Synthetic Studies Towards Chiral Analogues of Steganone

A thesis presented by

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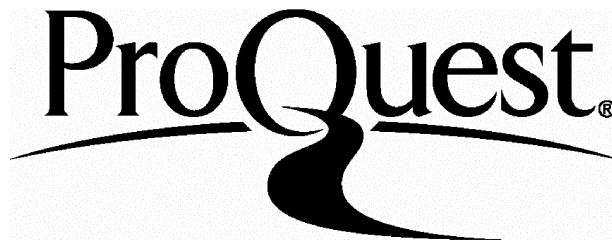
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Abstract

This thesis is divided into three chapters.

In the first chapter, following a brief overview of the isolation, structure and biological properties of steganone, the various strategies which have been adopted for the total synthesis of the racemate are presented. The more challenging problem of preparing the desired target as a single enantiomer is then examined by illustrating the variety of approaches used for the asymmetric synthesis of such lignans. In the second chapter, having introduced the efficient and highly convergent route to racemic analogues of steganone which had evolved within the group, some of the more problematic steps in this existing route are examined; namely, the synthesis of the key ynone utilising toxic organotin reagents and the low yielding, but absolutely crucial cobalt-mediated [2+2+2] cycloaddition of the tethered diyne with a third alkyne component. Although an approach that obviated the use of tin reagents was successfully accomplished, efforts to improve the cobalt-mediated cyclisation using a novel Trost reagent generated *in situ* from cobalt tris(acetylacetonate), triphenylphosphine, and triisobutylaluminum failed. In parallel with the above work, two approaches have been investigated to access chiral analogues of steganone. The first of these was based on a variety of modified literature routes to (*R*)-(+)-paraconic acid as a key intermediate. Although ultimately successful, multigram quantities of (*R*)-(+)-paraconic acid could not be prepared in this manner. In an entirely different strategy, the use of a chiral acyl anion equivalent developed by Enders in an addition to butenolide was investigated. The third chapter provides a formal description of the experimental results and procedures.

Contents

Acknowledgements

The last three years has undoubtedly been most challenging.

My deepest gratitude must go to my supervisor Willie Motherwell, for his enthusiasm, encouragement, and guidance during the past three years. Carrying out a PhD amidst a very difficult personal situation would not have been possible without your patience, your advice and help.

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On a personal level, I would like to thank my parents and my sister for the encouragement, love and support given throughout my education, and to Antony, Romano, Sarah and Shabano (for their trusted friendship).

Abbreviations

Ac	Acetyl
acac	Acetylacetonato
AIBN	Azoisobutyronitrile
aq	Aqueous
Ar	Aryl
atm	Standard Atmosphere
b.p.	Boiling point
Bn	Benzyl
br	Broad
Bu	Butyl
t-Bu	*tert*-Butyl
Bz	Benzoyl
cat.	Catalytic
ca.	(*circa*) About
CI	Chemical ionisation
cm^{-1}	Wavenumbers
Cp	η^5-Cyclopentadienyl ligand
Cp*	η^5-Pentamethylcyclopentadienyl ligand
Cy	Cyclohexyl
Δ	Heat
d	Doublet
DCM	Dichloromethane

dd	Double doublet
de	Diastereomeric excess
dec.	Decomposes
DIBAL-H	Diisobutylaluminum hydride
DIPA	Diisopropylamine
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
dt	Double triplet
E	Unspecified electrophile
ee	Enantiomeric excess
EI	Electron impact
eq.	Equivalents
Et	Ethyl
ether	Diethyl ether
FAB	Fast atom bombardment
FT-IR	Fourier transform-infrared
h	Hour
HMPA	Hexamethylphosphoramide
hν	Irradiation of unspecified wavelength
IR	Infrared
J	Coupling constant

K(L)HMDS	Potassium(lithium) bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
liq	Liquid
lit.	Literature value
M	Molar concentration
m	*meta*
m	Medium or multiplet
m.p.	Melting point
Me	Methyl
MEM	2-Methoxyethoxymethyl
min	Minutes
mmHg	Millimetres of mercury
mol%	Molar percentage
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
o	*ortho*
o/n	Overnight
p	*para*
P	Unspecified protecting group
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Petrol	Petroleum spirit, b.p. 40 – 60 $^\circ$C
Ph	Phenyl

ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
i-Pr	Isopropyl
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
q	Quartet
R_f	Retention factor
rt	Room temperature
s	Strong or singlet
sat.	Saturated
soln	Solution
t	Triplet
TBDMS	*tert*-Butyldimethylsilyl
tert	Tertiary
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
tlc	Thin layer chromatography
TMS	Trimethylsilyl
Tr	Trityl
Ts	*p*-Tolylsulfonyl
w	Weak

wt.%   Weight percentage

Stereochemical Notation

Graphical representation of stereochemistry in this thesis is in accordance with the conventions proposed by Maehr.[1] Accordingly, solid–broken lines indicate racemates.
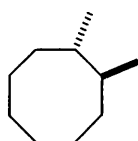
Racemate

Solid–broken wedges indicate the absolute configuration. The narrowing of solid-broken wedges indicates increasing distance from the viewer.
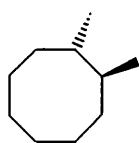
Single enantiomer

Chapter 1

Introduction

1.1 General Remarks

The present thesis is concerned with the ongoing development within our group of a flexible and highly convergent route to unnatural analogues of the antileukaemic lignan, steganone. In order to highlight the approach which has been adopted, the following introduction has been formally divided into two sections. In the first of these, following a brief overview of the isolation, structure and biological properties of steganone, the various strategies which have been adopted for the total synthesis of the racemate are examined. The second section then focuses on the more challenging problem of preparing the desired target as a single enantiomer by illustrating the variety of approaches used for the asymmetric synthesis of lignans.

1.2 Lignans: Definition

The lignans themselves constitute a structurally broad and a chemically diverse class of naturally occurring compounds. These phenolic plant derivatives are characterised by their dimeric relationship to cinnamic acid (1) or to its biogenetic congeners (Figure 1).[2]
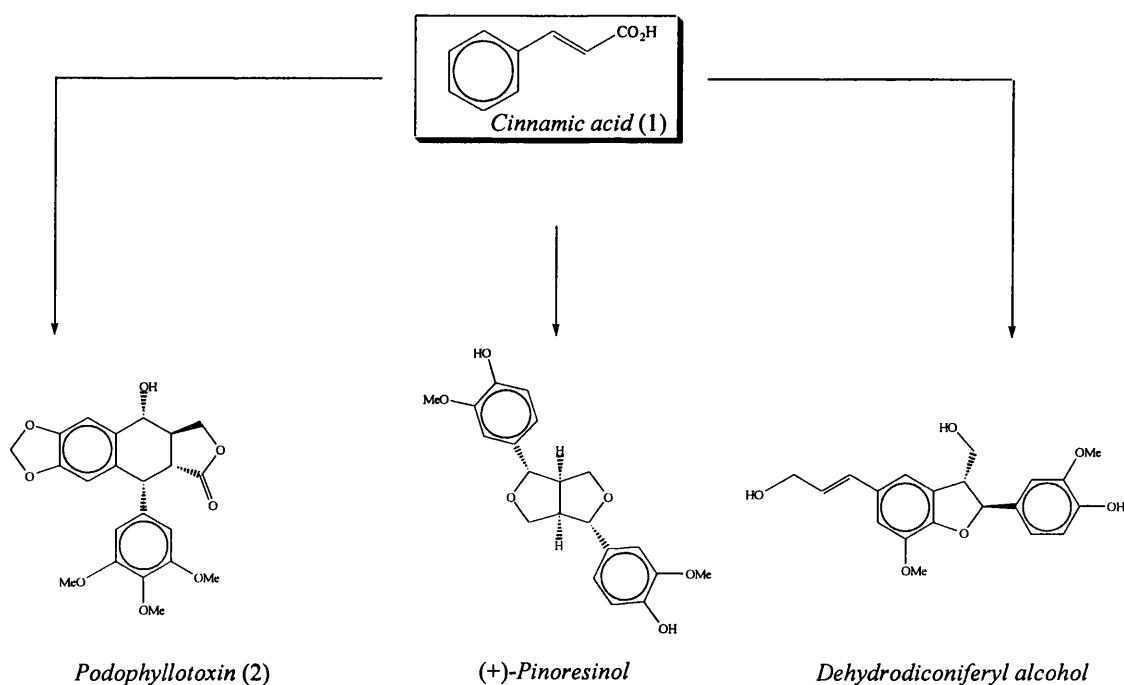
Figure 1: Some representative lignans

The structural variation evident in this class of natural products can be attributed to the following differences: *viz.*, the points of fusion of the cinnamate residues, the oxidation levels of the cinnamic acid carboxy terminus and to the degree and nature of the oxygenation pattern around the aromatic rings.[2]

1.3 Isolation and Characterisation of (–)-Steganone

In 1973 Kupchan and co-workers reported the isolation of (–)-steganone, one member of a family of four bisbenzocyclooctadiene lignan lactones from an alcoholic extract of *Steganotaenia araliacea* Hochst (Figure 2).[3]
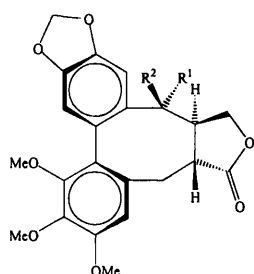
Lignans	R^1	R^2
Steganacin (3)	OAc	H
Steganangin (4)	Angelate	H
Steganol (5)	OH	H
Steganone (6)	=O	=O

Figure 2: Lignans isolated from *Steganotaenia araliacea* Hochst

Synthetic interest in these bisbenzocyclooctadiene lactones was immediately fuelled by the discovery that they demonstrated significant *in vivo* activity against the P-388 leukaemia in mice and displayed potent *in vitro* activity against cells derived from human carcinoma of the nasopharynx (KB).[4]

(–)-Steganone is composed of three stereochemical elements, two of which reside in the *trans*-fused γ-lactone ring while the third is the atropisomeric biaryl unit comprising rings A and B. The latter feature is relatively rare amongst natural products and leads to the generation of a somewhat 'propeller-shaped' molecule.

