393 (s), 1326 (s), 1196 (s), 1161 (s), 1107 (s), 1074 (s), 1020 (s), 919 (w), 796 (w) cm^{-1}; *m/z* (FAB) 324 (M^+, 100 %), 253 (3.5 %), 167 (4.6 %), 154 (14.6 %), 139 (10.8 %), 111 (7.7 %), 93 (5.5 %), 77 (5.9 %); Found C, 36.91; H, 3.94. $C_{10}H_{13}O_4I$ expected C, 37.1; H, 4.0 %.

Preparation of 2-[(trimethylsilyl)ethynyl]-3,4,5-trimethoxybenzenemethanol **(221)**

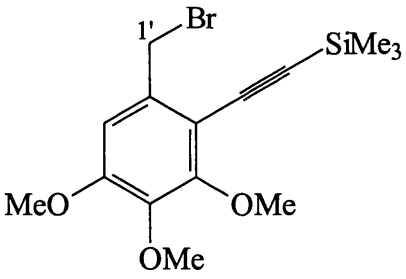


(221)

Trimethylsilylethyne (1.3 mL, 9.4 mmol) was added to a stirred solution of 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)** (2.0 g, 6.2 mmol), bis(triphenylphosphine)palladium(II) chloride (0.33 g, 0.47 mmol) and copper(I) iodide (0.18 g, 0.94 mmol) in diethylamine (12 mL). The solution was warmed to 50 °C, and stirred at this temperature for 2 h. After this time, the solution was allowed to cool to ambient temperature, and poured into water (25 mL). The aqueous mixture was extracted with ether (3 × 25 mL) and the combined organic extracts were washed with brine and dried over $MgSO_4$. The solution was filtered, and the solvents

removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol as eluent) to give **(221)** as a colourless solid,[134] m. pt. 71-73 °C (1.35 g, 74 %); NMR (400 MHz, $CDCl_3$) δ_H 6.73 (1H, s, ArH), 4.71 (2H, d, J=6.3, H-1'), 3.93 (3H, s, OMe), 3.85 (3H, s, OMe), 3.81 (3H, s, OMe), 2.23 (1H, t, J=6.3, OH), 0.24 (9H, s, $SiMe_3$); υ_{max} (KBr) 3484 (m, O-H), 2944 (m), 2145 (s, alkyne), 1595 (m), 1488 (m), 1460 (m), 1404 (m), 1327 (m), 1250 (m), 1130 (s), 1047 (m), 1022 (m), 895 (m), 847 (s) cm^{-1}; *m/z* (EI) 294 (M^+, 100 %), 279 (18.0 %), 249 (9.4 %), 221 (25.5 %), 203 (10.0 %), 132 (21.5 %), 75 (72.6 %); Found C, 60.76; H, 7.38. $C_{15}H_{22}O_4Si$ requires C, 61.2; H, 7.5 %.

Preparation of 1-(bromomethyl)-3,4,5-trimethoxy-2-[(trimethylsilyl)ethynyl]benzene **(204)**

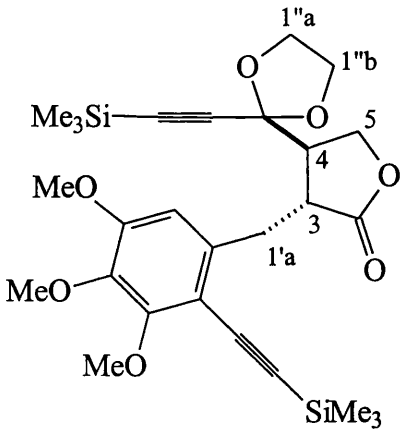


(204)

Triphenylphosphine (2.7 g, 10.2 mmol) and carbon tetrabromide (3.4 g, 10.2 mmol) were added to a stirred solution of **(221)** (1.5 g, 5.1 mmol) in ether (25 mL). The mixture was stirred for 24 h. at ambient temperature. After this time, the solution was filtered through a short pad of silica, and this was washed with ether (25 mL). The filtrate and washings were combined, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 20 %

ether in petrol as eluent) to give **(204)** as a pale brown solid (1.3 g, 72 %) m. pt 57-58 °C (lit.[128] 57-58 °C), NMR (400 MHz, $CDCl_3$) δ_H 6.70 (1H, s, ArH), 4.60 (2H, s, H-1'), 3.94 (3H, s, OMe), 3.85 (3H, s, OMe), 3.82 (3H, s, OMe), 0.26 (9H, s, $SiMe_3$); υ_{max} (KBr) 2939 (m), 2150 (m, alkyne), 1594 (w), 1460 (m), 1406 (m), 1338 (m), 1247 (m), 1078 (m), 845 (s) cm^{-1}; *m/z* (EI) 358 (M^+ (^{81}Br), 50.3 %), 357 (M^+ (^{79}Br), 46.3 %), 277 (100 %), 247 (44.9 %), 232 (27.0 %), 217 (29.8 %), 203 (39.1 %), 189 (43.2 %), 131 (50.8 %), 73 (94.5 %); Found C, 49.65; H, 5.86. $C_{15}H_{21}O_3BrSi$ requires C, 50.4; H, 50.9 %.

Preparation of (3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-[(trimethylsilyl)ethynyl]phenyl]methyl]-4-[2-[(trimethylsilyl)ethynyl]-1,3-dioxolan-2-yl] -2(3*H*)-furanone **(201)**

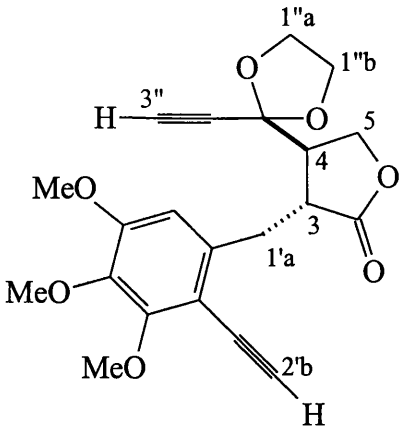


(201)

A freshly prepared 0.97 M solution of lithium diisopropylamide in THF/hexanes (2.06 mL, 2.0 mmol) was added over a period of 10 min. to a solution of **(202)** (0.57 g, 2.00 mmol) in THF (10 mL) at -78 °C. The solution was stirred for 30 min. at this temperature. After this time, a solution of **(204)** (0.71 g, 2.00 mmol) in THF (10 mL)

at -35 °C was added dropwise *via* cannula. Stirring was continued for 1 h. at -35 °C, and the solution was then allowed to warm to ambient temperature. The solution was stirred for a further 12 h. at ambient temperature. The reaction mixture was poured into sat. aq. NH_4Cl (25 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), and dried over $MgSO_4$. The solution was filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica, gradient elution; 20 % ether in petrol to 50 % ether in petrol) to give, in order of elution, recovered **(204)** (0.12 g, 17 %) and **(201)** as colourless needles, m. pt. 87-89 °C (lit.[128] 109.5-110 °C) (0.77 g, 72 %); NMR (400 MHz, $CDCl_3$) δ_H 6.58 (1H, s, ArH), 4.39 (1H, dd, J=9.9, 2.6, H-5), 4.02 (3H, m, H-5 and H-1"a or H-1"b), 3.94 (3H, s, OMe), 3.88 (2H, m, H-1"a or H-1"b), 3.84 (6H, s, 2 × OMe), 3.31 (1H, dd, J=17.1, 8.2, H-1'a), 3.08 (2H, m, H-1'a, H-3a), 2.91 (1H, dt, J=7.7, 2.4, H-4), 0.24 (9H, s, $SiMe_3$), 0.13 (9H, s, $SiMe_3$); υ_{max} (NaCl/Film) 2961 (m), 2179 (m, alkyne), 1772 (s, C=O) 1594 (w), 1493 (m), 1342 (m), 1250 (s), 1198 (s), 1129 (s), 1076 (s), 1023 (s), 845 (s) cm^{-1}; *m/z* (FAB) 553 (M^++Na, 27.5 %), 531 (MH^+, 100 %), 515 (13.2 %), 397 (6.2 %), 277(28.9 %); Found M^+ + H 531.2240; $C_{27}H_{39}O_7Si_2$ requires *M* 531.2244.

Preparation of (3*R**,4*R**)-4-[[2-ethynyl-3,4,5-trimethoxyphenyl]methyl]-3-[2-ethynyl-1,3-dioxolan-2-yl]-4,5-dihydro-2(3*H*)-furanone **(206)**

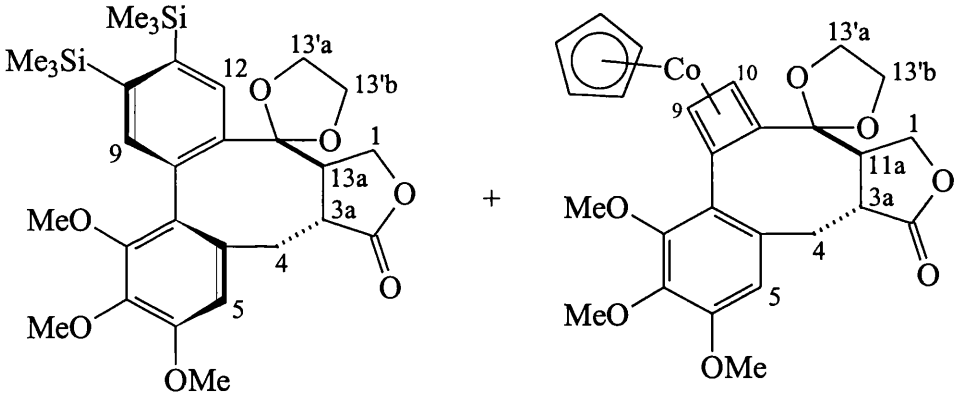


(206)

Potassium carbonate (24 mg, 0.18 mmol) was added to a stirred solution of **(201)** (0.75 g, 1.4 mmol) in methanol (10 mL). The solution was stirred for 15 h. at ambient temperature. The solution was poured into water (25 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 75 % ether in petrol as eluent) to give **(206)** as colourless needles, m. pt. 88.5-90 °C (lit.[128] 90.5-94.5 °C) (0.47 g, 88 %); NMR (400 MHz, $CDCl_3$) δ_H 6.60 (1H, s, ArH), 4.35 (1H, dd, J=10.0, 3.3, H-5), 4.10 (1H, dd, J=10.0, 8.1, H-5), 4.04 (2H, m, 2 × 1"a or 2 × 1"b), 3.94 (5H, m, 2 × 1"a or 2 × 1"b and OMe), 3.83 (6H, s, 2 × OMe), 3.41 (1H, s, H-2'b), 3.30 (1H, m, H-1'a), 3.13 (2H, m, H-1'a and H-3), 2.87 (1H, dt, J=7.9, 3.2, H-4), 2.42 (1H, s, H-3"); υ_{max} (KBr) 3267 (m), 2961 (m), 2107 (w, alkyne), 1766 (s, C=O), 1594 (m), 1492 (m), 1405 (m), 1124 (s), 1029 (m) cm^{-1}; *m/z* (EI) 386 (M^+, 4.2

%), 315 (1.6 %), 205 (7.4 %), 115 (5.1 %), 86 (98.2 %), 84 (100 %); Found, $M^+ + H$ 387.1450. $C_{21}H_{23}O_7$ requires *M* 387.1444

Preparation of (3a*R**, 13a*R**)-3a,4,13,13a-tetrahydro-6,7,8-trimethoxy-10,11-bis(trimethylsilyl)spiro[[1,3]dioxolane-1,13(1*H*)-dibenzo[1,5:6,7]cycloocta[1,2-c]furan-3-one **(209)** and (3a*R**, 11a*R**)-(η^5-2,4-cyclopentadien-1-yl)-[(8b,9,10,10a-η)-1,3,3a,4,11,11a-hexahydro-6,7,8-tetramethoxy-3-oxospiro[[1,3]dioxolane-2,11-benzo[4,5]cyclobuta[6,7]cycloocta[1,2-c]furanyl]]cobalt **(207)**



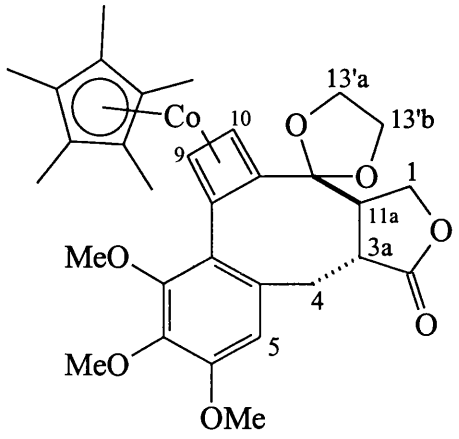
(209) **(207)**

A solution of **(206)** (40 mg, 104 μmol) in acetonitrile (1 mL) and a solution of η^5-cyclopentadienyl cobalt dicarbonyl (8.5 μL, 66 μmol) in acetonitrile (1 mL) were added over a period of 8 h. to a stirred solution of η^5-cyclopentadienyl cobalt dicarbonyl (8.5 μL, 66 μmol) in acetonitrile (2.5 mL) and bis(trimethylsilyl)ethyne (5 mL). The solution was irradiated throughout the time of reaction with a 300 W tungsten lamp, the proximity of the bulb to the reaction flask being such that the solution was caused to reflux. Irradiation of the stirred solution was continued for a further 8 h. after addition was complete. The solution was allowed to cool to ambient temperature, and the solvents were removed under reduced pressure. The residue was

purified by flash column chromatography (silica, gradient elution; 20 % ether in petrol to 50 % ether in petrol) to give, in order of elution, **(209)** as colourless needles, m. pt. 152-157.5 °C (lit.[128] 161.5-162 °C) (11 mg, 19 %); NMR (400 MHz, $CDCl_3$) δ_H 7.84 (1H, s, H-9), 7.33 (1H, s, H-12), 6.44 (1H, s, H-5), 4.24 (3H, m, H-1 and 2 × H-13'a or H-13'b), 3.90 (3H, s, OMe), 3.87 (2H, m, 2 × H-13'a or H-13'b), 3.84 (3H, s, OMe), 3.67 (1H, m, H-1), 3.65 (3H, s, OMe), 2.96 (1H, dd, J=13.8, 1.4, H-4), 2.83 (1H, m, H-13a), 2.63 (1H, m, H-3a), 2.53 (1H, dd, J=13.8, 9.5, H-4), 0.38 (9H, s, $SiMe_3$), 0.31 (9H, s, $SiMe_3$); υ_{max} 2955 (m), 1776 (s, C=O), 1654 (w), 1596 (w), 1404 (m), 1249 (m), 1194 (m), 1136 (s), 1098 (s), 1021 (m), 838 (s) cm^{-1}; *m/z* (FAB) 579 (M^++Na, 28.8 %), 556 (M^+, 100 %), 495 (23.0 %), 472 (46.4 %), 265 (15.4 %); Found M^+ + H 557.2370; $C_{29}H_{41}O_7Si_2$ requires *M* 557.2380, and **(207)** as yellow cubes, m. pt. 205-207 °C (lit.[128] 199.5-200.5 °C) (18.3 mg, 35 %); NMR indicated complex mixture of diastereomers; assignments are tentative for major component (400 MHz, $CDCl_3$) δ_H 6.58 (1H, s, ArH), 4.92 (5H, s, 5 × CpH), 4.49 (1H, s, H-9 or H-10), 4.35 (1H, t, J=8.3, H-1), 3.91 (7H, m, remaining protons), 3.83 (6H, s, 2 × OMe), 3.71 (3H, m, OMe), 3.53 (1H, dd, J=13.7, 5.3, H-4), 3.27 (1H, m, H-13a), 2.48 (1H, m, H-3a); υ_{max} (KBr) 2937 (m), 1773 (s, C=O), 1592 (m), 1464 (m), 1381 (m), 1321 (m), 1197 (s), 1102 (s), 1006 (m), 814.7 (m) cm^{-1}; *m/z* (FAB) 510 (M^+, 100 %), 391 (7.4 %), 149 (35.0 %), 136 (15.2 %), 124 (25.2 %); Found M^+ 510.1080; $C_{26}H_{27}O_7Co$ requires 510.1089

Preparation of (3a*R**, 11a*R**)-(η^5-pentamethyl-2,4-cyclopentadien-1-yl)-[(8b,9,10,10a-η)-1,3,3a,4,11,11a-hexahydro-6,7,8-tetramethoxy-3-

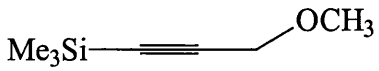
oxospiro[[1,3]dioxolane-2,11-benzo[4,5]cyclobuta[6,7]cycloocta[1,2-c]furanyl]]cobalt **(224)**



(224)

A solution of **(206)** (85 mg, 260 μmol) in THF (1 mL) and a solution of η^5-pentamethylcyclopentadienyl cobalt bis(ethene) (33 mg, 130 μmol) in THF (1 mL) were added over a period of 8 h. to a stirred solution of η^5-pentamethylcyclopentadienyl cobalt bis(ethene) (33 mg, 130 μmol) in THF (5 mL) and bis(trimethylsilyl)ethyne (10 mL) at ambient temperature. Stirring was continued for a further 8 h. after addition was complete. Solvents were removed under reduced pressure, and the residue was purified by flash column chromatography (silica, gradient elution; 20 % ether in petrol to 50 % ether in petrol as eluent) to give **(224)** as yellow crystals, m. pt. 83-84 °C (33 mg, 22 %); NMR indicated complex mixture of diastereomers; assignments are tentative for major component (400 MHz, $CDCl_3$) δ_H 6.63 (1H, s, ArH), 4.33 (1H, t, J=12.2, H-1), 3.90 (7H, m, remaining protons), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.73 (3H, s, OMe), 3.25 (1H, m, H-11a), 3.18 (1H, dd, J=13.6, 4.6, H-4), 3.10 (1H, m, H-3a), 2.98 (1H, m, H-4), 1.85 (15H, s, $CpMe_5$); υ_{max} 2902 (m), 2345 (w), 1781 (s, C=O), 1654 (m), 1560 (m), 1498 (m), 1458 (m), 1388 (m), 1210 (m), 1151 (m), 1102 (s), 1045 (m), 1023 (m) cm^{-1}; *m/z* (FAB) 580 (M^+, 100 %), 193 (6.7 %), 133 (13.2 %), 119 (5.8 %); Found M^+ 580.1880; $C_{31}H_{37}O_7Co$ requires *M* 580.1871.

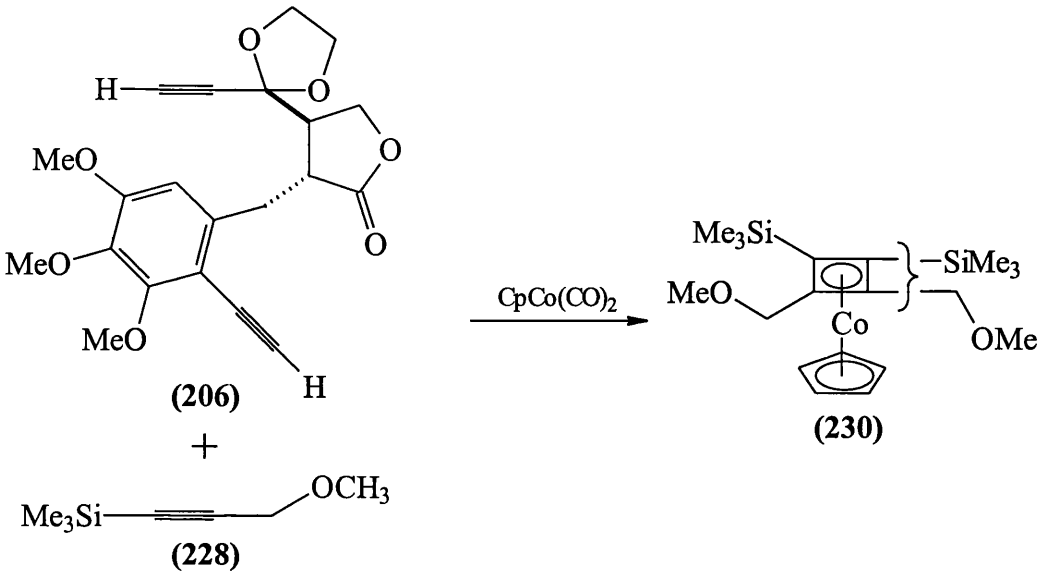
Preparation of 1-methoxy-3-(trimethylsilyl)prop-2-yne **(228)**



(228)

A 2.5 M solution of *n*-butyllithium in hexanes (24 mL, 60 mmol) was added to a stirred solution of methyl propargyl ether (5.0 mL, 60 mmol) in THF (50 mL) at -78 °C over a period of 15 min. The solution was stirred for an additional 15 min. at this temperature. Chlorotrimethylsilane (7.6 mL, 60 mmol) was added in one portion, and the solution was stirred for 1 h. at -78 °C. The solution was allowed to warm to ambient temperature, and stirring was continued for one hour. Tlc of the reaction mixture indicated that no starting material remained. Sat. aq. NH_4Cl (100 mL) and ether (100 mL) were added, and the aqueous and organic portions separated. The aqueous phase was extracted with two further portions of ether (100 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure. The residue was distilled (140–145 °C, 1 atm. (lit.[57] 144-145 °C)) to give **(228)** as a colourless oil (5.8 g, 67 %); NMR (400 MHz, $CDCl_3$) δ_H 4.07 (2H, s, CH_2), 3.36 (3H, s, OMe), 0.16 (9H, s, $SiMe_3$); υ_{max} (NaCl, film) 2950 (s), 2174 (m, alkyne), 1390 (m), 1243 (s), 1110 (s), 1003 (s), 995 (s), 856 (vs), 755 (s) cm^{-1}; *m/z* (EI) 142 (M^+, 1 %), 127 (M^+-Me, 100%), 97 (72 %), 73 (62 %), 58 (48 %), 41 (31 %); found C, 58.69; H, 10.25. $C_7H_{14}OSi$ requires C, 59.2; H, 9.9 %.

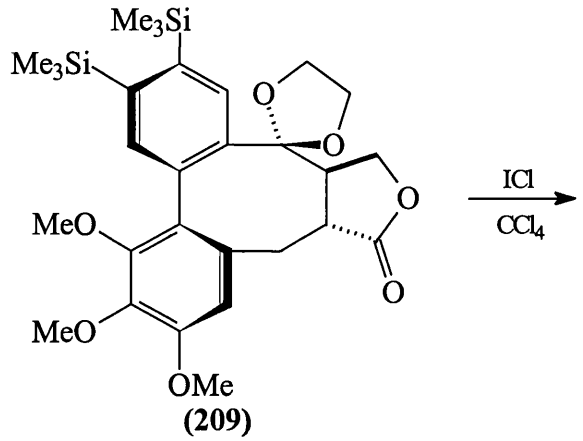
Attempted co-cyclisation of (206) with (228) and formation of (230)



Two separate solutions, one of diyne **(206)** (50 mg, 130 μmol) in THF (1 mL) and one of η^5-cyclopentadienyl cobalt dicarbonyl (17 μL, 130 μmol) in THF (1 mL) were added simultaneously over a period of 9 h. to a stirred solution of η^5-cyclopentadienyl cobalt dicarbonyl (17 μL, 130 μmol) in **(228)** (5 mL) and THF (2.5 mL). The reaction vessel was irradiated with a 300 W tungsten throughout the addition, with the bulb at such a distance from the vessel so as to maintain the solution at a temperature of 55 ± 5 °C. Irradiation of the solution was continued for a further 9 h. after the addition was complete. The solution was allowed to cool to ambient temperature, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, gradient elution; 20 % ether in petrol to 75 % ether in petrol as eluent) to give the cobalt cyclobutadiene complex **(230)** as red crystals, m. pt. 101-104.5 °C (10.2 mg, 9 % based on starting catalyst) as the only identifiable product; NMR (400 MHz, $CDCl_3$) δ_H 4.78 (5H, s, CpH), 3.84 (4H, m, 2 × CH_2), 3.26 (6H, s, 2

× OMe), 0.122 (18H, s, 2 × $SiMe_3$); υ_{max} (KBr) 2954 s, 1464 m, 1246 s, 1095 s, 840 vs cm^{-1}; satisfactory mass spectral data could not be obtained for this compound.

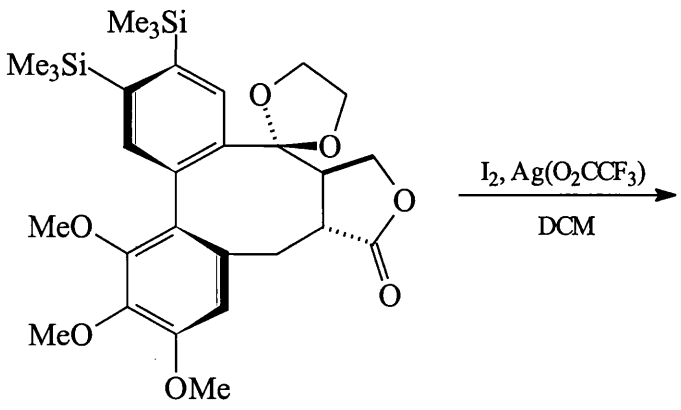
Attempted iodination of (209)



(209)

Iodine monochloride (3.0 mg, 18.5 μmol) in carbon tetrachloride (0.1 mL) was added to a stirred solution of **(209)** (6.9 mg, 12.3 μmol) in carbon tetrachloride (0.5 mL). The solution was heated at reflux for 24 h. After this time, the mixture was allowed to cool to ambient temperature, and the solution was poured into 1 M aq. $Na_2S_2O_3$ solution (5 mL). The aqueous and organic layers were separated, and the aqueous phase was extracted with DCM (2 × 5 mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 66 % ether in petrol) to recover unchanged **(209)** (5.8 mg, 84 %) as the only product.

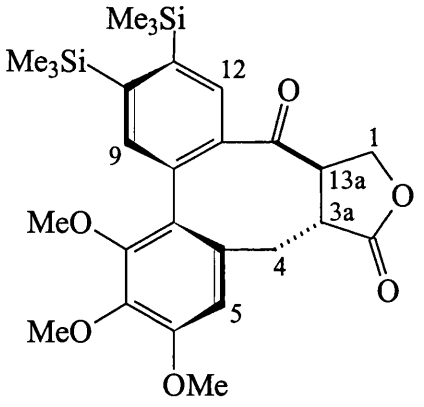
Attempted Iodination of **(209)**



(209)

A solution of iodine (6.1 mg, 23 μmol) in DCM (1.15 mL) was added over a period of 3 h. to a stirred solution of **(209)** (8.8 mg, 15 μmol) in DCM (1 mL) at ambient temperature. The solution was stirred at this temperature for an additional 5 h. after addition was complete. The solution was filtered, washed with 1 M aq. $Na_2S_2O_3$ (1 mL) and brine (1 mL), and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol) to give recovered **(209)** (6.3 mg, 72 %) as the only product.

Preparation of (3a*R**, 13a*R**)-3a,4,13,13a-tetrahydro-6,7,8-trimethoxy-10,11-bis(trimethylsilyl)spiro[oxo-1,13(1*H*)-dibenzo[1,5:6,7]cycloocta[1,2-c]furan-3-one (239)

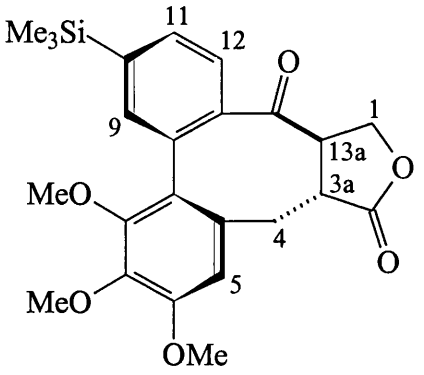


(239)

Ketal **(209)** (7.0 mg, 12.6 μmol) was stirred in formic acid (1 mL) at ambient temperature for 24 h. After this time, tlc indicated complete consumption of starting material. The solvent was removed under reduced pressure, and DCM was added. The solvent was again removed under reduced pressure, and this procedure was repeated once more to remove traces of formic acid. The residue was purified by flash column chromatography (silica, 50 % petrol in ether) to afford **(239)** as a colourless gum (3.5 mg, 54 %); NMR (400 MHz, $CDCl_3$) δ_H 8.29 (1H, s, H-12), 7.46 (1H, s, H-9), 6.57 (1H, s, H-5), 4.50 (1H, dd, J=10.3, 9.9, H-1), 4.43 (1H, m, H-1), 3.91 (3H, s, OMe), 3.90 (3H, s, OMe), 3.64 (3H, s, OMe), 3.24 (1H, d, J=12.9, H-4), 3.18 (1H, m, H-13a), 2.83 (1H, dd, J=13.1, 9.0, H-4), 2.77 (1H, dd, J=12.6, 9.0, H-3a), 0.44 (9H, s, $SiMe_3$), 0.37 (9H, s, $SiMe_3$); υ_{max} 2950 (m), 1778 (m, lactone C=O), 1674 (m, ketone C=O), 1400 (w), 1250 (m), 1137 (s), 1017 (m), 838 (s), 756 (w) cm^{-1}; *m/z* (FAB) 512

(M^+, 100 %), 496 (11.0 %), 154 (20.9 %), 136 (29.2 %); Found M^+ 512.2040; $C_{27}H_{36}O_6Si_2$ requires *M* 512.2050.

Preparation of (3a*R**, 13a*R**)-3a,4,13,13a-tetrahydro-6,7,8-trimethoxy-10-(trimethylsilyl)spiro[oxo-1,13(1*H*)-dibenzo[1,5:6,7]cycloocta[1,2-c]furan-3-one **(240)**

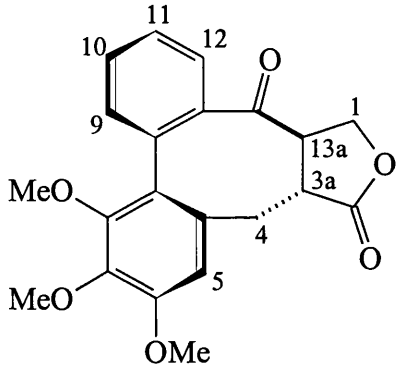


(240)

A solution of **(209)** (9.5 mg, 17 μmol) in trifluoroacetic acid (1 mL) was stirred at ambient temperature for 12 h. After this time, the solvent was removed under reduced pressure. Dichloromethane (1 mL) was added to the residue, and this was removed under reduced pressure. This procedure was repeated twice to remove traces of trifluoroacetic acid. The residue was purified by flash column chromatography (silica, 50 % ether in petrol as eluent) to give **(240)** as a colourless gum (5.5 mg, 73 %); NMR (300 MHz, C_6D_6) δ_H 8.31 (1H, d, J=7.7, H-12), 7.57 (1H, d, J=0.8, H-9), 7.51 (1H, dd, J=7.8, 1.3, H-11), 6.59 (1H, s, H-5), 4.14 (1H, dd, J=10.4, 9.2, H-1), 3.80 (3H, s, OMe), 3.76 (1H, dd, J=9.2, 7.14, H-1), 3.53 (3H, s, OMe), 3.29 (3H, s, OMe),3.25 (1H, d, J=14.1, H-4), 3.04 (1H, ddd, J=13.9, 10.4, 7.0, H-13a), 2.53 (1H, dd, J=13.7, 9.3, H-4), 1.93 (1H, dd, J=13.9, 8.60, H-3a), 0.44 (9H, s, $SiMe_3$); υ_{max} 2917 (s), 1776 (s, lactone C=O), 1673 (s, ketone C=O), 1593 (m), 1458 (m), 1401

(m), 1244 (m), 1135 (s), 1017 (s), 840 (s) cm^{-1}; *m/z* (FAB) 463 (MNa^+, 13.5 %), 440 (M^+, 91.1 %), 307 (13.3 %), 176 (27.0 %), 154 (92.6 %), 136 (100 %), 120 (22.0 %); Found M^+ 440.1655; $C_{24}H_{28}O_6Si$ requires *M* 440.1650.

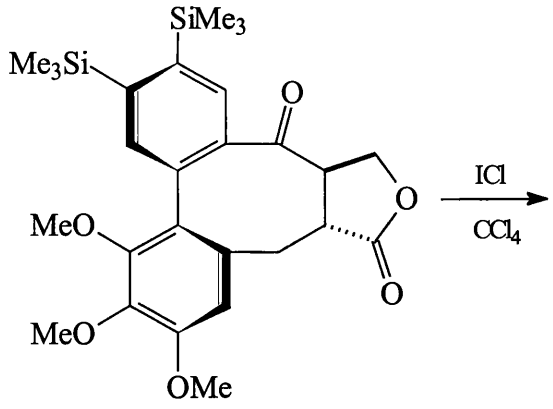
Preparation of (3a*R**, 13a*R**)-3a,4,13,13a-tetrahydro-6,7,8-trimethoxy-10-spiro[oxo-1,13(1*H*)-dibenzo[1,5:6,7]cycloocta[1,2-c]furan-3-one **(241)**



(241)

A solution of **(209)** (7.7 mg, 13.8 μmol) in trifluoroacetic acid (2 mL) was heated at reflux for 12 h. After this time, the solution was allowed to cool to ambient temperature, and the solvent was removed under reduced pressure. The residue was re-dissolved in DCM, and this was removed under reduced pressure. This procedure was repeated twice, to remove traces of trifluoroacetic acid. The residue was purified by flash column chromatography (silica, 50 % ether in petrol) to give **(241)** as a colourless gum (2.1 mg, 41 %); NMR (400 MHz, $CDCl_3$) δ_H 8.03 (1H, dd, J=7.9, 1.2, H-12), 7.58 (1H, dt, J=7.8, 1.2, H-11), 7.47 (1H, dt, J=7.9, 0.8, H-10), 7.21 (1H, dd, J=7.7, 0.8, H-9), 6.54 (1H, s, H-5), 4.44 (2H, m, 2 × H-1), 3.878 (3H, s, OMe), 3.874 (3H, s, OMe), 3.55 (3H, s, OMe), 3.22 (1H, d, J=13.2, H-4), 3.15 (1H, m, H-13a), 2.76 (1H, dd, J=13.1, 9.6, H-4), 2.73 (1H, dd, J=13.0, 9.5, H-3a); υ_{max} 2936 (m), 1776 (s, lactone C=O), 1674 (s, ketone C=O), 1595 (m), 1455 (m), 1402 (m), 1348 (m), 1236 (m), 1144 (s), 1114 (s), 1012 (s), 756 (w) cm^{-1}; *m/z* (FAB) 391 (M^++Na, 6.8 %), 368 (M^+, 53.2 %), 307 (11.8 %), 289 (11.5 %), 176 (29.8 %), 154 (100 %), 136 (99.2 %), 107 (47.0 %); Found M^+ 368.1250; $C_{21}H_{20}O_6$ requires *M* 368.1260.

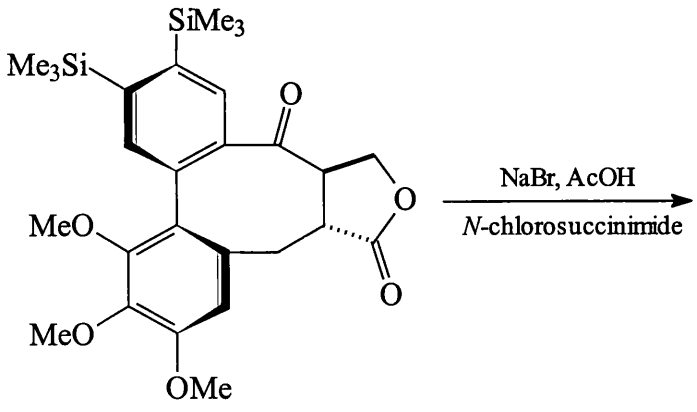
Attempted Iodination of (239)



(239)

A solution of iodine monochloride (4.4 mg, 27 μmol) in carbon tetrachloride (0.1 mL) was added to a stirred solution of **(239)** (9.2 mg, 18 μmol) in carbon tetrachloride (1 mL). The solution was stirred at ambient temperature for 12 h. Tlc indicated no reaction had occurred after this time. The solution was then heated at reflux for 12 h. After this time, tlc indicated complete decomposition of starting material had occurred.

Attempted Bromination of (239)

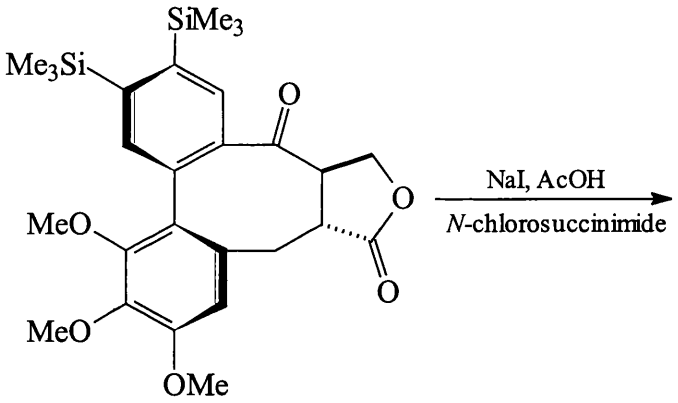


(239)

Sodium bromide (2.7 mg, 26 μmol) and *N*-chlorosuccinimide (3.6 mg, 26 μmol) were added to a stirred solution of **(239)** (10 mg, 19 μmol) in acetic acid (1 mL) at ambient temperature. The solution was stirred at this temperature for 12 h. After this time, the

solvent was removed under reduced pressure, and the residue was re-dissolved in DCM (5 mL). The solution was washed with sat. aq. $NaHCO_3$ (5 mL), 1 M aq. $Na_2S_2O_3$ (5 mL) and brine (5 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol) to give starting **(239)** (6.7 mg, 67 %) as the only product.

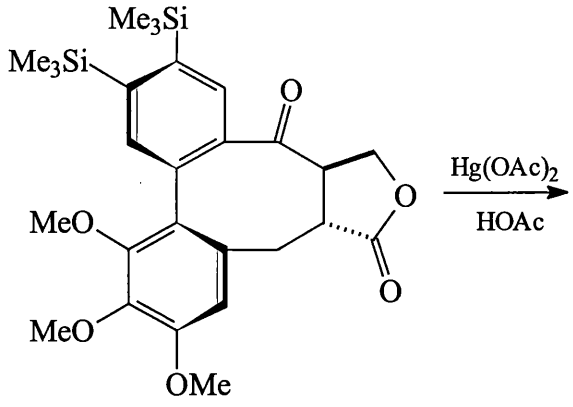
Attempted Iodination of (239)



(239)

Sodium iodide (4.0 mg, 25 μmol) and *N*-chlorosuccinimide (3.4 mg, 25 μmol) were added to a stirred solution of **(239)** (13 mg, 25 μmol) in acetic acid (1 mL) at ambient temperature. The solution was warmed to 60 °C and was stirred at this temperature for 20 h. After this time, the solution was allowed to cool to ambient temperature, the solvent was removed under reduced pressure, and the residue was re-dissolved in DCM (5 mL). The solution was washed with sat. aq. $NaHCO_3$ (5 mL), 1 M aq. $Na_2S_2O_3$ (5 mL) and brine (5 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol) to give starting **(239)** (9.7 mg, 73 %) as the only product.