Steganone (6)

Figure 3

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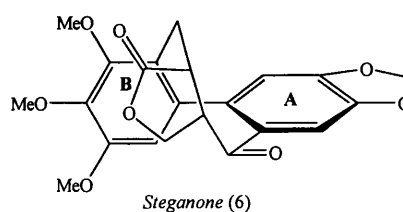
The almost orthogonal nature of the two aromatic rings, which is now familiar to all organic chemists in the form of ligands such as (*R*) and (*S*)-BINAP, is shown in Figure 3.

(S)-(–)-BINAP
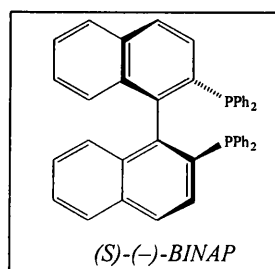
1.4 Mode of Biological Action

The lignan lactones isolated from the alcoholic extract of *Steganotaenia araliacea* Hochst are cytotoxins and belong to the class of spindle poisons. All eukaryotic cells contain the dimeric protein tubulin, which during most of the cell's life polymerises to form microtubules which form the cytoskeleton.[5,6] During cell division, microtubules in the form of spindle fibres undergo contraction thus 'pulling' the newly formed daughter chromosomes to make up the nuclei of the two daughter cells. Steganone (6) and the companion lignans, steganacin (3) and steganangin (4) are known to bind to tubulin at the colchicine-binding site. A number of other spindle toxins including the intriguing biaryl derived colchicine (7)[7] and podophyllotoxin (2) (Figure 4) bind to tubulin, preventing formation of spindle fibres, causing metaphase arrest, thus inhibiting mitosis. It is intriguing to record the observation that all of the spindle poisons noted above possess two non-coplanar aromatic rings as a common structural motif.

Colchicine (7)   Podophyllotoxin (2)   Steganacin (3)
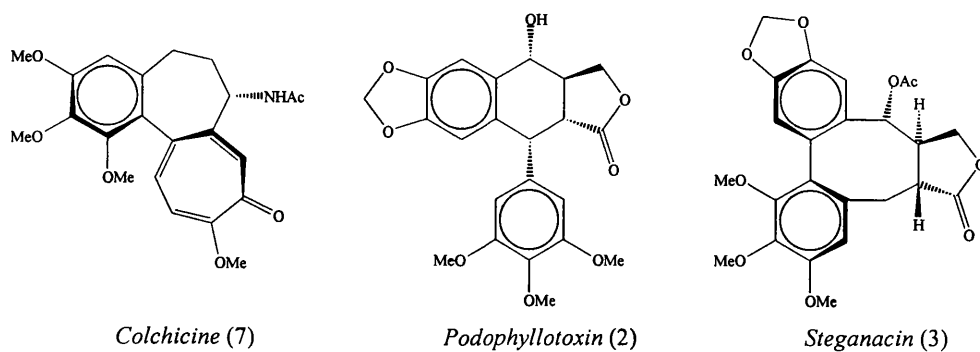
Figure 4: Spindle poisons

1.5 Previous Synthetic Routes to (±)-Steganone

Of the thirteen published total and formal syntheses of steganone six have focused on furnishing the racemic product. The nub of any synthetic plan has logically centred on establishing an efficient route for assembling the highly functionalised eight-membered carbocycle. A wide variety of synthetic strategies have thus culminated over almost three decades in pursuit of achieving this goal. Our discussion of published routes to (±)-steganone highlights the various strategies employed.
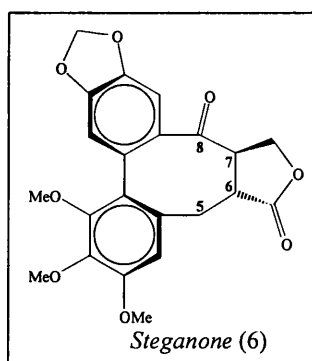
Steganone (6)

1.5.1 The Kende Synthesis of (±)-Steganone

The first successful total synthesis of (±)-steganone and the companion lignans,

steganacin (3) and steganol (5) were reported by Kende and Liebeskind from

Rochester, USA in 1976.[8] Their synthetic approach was based on the following

strategic principles: *viz.* 1) utilisation of diethyl malonate as a 'lynch-pin' unit for

elaboration of both aromatic residues, 2) concomitant construction of the biaryl axis

and the eight-membered carbocycle by a vanadium(V) oxytrifluoride assisted non-

phenolic oxidative coupling, and 3) late introduction of functionality at C-8, followed

by the elaboration of the *trans*-fused γ-lactone ring.

The synthesis commenced from homopiperonyl alcohol (8), which was

obtained in 5 steps from readily available piperonal (Scheme 1). The alcohol (8) was

transformed to the *gem*-diester (9) in a moderate yield in 3 steps involving

mesylation, and a sequential double alkylation. The non-phenolic, intramolecular

oxidative coupling assisted by vanadium(V) oxytrifluoride constructed both the

crucial biaryl bond and the eight-membered ring, furnishing the

dibenzocyclooctadiene (10) in a yield of 45%. An attractive design element in the

synthesis was the selective functionalisation of dibenzocyclooctadiene (10) at C-8

rather than at C-5, by virtue of the bulky *gem*-dicarbethoxy substituents on C-6. In

order to introduce the oxygen functionality at C-8 of the dibenzocyclooctadiene (10),

Kende found it essential to perform a three-stage operation involving

monobromination of the dibenzocyclooctadiene (10), followed by sequential

hydroxylation and oxidation to generate the keto-diester (11).
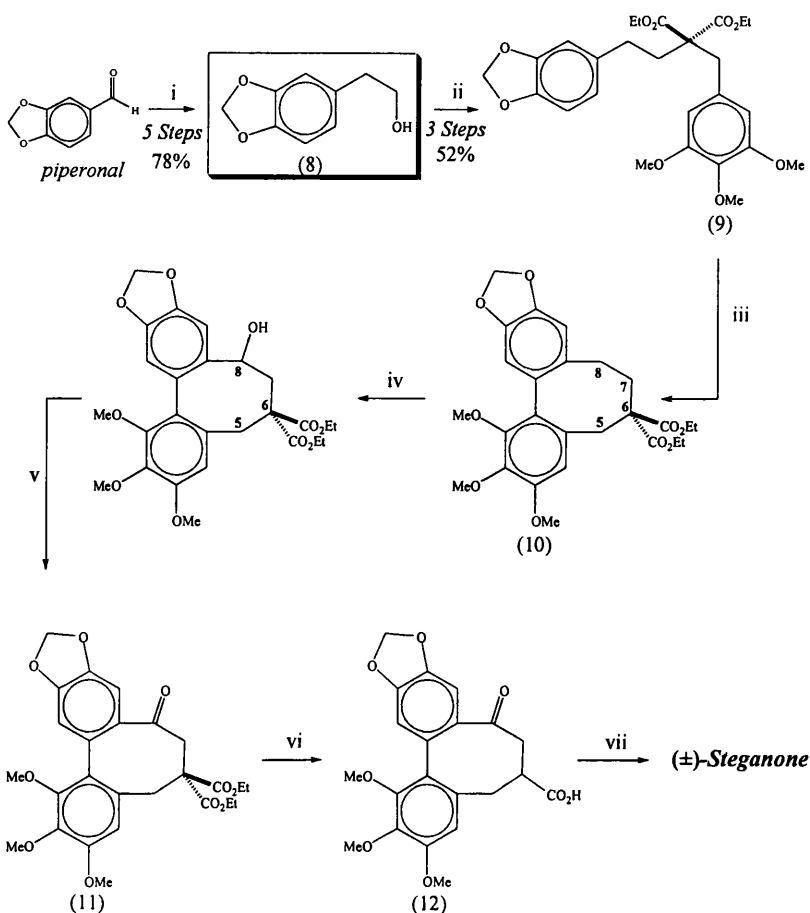
Scheme 1: Reagents and Conditions
i) a) NaBH₄ reduction of piperonal; b) HBr gas on a chloroform solution of piperonyl alcohol; c) phase-transfer catalysed reaction of the resulting benzyl bromide with NaCN; d) hydrolysis (6 N NaOH, 40% EtOH, reflux, 18 h) of the nitrile; e) LiAlH₄ reduction of the resulting 3,4-methylenedioxyphenylacetic acid; ii) a) CH₃SO₂Cl-Et₃N, CH₂Cl₂, 0 °C, 20 min; b) sodiodiethyl malonate, benzene, reflux, 18 h; c) 3,4,5-trimethoxybenzyl bromide, NaH, DMF, 0 °C, 30 min, 52% overall yield from (8); iii) 3.5 eq VOF₃, 5% trifluoroacetic anhydride/CH₂Cl₂, 25 °C, 1 h, 45%; iv) a) NBS, benzoyl peroxide, CCl₄, reflux, 2 h; b) AgOCOCF₃, DMSO, 25 °C, 1 h, basic aq work-up; v) dipyridine-chromium trioxide, CH₂Cl₂, 60% from (10); vi) 2.7 N KOH, 50% EtOH, reflux, 6 h, 95%; vii) 37% aq formaldehyde, 0.4 N KOH, H₂O, 25 °C, 1 h, 3 successive cycles, 77%.