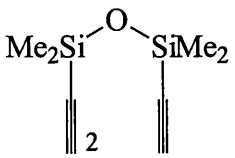
Attempted mercuration of **(239)**



(239)

Mercury(II) acetate (3.6 mg, 12 μmol) was added to a stirred solution of **(239)** (5.8 mg, 11 μmol) in acetic acid (1 mL). The solution was heated at reflux overnight. The solution was allowed to cool to ambient temperature, and the solvent was removed under reduced pressure. The residue was dissolved in DCM, and the solvent was removed under reduced pressure. This procedure was repeated twice, to remove traces of formic acid. The residue was purified by flash column chromatography (silica, 66 % ether in petrol as eluent) to give starting **(239)** (5.5 mg, 95 %) as the only product.

Preparation of 1,3-bis(ethynyl)tetramethyldisiloxane **(260)**

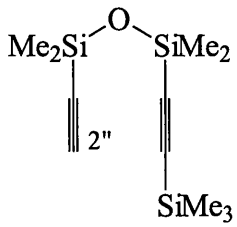


(260)

1,3-dichlorotetramethyldisiloxane **(258)** (5.0 g, 26.7 mmol) was added over a period of 1 h. to a stirred solution of ethynylmagnesium bromide (106 mL of a 0.5 M solution, 53 mmol) in THF at 0 °C. The mixture was stirred at this temperature for 1

h. The solution was then allowed to warm to ambient temperature, and was stirred for a further 5 h. The solution was poured into sat. aq. NH_4Cl (250 mL), and this mixture was extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 100 % petrol as eluent), and by bulb-to-bulb distillation (10 mmHg, oven temperature 100 °C), to afford **(260)** as a colourless, mobile liquid (2.86 g, 66 %); NMR (400 MHz, $CDCl_3$) δ_H 2.43 (2H, s, 2 × H-2), 0.31 (12H, s, 2 × $SiMe_2$); υ_{max} 3285 (s, alkyne), 2966 (m), 2039 (m, alkyne), 1406 (w), 1250 (s), 1063 (s), 840 (s), 802 (s), 695 (s) cm^{-1}; *m/z* (EI) 167 (M^+-Me, 100 %), 157 (11.9 %), 133 (16.2 %), 93 (21.2 %), 83 (54.3 %), 73 (63.0 %); Found C, 52.22; H, 8.00. $C_8H_{14}Si_2O$ requires C, 52.7; H, 7.7 %.

Preparation of 1-[(trimethylsilyl)ethynyl]-3-(ethynyl)tetramethyldisiloxane **(257)**

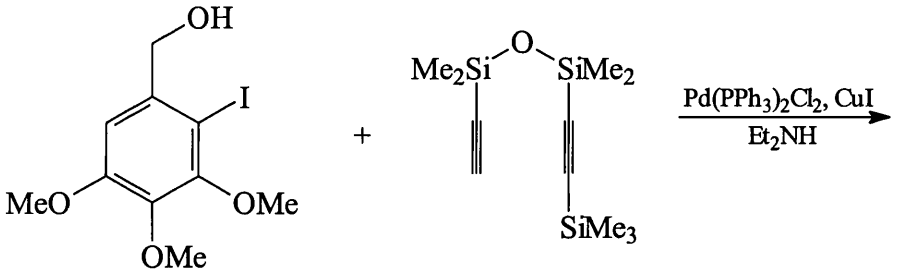


(257)

A solution of *n*-butyllithium in hexanes (3.8 mL of a 1.6 M solution, 6.1 mmol) was added over a period of 10 min. to a stirred solution of **(260)** (1.1 g, 6.1 mmol) in THF (15 mL) at -78 °C. The solution was stirred at this temperature for 1 h. Chlorotrimethylsilane (0.78 mL, 6.1 mmol) was added in one portion. The solution was allowed to warm to ambient temperature, and stirring was continued for a further 1 h. The solution was poured into sat. aq. NH_4Cl (25 mL), and the mixture was

extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 100 % petrol as eluent) and subsequently by bulb-to-bulb distillation (10 mmHg, oven temperature 110 °C) to give **(257)** as a colourless oil (0.78 g, 51 %); NMR (400 MHz, $CDCl_3$) δ_H 2.41 (1H, s, H-2"), 0.28 (12H, s, 2 × $SiMe_2$), 0.18 (9H, s, $SiMe_3$); υ_{max} 3296 (m, alkyne), 2962 (s), 2039 (s, alkyne), 1409 (w), 1253 (s), 1056 (s), 836 (s), 801 (s), 752 (s), 701 (m), 602 (m) cm^{-1}; *m/z* (EI) 253 (M^+-H, 1.3 %), 239 (6.5 %), 223 (16.5 %), 147 (9.1 %), 97 (11.0 %), 83 (12.9 %), 73 (100 %); Found C, 51.16; H, 9.02. $C_{11}H_{22}OSi_3$ requires C, 51.9; H, 8.7 %.

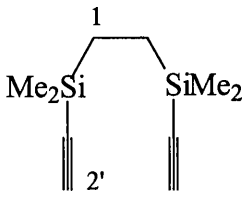
Attempted coupling of **(257)** with 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)**



(220) **(257)**

Diyne **(257)** (0.15 g, 0.60 mmol) was added to a stirred solution of 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)** (0.20 g, 0.6 mmol), bis(triphenylphosphine)palladium(II) chloride (42 mg, 60 μmol) and copper(I) iodide (21 mg, 0.11 mmol) in diethylamine (2 mL) at ambient temperature. After 12 h., tlc indicated a complex and inseparable mixture of products had formed.

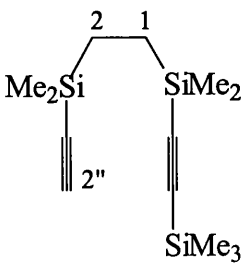
Preparation of 1,2-bis(ethynyldimethylsilyl)ethane **(361)**



(361)

A solution of 1,2-bis(chlorodimethylsilyl)ethane (4.3 g, 20 mmol) in benzene (5 mL) was added over 5 min. to a stirred, freshly prepared 1 M solution of ethynyl magnesium bromide in THF (40 mL, 40 mmol) at 0 °C. The solution was stirred at this temperature for 30 min. The solution was allowed to warm to ambient temperature, and left to stand overnight. Sat. aq. NH_4Cl (50 mL) was added, and the mixture extracted with petrol (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica, 100 % petrol as eluent). The product was distilled (75 °C, 10 mmHg) to afford **(361)** as a colourless oil (1.65 g, 42 %). NMR (400 MHz, $CDCl_3$) δ_H 2.35 (2H, s, 2 × H-2'), 0.59 (4H, s, 4 × H-1), 0.15 (12H, s, 2 × Si$\underline{Me}_2$); υ_{max} (Film) 3281 (s, alkyne), 2961 (s), 2914 (m), 2035 (s, alkyne), 1405 (m), 1251 (s), 1107 (s), 1057 (m) cm^{-1}; *m/z* (EI) 194 (M^+, 2.6 %), 179 (21.5 %), 166 (19.1 %), 151 (8.6 %), 83 (100 %); Found M^+ 194.0940; $C_{10}H_{18}Si_2$ requires M^+ 194.0947; Found C, 60.88; H, 9.56. $C_{10}H_{18}Si_2$ requires C, 61.7; H, 9.3 %.

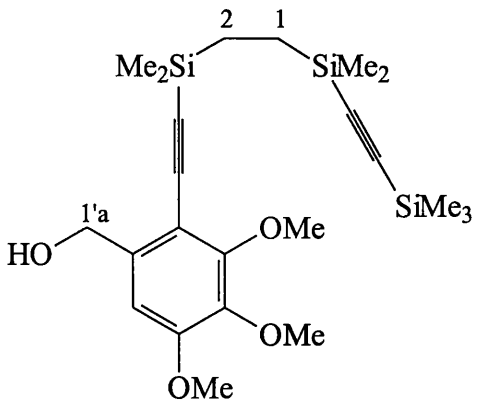
Preparation of 1-[2-[(trimethylsilyl)ethynyl]dimethlsilyl]-2-(ethynyldimethylsilyl)ethane **(261)**



(261)

A 1.0 M solution of *n*-butyllithium in hexanes (5.5 mL, 5.5 mmol) was added over a period of 10 min. to a stirred solution of **(361)** (1.0 g, 5 mmol) in THF (25 mL) at -78 °C. The solution was stirred at this temperature for 30 min. Chlorotrimethylsilane (0.7 mL, 5.5 mmol) was added over a period of 10 min. The solution was allowed to warm to ambient temperature, poured into sat. aq. NH_4Cl (25 mL) and extracted with DCM (3 × 25 mL). The combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica, 100 % petrol as eluent), and subsequently by distillation (0.1 mmHg, 75 °C oven temperature) to give **(261)** as a colourless oil (0.67 g, 50 %); NMR (400 MHz, $CDCl_3$) δ_H 2.36 (1H, s, H-2"), 0.59 (2H, d, J=9.0, H-2 or H-1), 0.56 (2H, d, J=8.4, H-2 or H-1), 0.16 (6H, s, $SiMe_2$), 0.15 (9H, s, $SiMe_3$), 0.12 (6H, s, $SiMe_2$); υ_{max} (Film) 3292 (m, alkyne), 2964 (s), 2902 (m), 2036 (m, alkyne), 1405 (m), 1251 (s), 1135 (m), 1056 (m), 841 (s) cm^{-1}; *m/z* (EI) 266 (M^+, 9.0 %), 265 (25.7 %), 251 (22.5 %), 156 (26.9 %), 155 (100 %), 140 (27.1 %), 97 (11.2 %), 83 (11.5 %), 73 (45.9 %);

Preparation of 1-[2-[(trimethylsilyl)ethynyl]dimethlsilyl]-2-[[2-[(2-hydroxymethyl-4,5,6-trimethoxy)phenyl]ethynyl]dimethylsilyl]ethane **(263)**

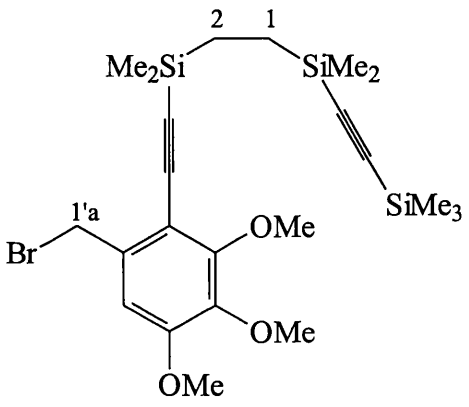


(263)

(261) (0.41 g, 1.5 mmol) was added to a stirred solution of 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)** (0.5 g, 1.5 mmol), bis(triphenylphosphine)palladium(II) chloride (0.1 g, 0.15 mmol) and copper(I) iodide (0.05 g, 0.26 mmol) in diethylamine (5 mL) at 50 °C. The solution was stirred at this temperature for 2 h. After this time, the solution was allowed to cool to ambient temperature, and was poured into sat. aq. NH_4Cl (10 mL). The aqueous mixture was extracted with ether (3 × 10 mL) and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol as eluent) to give **(263)** as a colourless gum (0.12 g, 18 %); NMR (400 MHz, $CDCl_3$) δ_H 6.74 (1H, s, ArH), 4.73 (2H, s, H-1'a), 3.94 (3H, s, OMe), 3.86 (3H, s, OMe), 3.82 (3H, s, OMe), 0.65 (4H, s, 2 × H-1 and 2 × H-2), 0.22 (6H, s, $SiMe_2$), 0.14 (9H, s, $SiMe_3$), 0.13 (6H, s, $SiMe_2$); υ_{max} (Film) 3448 (w, O-H), 2959 (m), 2149 (m, alkyne), 1595 (w), 1490 (m), 1405 (m),

1330 (m), 1250 (s), 1130 (s), 1052 (m), 842 (s) cm^{-1}; *m/z* (CI, NH_3) 463 (100 %, MH^+), 365 (25 %), 258 (32 %), 222 (27 %), 176 (15 %), 55 (57 %):· Found M^+ + Na 485.1970; $C_{23}H_{38}O_4Si_3Na$ requires *M* 485.1976.

Preparation of 1-[2-[(trimethylsilyl)ethynyl]dimethlsilyl]-2-[[2-[(2-bromomethyl-4,5,6-trimethoxy)phenyl]ethynyl]dimethylsilyl]ethane **(264)**

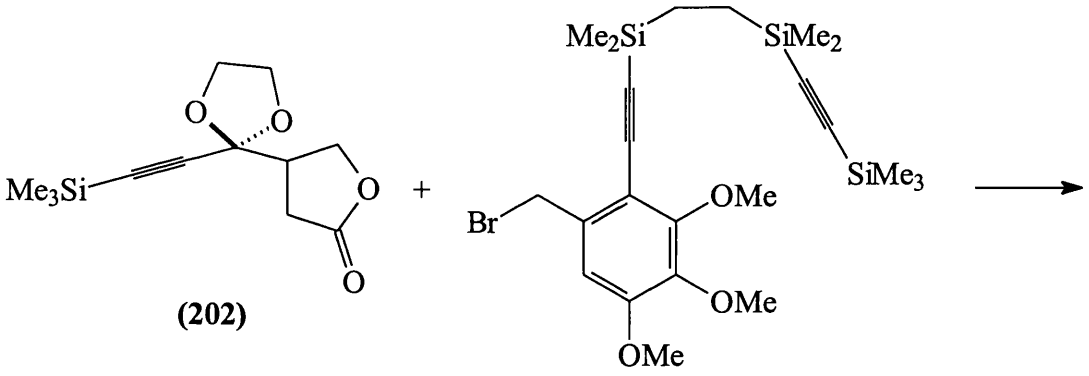


(264)

Carbon tetrabromide (0.20 g, 0.6 mmol) and triphenylphosphine (0.15 g, 0.6 mmol) were added to a stirred solution of **(263)** (0.13 g, 0.3 mmol) in ether (2.5 mL) at ambient temperature. The suspension was stirred at this temperature for 24 h. After this time, the mixture was filtered through a pad of celite, and washed with ether (3 × 5 mL). The filtrate and washings were combined, and the solvent was removed under reduced pressure. The residue purified by flash column chromatography (silica, 20 % ether in petrol as eluent) to afford **(264)** as a pale yellow gum (0.102 g, 64 %); NMR (400 MHz, $CDCl_3$) δ_H 6.71 (1H, s, ArH), 4.62 (2H, s, H-1'a), 3.97 (3H, s, OMe), 3.88 (3H, s, OMe), 3.85 (3H, s, OMe), 0.70 (4H, s, 2 × H-1 and 2 × H-2), 0.27 (6H, s, $SiMe_2$), 0.16 (9H, s, $SiMe_3$), O.15 (6H, s, $SiMe_2$); υ_{max} 2959 (m), 2199 (w, alkyne),

1593 (w), 1492 (m), 1405 (m), 1339 (m), 1250 (m), 1193 (s), 841 (s) cm^{-1}; *m/z* (FAB) 511 (M^+-Me (^{81}Br), 8.4 %), 509 (M^+-Me (^{79}Br), 6.7 %), 445 (10.1 %), 429 (6.6 %), 357 (5.0 %), 327 (5.7 %), 241 (100 %), 213 (17.1 %), 155 (91.5 %), 145 (31.0 %); Found M^+-Me 509.0990; $C_{22}H_{34}O_3Si_3Br$ requires *M* 509.0999.

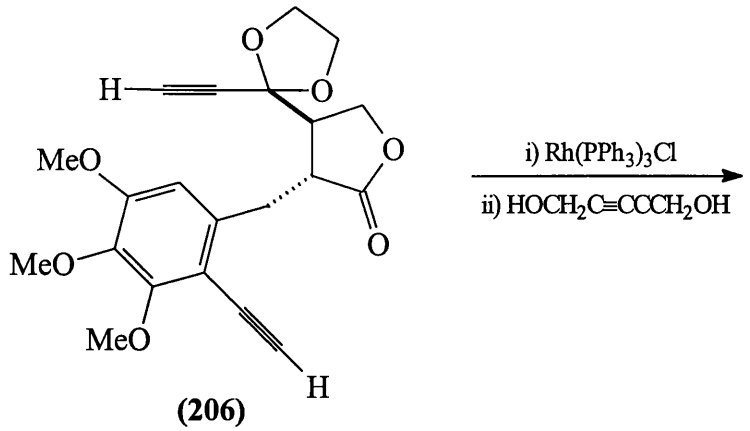
Attempted coupling of (264) and (202)



(202) **(264)**

A freshly prepared solution of lithium diisopropylamide in THF/hexanes (1.15 mL of a 0.17 M solution, 0.20 mmol) was added to a stirred solution of **(202)** (48 mg, 0.20 mmol) in THF (1 mL) at -78 °C. The solution was stirred at this temperature for 1 h. After this time, the solution was transferred *via* cannula to a stirred solution of **(264)** (100 mg, 0.20 mmol) in THF (5 mL) at -78 °C. The solution was stirred at this temperature for 1 h. After this time, the solution was allowed to warm to ambient temperature, and was stirred for a further 12 h. The solution was poured into sat. aq. NH_4Cl (10 mL), and this aqueous mixture was extracted with ether (3 × 5 mL). The combined organic phases were washed with brine (10 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography to give starting **(264)** (35 mg, 35 %) as the only product.

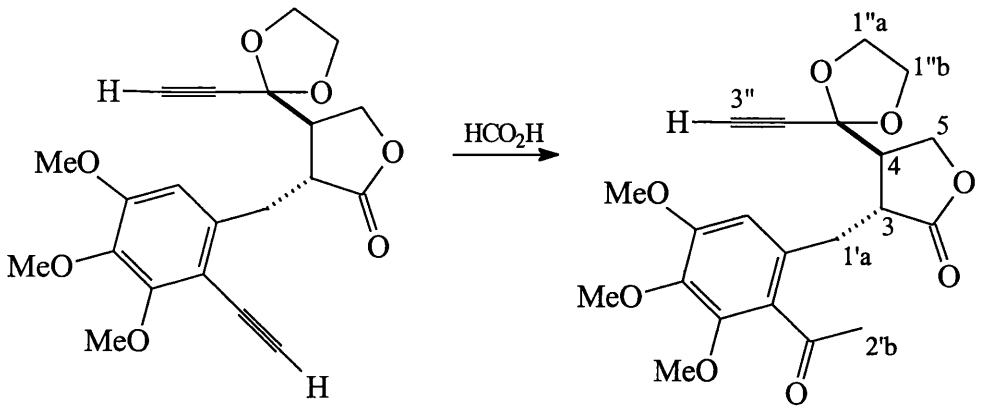
Typical attempted reaction of **(206)** with but-2-yne-1,4-diol



(206)

A solution of **(206)** (50 mg, 130 μmol) in degassed xylene (1 mL) was added to a stirred solution of tris(triphenylphosphine)rhodium(I) chloride (120 mg, 130 μmol) in xylene (4 mL). An orange precipitate formed. The solution was stirred at ambient temperature for 1 h., after which time tlc indicated that the starting diyne **(206)** had been completely consumed. The mixture was brought to reflux, giving a brown/red solution. A solution of but-2-yne-1,4-diol (110 mg, 1.3 mmol) in xylene (1 mL) was added over a period of 12 h. A black precipitate was formed. Tlc indicated that only baseline material was present in solution.

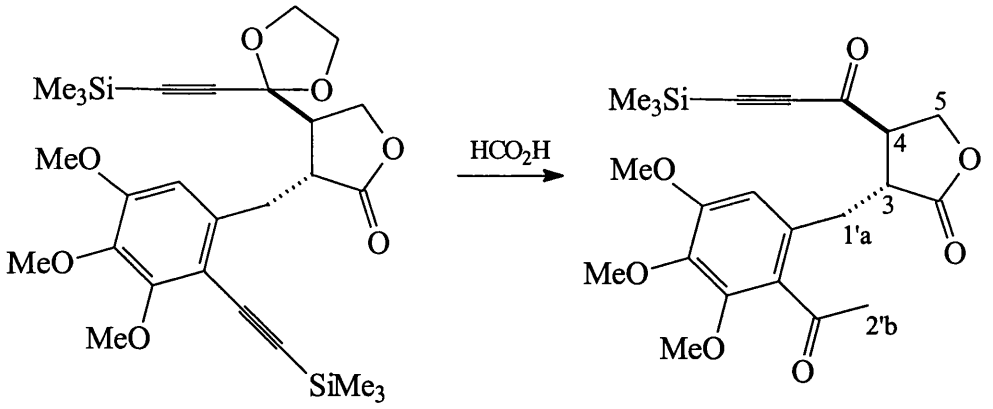
Attempted deprotection of **(206)** and formation of (3*R**,4*R**)-4-[[2-(ethan-1-oyl)-3,4,5-trimethoxyphenyl]methyl]-3-[2-ethynyl-1,3-dioxolan-2-yl]-4,5-dihydro-2(3*H*)-furanone **(271)**



(206) **(271)**

A solution of **(206)** (50 mg, 0.13 mmol) in formic acid (1 mL) was stirred at ambient temperature for 1h. After this time, tlc indicated complete consumption of starting material. The solvent was removed under reduced pressure. The residue was dissolved in DCM, and the solvent was removed under reduced pressure. This procedure was repeated twice, to remove traces of formic acid. The residue was purified by flash column chromatography (silica, 66 % ether in petrol as eluent) to afford **(271)** as a colourless solid, m. pt. 84-87 °C (38 mg, 72 %); NMR (400 MHz, $CDCl_3$) δ_H 6.68 (1H, s, ArH), 4.36 (1H, dd, J=9.9, 4.2, H-5), 4.26 (1H, dd, J=9.9, 8.0, H-5), 4.08 (2H, m, 2 × H-1"a or H-1"b), 3.96 (2H, m, 2 × H-1"a or H-1"b), 3.90 (3H, s, OMe), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 2.89 (4H, m, 2 × H-1'a, H-4 and H-3), 2.50 (3H, s, 3 × H-2'b), 2.48 (1H, s, H-3"); υ_{max} 3267 (m, alkyne), 2941 (m), 2108 (w, alkyne), 1770 (s, lactone C=O), 1689 (m, ketone C=O), 1595 (m), 1573 (w), 1496 (m), 1454 (m), 1400 (m), 1352 (m), 1323 (m), 1268 (m), 1196 (s), 1152 (s), 1104 (s), 1026 (s), 945 (m), 667 (w) cm^{-1}; *m/z* (EI) 405 (MH^+, 34.2 %), 404 (M^+, 25.3 %), 359 (21.0 %), 255 (13.0 %), 223 (29.8 %), 181 (39.7 %), 97 (100 %); Found, M^+ + H 405.1540 $C_{21}H_{25}O_8$ requires *M* 405.1549.

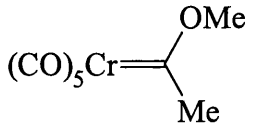
Attempted deprotection of (201) and formation of (3*R**,4*R**)-4-[[2-(ethan-1-oyl)-3,4,5-trimethoxyphenyl]methyl]-3-[[(trimethylsilyl)ethynyl]carbonyl]-4,5-dihydro-2(3*H*)-furanone (272)



(201) **(272)**

A solution of **(201)** (50 mg, 94 μmol) in formic acid (1 mL) was stirred at ambient temperature for 18 h. After this time, tlc indicated complete consumption of starting material. The solvent was removed under reduced pressure. The residue was dissolved in DCM, and the solvent was removed under reduced pressure. This procedure was repeated twice, to remove traces of formic acid. The residue was purified by flash column chromatography (silica, 66 % ether in petrol as eluent) to afford **(272)** as a colourless gum (24 mg, 58 %); NMR (400 MHz, $CDCl_3$) δ_H 6.58 (1H, s, ArH), 4.43 (1H, dd, J=9.0, 8.9, H-5), 4.30 (1H, dd, J=9.3, 7.4, H-5), 3.91 (3H, s, OMe), 3.87 (3H, s, OMe), 3.86 (3H, s, OMe), 3.61 (1H, dd, J=12.0, 7.9, H-4), 3.46 (1H, ddd, J=12.2, 8.1, 5.5, H-3), 3.05 (1H, dd, J=14.0, 5.5, H-1'a), 2.83 (1H, dd, J=13.9, 8.0, H-1'a), 2.49 (3H, s, 3 × H-2'b), 0.23 (9H, s, $SiMe_3$); υ_{max} 2963 (m), 2150 (w, alkyne), 1778 (s, lactone C=O), 1677 (s, ketone C=O), 1594 (m), 1570 (m), 1496 (m), 1454 (w), 1400 (m), 1352 (m), 1326 (m), 1253 (m), 1196 (m), 1152 (s), 1104 (s), 1029 (m), 849 (s), 763 (w) cm^{-1}; *m/z* (FAB) 455 (M^++Na, 43.5 %), 432 (M^+, 69.1 %), 417 (25.4 %), 391 (20.7 %), 373 (71.7 %), 223 (50.4 %), 181 (58.4 %), 125 (100 %); Found M^+, 432.1610; $C_{22}H_{28}O_7Si$ requires *M* 432.1604.

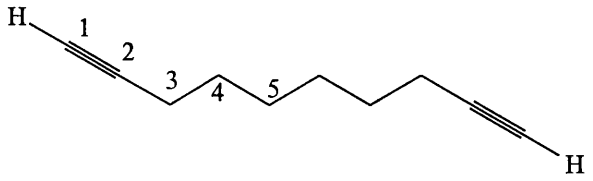
Preparation of pentacarbonyl(methoxymethylcarbene)-chromium(0) **(292)**



(292)

Methyllithium (18 mL of a 1.4 M solution in hexanes) was added over a period of 15 min. to a stirred suspension of chromium hexacarbonyl **(293)** (5 g, 23 mmol) in ether (100 mL) at ambient temperature. Five minutes after the addition was complete, the suspended solid had dissolved and a yellow solution had formed. The solution was cooled to -10° C, and methyl triflate (2.8 mL, 25 mmol) was added in one portion. The mixture was stirred at this temperature for 10 min., and was then allowed to warm to ambient temperature. The solution became orange over this period. The mixture was poured into sat. aq. $NaHCO_3$ (100 mL), the aqueous and organic phases separated, and the aqueous phase re-extracted with petrol (2 × 100 mL). The combined organic extracts were washed with brine (100 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure to afford **(292)** as orange/yellow crystals, decomposing in air, m. pt. 30-31 °C (lit.[152] 34 °C), (4.7 g, 82 %); NMR (400 MHz, $CDCl_3$) δ_H 4.72 (3H, br. s, Me), 2.96 (3H, br. s, OMe); υ_{max} (KBr) 1936 (vs, br, C=O), 1452 (m), 1257 (s), 1103 (m), 1019 (m), 895 (m), 655 (s) cm^{-1}; *m/z* (EI) 250 (M^+, 39.1 %), 222 (39.8 %), 194 (38.5 %), 165 (33.5 %), 138 (53.1 %), 110 (100 %), 95 (83.8 %), 80 (82.8 %)

Preparation of deca-1,9-diyne **(289)**

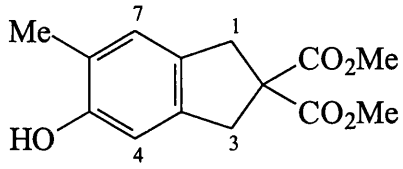


(289)

Sodium (2 g, 86 mmol) was added to a stirred solution of iron(III) nitrate (0.3 g, 1.2 mmol) in refluxing liquid ammonia (1 L). An intense blue coloration developed, and this gradually changed to a dark grey suspension. When the blue colour had completely disappeared, a further portion of sodium (13 g, 565 mmol) was added, and stirring was continued for 15 min. After this time, triphenylmethane (0.1 g) was added; the solution became dark red. Dry acetylene was bubbled through the mixture until the colour of the solution changed from red to grey. 1,6-dibromohexane (40 mL, 250 mmol) was added over a period of 45 min. The mixture was stirred for a further 4 h., and after this time ice/water (500 mL) was added (a small portion of ether was also added to prevent foaming). The aqueous mixture was extracted with petrol (4 × 250 mL), and the combined organic extracts were washed with 1 M hydrochloric acid (250 mL), sat. aq. $NaHCO_3$ (250 mL) and brine (250 mL). The solution was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude product was distilled to give **(289)** as a colourless oil (18 g, 53 %) b. pt. 78 °C/10 mmHg; NMR (400 MHz, $CDCl_3$) δ_H 2.19 (4H, dt, J=7.0, 2.7, 2 × H-3), 1.90 (2H, t, J=2.7, 2 × H-1), 1.48 (4H, m, 2 × H-4 or H-5), 1.31 (4H, m, 2 × H-4 or H-5); υ_{max} (NaCl, film) 3297 (s, alkyne), 2937 (s), 2860 (s), 2117 (m, alkyne), 1463 (m), 1432 (m), 1237 (m), 636 (vs) cm^{-1}; *m/z* (EI) 133 (M^+-H, 1.5 %), 119 (6.1 %), 105

(28.9 %), 91 (98.5 %), 79 (88.2 %), 67 (74.6 %), 55 (74.9 %), 41 (100 %), 39 (100 %); found C, 89.46; H, 10.64. $C_{10}H_{14}$ requires C, 89.5; H, 10.4%.

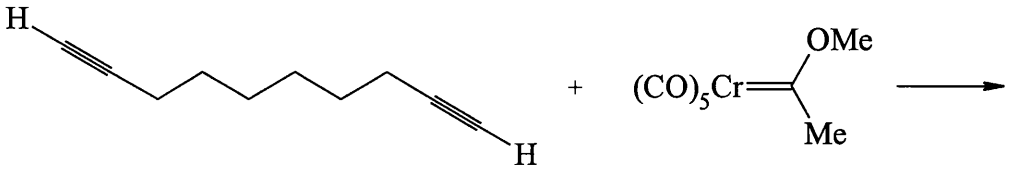
Preparation of dimethyl 5-hydroxy-6-methylindane-2,2-dicarboxylate **(295)**



(295)

A mixture of pentacarbonyl(methoxymethylcarbene)-chromium(0) **(292)** (0.42 g, 2.0 mmol) and diyne **(294)** (0.50 g, 2.0 mmol) in THF (50 mL) was stirred at 70 °C. After 2 h., the solution was allowed to cool to ambient temperature, and the mixture was poured into water (50 mL). The aqueous mixture was extracted with ether (3 × 25 mL), and the combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol as eluent) to give **(295)** as colourless needles, m. pt. 112.5-116 °C (255 mg, 48 %); NMR (400 MHz, $CDCl_3$) δ_H 6.91 (1H, s, H-4 or H-7), 6.58 (1H, s, H-4 or H-7), 4.80 (1H, br s, O<u>H</u>), 3.72 (6H, s, 2 × CO_2<u>Me</u>), 3.48 (2H, s, H-1 or H-3), 3.46 (2H, s, H-1 or H-3), 2.17 (3H, s, <u>Me</u>); υ_{max} 3488 (s, O-H), 3020 (m), 2965 (m), 1718 (s, C=O), 1621 (w), 1507 (m), 1439 (s), 1266 (s), 1186 (s), 1068 (s), 886 (m); *m/z* (FAB) 287 (MNa^+, 9 %), 264 (M^+, 70 %), 233 (15 %), 204 (57 %), 180 (100 %), 154 (62 %), 145 (33 %), 136 (63 %), 135 (63 %); Found M^+, 264.0980; $C_{14}H_{16}O_5$ requires 264.0990

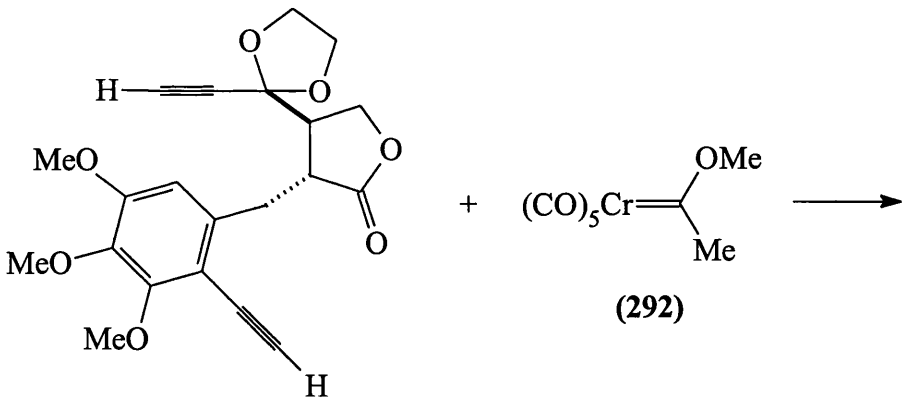
Attempted Dötz benzannulation of deca-1,9-diyne (289)



(289) **(292)**

A solution of deca-1,9-diyne **(289)** (0.50 g, 3.7 mmol) in THF (1 mL) was added over a period of 24 h. to a stirred solution of pentacarbonyl(methoxymethylcarbene)-chromium(0) **(292)** (0.77 g, 3.7 mmol) in THF (50 mL) at 70 °C. After addition was complete, tlc of the reaction mixture indicated only baseline material was present in solution.

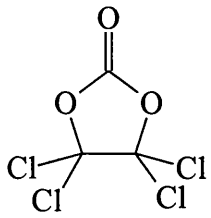
Attempted Dötz benzannulation of (206)



(206) **(292)**

A solution of **(206)** (100 mg, 0.2 mmol) in THF (1 mL) was added to a stirred solution of **(292)** (40 mg, 0.2 mmol) in THF (20 mL) at 70°C over a period of 8 h. After this time, tlc indicated that only baseline material was present in solution.

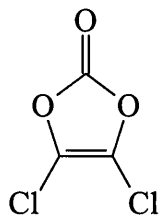
Preparation of tetrachloro-1,3-dioxolan-2-one **(308)**



(308)

Chlorine gas was bubbled through a solution of 1,3-dioxolan-2-one (17.6 g, 100 mmol) in carbon tetrachloride (40 mL) in a quartz reaction vessel. The solution was irradiated with a 400 W ultraviolet lamp. The flow of chlorine was adjusted to maintain the solution at a gentle reflux. After 24 h. a permanent yellow coloration, which did not disappear on cessation of passage of chlorine, had developed. Irradiation was ceased, and the passage of chlorine was halted. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. The residue was distilled to give **(308)** (26.2 g, 58 %) as a colourless oil, b. pt. 49 °C (7 mmHg) (lit.[171] 155 °C (760 mmHg)); NMR (133 MHz, $CDCl_3$) δ_C 143.05 (<u>C</u>=O), 113.57 (<u>C</u>Cl_2); υ_{max} (NaCl, film) 2092 (m), 1887 (vs, C=O), 1182 (s), 1036 (s), 911 (s), 781 (s), 718 (m) cm^{-1}; *m/z* (FAB) 181 (M^+-CO_2, 2.2 %), 167 (12.2 %), 149 (100 %), 136 (53.7 %), 113 (10.5 %); found C, 15.99; Cl, 61.91. $C_3O_3Cl_4$ requires C, 16.0; Cl, 62.5 %.

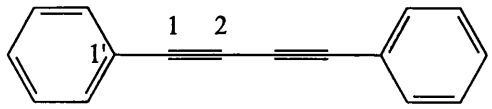
Preparation of 4,5-dichloro-1,3-dioxol-2-one **(304)**



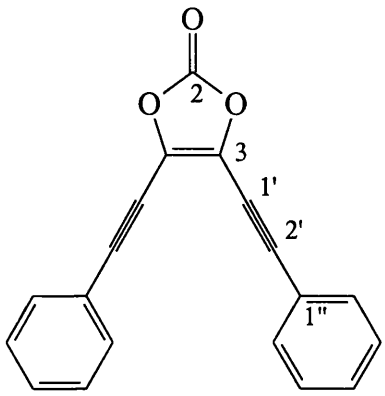
(304)

A solution of **(308)** (10.0 g, 44 mmol) in ether (25 mL) was brought to reflux. Zinc-copper amalgam[156] (7.8 g) was added portionwise over five minutes. DMF (50 μL) was added, and the solution was heated at reflux for 10 h. After this time, the solution was allowed to cool to ambient temperature and was filtered. The residue was washed with ether (3 × 10 mL), and the filtrate and washings combined. The solvent was removed under reduced pressure, and the residue was distilled to afford **(304)** (5.2 g, 76 %) as a colourless, unstable oil, solidifying on storage below 20 °C, b. pt. 70 °C (15 mmHg) (lit.[171] 147 °C (760 mmHg)); NMR (400 MHz, $CDCl_3$) δ_C 147.2 (C=O), 125.7 (CCl); υ_{max} (NaCl, film) 2181 (w), 2090 (w), 1874 (vs, C=O), 1713 (m), 1683 (s, C=C), 1173 (s), 1127 (s), 1040 (s), 932 (m), 788 (m), 750 (m) cm^{-1}.