The diester (11) when subjected to saponification followed by mono-decarboxylation, and treatment of the resultant oxo-acid (12) with aqueous formaldehyde delivered (±)-steganone in an overall yield of 10% from homopiperonyl alcohol (8).

Although this approach was somewhat curtailed by the apparent inability to perform the oxidative coupling of the *gem*-diester (9) in the presence of a benzylic oxygen substituent at C-8, the Kende-Liebeskind strategy has been suggested as the most interesting strategy from a biosynthetic point of view.[9]

1.5.2 *The Raphael Synthesis of (±)-Steganone*

Just three months after Kende's route to (±)-steganone was published, Raphael and co-workers then revealed their own highly original strategy (Scheme 2).[10,11] Their route proceeded *via* the 9-pyrrolidinophenanthrene derivative (15) as a key intermediate, which was constructed by the photochemically induced conrotatory cyclisation of a stilbene derivative (14) (Scheme 2).
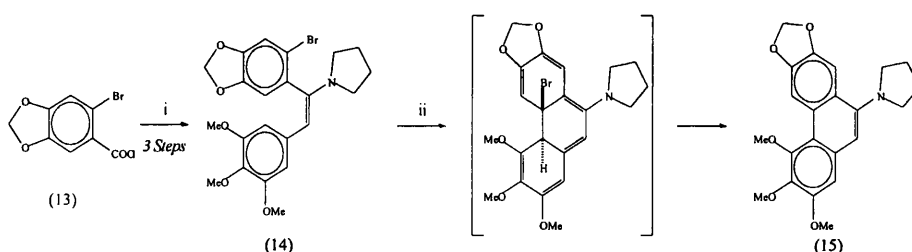
Scheme 2: **Reagents and Conditions**
i) a) *t*-Butyl-3,4,5-trimethoxyphenylacetate, LDA, THF, then add (13), –78 °C, 1 h, 95%; b) aq DMSO, heat, 74%; c) pyrrolidine, *p*-TSA, benzene, 18 h, 88%; ii) liq NH₃, *t*-BuOK, hv, 65%.

The highly functionalised eight-membered carbocycle was then assembled by a 2-carbon ring expansion sequence involving a stepwise [2+2] cycloaddition of an enamine with dimethyl acetylenedicarboxylate followed by electrocyclic ring opening of the resultant cyclobutene (Scheme 3).

(15) → (16)
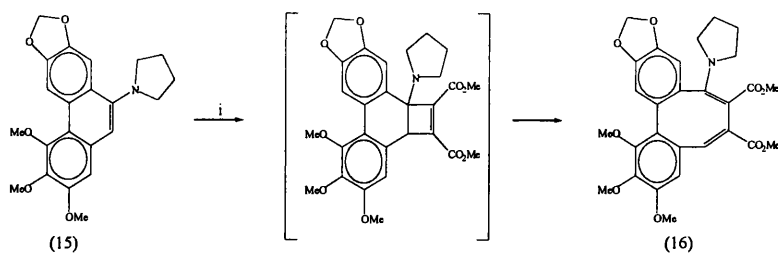
Scheme 3: **Reagents and Conditions**
i) Dimethyl but-2-ynedioate, 1,4-dioxane, heat, 91%.

An elegant feature of the Raphael approach was that it permitted the direct, regiospecific introduction of benzylic oxygen functionality at C-8 and also differed from the Kende approach inasmuch as the biaryl axis was formed at a very early stage in the synthesis.

(16)

(17)

Oxo-acid (12)

(±)-*Steganone* (6)

(±)-*Isosteganone* (18)
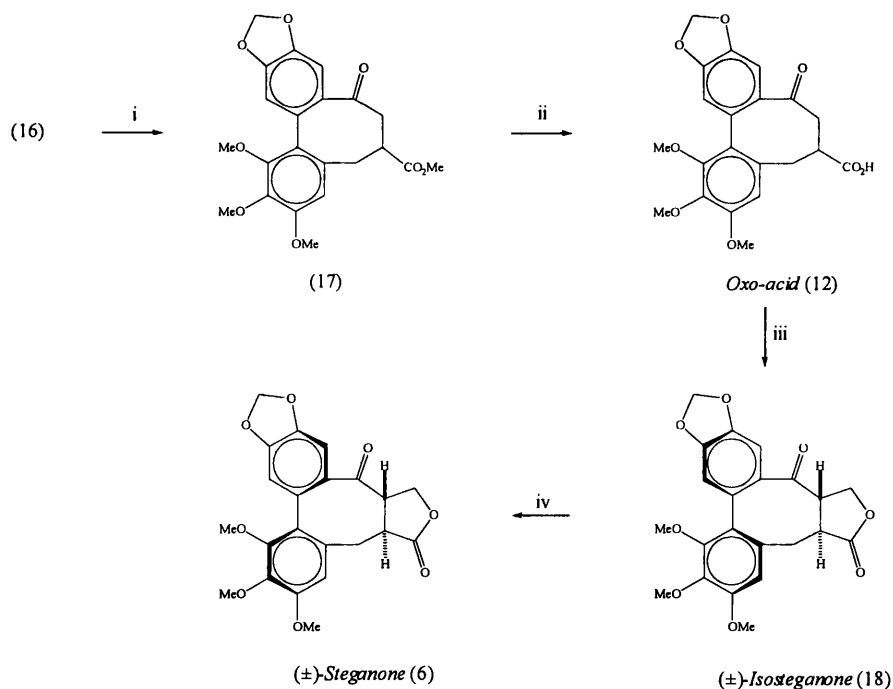
Scheme 4: **Reagents and Conditions**
i) a) 5% HCl, MeOH, reflux, 48 h, 90%; b) H₂, Raney® Ni, 1 atm, 12 h, 93%; ii) LiOH, H₂O, 12 h, 95%; iii) aq 5% KOH, formaldehyde, H₂O then Jones reagent, 75% over two steps; iv) xylene, reflux, 1 h, quantitative.

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The dibenzocyclooctadiene (16) formed by the ring expansion protocol was then smoothly converted into the 'same' oxo-acid (12) encountered in the Kende synthesis by a three step sequence involving acidic hydrolysis, hydrogenation over Raney® nickel and saponification (Scheme 4). Completion of the synthesis by base catalysed condensation with formaldehyde followed by Jones oxidation however did not lead to (±)-steganone but to its diastereoisomer (±)-isosteganone (18) in which the atropisomeric biaryl unit has the unnatural relative configuration. Fortunately, this curious stereochemical "twist in the tail" was overcome when it was discovered that simple thermolysis in xylene led to highly efficient isomerisation to racemic steganone itself, thereby averting catastrophe at the final stage of the synthesis!

Although at first sight the isomerisation can be regarded as a thermodynamically driven conformational change, a more subtle explanation was subsequently advanced by Magnus[12] and co-workers during their own independent approach to steganone several years later (*vide infra*).

Thus, as shown in Scheme 5, it was speculated that isomerisation could involve β-elimination to give methylene-oxo-acid (19) followed by rotation around the biaryl axis and a final recyclisation reaction. The overall driving force for this sequence of events is provided by the movement of the C-8 carbonyl group into planarity with the piperonyl ring.