Preparation of 1,4-biphenylbuta-1,3-diyne **(311)** and 4,5-bis[(phenyl)ethynyl]-1,3-dioxol-2-one **(310)**



(311)

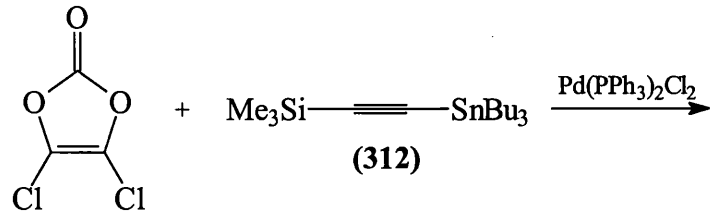


(310)

Phenylethyne (0.30 mL, 2.6 mmol) was added to a stirred solution of 4,5-dichloro-1,3-dioxol-2-one (0.25 g, 1.6 mmol), copper(I) iodide (50 mg, 0.3 mmol), tetrakis(triphenylphosphine)palladium(0) (50 mg, 80 μmol) and ethyl diisopropylamine (0.42 mL, 2.7 mmol) in benzene (2 mL). A slight effervescence was observed, and the solution turned black over a period of 30 min. After 24 h., tlc indicated that the starting phenylethyne had been completely consumed. The mixture was poured into sat. aq. NH_4Cl (25 mL), and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica, 5 % ether in petrol) to afford, in order of elution, **(311)** (76 mg, 28 % based on consumed phenylethyne) as colourless needles, m. pt. 84-86 °C, NMR (400 MHz, $CDCl_3$) δ_H 7.52 (4H, m, 2 × ArH), 7.34 (6H, m, 3 × ArH); (133 MHz, $CDCl_3$) δ_C 132.4 (ArC), 129.2 (ArC), 128.4 (ArC), 121.7 (C-1'), 81.53 (C-1), 76.7 (C-2); υ_{max} (KBr) 3048 (w), 1484 (m), 1439 (m), 915 (m), 756 (s), 686 (m) cm^{-1}; *m/z* (FAB) 202 (M^+, 100 %), 149 (19.1 %),

71 (7.8 %), 41 (17.3 %); found C, 94.86; H, 5.18. $C_{16}H_{10}$ requires C, 95.0; H, 4.9 % and **(310)** (54 mg, 12 % based on consumed dichlorovinylene carbonate) as yellow cubes, m. pt. 115-117 °C, NMR (400 MHz, $CDCl_3$) δ_H 7.54 (4H, m, 2 × ArH), 7.37 (6H, m, 3 × ArH); NMR (133 MHz, $CDCl_3$) δ_C 149.7 (C-2), 131.8 (ArC), 130.2 (ArC), 129.5 (C-3), 128.6 (ArC), 120.3 (C-1"), 103.3 (C-2'), 72.9 (C-1'); υ_{max} (KBr) 2237 (s), 2209 (m, alkyne), 1839 (s, C=O), 1490 (m), 1280 (m), 1211 (m), 1150 (s), 764 (m) cm^{-1}; *m/z* (EI) 286 (M^+, 60.8 %), 214 (100 %), 129 (21.7 %), 107 (19.1 %), 75 (14.5 %), 49 (22.0 %), 28 (30.2 %); found C, 79.90; H, 3.69. $C_{19}H_{10}O_3$ requires C, 79.7; H, 3.5 %.

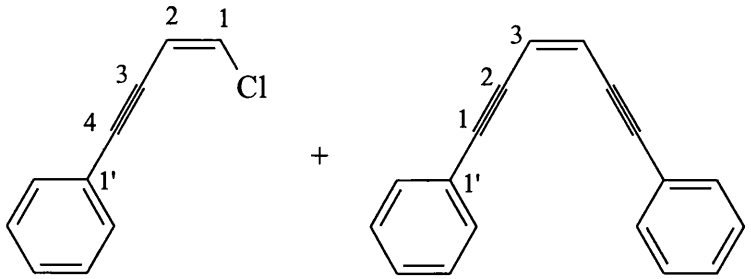
Attempted coupling of 4,5-dichloro-1,3-dioxol-2-one **(304)** and [(trimethylsilyl)ethynyl]tributylstannane **(312)**



(304) **(312)**

[(Trimethylsilyl)ethynyl]tributylstannane **(312)** (0.68 g, 1.8 mmol) was added to a stirred solution of 4,5-dichloro-1,3-dioxol-2-one **(304)** (0.25 g, 1.6 mmol) and bis(triphenylphosphine)palladium(II) chloride (5 mL) in 1,2-dichloroethane (5 mL) at ambient temperature. The yellow solution darkened rapidly. After 24 h., tlc indicated a complex mixture of products had formed; it did not prove possible to isolate or identify these.

Preparation of (*Z*)-1-chloro-4-phenylbuta-1-en-3-yne **(315)** and (Z)-1,6-diphenylhex-3-ene-1,5-diyne **(314)**

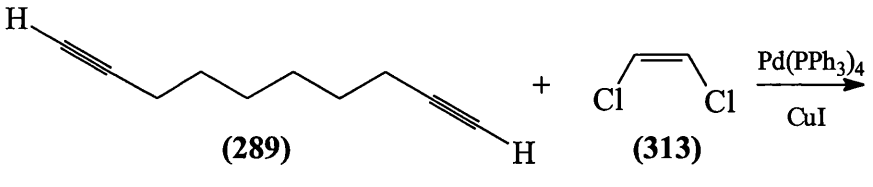


(315) **(314)**

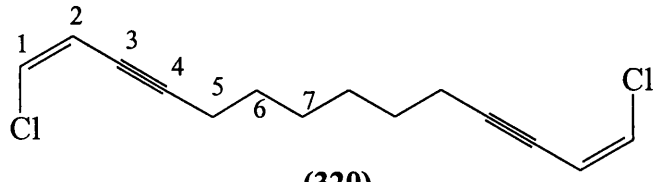
Phenylethyne (1.2 mL, 11 mmol) was added to a stirred solution of *n*-propylamine (0.9 mL, 11 mmol), (*Z*)-1,2-dichloroethene (0.38 mL, 5 mmol), copper(I) iodide (0.2 g, 1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.2 g, 0.25 mmol) in benzene (10 mL). The reaction was exothermic, and the reaction vessel was cooled with an ice bath to maintain a temperature of less than 20 °C. The mixture was stirred at ambient temperature for 20 h. After this time, the reaction mixture was poured into sat. aq. NH_4Cl (25 mL), and the aqueous and organic phases were separated. The aqueous phase was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 1 % ether in petrol as eluent) to afford, in order of elution, **(315)** (250 mg, 30 %) as a colourless oil; NMR (400 MHz, $CDCl_3$) δ_H 7.50 (2H, m, 2 × Ar<u>H</u>), 7.32 (3H, m, 3 × Ar<u>H</u>), 6.43 (1H, d, J=7.3, H-1), 6.08 (1H, d, J=7.5, H-2); (133 MHz, $CDCl_3$) δ_C 132.4 (C-1'), 131.7 (Ar<u>C</u>), 128.7 (Ar<u>C</u>), 128.3 (Ar<u>C</u>), 122.7 (C-1), 112.1 (C-2), 97.4 (C-4), 83.3 (C-3); υ_{max} (NaCl, film); 3082 (m), 2203

(m, alkyne), 1580 (m, C=C), 1488 (s), 1441 (m), 1342 (m), 1070 (m), 1028 (m), 806 (s), 756 (s), 721 (s), 689 (s), 636 (s) cm^{-1}; *m/z* (EI) 164 (M^+ (^{37}Cl), 89.3 %), 162 (M^+ (^{35}Cl), 100 %), 127 (100 %), 101 (24.1 %), 87 (21.4 %), 77 (61.4 %), 63 (51.7 %), 51 (38.9 %), 39 (16.4 %), and **(314)** as a colourless oil,[172] (570 mg, 49 %) (isomerising on standing to red needles of the *trans* isomer, m. pt. 106-109 °C); NMR (400 MHz, $CDCl_3$) δ_H 7.49 (4H, m, 4 × ArH), 7.31 (6H, m, 6 × ArH), 6.10 (2H, s, 2 × H-3); (133 MHz, $CDCl_3$) δ_C 131.7 (ArC), 128.6 (ArC), 128.4 (ArC), 123.1 (C-1'), 119.4 (C-3), 97.6 (C-1), 87.3 (C-2); υ_{max} (KBr) 3080 (m), 2174 (m, Alkyne), 1560 (m, C=C), 1485 (m), 1437 (m), 752 (s), 688 (s); *m/z* (EI) 229 (MH^+, 25.0 %), 228 (M^+, 100 %), 226 (71.6 %), 202 (19.2 %), 150 (6.3 %), 126 (23.1 %), 113 (12.6 %); Found M^+ 228.0930; $C_{18}H_{12}$ requires *M* 228.0930.

Attempted co-cyclisation of (*Z*)-1,2-dichloroethene **(313)** and deca-1,9-diyne **(289)** and formation of 1,14-dichlorotetradeca-1,13-dien-3,11-diyne **(320)**



(289) **(313)**

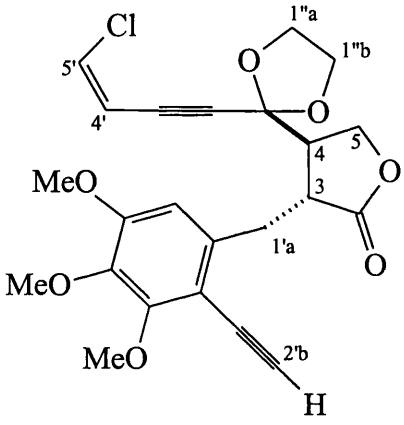


(320)

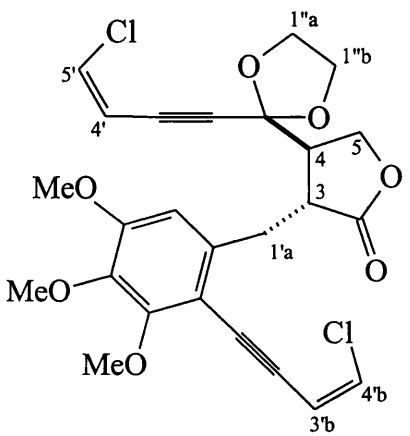
Separate solutions of deca-1,9-diyne (0.5 g, 3.7 mmol) in benzene (1 mL) and (*Z*)-1,2 dichloroethene (0.27 mL, 3.7 mmol) in benzene (1 mL) were added simultaneously over a period of 18 h. to a stirred solution of tetrakis (triphenylphosphine)palladium(0) (0.3 g, 0.37 mmol) and copper(I) iodide (0.3 g, 1.48

mmol) in diethylamine (20 mL). The solution was stirred for an additional 12 h. at ambient temperature. After this time, the mixture was poured into sat. aq. NH_4Cl (50 mL), and the aqueous and organic phases separated. The aqueous phase was extracted with ether (3 × 25 mL), and the combined organic extracts were washed with brine (25 mL), and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica, 1 % ether in petrol as eluent) to give **(320)** as a colourless oil (200 mg, 21 %); NMR (400 MHz, $CDCl_3$) δ_H 6.29 (2H, d, J=7.4, 2 × H-1), 5.85 (2H, dt, J=7.3, 2.2, 2 × H-2), 2.39 (4H, dt, J=7.0, 2.1, 4 × H-5), 2.59 (4H, m, 4 × H-6 or H-7), 1.45 (4H, m, 4 × H-6 or H-7); (133 MHz, $CDCl_3$) δ_C 126.7 (C-1), 112.5 (C-2), 99.2 (C-3), 74.7 (C-4), 28.3 (C-5, C-6 or C-7), 28.2 (C-5, C-6 or C-7), 19.6 (C-5, C-6 or C-7); υ_{max} (NaCl, film) 2936 (s), 2859 (m), 2214 (m, alkyne), 1590 (m, C=C), 1334 (m), 1131 (w), 722 (s) cm^{-1}; *m/z* (EI) 219 (M^+-HCl, 15.1 %), 177 (27.6 %), 163 (33.1 %), 155 (56.9 %), 141 (88.1 %), 73 (100 %); satisfactory microanalytical data could not be obtained for this compound.

Attempted co-cyclisation of **(206)** and (*Z*)-1,2-dichloroethene and formation of (*Z*)-(3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-(ethynyl)phenyl]methyl]-4-[2-(4-chlorobut-3-en-1-ynyl)-1,3-dioxolan-2-yl] -2(3*H*)-furanone **(322)** and (*Z,Z'*)-(3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-(4-chlorobut-3-en-1-ynyl)phenyl]methyl]-4-[2-(4-chlorobut-3-en-1-ynyl)-1,3-dioxolan-2-yl] -2(3*H*)-furanone **(362)**



(321)

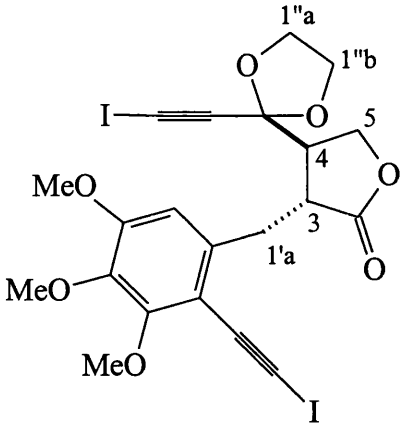


(322)

A solution of (*Z*)-1,2-dichloroethene (21 μL, 280 μmol) and **(206)** (100 mg, 260 μmol) in benzene (1 mL) was added over a period of 24 h. to a stirred solution of tetrakis(triphenylphosphine)palladium(0) (9.1 mg, 13 μmol), copper(I) iodide (5.0 mg, 26 μmol) and *n*-butylamine (50 μL, 520 μmol) in benzene (5 mL) at ambient temperature. The solution was allowed to stir at this temperature for an additional 12 h. after addition was complete. After this time, tlc indicated complete consumption of **(206)**. The mixture was poured into sat. aq. NH_4Cl (10 mL), and the aqueous and organic layers were separated. The aqueous phase was extracted with ether (2 × 10 mL), and the combined organic phases were washed with brine and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure to afford 7 mg of a substance which appeared as a single spot on tlc. NMR, however, indicated the presence of two compounds; NMR (400 MHz, $CDCl_3$) δ_H 6.66 (1H, s, ArH of **(322)** or **(362)**), 6.63 (1H, s, ArH of **(322)** or **(362)**), 6.47 (1H, d, J=7.5, vinyl CH of **(322)** or **(362)**), 6.46 (1H, d, J=7.6, vinyl CH of **(322)** or **(362)**),

6.44 (1H, d, J=7.5, vinyl CH of **(322)** or **(362)**), 6.17 (1H, d, J=7.5, vinyl CH of **(322)** or **(362)**), 5.80 (1H, d, J=7.5, vinyl CH of **(322)** or **(362)**),5.78 (1H, d, J=7.1, vinyl CH of **(322)** or **(362)**), 4.41 (1H, dd, J=9.9, 3.5, H-5 of **(322)** and **(362)**), 4.15 (1H, dd, J=9.8, 8.3, H-5 of **(322)** and **(362)**), 4.11-3.93 (8H, m, 2 × H-1"a of **(322)**, 2 × H-1"b of **(322)**, 2 × H-1"a of **(362)** and 2 × H-1"b of **(362)**) 3.98 (3H, s, OMe of **(322)** or **(362)**), 3.97 (3H, s, OMe of **(322)** or **(362)**), 3.96 (3H, s, OMe of **(322)** or **(362)**), 3.87 (3H, s, OMe of **(322)** or **(362)**), 3.86 (6H, s, 2 × OMe of **(322)** or **(362)**), 3.44 (1H, s, H-2'b of **(322)**), 3.35-2.94 (4H, m, remaining protons); υ_{max} 3278 (w), 2925 (m), 2360 (w, alkyne), 1770 (s, C=O), 1594 (m, C=C), 1492 (m), 1458 (m), 1405 (m), 1325 (m), 1248 (m), 1195 (s), 1124 (s), 1029 (m), 729 (w), 688 (w) cm^{-1}; *m/z* (FAB) 531 (M^++Na of **(362)** ($^{35}Cl^{37}Cl$), 13.4 %), 529 (M^++Na of **(362)** ($^{35}Cl^{35}Cl$), 14.2 %), 471 (M^++Na of **(322)** (^{37}Cl), 19.1 %), 469 (M^++Na of **(322)** (^{35}Cl), 60 %), 447 (M^+ of **(322)** (^{35}Cl), 22.1 %), 329 (13.4 %), 176 (100 %), 154 (48.0 %), 136 (58.3 %); Found M^+ + Na **(322)**, 469.1040; $C_{23}H_{23}O_7ClNa$ requires *M* 469.1030.

Preparation of (3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-[(iodo)ethynyl]phenyl]methyl]-4-[2-[(iodo)ethynyl]-1,3-dioxolan-2-yl]-2(3*H*)-furanone **(325)**

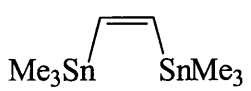


(325)

N-iodosuccinimide (0.11 g, 0.5 mmol) and silver(I) nitrate (70 mg, 0.04 mmol) were added to a stirred solution of **(206)** (0.10 g, 0.2 mmol) in THF (2 mL) at ambient

temperature. The solution was stirred at this temperature for 24 h. After this time, tlc indicated complete consumption of **(206)**. The solution was filtered through a short pad of celite, and the residue washed with ether (10 mL). The combined filtrate and washings were poured into water (10 mL), and the aqueous and organic phases were separated. The aqueous phase was extracted with further ether (2 × 10 mL), and the combined organic phases were washed with brine (15 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 66 % ether in petrol as eluent) to give **(325)** as yellow crystals (0.11 g, 65 %), m. pt. 158.0-159.9 °C, NMR (400 MHz, $CDCl_3$) δ_H 6.56 (1H, s, ArH), 4.32 (1H, dd, J=10.0, 3.1, H-5), 4.10 (1H, dd, J=10.0, 7.9, H-5), 4.05 (2H, m, H-1"a or H-1"b), 3.96 (2H, m, H-1"a or H-1"b), 3.92 (3H, s, OMe), 3.83 (3H, s, OMe), 3.82 (3H, s, OMe), 3.17 (1H, dd, J=13.1, 5.0, H-1'a), 3.10 (2H, m, H-1'a and H-3), 2.84 (1H, dt, J=7.8, 3.2, H-4); υ_{max} 2934 (m), 2172 (w, alkyne), 1750 (s, C=O), 1592 (m), 1490 (m), 1404 (m), 1343 (m), 1199 (s), 1124 (s), 1026 (s), 879 (m) cm^{-1}; *m/z* (EI) 638 (M^+, 34.7 %), 511 (38.7 %), 384 (19.6 %), 331 (23.5 %), 254 (85.7 %), 223 (93.5 %), 179 (52.0 %), 127 (25.1 %), 97 (20.6 %); Found M^+ 638.9370; $C_{21}H_{20}O_7I_2$ requires *M* 638.9377.