(±)-*Isosteganone* (18)   (19)   (±)-*Steganone* (6)
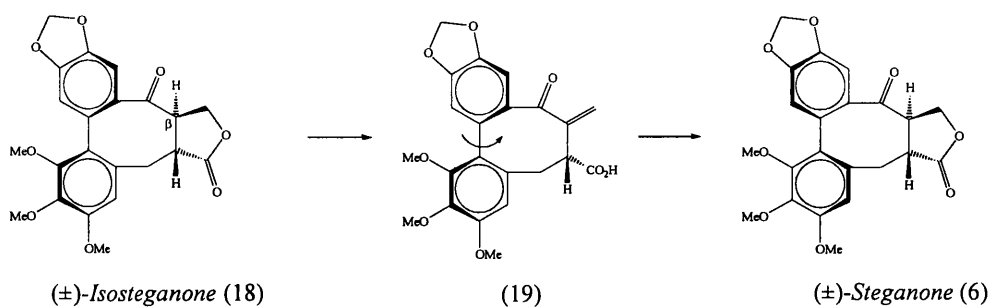
Scheme 5

1.5.3 The Krow Synthesis of (±)-Steganone

In 1978, Krow and co-workers reported an independent synthetic route (Scheme 6) to an almost identical unsaturated oxo-ester intermediate (17), encountered in the Raphael synthesis of steganone.[13] The two key reactions, viz., the photochemical ring closure of a stilbenecarboxylic acid to generate a phenanthrene derivative and the two-carbon ring expansion of a 9-phenanthrylamine with dimethyl but-2-ynedioate, utilised in Krow's synthetic sequence to (±)-steganone, are, of course, conceptually similar to the Raphael strategy, and the minor modification is that the enamine required for the [2+2] cycloaddition step is formed by a modified Curtius reaction.
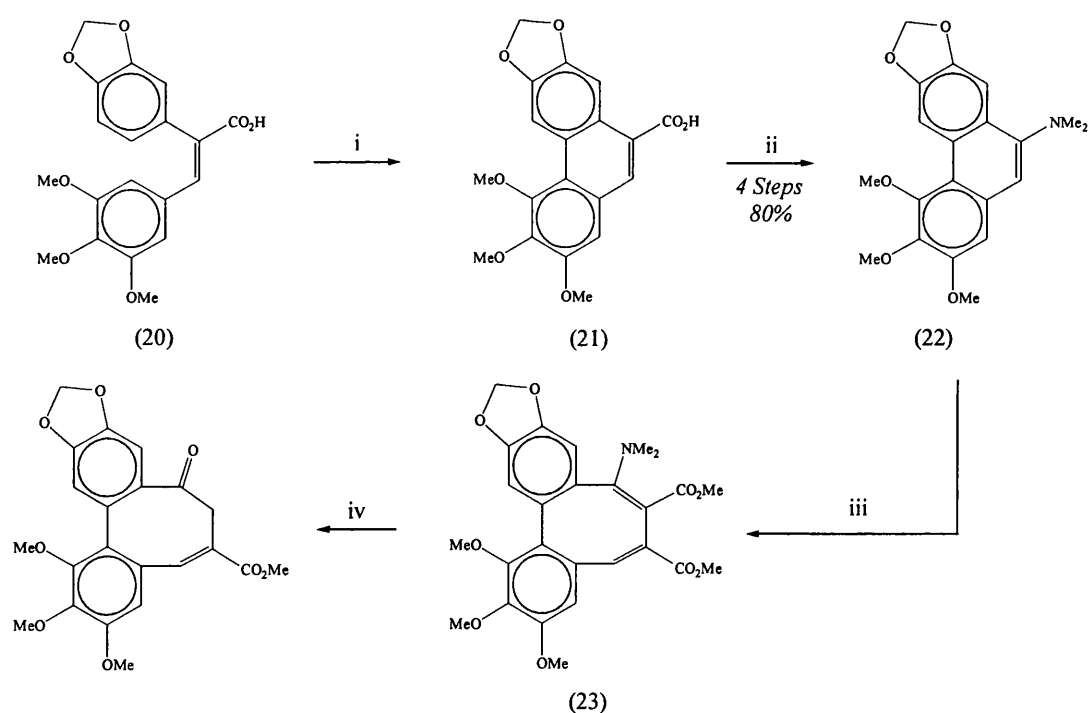
Scheme 6: Reagents and Conditions
i) I_2, benzene, hv, 20 h, 81%; ii) a) NaOMe, MeOH, then sodium salt of (21), (COCl)$_2$, benzene, reflux 2 h; b) trimethylsilyl azide, benzene, rt, 1 h, reflux, 24 h; c) LiAlH$_4$, THF, rt for 1 h, then reflux, 1 h, 84%; d) trimethyl phosphate, reflux, 2 h, then 10% NaOH, EtOH, reflux, 1.5 h, 87%; iii) dimethyl but-2-ynedioate, dioxane, reflux, 5 days, 50%; iv) (5:1) (v/v) methanol/6 N hydrochloric acid, reflux, 8 h, 80%.

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Thus, entry to phenanthrene-9-carboxylic acid (21) was straightforward *via* the intramolecular oxidative photochemical ring closure of 3,4-methylenedioxy-3',4',5'-trimethoxy-α-carboxystilbene (20) and was obtained in high yield.[13] Phenanthrene-9-carboxylic acid (21) was then transformed in 4 steps to the enamine (22) *via* conversion of the derived acid chloride into the isocyanate followed by hydride reduction and subsequent methylation in high overall yield. The 2-carbon ring expansion was then performed by the thermal cycloaddition of the enamine (22) and dimethyl but-2-ynedioate in moderate yield, and, as before hydrolysis afforded the unsaturated oxo-ester (17) in high yield.

1.5.4 The Ghera Synthesis of (±)-Steganone

The approach adopted by Ghera and co-workers relied on an adventurous eight membered ring closure step of a 2,2'-bis(bromoacyl)-1,1'-biaryl derivative (26) *en route* to (±)-steganone (Scheme 7).[14]

The stilbene (24) was readily available in a moderate yield from the hitherto unreported 2-bromopiperonal in 2 steps, entailing the Wittig reaction and photocyclisation. Oxidative cleavage of diol (25) followed by α-bromination afforded the dibromide (26) in a high yield. The necessary intramolecular cyclisation of the dibromide (26) was then achieved using zinc/silver couple to install the eight-membered carbocycle in a moderate yield. Interestingly, the key bisbenzocyclooctadiene intermediates (27 and 28) were obtained as a rapidly interconverting mixture of atropisomers since, in this instance, each aromatic ring is

flanked by a carbonyl group. Elaboration of the key intermediates (27 and 28) was achieved in a further 10 steps to deliver (±)-steganone.

(24)   (25)   (26)

Oxo-acid (12)   (28)   (27)

2-Bromopiperonal

(±)-Steganone
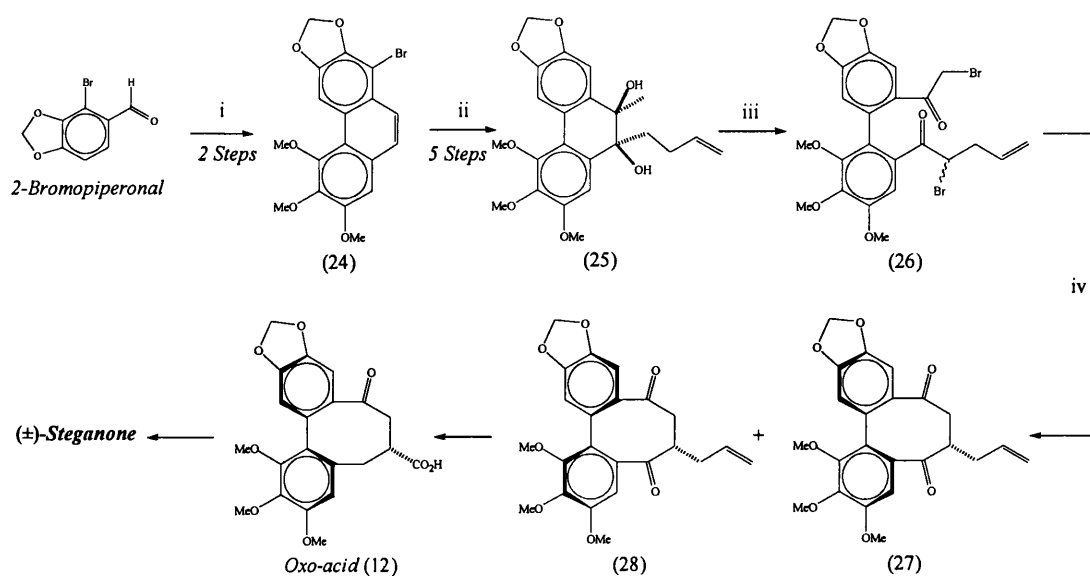
Scheme 7: **Reagents and Conditions**
i) a) 3,4,5-Trimethoxybenzylphosphonium bromide, DMF, MeOLi, 90 °C, 96%; b) I_2, THF-cyclohexane, hv, 91%; ii) OsO_4, pyridine, 240 h, rt, then 4 steps; iii) a) Pb(OAc)$_4$, (1:1) benzene/pyridine, 25 °C, 1 h, 91%; b) n-BuLi, −78 °C, then Me$_3$SiCl in (10:1) THF/HMPA; c) NBS, THF, 0 °C, 79% over steps b) and c); iv) Zn/Ag, DMSO, 57%.

1.5.5 The Ziegler Synthesis of (±)-Steganone

In a similar manner to a second approach adopted by Raphael (*vide infra*), Ziegler also envisaged construction of the biaryl axis at an embryonic stage by employing Ullmann type methodology. Prior to launching their synthesis of racemic steganone, Ziegler and co-workers had investigated the feasibility of applying the classical Ullmann reaction towards the synthesis of the steganes.[15] Despite exhaustive experimentation however, they were unsuccessful in this area and therefore turned to generating unsymmetrical-biphenyls *via* an intramolecular

heteroatom-stabilised arylcopper(I) species (29) (Scheme 8). The required arylcopper(I) species (29) was generated by transmetallation from the appropriate organolithium reagent.

Z = NR$_2$ or SR

(29)

Scheme 8
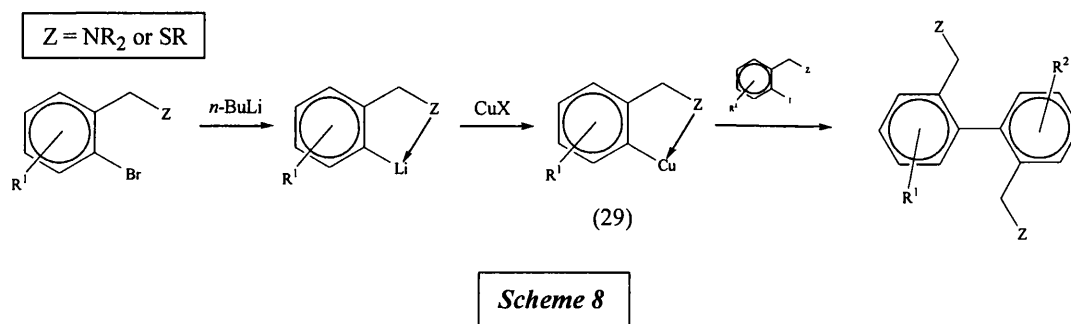
From their studies, the Ziegler group concluded that sulphur based intramolecular-ligands, namely dithioketals and oxathioketals, when employed as masking agents for acetophenones, had a distinct advantage over their nitrogen counterparts, predominantly due to their stability and subsequent ease of removal.

On completion of their study of the scope of this ambient temperature Ullmann reaction, work then commenced on the synthesis of steganone and the companion lignans, steganacin (3) and steganol (5).[15]

Thus, as shown in Scheme 9, the 1,3-oxathiolane derivative (30) was conveniently chosen as the starting point for the synthesis, and was prepared from readily available 6-bromopiperonal in moderate yield through sequential treatment with methylmagnesium bromide, oxidation and hemithioacetal formation with β-mercaptoethanol. Initial metal-halogen exchange and subsequent lithium-copper transmetallation transformed the oxathiolane (30) to the arylcopper(I) species (31). On treatment of the arylcopper(I) species (31) with the imine (32), the biaryl (33) was generated and on further subjection to acid hydrolysis, delivered the monoprotected biaryl aldehyde (34) in a high yield.

(30)　　　　　　(31)

+

(32)　　　　　　(33)　　　　　　(34)
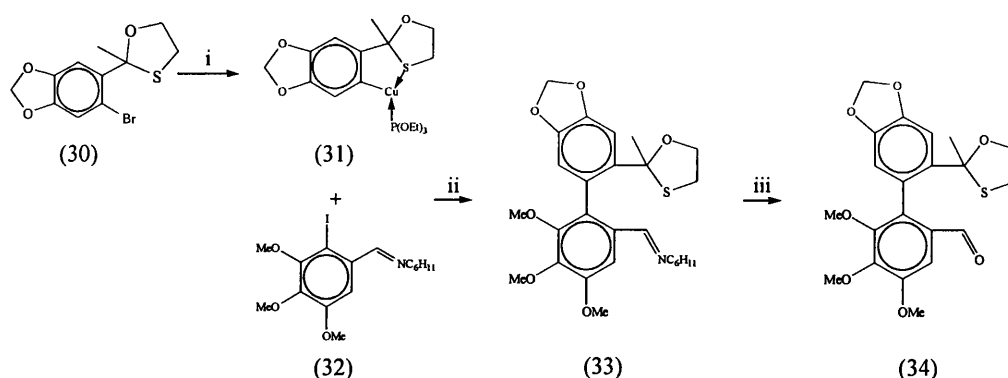
Scheme 9:　Reagents and Conditions
i) a) n-BuLi, THF, −78 °C, 10 min; b) cuprous iodide-triethylphosphate complex, −78 °C, 10 min, (31) used *in situ*; ii) THF, −78 to 25 °C, over 20 h; iii) 15% aq AcOH, 12 h, 82% over steps ii) and iii).

The Knoevenagel condensation of the aldehyde with dimethyl malonate, followed by sequential hydrolytic deprotection (Fetizon deprotection), catalytic hydrogenation over Raney® Nickel and α–bromination then afforded the cyclisation precursor (35). As both methine and methylene protons on the α–bromo ketone (35) are susceptible to exchange with base, the α–bromo ketone (35) was treated with a *tert*-potassium butoxide/*tert*-butanol/THF system in order to ensure proton exchange in the event of methylene deprotonation thereby affecting the crucial intramolecular ring closure and generating the dicarboxylate (36) in a high yield (Scheme 9, continued). Saponification, thermal monodecarboxylation, and a final esterification provided the ester (17), previously encountered by both Kende[8] and Raphael.[10,11] Refluxing either diastereomer in xylene led to the known thermal interconversion of the esters resulting in a 1:1 mixture of both diastereomers *via* rotation about the biphenyl bond, and the γ-lactone ring was then assembled as described previously using the aqueous formaldehyde protocol.[15]

$(34) \xrightarrow{iv}$ (35) $\xrightarrow{v}$ (36) $\longrightarrow$ (±)-*Steganone*

(35)

(36)
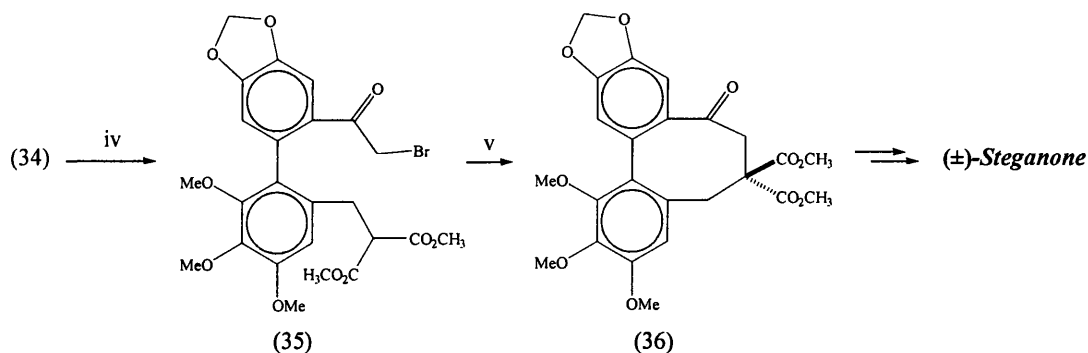
Scheme 9 (continued): Reagents and Conditions
iv) a) dimethyl malonate, piperidine, benzene, reflux, 10 h, 78%; b) methyl iodide, 90% aq acetone, reflux, 12 h, 91%; c) Raney® Ni, H_2 1 atm, EtOH, 95%; d) pyridinium perbromide, CF_3CO_2H, CH_2Cl_2, 3.5 h, 85%; v) t-BuOK, t-BuOH, THF, addition of (35) over 45 min, stir for 45 min, 25 °C, 73%.

1.5.6 The Magnus Synthesis of (±)-Steganone

In similar fashion to Kende and Liebeskind, albeit some nine years later, Magnus and co-workers[12] also decided to adopt a somewhat surprising non-phenolic oxidative coupling strategy in the presence of a benzylic oxygen atom substituent at C-8. In spite of the extensive experimentation however their efforts were equally unsuccessful. These failures did however inspire a very ingenious subsequent approach in which a cyclopropane was used as a source of latent functionality for introduction of the oxo group.

In the first instance, commencing from readily available 3,4,5-trimethoxybenzyl bromide, the coupling precursor cyclopropane (38) was prepared in several steps. Treatment of (38) with thallium(III) tris(trifluoroacetate) in trifluoroacetic acid then produced the biaryl (39) as a single stereoisomer in moderate yield (Scheme 10).