Preparation of (*Z*)-1,2-bis(trimethylstannyl)ethene **(323)**

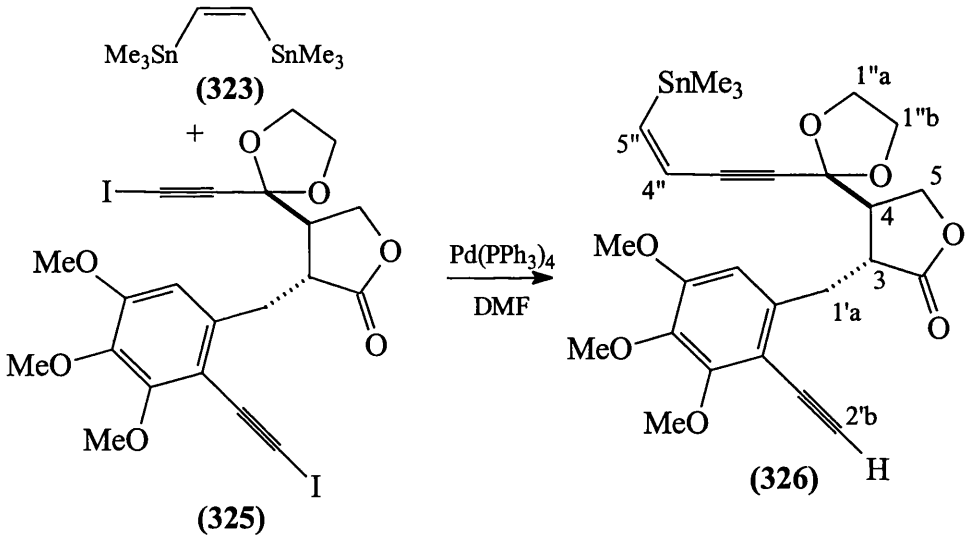


(323)

Dry acetylene was bubbled through a stirred solution of hexamethylditin (1.0 g, 3.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.1 g, 0.15 mmol) in freshly

purified 1,4-dioxan at 60 °C. After 3.5 h, the solution had turned from yellow to dark brown. The flow of acetylene was halted, the solution was allowed to cool to ambient temperature, and filtered through a pad of celite. The residue was washed with ether, and the filtrate and washings combined. The solvent was removed under reduced pressure and the residue was purified by bulb-to-bulb distillation (0.1 mmHg, oven temperature 100 °C) (lit.[130] 37 °C, 0.005 mmHg) to give **(323)** as a colourless, very unstable oil (0.73 g, 69 %) which was used without delay; NMR (400 MHz, $CDCl_3$) δ_H 7.31 (2H, s, 2 × vinyl C<u>H</u>), 0.10 (18H, s, Sn<u>Me</u>$_3$); υ_{max} 2979 (s), 2910 (s), 1788 (w), 1712 (w), 1526 (w), 1288 (m), 1189 (m), 764 (s), 586 (s), 526 (s) cm^{-1}.

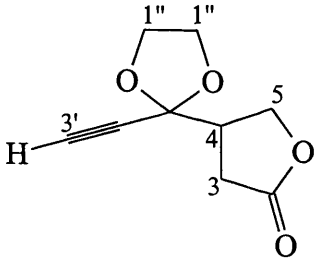
<u>Typical attempted cyclisation of **(325)** and (*Z*)-1,2-bis(trimethylstannyl)ethene **(323)** and formation of (*Z*)-(3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-(ethynyl)phenyl]methyl]-4-[2-[5-(trimethylstannyl)-4-en-2-ynyl]-1,3-dioxolan-2-yl]-2(3*H*)-furanone **(326)**</u>



A solution of (*Z*)-1,2-bis(trimethylstannyl)ethene **(323)** (30 mg, 80 μmol) in DMF (4 mL) was added to a stirred solution of **(325)** (50 mg, 78 μmol) in DMF (5 mL) at 60 °C over a period of 1 h. The solution was stirred at this temperature for 1h. after the addition was complete. The solution was allowed to cool to ambient temperature, and was poured into sat. aq. NH_4Cl (10 mL). The aqueous mixture was extracted with DCM (3 × 5 mL), and the combined organic extracts were washed with brine and

dried over $MgSO_4$. The solution was filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica, gradient elution; 20 % ether in petrol to 50 % ether in petrol as eluent) to give, in order of elution, **(326)** as brown gum (2.5 mg, 5 %) which decomposed slowly upon standing; NMR (400 MHz, $CDCl_3$) δ_H 6.66 (1H, d, J=14.3, H-4"), 6.59 (1H, s, ArH), 6.30 (1H, d, J=14.1, H-5"), 4.36 (1H, dd, J=10.0, 3.1, H-5), 4.12 (1H, dd, J=10.2, 8.1, H-5), 4.03 (2H, m, 2 × H-1"a or 2 × H-1"b), 3.94 (5H, m, OMe and 2 × H-1"a or 2 × H-1"b), 3.83 (6H, s, 2 × OMe), 3.40 (1H, s, H-2'b), 3.28 (1H, m, H-1'a), 3.12 (2H, m, H-1'a and H-3), 2.86 (1H, m, H-4), 0.19 (9H, s, $SnMe_3$); υ_{max} 2923 (s), 1770 (s, C=O), 1454 (m), 1403 (m), 1196 (s), 1124 (s) cm^{-1}; *m/z* (FAB) 577 (MH^+, 100%), 561 (38.7 %), 451 (31.1 %), 413 (39.9 %), 391 (36.9 %), 367 (33.4 %), 329 (29.2 %), 307 (80.2 %); Found M^+ + H, 577.1240, $C_{26}H_{33}O_7Sn$ requires 577.1248; and **(206)** (6.5 mg, 21 %).

Preparation of 4,5-dihydro-4-(2-ethynyl-1,3-dioxolan-2-yl)-2(3*H*)-furanone **(331)**

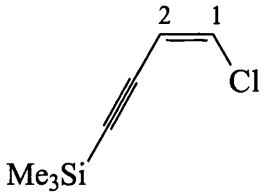


(331)

Potassium carbonate (0.1 g, 0.78 mmol) was added to a stirred solution of **(202)** (1.84 g, 7.8 mmol) in methanol (50 mL). The solution was stirred at ambient temperature for 12 h. After this time, the solution was poured into sat. aq. NH_4Cl (100 mL). The aqueous mixture was extracted with ether (3 × 50 mL) and the combined organic extracts were washed with brine (100 mL) and dried over $MgSO_4$. The solution was filtered and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica, 60 % ether in petrol as

eluent) to give **(331)** (1.00 g, 70 %) as a colourless solid, m. pt. 66-68 °C, NMR (400 MHz, $CDCl_3$) δ_H 4.39 (2H, d, J=6.7, H-5), 4.12 (2H, m, 2 × H-1"), 4.02 (2H, m, 2 × H-1"), 3.07 (1H, m, H-4), 2.66 (2H, m, H-3), 2.56 (1H, s, H-3'); υ_{max} (KBr) 3231 (s), 2989 (m), 2909 (m), 2101 (m, alkyne C-H), 1757 (s, C=0), 1474 (s), 1414 (m), 1381 (s), 1203 (s), 1105 (s), 1058 (s), 1020 (s), 945 (s), 849 (m), 743 (m), 685 (s), 522 (m) cm^{-1} ; *m/z* (EI) 183 (MH^+, 1.6 %), 110 (20.8 %), 97 (100 %), 64 (53.8 %), 53 (98 %), 43 (30.7 %), 27 (36.9 %), 18 (68.0 %); found C, 58.99; H, 5.55. $C_9H_{10}O_4$ requires C, 59.3; H, 5.5 %.

Preparation of (*Z*)-1-chloro-4-trimethylsilylbut-1-en-3-yne **(332)**[157]

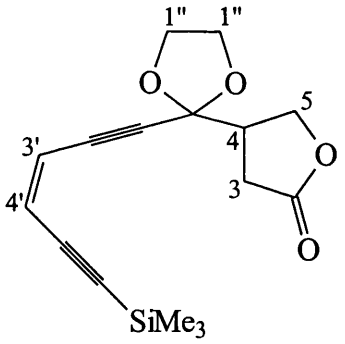


(332)

Trimethylsilylethyne (4.15 mL, 30 mmol) was added over a period of 5 min. to a stirred mixture of (*Z*)-1,2-dichloroethene (4.5 mL, 60 mmol), tetrakis(triphenylphosphine)palladium(0) (1.73 g, 1.5 mmol), copper(I) iodide (0.57 g, 3 mmol) and *n*-butylamine (6.0 mL) in ether (40 mL). The reaction was exothermic, and the temperature of the mixture was maintained at approximately 20 °C by use of a cooling bath. After 30 min., there was no further heat evolved, and the reaction mixture was stirred at ambient temperature for a further 12 h. The reaction mixture was poured into sat. aq. NH_4Cl (50 mL), and the aqueous and organic layers were separated. The aqueous phase was re-extracted with ether (2 × 50 mL), and the

combined organic extracts were washed with brine (50 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent removed under reduced pressure, maintaining the water bath temperature at 0 °C. The crude material was purified by flash column chromatography (silica, 100 % petrol), and subsequently by bulb-to-bulb distillation (1 atm., 100 °C oven temperature) to afford **(332)**[157] (2.97 g, 62 %) as a colourless oil; NMR (400 MHz, $CDCl_3$) δ_H 6.38 (1H, d, J=7.5, H-1), 5.87 (1H, d, J=7.5, H-2), 0.21 (9H, s, $SiMe_3$); υ_{max} (NaCl, film) 2961 (s), 2158 (s, alkyne), 1595 (m), 1339 (m), 1251 (s), 1040 (s), 1010 (s), 845 (s), 792 (m), 760 (m), 724 (m) cm^{-1}; *m/z* (EI) 158 (M^+, 21.7 %), 145 (67.2 %), 143 (100 %), 117 (59.4 %), 93 (10.4 %), 71 (11.3 %), 63 (28.2 %), 43 (20.7 %); Found C, 53.56; H, 7.12. $C_7H_{11}ClSi$ requires C, 53.9; H, 7.0 %.

Preparation of (*Z*)-4,5-dihydro-4-[2-[6-(trimethylsilyl)-hex-3-ene-1,5-diyne]-1,3-dioxolan-2-yl]-2(3*H*)-furanone **(333)**

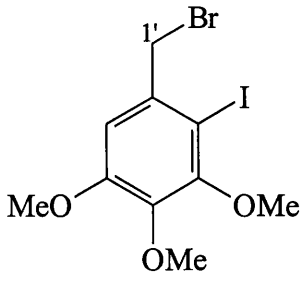


(333)

(331) (0.22 g, 1.2 mmol) was added to a stirred solution of **(332)** (0.20 g, 1.2 mmol), tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.06 mmol), copper(I) iodide (25 mg, 0.12 mmol) and *n*-butylamine (0.24 mL, 2.4 mmol) in benzene (2 mL) at ambient

temperature. The mixture was stirred at this temperature for 5 h. After this time, the dark brown solution was poured into sat. aq. NH_4Cl (15 mL), and the aqueous and organic phases separated. The aqueous phase was re-extracted with ether (3 × 15 mL), and the combined organic extracts washed with brine (15 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol) to afford **(333)** as a pale yellow oil (130 mg, 37 %); NMR (400 MHz, $CDCl_3$) δ_H 5.91 (1H, d, J=11.1, H-3'), 5.79 (1H, d, J=11.0, H-4'), 4.42 (2H, m, 2 × H-3), 4.15 (2H, m, 2 × H-1"), 4.02 (2H, m, 2 × H-1"), 3.07 (1H, m, H-4), 2.71 (1H, dd, J=18.0, 8.0, H-5), 3.62 (1H, dd, J=18.0, 9.6, H-5), 0.20 (9H, s, $SiMe_3$); υ_{max} (Film, NaCl) 2766 (m), 1781 (s, C=O), 1260(s), 1145(s), 1026(s), 844(s), 750 (s) cm^{-1}; *m/z* (FAB) 327 (M^++Na, 100 %), 305 (MH^+, 97 %), 289 (28 %), 219 (79 %), 187 (40 %), 157 (96 %), 136 (61 %), 115 (32 %), 107 (38 %); Found M^+ + H 305.1209; $C_{16}H_{21}O_4Si$ requires *M* 305.1204.

Preparation of 1-(bromomethyl)-2-iodo-3,4,5-trimethoxybenzene **(334)**

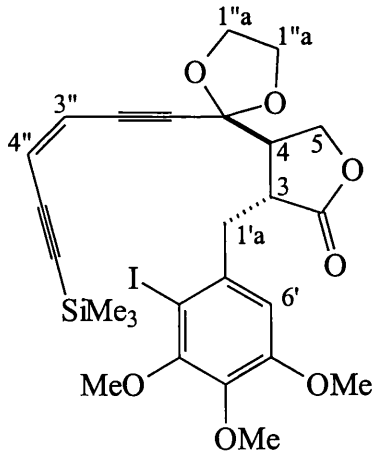


(334)

Carbon tetrabromide (1.73 g, 5.2 mmol) and triphenylphosphine (1.37 g, 5.2 mmol) were added simultaneously to a stirred solution of 2-iodo-3,4,5-trimethoxybenzyl

alcohol **(220)** (0.85 g, 2.6 mmol) in ether (20 mL). The mixture was stirred at ambient temperature for 18 h. After this time, a thick, pale brown suspension had formed. The suspension was filtered, the residue was washed with ether (2 × 25 mL), and the washings and filtrate combined. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (silica, 20 % ether in petrol as eluent). Bromide **(334)** was collected as colourless, thermally unstable needles, m. pt. 88 °C (dec.) (0.48 g, 48 %); NMR (400 MHz, $CDCl_3$) δ_H 6.87 (1H, s, ArH), 4.61 (2H, s, H-1'), 3.86 (9H, s, 3 × OMe); υ_{max} (KBr) 2937 (m), 1576 (m), 1560 (m), 1482 (m), 1386 (s), 1337 (s), 1201 (m), 1097 (s), 1006 (m), 926 (m) cm^{-1}; *m/z* (EI) 388 (M^+ (^{81}Br), 8.8 %), 386 (M^+ (^{79}Br), 8.9 %), 308 (9.6 %), 307 (100 %), 165 (7.3 %); found C, 31.00; H, 2.96. $C_{10}H_{12}O_3IBr$ requires C, 31.0; H, 3.1 %.

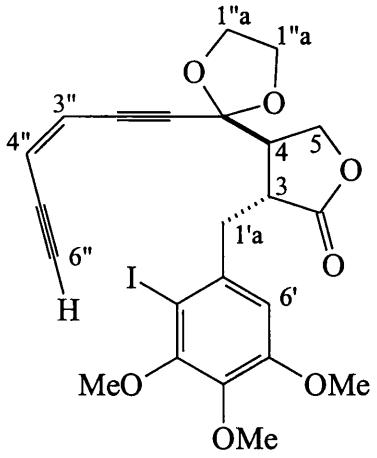
Preparation of (*Z*)-(3*R**,4*R**)-3-[[2-iodo-3,4,5-trimethoxyphenyl]methyl]-4-[2-[6-(trimethylsilyl)-hex-3-ene-1,5-diyne]-1,3-dioxolan-2-yl]-4,5-dihydro-2(3*H*)-furanone **(335)**



(335)

A freshly prepared solution of lithium diisopropylamide in THF/hexanes (3.3 mL of a 0.26 M solution) was added dropwise to a stirred solution of **(333)** (0.29 g, 1.0 mmol) in THF (5 mL) at -100 °C. The solution was stirred at this temperature for 30 min. After this time, the mixture was added dropwise, *via* cannula, to a stirred solution of **(334)** (0.37 g, 1.0 mmol) in THF (5 mL) at -100 °C. The mixture was stirred at this temperature for 1 h. It was then allowed to warm to ambient temperature, and stirred for a further 12 h. The mixture was poured into sat. aq. NH_4Cl (20 mL), and the aqueous mixture was extracted with ether (3 × 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica, gradient elution, 20 % ether in petrol to 50 % ether in petrol as eluent) to give, in order of elution, the starting bromide **(334)** (0.20 g, 54 %) and **(335)** as a colourless solid, m. pt. 86-89 °C (75 mg, 12 %); NMR (400 MHz, $CDCl_3$) δ_H 6.71 (1H, s, ArH), 5.88 (1H, d, J=11.1, H-4"), 5.70 (1H, d, J=11.0, H-3"), 4.44 (1H, dd, J=8.2, 3.7, H-5), 4.28 (1H, dd, J=8.0, 5.2, H-5), 4.10 (2H, m, 2 × H-1"a), 3.84 (2H, m, 2 × H-1"a), 3.84 (3H, s, OMe), 3.83 (3H, s, OMe), 3.81 (3H, s, OMe), 3.27 (1H, m, H-1'a), 3.15 (2H, m, H-1'a and H-3), 2.82 (1H, dt, J=7.9, 4.0, H-4), 0.18 (9H, s, $SiMe_3$); υ_{max} (KBr) 2960 (m), 1772 (s, C=0), 1481 (s), 1387 (s), 1250 (m), 1196 (s), 1104 (s), 1026 (m), 1006 (m), 645 (s), 759 (m) cm^{-1}; *m/z* (EI) 611 (M^+, 16 %), 610 (M^+-H, 49 %), 484 (19 %), 483 (55 %), 373 (17 %), 307 (75 %), 263 (19 %), 220 (22 %), 219 (100 %), 181 (48 %), 117 (19 %), 73 (52 %); Found M^+ + Na 633.0790; $C_{26}H_{31}O_7ISiNa$ requires *M* 633.0782.

Preparation of (*Z*)-(3*R**,4*R**)-3-[[2-iodo-3,4,5-trimethoxyphenyl]methyl]-4-[2-(hex-3-ene-1,5-diyne)-1,3-dioxolan-2-yl]-4,5-dihydro-2(3*H*)-furanone **(330)**

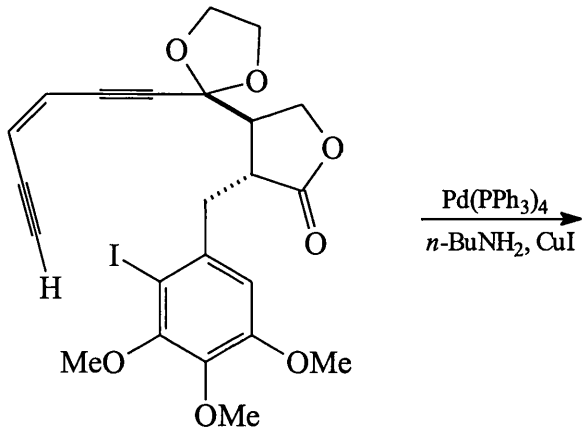


(330)

Tetra-*n*-butylammonium fluoride (75 μL of a 1.0 M solution in THF) was added in one portion to a stirred solution of **(335)** (30 mg, 50 μmol) in methanol (0.5 mL). The solution was stirred at ambient temperature for 1h. After this time, the solution was poured into water (5 mL), and extracted with DCM (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), and dried over $MgSO_4$. The solution was filtered, and the solvent removed under reduced pressure. The residue was purified by flash column chromatography (silica, 70 % ether in petrol as eluent) to give **(330)** as an unstable, yellow gum (14 mg, 52 %); NMR (400 MHz, $CDCl_3$) δ_H 6.71 (1H, s, ArH), 5.86 (1H, dd, J=11.0, 2.0, H-4"), 5.80 (1H, d, 11.0, H-3"), 4.44 (1H, dd, J=10.0, 4.1, H-3), 4.25 (1H, dd, J=9.8, 8.1, H-4), 4.08 (2H, m, 2 × 1"a), 3.96 (2H, m, 2 × 1"a), 3.84 (3H, s, OMe), 3.83 (3H, s, OMe), 3.81 (3H, s, OMe), 3.35 (1H, d, J=2.2, H-6"), 3.30 (1H, dd, J=12.9, 5.0, H-1'a), 3.19 (2H, m, H-1'a and H-3), 2.84 (1H, m, H-4); υ_{max} (Film, NaCl) 2936 (m), 1769 (s, C=O), 1563 (m), 1481 (s), 1387

(s), 1338 (m), 1328 (m), 1197 (s), 1103 (s), 1010 (m), 913 (w), 736 (w) cm^{-1}; *m/z* (EI) 539 (MH^+, 1 %), 481 (3 %), 464 (1 %), 390 (11 %), 307 (51 %), 263 (72 %), 205 (25 %), 181 (35 %), 147 (50 %), 85 (37 %), 71 (61 %), 57 (100 %), 43 (74 %); Found $M^+ + Na$ 561.0381; $C_{23}H_{23}O_7INa$ requires *M* 561.0386.