(2:1) mixture of E and Z isomers
(37)

(38)

(39)
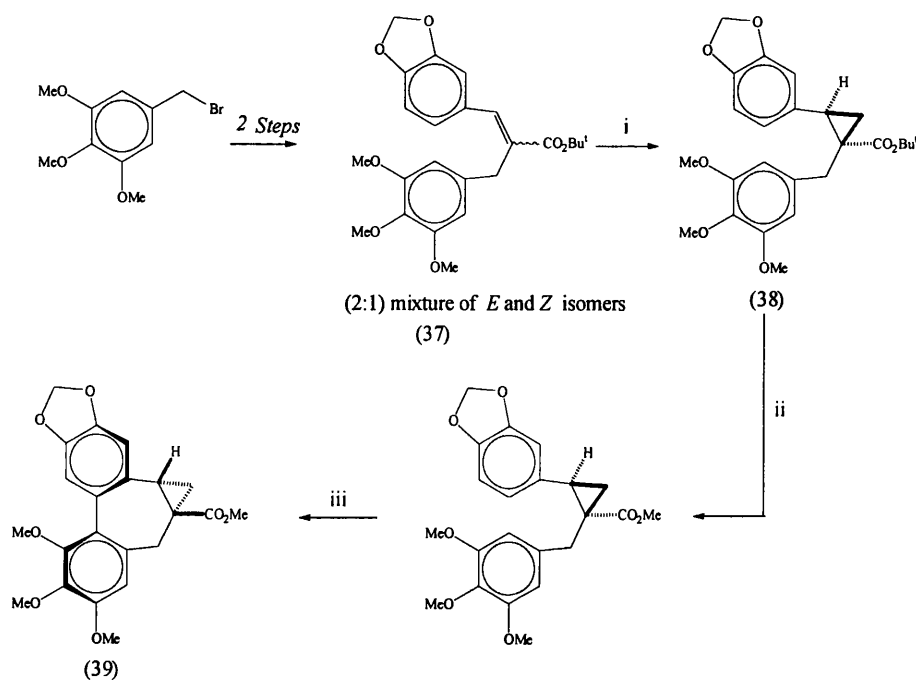
Scheme 10: **Reagents and Conditions**
i) Dimethylsulfoxonium methylide, DMSO, 20 °C for 2 h and then 15 min at 60 °C, 82%; ii) a) *p*-TsOH, toluene, reflux, 10 h, 76%; b) CH_2N_2, CH_2Cl_2, 0 °C, 92%; iii) $Tl(OCOCF_3)_3$, trifluoroacetic acid, −18 °C, 25 min, 43%.

At a later stage the authors were able to devise a much more efficient route[12] to the same key precursor (39) by involving a non-phenolic oxidative coupling step prior to the cyclopropanation of the cinnamate derivative (37) (Scheme 11).

The non-phenolic oxidative coupling of the biaryl (37) was performed by employing thallium(III) tris(trifluoroacetate) oxidant to generate the cycloheptatriene (40) in almost twice the yield of similar couplings used for steganone. A hydride reduction of (40) followed by a Simmons-Smith cyclopropanation of the allylic alcohol gave the cyclopropylcarbinol (41) as a single diastereomer in high yield. Solvolysis of (41) under acidic conditions not only accomplished ring expansion but also achieved the regio- and stereospecific introduction of the acetoxy group in acetate (42). Sequential hydroboration, base hydrolysis and Jones oxidation generated the oxo-acid (12) previously encountered by both Kende[8] and Raphael.[10,11]
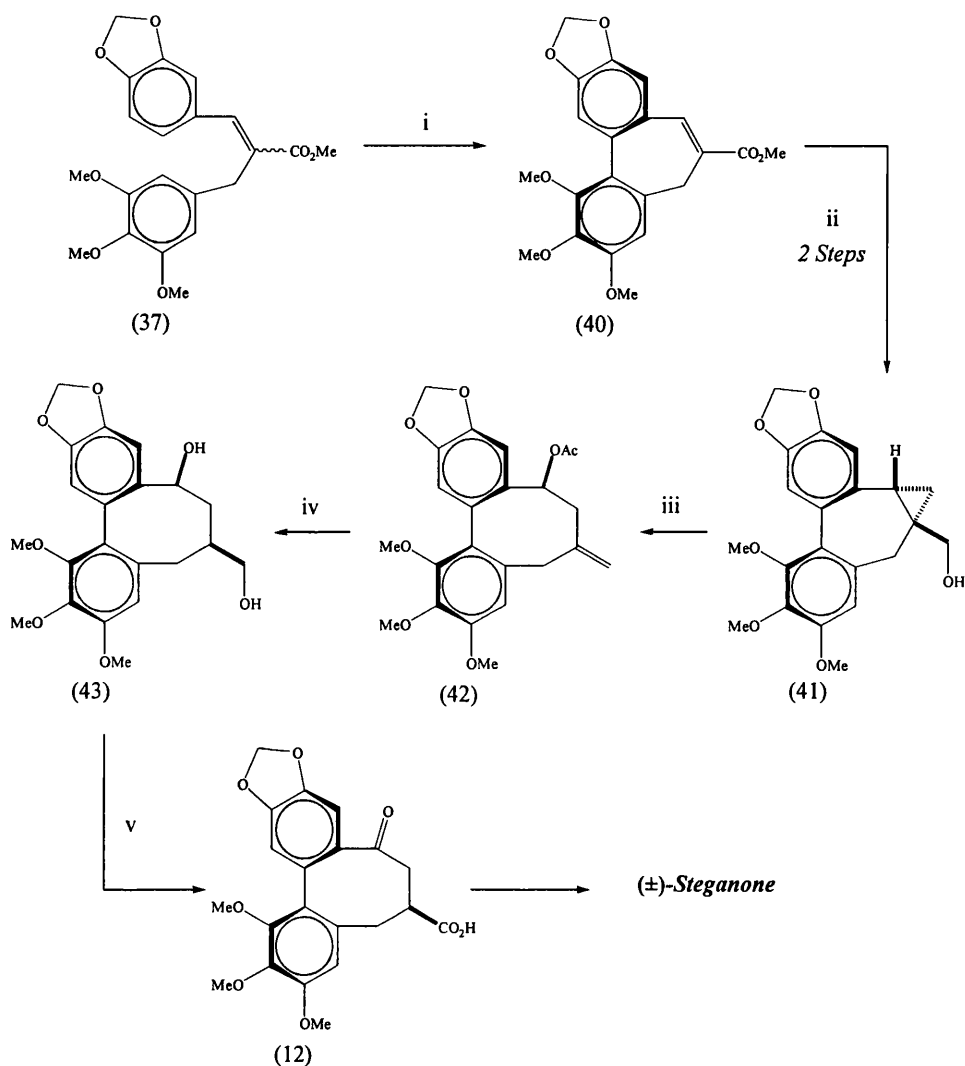
Scheme 11: Reagents and Conditions
i) Tl(OCOCF$_3$)$_3$, trifluoroacetic acid, −18 °C, 30 min, 81%; ii) a) LiAlH$_4$, THF, −78 to 0 °C, 71%; b) Zn(Cu), CH$_2$I$_2$, Et$_2$O, reflux, 1 h, 74%; iii) AcOH, NaOAc, HClO$_4$, 45 °C, 3 h, 37% (97% based on recovered s/m); iv) a) BH$_3$, THF, 0 to 20 °C, 30 min; b) 3 *N* NaOH, 30% H$_2$O$_2$, 0 to 20 °C, 20 min; c) K$_2$CO$_3$, MeOH, H$_2$O, 25 °C, 24 h, 92% overall; v) Jones reagent, acetone, 20 °C, 2.5 h, 80%.

1.5.7 The Narasimhan Formal Synthesis of (±)-Steganone

Narasimhan and Aidhen[16,17] also considered that an intermediate of the phenanthrene enamine type (15) as originally envisaged by Raphael co-workers in their synthesis of (±)-steganone and also used by Krow, could be a valuable intermediate. The bromoenamine (44) was generated in four steps from readily available piperonal. A radical mediated intramolecular biaryl coupling reaction was then used to forge the aryl-aryl bond generating the phenanthrene (15) in good yield (Equation 1).

(44)   (15)
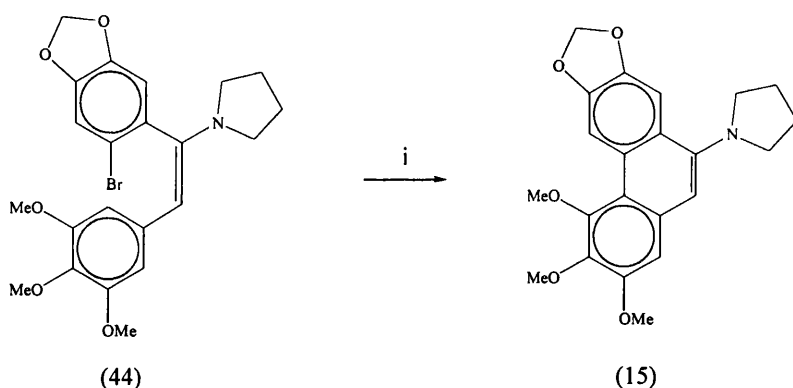
> *Equation1:* **Reagents and Conditions**
> i) Tributyltin hydride, AIBN, benzene, reflux, 2 – 2.5 h, 66%.

The most likely mechanism for the formation of phenanthrene intermediate (15) as suggested by Narasimhan and Aidhen was that *via* the spirocyclohexadienyl radical (45) derived from [1,5]-*ipso*-attack (Scheme 12). The *ipso*-attack was thought to be favoured over the alternative *ortho*-attack as the former was more free of steric crowding between the $C_{5'}$-OMe and C_5-H. A 3-*exo-trig* cyclisation followed by β-fragmentation can then give the phenanthrene as the formal product of 1,6-addition.