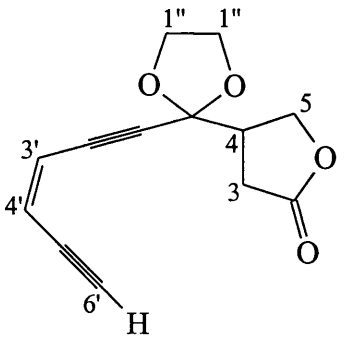
Attempted cyclisation of **(330)**



(330)

A solution of **(330)** (7 mg, 13 μmol) in benzene (1 mL) was added over a period of 24 h. to a stirred solution of tetrakis(triphenylphosphine)palladium(0) (9 mg, 52 μmol), copper(I) iodide (2 mg, 52 μmol) and *n*-butylamine (2 μL, 20 μmol) in benzene (5 mL) at ambient temperature. After this time, tlc indicated that only baseline solution existed in solution.

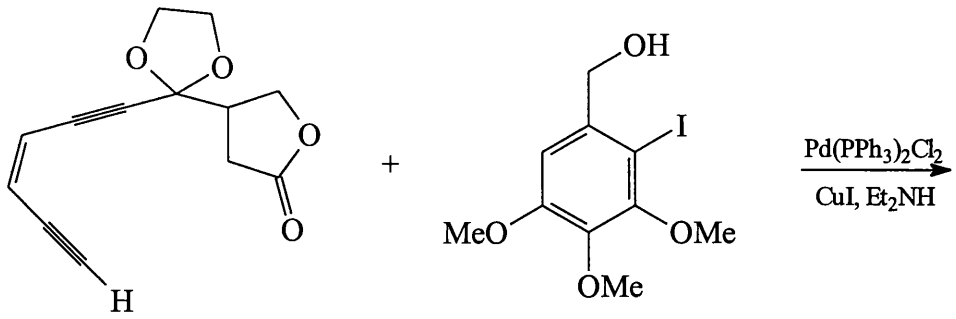
Preparation of (*Z*)-4,5-dihydro-4-[2-(hex-3-ene-1,5-diyne)-1,3-dioxolan-2-yl]-2(3*H*)-furanone (336)



(336)

Tetra-*n*-butyl ammonium fluoride (1.8 mL of a 1.1 M THF solution, 2.0 mmol) was added over a period of 5 min. to a stirred solution of **(333)** (0.58 g, 1.9 mmol) in THF (10 mL) at ambient temperature. The solution was stirred at this temperature for 2 h. After this time, the solution was poured into sat. aq. NH_4Cl (25 mL) and extracted with ether (3x10 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica, 70 % ether in petrol as eluent) to give **(336)** as an unstable, pale yellow gum (0.21 g, 45 %); NMR (400 MHz, $CDCl_3$) δ_H 5.95 (1H, d, J=12.2, H-3'), 5.53 (1H, dd, J=12.3, 2.5, H-4'), 4.24 (1H, dd, J=11.2, 2.8, H-4), 4.06 (1H, dd, J=11.2, 5.7, H-4), 3.97 (2H, m, H=1"), 3.87 (2H, m, H-1"), 3.30 (1H, d, J=2.8, H-6'), 2.54 (2H, m, H-5 and H-4), 2.28 (1H, dd, J=15.8, 7.0, H-5); υ_{max} (Film, NaCl) 3277 (m), 2899 (m), 1773 (s, C=O), 1384 (w), 1178 (m), 1020 (s), 947 (m), 844 (w), 753 (w) cm^{-1}; *m/z* (EI) 233 (M^+, 17.4 %), 205 (15.2 %), 189 (37.8 %), 171 (64.3 %), 113 (48.0 %), 79 (45.04 %), 31 (100 %); Found M^+ 233.0810; $C_{13}H_{12}O_4$ requires *M* 233.0814.

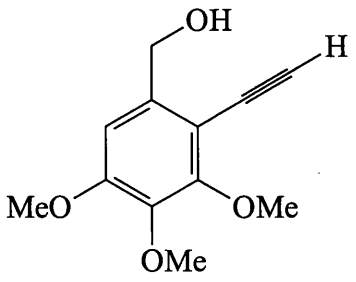
Attempted coupling of **(336)** with 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)**



(336) **(220)**

A solution of **(336)** (0.2 g, 0.8 mmol) in benzene (0.5 mL) was added to a stirred solution of 2-iodo-3,4,5-trimethoxybenzyl alcohol **(220)** (0.32 g, 1.0 mmol), copper(I) iodide (50 mg, 0.26 mmol) and bis(triphenylphosphine)palladium(II) chloride (0.1 g, 0.14 mmol) in diethylamine (2 mL) at ambient temperature. The mixture was heated to 55 °C, and stirred at this temperature for 1 h. After this time, tlc indicated only baseline material was present in solution.

Preparation of 2-ethynyl-3,4,5-trimethoxybenzyl alcohol **(340)**

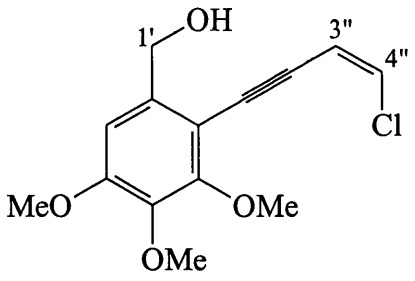


(340)

Potassium carbonate (28 mg, 0.20 mmol) was added to a stirred solution of **(221)** (0.5 g, 1.7 mmol) in methanol (10 mL). The solution was stirred for 12 h. at ambient temperature. The solution was poured into water (25 mL) and extracted with DCM (3

× 20 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol as eluent) to give **(340)**[128] as a colourless gum, decomposing on standing (0.31 g, 88 %); NMR (400 MHz, $CDCl_3$) δ_H 6.78 (1H, s, ArH), 4.74 (2H, d, J=5.3, H-1'), 3.95 (3H, s, OMe), 3.88 (3H, s, OMe), 3.84 (3H, s, OMe), 3.45 (1H, s, H-2"), 2.09 (1H, br. s, OH); υ_{max} (NaCl/Film) 3430 (s, O-H), 3283 (w), 2206 (m, alkyne) cm^{-1}; *m/z* (EI) 222 (M^+, 100 %), 193 (9.1 %), 151 (13.4 %), 119 (12.9 %), 29 (80 %); Found C, 64.26; H, 6.38. $C_{12}H_{14}O_4$ requires C, 64.8; H, 6.3 %.

Preparation of (*Z*)-2-(4-chlorobut-3-en-1-ynyl)-3,4,5-trimethoxybenzyl alcohol **(341)**

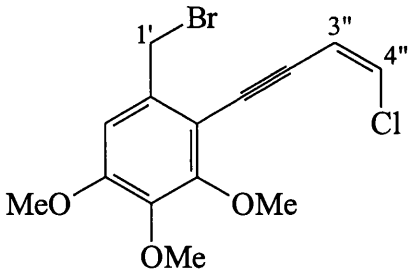


(341)

n-Butylamine (0.53 mL, 5.4 mmol) was added to a stirred solution of **(340)** (0.60 g, 2.7 mmol), copper(I) iodide (0.10 g, 0.5 mmol), tetrakis(triphenylphosphine)palladium(0) and (*Z*)-1,2-dichloroethene (0.40 mL, 5.4 mmol) in benzene (10 mL) at ambient temperature. The orange mixture was stirred at this temperature for 3 h. After this time, the mixture was poured into sat. aq. NH_4Cl (15 mL), and the aqueous and organic layers were separated. The aqueous phase was extracted with ether (2 × 10 mL), and the combined organic extracts were washed

with brine and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % petrol in ether as eluent) to afford **(341)** as a colourless gum (0.40 g, 52 %); NMR (400 MHz, $CDCl_3$) δ_H 6.78 (1H, s, ArH), 6.38 (1H, d, J=7.4, H-4"), 6.10 (1H, d, J=7.3, H-3"), 4.75 (2H, s, H-1'), 3.92 (3H, s, OMe), 3.82 (3H, s, OMe), 3.80 (3H, s, OMe), 2.67 (1H, br s, OH); υ_{max} 3416 (m, br, O-H), 2939 (m), 2199 (m, alkyne), 1598 (m, C=C), 1583 (m), 1489 (m), 1408 (s), 1322 (s), 1196 (m), 1135 (s), 1094 (m), 1067 (m), 847 (w), 723 (w) cm^{-1}; *m/z* (FAB) 284 (M^+ (^{37}Cl), 28.9 %), 283 (31.0 %), 282 (M^+ (^{35}Cl), 100 %), 267 (26.1 %), 265 (42.1 %), 136 (16.6 %), 115 (12.2 %); Found M^+ 282.0650; $C_{14}H_{15}O_4Cl$ requires *M* 282.0659.

Preparation of (*Z*)-1-bromomethyl-2-(4-chlorobut-3-en-1-ynyl)-3,4,5-trimethoxy benzene **(339)**

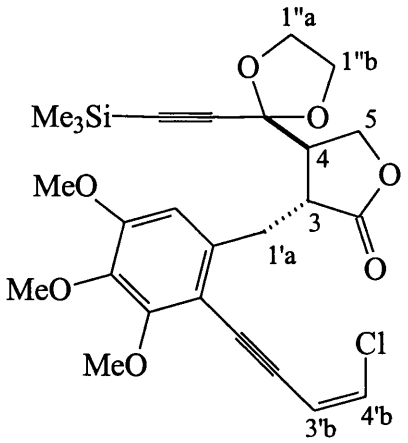


(339)

Carbon tetrabromide (0.70 g, 2.0 mmol) and triphenylphosphine (0.56 g, 2.0 mmol) were added to a solution of **(341)** (0.30 g, 1.0 mmol) in ether (5 mL). The suspension was stirred at this temperature for 24 h. After this time, the reaction mixture was filtered through a pad of celite, and the residue washed with ether (2 × 10 mL). The filtrate and washings were combined, and the solvents removed under reduced

pressure. The residue was purified by flash column chromatography (silica, 20 % ether in petrol as eluent) to afford **(339)** as a pale yellow gum (235 mg, 68 %); NMR (400 MHz, $CDCl_3$) δ_H 6.74 (1H, s, ArH), 6.44 (1H, d, J=7.4, H-4"), 6.15 (1H, d, J=7.5, H-3"), 4.68 (2H, s, H-1'), 3.96 (3H, s, OMe), 3.87 (3H, s, OMe), 3.85 (3H, s, OMe); υ_{max} 2200 (w, alkyne), 1596 (m, C=C), 1492 (s), 1460 (m), 1346 (s), 1139 (s), 1089 (s), 997 (w), 914 (w), 743 (w) cm^{-1}; *m/z* (FAB) 348 (M^+ ($^{81}Br^{37}Cl$), 8.3 %), 346 (M^+ ($^{79}Br^{37}Cl$)($^{81}Br^{35}Cl$), 29.0 %), 344 (M^+ ($^{79}Br^{35}Cl$), 22.0 %), 267 (40 %), 265 (100 %), 251 (10.6 %), 154 (17.2 %), 136 (16.8 %), 115 (11.5 %); Found M^+ 345.9960; $C_{14}H_{14}O_3ClBr$ requires *M* 345.9971.

Preparation of (*Z*)-(3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-(4-chlorobut-3-en-1-ynyl)phenyl]methyl]-4-[2-[(trimethylsilyl)ethynyl]-1,3-dioxolan-2-yl] -2(3*H*)-furanone **(347)**



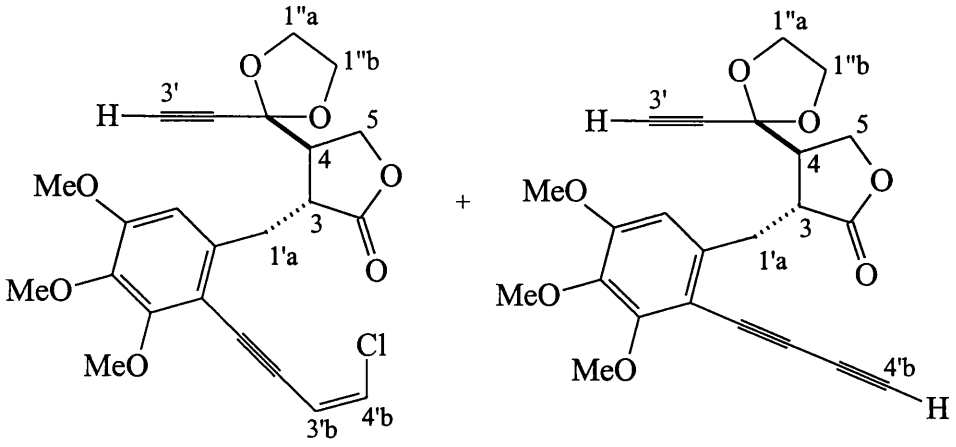
(347)

A freshly prepared solution of lithium diisopropylamide in THF/hexanes (5.43 mL of a 0.15 M solution, 0.80 mmol) was added dropwise to a stirred solution of **(202)** (0.21 g, 0.80 mmol) in THF (5 mL) at -78 °C. The solution was stirred at this

temperature for 30 min. After this time, the solution was added *via* cannula to a stirred solution of **(339)** (0.26 g, 0.70 mmol) in THF (5 mL) at -78 °C. The solution was stirred at this temperature for 1 h., and was then allowed to warm to ambient temperature and stirred for 12 h. at this temperature. The solution was poured into sat. aq. NH_4Cl (25 mL), and the aqueous mixture was extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, gradient elution; 20 % ether in petrol to 50 % ether in petrol as eluent) to give, in order of elution, the starting bromide **(339)** (52 mg, 25 %) and **(347)** as a colourless solid, m. pt. 100-101 °C (0.19 g, 45 %); NMR (400 MHz, $CDCl_3$) δ_H 6.63 (1H, s, ArH), 6.40 (1H, d, J=7.3, H-4'b), 6.14 (1H, d, J=7.3, H-3'b), 4.35 (1H, dd, J=9.9, 3.3, H-5), 4.10 (1H, dd, J=9.8, 7.9, H-5), 4.00 (2H, m, 2 × H-1"a or 2 × H-1"b), 3.95 (3H, s, OMe), 3.84 (8H, m, 2 × OMe and 2 × H-1"a or 2 × H-1"b), 3.30 (1H, dd, J=13.5, 5.4, H-1'a), 3.19 (1H, dd, J=13.8, 8.1, H-1'a), 3.10 (1H, m, H-4), 2.81 (1H, dt, J=8.1, 4.3, H-3), 0.13 (9H, s, $SiMe_3$); υ_{max} 3082 (m), 2946 (m), 2201 (m, alkyne), 1765 (s, C=O), 1596 (m), 1493 (s), 1408 (m), 1349 (m), 1246 (m), 1199 (s), 1137 (m), 1023 (m), 846 (s), 762 (m) cm^{-1}; *m/z* (FAB) 541 (MNa^+ (^{35}Cl), 29.1 %), 520 (M^+ (^{37}Cl), 52.5 %), 519 (64.1 %), 518 (M^+ (^{35}Cl), 100 %), 504 (10.0 %), 295 (12.5 %), 267 (22.9 %), 265 (50.8 %), 251 (23.4 %), 235 (18.0 %); Found M^+ + Na 541.1420; $C_{26}H_{31}O_7SiClNa$ requires *M* 541.1425.

Preparation of (*Z*)-(3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-(4-chlorobut-3-en-1-ynyl)phenyl]methyl]-4-[2-(ethynyl)-1,3-dioxolan-2-yl]-2(3*H*)-furanone **(343)** and

(3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-(buta-1,3-diynyl)phenyl]methyl]-4-[2-(ethynyl)-1,3-dioxolan-2-yl]-2(3*H*)-furanone **(344)**

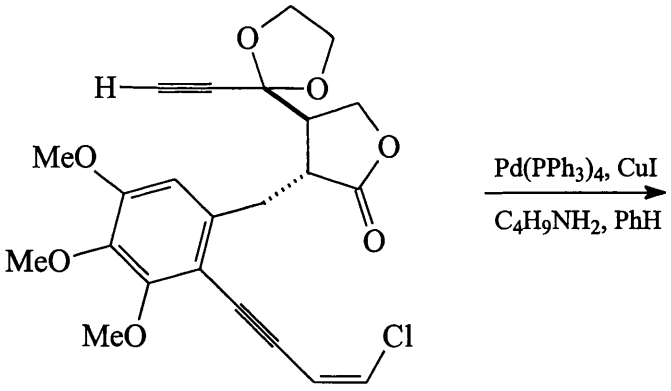


(343) **(344)**

Tetra-*n*-butylammonium fluoride in THF (0.2 mL of a 1.0 M solution, 0.2 mmol) was added over a period of 5 min. to a stirred solution of **(347)** (67 mg, 0.13 mmol) in THF (5 mL) at ambient temperature. The mixture was stirred at this temperature for 10 min. After this time, the mixture was poured into water (10 mL) and the mixture extracted with DCM (2 × 10 mL) and ether (10 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica, 33 % ether in petrol as eluent) to give an inseparable mixture of **(343)** and **(344)** as a colourless solid (39 mg, 67 %), m. pt. 65-72 °C, NMR (400 MHz, $CDCl_3$) $\delta_{H,}$ 6.65 (1H, s, ArH of **(344)** or **(343)**), 6.63 (1H, d, J=7.4, H-4'b of **(343)**), 6.16 (1H, d, J=7.4, H-3'b of **(343)**), 4.36 (2H, dd, J=9.9, 3.8, H-5 of **(344)** and **(343)**), 4.14 (2H, dd, J=9.9, 8.2, H-5 of **(344)** and **(343)**), 4.09-3.92 (8H, m, 2 × H-1"a of **(344)**, 2 × H-1"b of **(344)**, 2 × H-1"a of **(343)** and 2 × H-1"b of **(343)**), 3.98 (3H, s, OMe of **(344)** or **(343)**), 3.97 (3H, s, OMe of **(344)** or **(343)**), 3.87 (3H, s, OMe of

(344) or **(343)**), 3.86 (3H, s, OMe of **(344)** or **(343)**), 3.85 (3H, s, OMe of **(344)** or **(343)**), 3.84 (3H, s, OMe of **(344)** or **(343)**), 3.37-3.12 (6H, m, 2 × H-1'a of **(344)**, 2 × H-1'a of H-4 of **(344)** and H-4 of **(343)**), 2.88 (1H, dt, J=7.9, 3.26, H-3 of **(344)**), 2.82 (1H, dt, J=8.2, 4.2, H-3 of **(343)**), 2.57 (1H, s, H-4'b of **(344)**), 2.49 (1H, s, H-3' of **(344)**), 2.42 (1H, s, H-3' of **(343)**); υ_{max} 3252 (m), 2164 (w, alkyne), 1768 (s, C=O), 1596 (C=C), 1496 (m), 1348 (m), 1176 (s), 1094 (s) cm^{-1}; *m/z* (FAB) 469 (M^++Na, 44.8 %), 446 (M^+ of **(343)**, 100 %), 433 (44.2 %), 411 (M^+ of **(344)**, 77.0 %), 329 (12.1 %), 307 (22.1 %), 289 (17.5 %), 265 (38.6 %), 229 (37.0 %), 215 (23.4 %); Found M^+ + Na **(343)** 469.1040; $C_{23}H_{23}O_7ClNa$ requires *M* 469.1030.

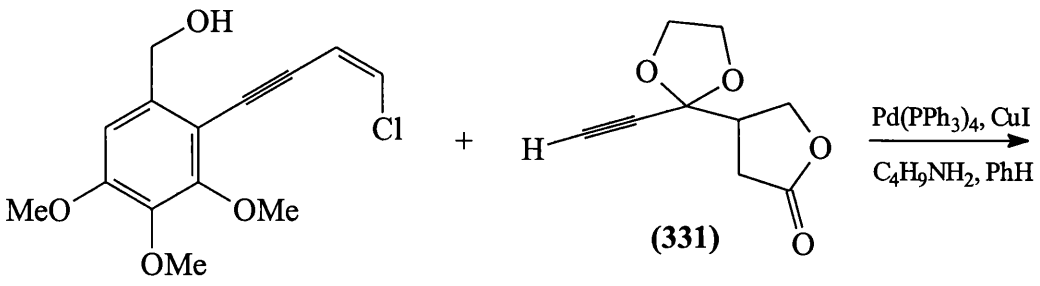
Attempted cyclisation of (343)



(343)

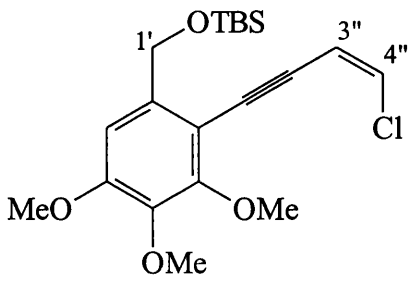
A mixture of **(343)** and **(344)** (35.0 mg) in benzene (1 mL) was added to a stirred solution of tetrakis(triphenylphosphine)palladium(0) (5.5 mg, 7.8 μmol), copper(I) iodide (2.8 mg, 15.6 μmol) and *n*-butylamine (16 μL, 156 μmol) in benzene (5 mL) over a period of 8 h. at ambient temperature. After this time, tlc indicated that only baseline material was present in solution.

Attempted coupling of **(341)** and **(331)**



n-Butylamine (0.31 mL, 3 mmol) was added to a stirred solution of **(341)** (0.43 g, 1.5 mmol), **(331)** (0.28 g, 1.5 mmol), copper(I) iodide (0.03 g, 0.15 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.05 g, 0.08 mmol) in benzene (5 mL) at ambient temperature. The solution was stirred at this temperature for 18 h. After this time, tlc indicated complete consumption of **(331)** . The reaction mixture was poured into sat. aq. NH_4Cl (10 mL), and the aqueous phase extracted with ether (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol as eluent) to afford the starting chloride **(341)** (0.13 g, 30 %) as the only product.

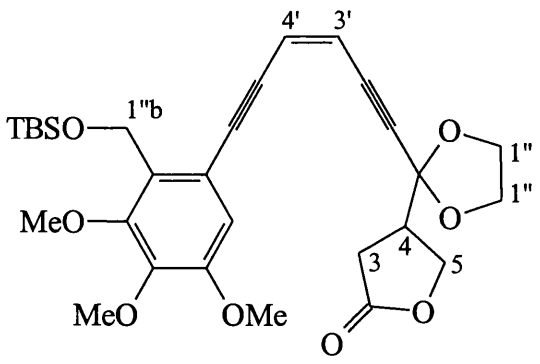
Preparation of (*Z*)-1-[[(1,1-dimethylethyl)dimethylsiloxy]methyl]-2-(4-chlorobut-3-en-1-ynyl)-3,4,5-trimethoxybenzene **(347)**



(347)

A solution of *tert*-butyldimethylchlorosilane (0.13 g, 0.83 mmol) in DCM (1 mL) was added to a stirred solution of **(341)** (0.22 g, 0.76 mmol), 4-(dimethylamino)pyridine (10 mg, 76 μmol) and triethylamine (0.2 mL, 1.5 mmol) in DCM (2 mL) at 0 °C. The mixture was stirred at this temperature for 30 min. After this time, tlc indicated complete consumption of **(341)**. The mixture was poured into sat. aq. NH_4Cl (5 mL), and the aqueous and organic phases were separated. The aqueous phase was extracted with DCM (2 × 5 mL), and the combined organic extracts were washed with brine, and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 20 % ether in petrol) to give **(347)** as a colourless gum (0.27 g, 91 %); NMR (400 MHz, $CDCl_3$) δ_H 6.98 (1H, s, ArH), 6.42 (1H, d, J=7.3, H-4"), 6.16 (1H, d, J=7.3, H-3"), 4.88 (2H, s, H-1'), 3.98 (3H, s, OMe), 3.90 (3H, s, OMe), 3.86 (3H, s, OMe), 0.97 (9H, s, $SiCMe_3$), 0.13 (6H, s, $SiMe_2$); υ_{max} 2932 (s), 2856 (s), 2198 (m, alkyne), 1582 (m, C=C), 1489 (s), 1462 (s), 1409 (m), 1343 (s), 1324 (s), 1256 (m), 1196 (m), 1138 (s), 1083 (s), 1038 (m), 1003 (m), 839 (s), 779 (m) cm^{-1}; *m/z* (FAB) 397 (M^+-H (^{37}Cl), 18.0 %), 395 (M^+-H (^{35}Cl), 22.7 %), 339 (83.1 %), 267 (44.3 %), 265 (100 %), 229 (11.2 %), 115 (20.1 %); Found M^+ - H 395.1455; $C_{20}H_{28}O_4SiCl$ requires *M* 395.1455.

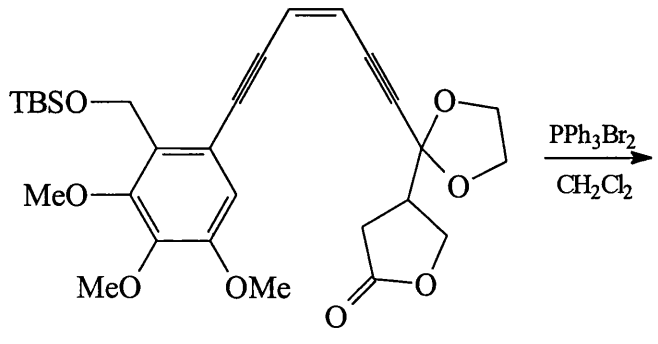
Preparation of (*Z*)-4,5-dihydro-4-[2-[6-[[(1,1-dimethylethyl)dimethylsiloxy]methyl]-3,4,5-trimethoxybenzyl]-hex-3-ene-1,5-diynyl]-1,3-dioxolan-2-yl]-2(3*H*)-furanone **(348)**



(348)

A solution of **(331)** (0.13 g, 0.70 mmol) in benzene (0.5 mL) was added to a stirred solution of **(347)** (0.18 g, 0.47 mmol), tetrakis(triphenylphosphine)palladium(0) (34 mg, 50 μmol), copper(I) iodide (20 mg, 0.11 mmol) and *n*-butylamine (0.1 mL, 1.0 mmol) in benzene (10 mL) at ambient temperature. The solution was stirred at this temperature for 5 h., after which time tlc indicated complete consumption of **(331)**. The solution was poured into sat. aq. NH_4Cl (10 mL), and the aqueous and organic phases were separated. The aqueous phase was extracted with ether (2 × 10 mL), the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, gradient elution; 20 % ether in petrol to 50 % ether in petrol as eluent) to give, in order of elution, **(347)** (30 mg, 16 %) and **(348)** as a colourless gum (130 mg, 50 %); NMR (400 MHz, $CDCl_3$) δ_H 6.95 (1H, s, ArH), 6.20 (1H, d, J=11.0, H-4'), 5.83 (1H, d, J=11.0, H-3'), 4.80 (2H, s, H-1"b), 4.42 (2H, m, H-5), 4.15 (2H, m, 2 × H-1"a), 3.99 (2H, m, 2 × H-1"a), 3.97 (3H, s, OMe), 3.89 (3H, s, OMe), 3.85 (3H, s, OMe), 3.11 (1H, m, H-4), 2.68 (2H, m, 2 × H-3), 0.97 (9H, s, $SiCMe_3$), 0.12 (6H, s, $SiMe_2$); υ_{max} 2933 (m), 2856 (m), 2183 (m, alkyne), 1784 (s, C=O), 1595 (m, C=C), 1489 (m), 1463 (m), 1412 (m), 1332 (s), 1135 (s), 1081 (m), 1027 (m), 840 (m), 779 (m) cm^{-1}; *m/z* (FAB) 565 (M^++Na, 4.2 %), 543 (MH^+, 2.16 %), 485 (10.8 %), 411 (14.0 %), 157 (100 %), 113 (10.1 %); Found M^+ + Na 565.2244; $C_{29}H_{38}O_8SiNa$ requires *M* 565.2234.

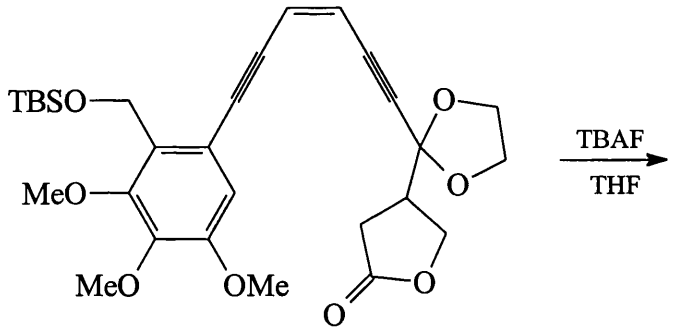
Attempted bromination of **(348)**



(348)

A solution of **(348)** (60 mg, 0.11 mmol) in DCM (1 mL) was added to a stirred solution of dibromotriphenylphosphorane (51 mg, 0.12 mmol) in DCM (2 mL) at ambient temperature. The solution was stirred at ambient temperature for 2 h. After this time, the mixture was filtered and poured into water (5 mL). The aqueous and organic phases were separated, the aqueous phase was extracted with DCM (2 × 2 mL) and the combined organic extracts were washed with brine and dried over $MgSO_4$. The solution was filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol), to give recovered **(348)** (11 mg, 18 %) as the only product.

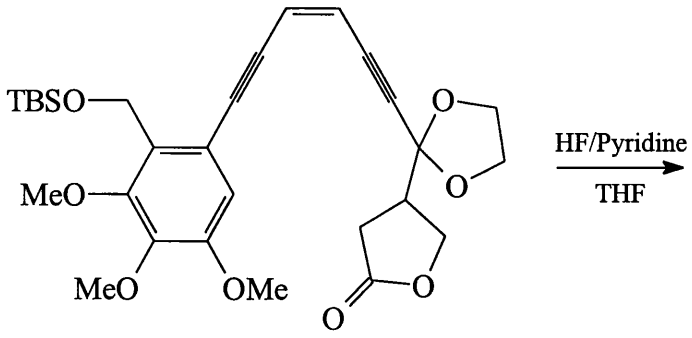
Attempted deprotection of **(348)**



(348)

A solution of tetra-*n*-butylammonium fluoride in THF (0.11 mL of a 1.0 M solution, 0.11 mmol) was added to a stirred solution of **(348)** (60 mg, 0.1 mmol) in THF (10 mL) at -78 °C. The solution was stirred at this temperature for 1 h. After this time, tlc indicated no consumption of starting **(348)**. The solution was warmed to 0 °C, and stirred for a further 1 h. After this time, tlc indicated only baseline material existed in solution.

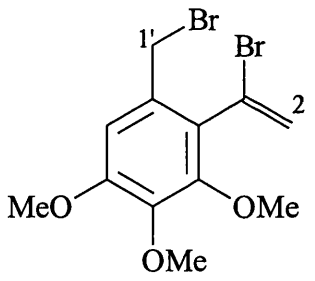
Attempted deprotection of **(348)**



(348)

A buffered solution of HF/Pyridine complex in THF (0.35 mL of a stock solution made from HF/pyridine complex (0.21 g), pyridine (0.7 mL) and THF (2 mL)) was added to a stirred solution of **(348)** (60 mg, 0.1 mmol) in THF (10 mL) at 0 °C. The solution was stirred at this temperature for 10 min. After this time, tlc indicated that only baseline material existed in solution.

Preparation of 1-bromo-1-(2-bromomethyl-4,5,6-trimethoxyphenyl)ethene **(357)**

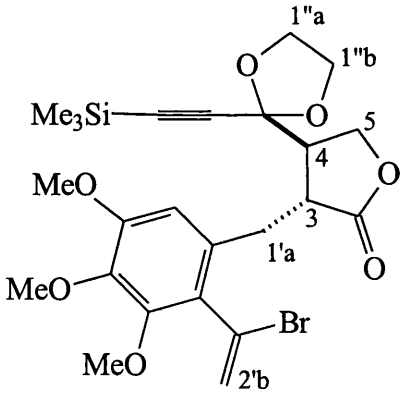


(357)

Carbon tetrabromide (1.5 g, 4.6 mmol) and triphenylphosphine (1.2 g, 4.6 mmol) were added to a stirred solution of **(340)** (0.5 g, 2.3 mmol) in ether (20 mL). The solution was stirred for 18 h. at ambient temperature. After this time, the solution was filtered through a pad of celite, and the residue was washed with ether (3x10 mL). The filtrate and washings were combined, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica, 20 %

ether in petrol as eluent) to give **(357)** as a colourless solid, m. pt. 62-63 °C (0.35 g, 41 %); NMR (400 MHz, $CDCl_3$) δ_H 6.70 (1H, s, ArH), 6.05 (1H, d, J=1.6, H-2"), 5.90 (1H, d, J=1.6, H-2"), 4.53 (2H, s, H-1'), 3.97 (3H, s, OMe), 3.89 (3H, s, OMe), 3.88 (3H, s, OMe); υ_{max} 2939 (m), 1593 (m, C=C), 1492 (m), 1466 (m), 1404 (s), 1336 (s), 1214 (m), 1196 (m), 1121 (s), 1070 (m), 1024 (m), 932 (w), 872 (w), 670 (w), 600 (w) cm^{-1}; *m/z* (EI) 368 (M^+ ($^{81}Br^{81}Br$), 5.7 %), 366 (M^+ ($^{79}Br^{81}Br$), 11.5 %), 364 (M^+ ($^{79}Br^{79}Br$), 5.9 %), 287 (72.8 %), 285 (71.4 %), 207 (100 %), 191 (27.6 %), 176 (25.2 %), 115 (16.0 %), 77 (17.3 %); Found M^+ 364.9380; $C_{12}H_{14}O_3Br_2$ requires *M* 364.9388.

Preparation of (3*R**,4*R**)-4,5-dihydro-3-[[3,4,5-trimethoxy-2-(1-bromoethenyl)phenyl]methyl]-4-[2-[(trimethylsilyl)ethynyl]-1,3-dioxolan-2-yl] -2(3*H*)-furanone **(358)**

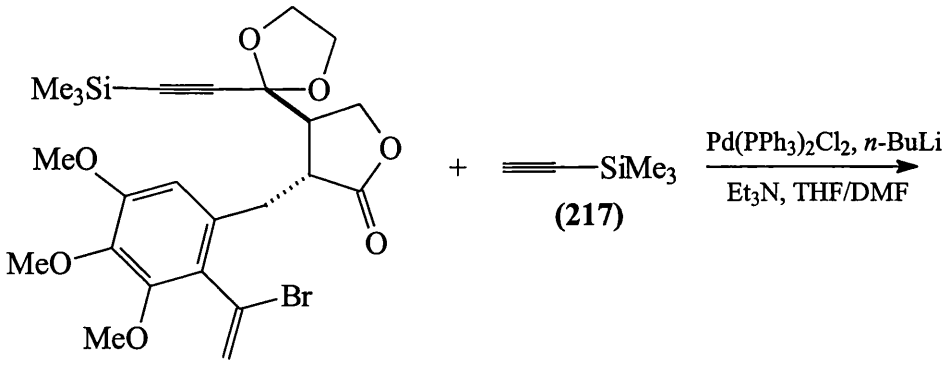


(358)

A freshly prepared solution of lithium diisopropylamide in THF/hexanes (1.41 mL of a 0.38 M solution, 0.54 mmol) was added dropwise to a solution of **(202)** (0.14 g, 0.54 mmol) in THF (2.5 mL) at -78 °C. The solution was stirred at this temperature for 1 h. After this time, the solution was added *via* cannula to a stirred solution of **(357)** (0.2 g, 0.54 mmol) in THF (2.5 mL) at -78 °C. The solution was stirred at this temperature for 1h., and was then allowed to warm to ambient temperature, and was

stirred for a further 12 h. The solution was poured into sat. aq. NH_4Cl (10 mL), and the aqueous mixture was extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine, and dried over $MgSO_4$. The solution was filtered, and the solvents removed under reduced pressure. The residue was purified by flash column chromatography (silica, gradient elution; 20 % ether in petrol to 50 % ether in petrol as eluent) to give, in order of elution, **(357)** (46 mg, 23 %), and **(358)** as a pale yellow gum (0.19 g, 65 %); NMR (400 MHz, $CDCl_3$) δ_H 6.62 (1H, s, ArH), 5.97 (1H, d, J=1.2, H-2'b), 5.71 (1H, d, J=1.1, H-2'b), 4.38 (1H, dd, J=9.8, 3.5, H-5), 4.17 (1H, dd, J=9.7, 8.3, H-5), 4.04 (2H, m, 2 × H-1"a or H-1"b), 3.93 (3H, s, OMe), 3.90 (2H, m, 2 × H-1"a or H-1"b), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.11 (3H, m, 2 × H-1'a and H-3), 2.75 (1H, m, H-4), 0.15 (9H, s, $SiMe_3$); υ_{max} 2958 (m), 2215 (w, alkyne), 1777 (s, C=O), 1593 (w, C=C), 1324 (m), 1250 (m), 1127 (s), 1024 (s), 913 (m), 849 (s), 745 (m) cm^{-1}; *m/z* (FAB) 540 (M^+ (^{81}Br), 14.8 %), 538 (M^+ (^{79}Br), 12.9 %), 491 (21.0 %), 481 (15.6 %), 459 (100 %), 434 (27.0 %), 307 (7.4 %), 285 (6.1 %); Found M^+ 538.1030; $C_{24}H_{31}O_7BrSi$ requires *M* 538.1022.

Attempted cyclisation of **(358)**



(358)

A solution of *n*-butyllithium in hexanes (20 μL of a 1.0 M solution, 20 μmol) was added to a stirred solution of bis(triphenylphosphine)palladium(II) chloride (7 mg, 10 μmol) in THF (0.1 mL) at -78 °C. The solution was stirred at this temperature for 10 min. After this time, trimethylsilylethyne (60 μL, 0.5 mmol), triethylamine (28 μL, 0.2 mmol) and DMF (0.2 mL) were added. A solution of **(358)** (50 mg, 93 μmol) in DMF (0.2 mL) was then added, and the solution was heated to 100 °C. The mixture

was stirred at this temperature for 2 h. After this time, the solution was allowed to cool to ambient temperature, and was poured into sat. aq. NH_4Cl (5 mL). The solution was extracted with ether (3 × 5 mL), the combined organic extracts were washed with brine, and dried over $MgSO_4$. The solution was filtered, and the solvents were removed under reduced pressure. The residue was purified by flash column chromatography (silica, 50 % ether in petrol as eluent) to give recovered **(358)** (12 mg, 24 %) as the only product.

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