(44) ⟶ [structure (45)] $\xrightarrow{\text{3--exo trig}}$ [structure]

(45)

β-fragmentation

(15) ⟵ [structure]
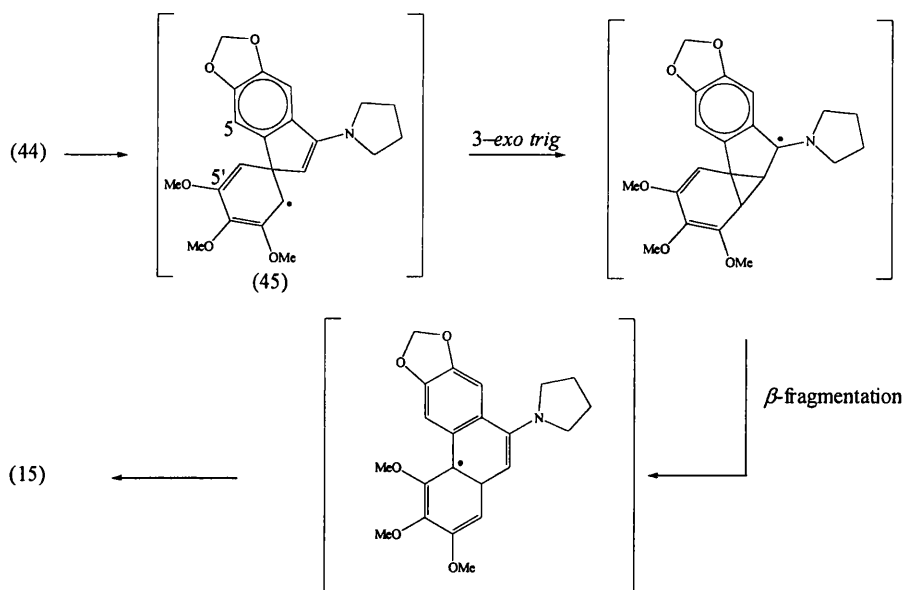
Scheme 12

1.6 Asymmetric Syntheses of Lignans

The present state of the art in organic synthesis requires that the preparation of the correct enantiomer is achieved, and indeed, this objective forms a significant part of the present thesis. At this stage, it is therefore appropriate to consider the methods and substrates which have been used in asymmetric syntheses of lignans.

The fact that these phenolic plant derivatives have surfaced as highly attractive targets for asymmetric syntheses has almost certainly been greatly influenced by the important biological properties of some lignans, coupled with their intriguing molecular architecture and the inherent close juxtaposition and well defined relative configuration of their chiral centres. Although the main focal point has been to deliver the target molecule, the lignans have also provided a framework for

developing asymmetric methodology, which is applicable especially to saturated substituted aromatic and heterocyclic compounds.[18]

The methodologies employed to deliver enantioselective lignans can be subdivided into five conceptual classes based on the strategic approach adopted as outlined below. Whilst, a detailed discussion of each class is outside the scope of this account, we have chosen to highlight the main features of each class and then to illustrate them within the specific context of enantioselective synthetic approaches to (−)-steganone.

1.6.1 *Diastereoselective Alkylation of Chiral Butyrolactones*

This method represents one of the earliest approaches to asymmetric syntheses of lignans and was pioneered in particular by the research groups of Koga,[19,20] in Japan and Brown,[21,22] in France. The required monosubstituted butyrolactones shown in Scheme 13 were obtained by Koga and co-workers from readily available L-glutamic acid by a multistep sequence involving diastereoselective alkylation of either the benzyl ether (46) or the trityl ether of 4-hydroxymethyl butyrolactone, followed by a carbonyl transposition sequence.[19,20]
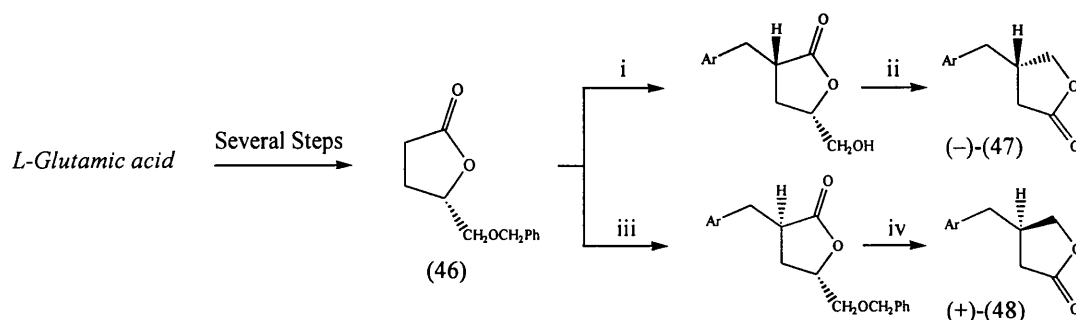
Scheme 13: **Reagents and Conditions**
i) (a) LDA (2 eq), then ClPO(OEt)$_2$, then piperonal (ArCHO); (b) 5% Pd/C, H$_2$, EtOH:EtOAc (1:1); ii) (a) LiAlH$_4$; (b) NaIO$_4$; (c) Collins oxidation, iii) (a) LDA, then ArCH$_2$Br; iv) (a) LiAlH$_4$; (b) 5% Pd/C, H$_2$; (c) NaIO$_4$; (d) Collins oxidation.

Koga's "self-immolative" synthesis of the butyrolactones (–)-(47) and (+)-(48), described above was by a five step sequence from optically active (46).[20] The Brown group obtained both (47) and (48), by firstly resolving readily available hemiester (49) into its (S)-(–)- and (R)-(+)-isomers by (+)-ephedrine and (–)-ephedrine respectively, and then subjecting each isomer to reduction by calcium borohydride (Scheme 14).[22]

Scheme 14: Reagents and Conditions
i) a) Resolve with (+)-ephedrine, 95% EtOH, then dilute hydrochloric acid 54%; b) Ca(BH₄)₂, 82%; ii) a) Resolve with (–)-ephedrine, 95% EtOH, then dilute hydrochloric acid 48%; b) Ca(BH₄)₂, 80%.
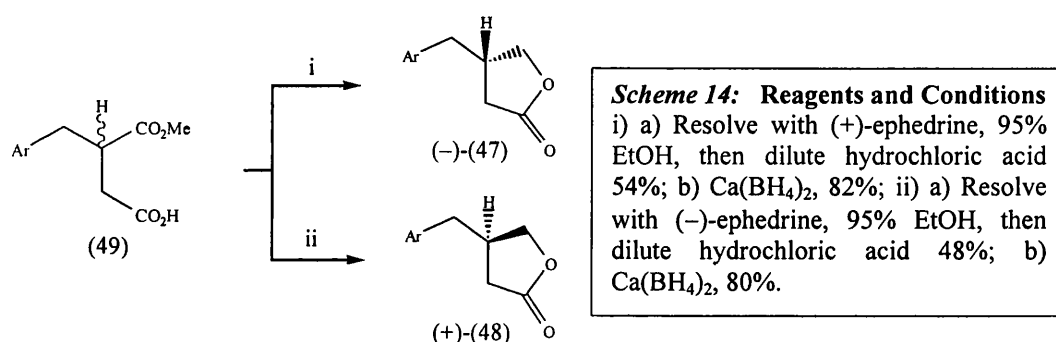
Kosugi and co-workers[23] revealed an intriguing route to the identical butyrolactones via 2-substituted ethylenic p-tolyl sulphoxides. The Horner-Wittig reaction of homopiperonal with (R)-(50) generated a mixture of Z- and E-ethylenic sulfoxides, which were easily separated and then subjected to sequential additive Pummerer rearrangement, dechlorination and desulphurisation, generating the desired butyrolactones (–)-(47) and (+)-(48) (Scheme 15).
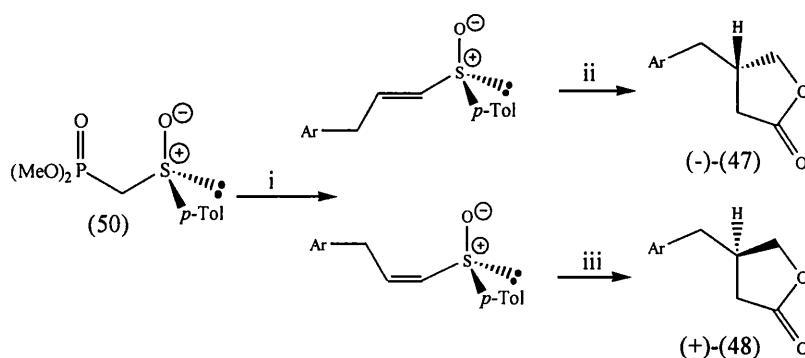
Scheme 15: Reagents and Conditions
i) n-BuLi, THF, –70 to –75 °C, add homopiperonal, 30 min, separate the Z/E-alkenyl sulfoxides; ii) a) Cl₃CCOCl, Zn, THF, –25 °C for Z-isomer and –45 °C for E-isomer; b) Zn-AcOH, rt; c) Bu₃SnH, AIBN, toluene, 90 °C.

1.6.1.1 The Robin Synthesis of (–)-Steganone

The diastereoselective alkylation methodology developed by the Robin[24] group for chiral butyrolactones was subsequently exploited in a chiral variant of their earlier racemic synthesis of steganone.[25]

Ar = 3,4,5-trimethoxybenzene

(53)

Diastereomeric mixture (1:1)
(52)

(51)

2 Steps

(12)

(–)-Steganone
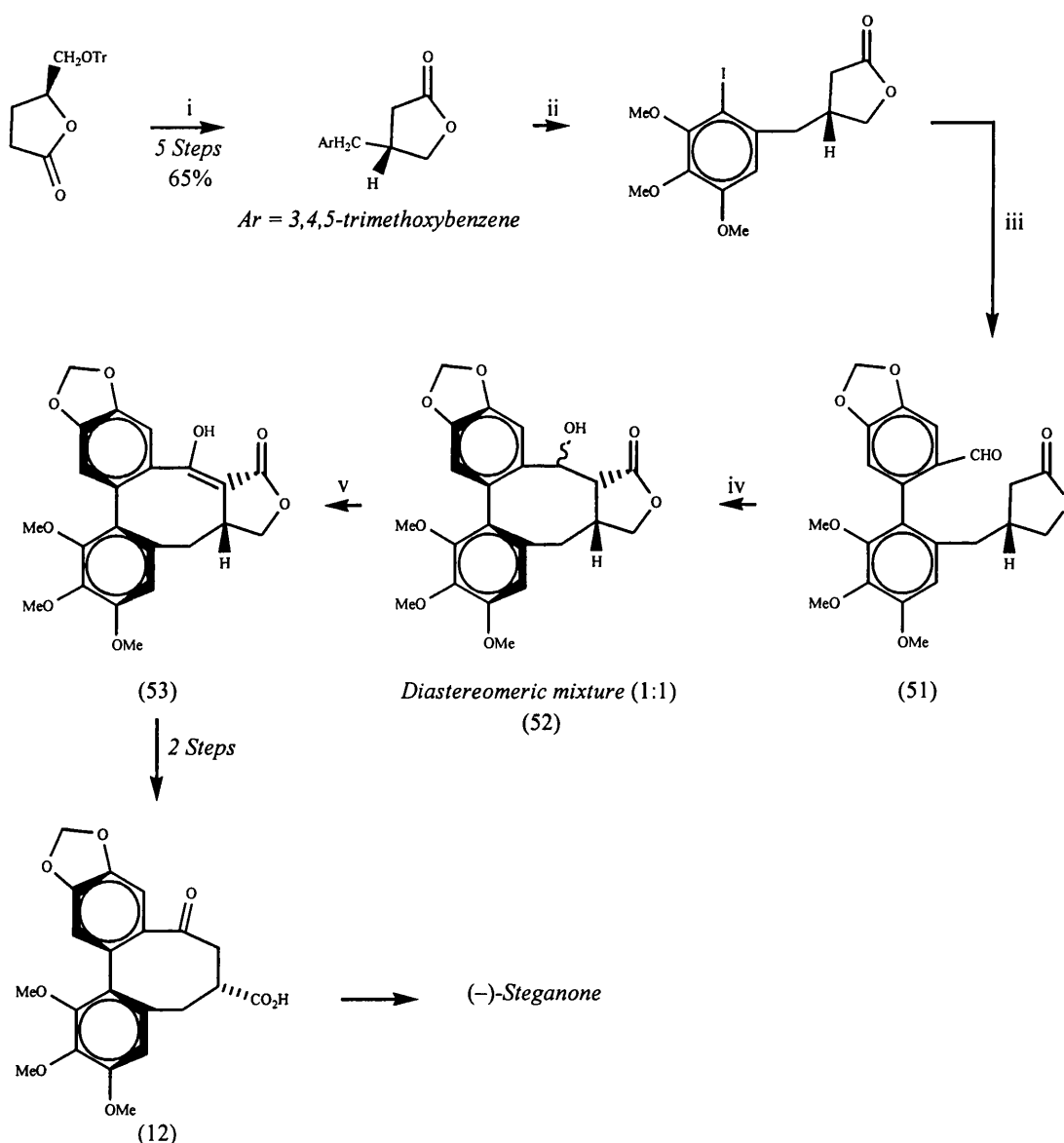
Scheme 16: **Reagents and Conditions**
i) See Scheme 13; ii) I$_2$, AgOCOCF$_3$, CHCl$_3$, 100%; iii) 6-bromopiperonal, Cu, 230 °C, 20 min, 59%; iv) LHMDS, benzene, 10 °C, 5 min, overall yield 67%; v) Jones reagent, acetone, 0 °C, 2 h, 66%.

Thus, as shown in Scheme 16 the biaryl was constructed at an early stage in moderate yield by Ullmann coupling and then subjected to an intramolecular aldol-like condensation which gave a mixture of two diastereoisomeric dibenzocyclooctadienes both of which possessed a *cis*-fused γ-lactone ring junction. Subsequent Jones oxidation then furnished the enolic derivative (53) and decarboxylation with barium hydroxide followed by Jones oxidation gave the well known oxo-acid (12) which was transformed into racemic steganone using the established method of Raphael. Although the overall yield of (–)-steganone from 3,4,5-trimethoxybenzaldehyde was 7%, the authors did not determine the optical purity of their sample!

1.6.2 *Diastereoselective Conjugate Addition to Chiral 2(5H)-Furanones*

1.6.2.1 The Koga Synthesis of (–)-Steganone

As an alternative to the diastereoselective alkylation method outlined above, Koga and co-workers have transformed the butyrolactone into the corresponding butenolide.[26] Koga *et al.*, obtained the required chiral trityl butenolide (56) by phenylselenation of the corresponding butyrolactone (54) (Scheme 17).

(54)   (55)   (56)
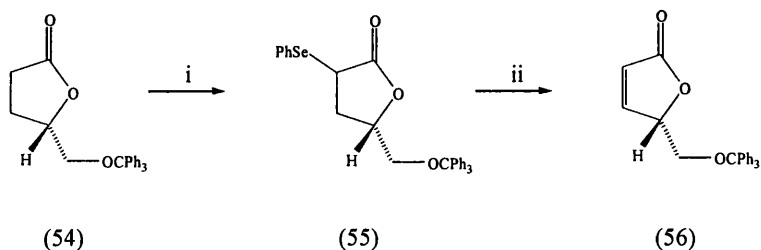
Scheme 17: **Reagents and Conditions**
i) LDA, THF, –78 °C, 35 min followed by the addition of phenylselenyl bromide, THF, –78 °C, 1.5 h, 94%; ii) NaIO₄, 18-crown-6, ethyl acetate, 50 °C, 14 h, 87%.

Like Kende,[8] Koga and co-workers were attracted by an approach involving non-phenolic oxidative coupling assisted by vanadium(V) oxytrifluoride to achieve simultaneous biaryl bond formation and eight-membered carbocyclic ring closure in their approach to (–)-steganone.[26] The absolute stereochemistry however was derived *via* a tandem 1,2-induction strategy. Thus 1,4-addition of the lithio dithiane anion (57) to the chiral trityl butenolide (56) and *in situ* trapping of anion which resulted with piperonyl bromide commenced the reaction sequence (Scheme 18).

(57)   (56)   (58)
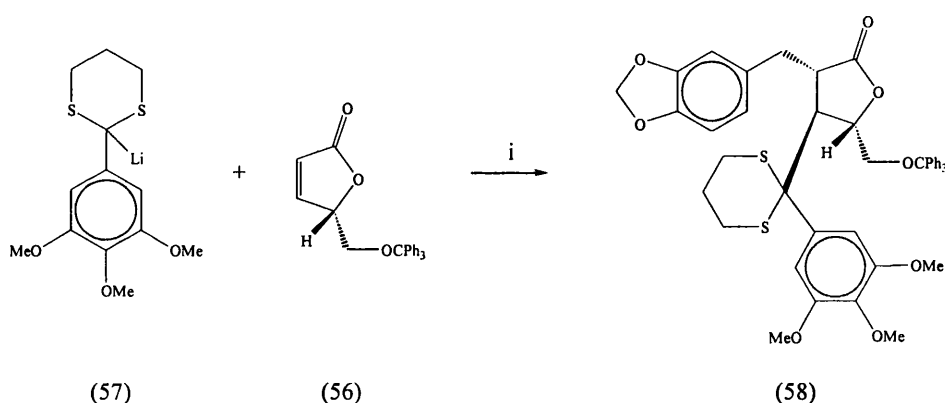
Scheme 18: Reagents and Conditions
i) THF, –78 °C, 1 h, then add piperonyl bromide –78 °C, 5 h, then at ambient temperature, 9.5 h, crude (58).

Although the reaction proceeded with essentially complete stereocontrol, the poor chemical yield encouraged the authors to investigate the use of benzyl ether protected butenolides. In the event however, although there was a notable increase in the chemical yield, this was accompanied by a decrease in the diastereomeric purity.[26] The four-step sequence, unmasking of the dithiane group by desulphurisation, hydride reduction and double oxidation delivered the natural product (+)-deoxypodorhizon (60) (Scheme 18, continued). Vanadium(V) oxytrifluoride assisted intramolecular oxidative coupling, then furnished the

dibenzocyclooctadiene, (+)-isostegane (61) in good yield. As in the Kende[8] study Koga and co-workers were also unable to effect this transformation in the presence of oxygen substituents at the C-8 benzylic position and further manipulations involving a high temperature thermal atropisomerisation to (−)-stegane (62) followed by bromination, hydroxylation and oxidation were required to deliver (−)-steganone.[26]
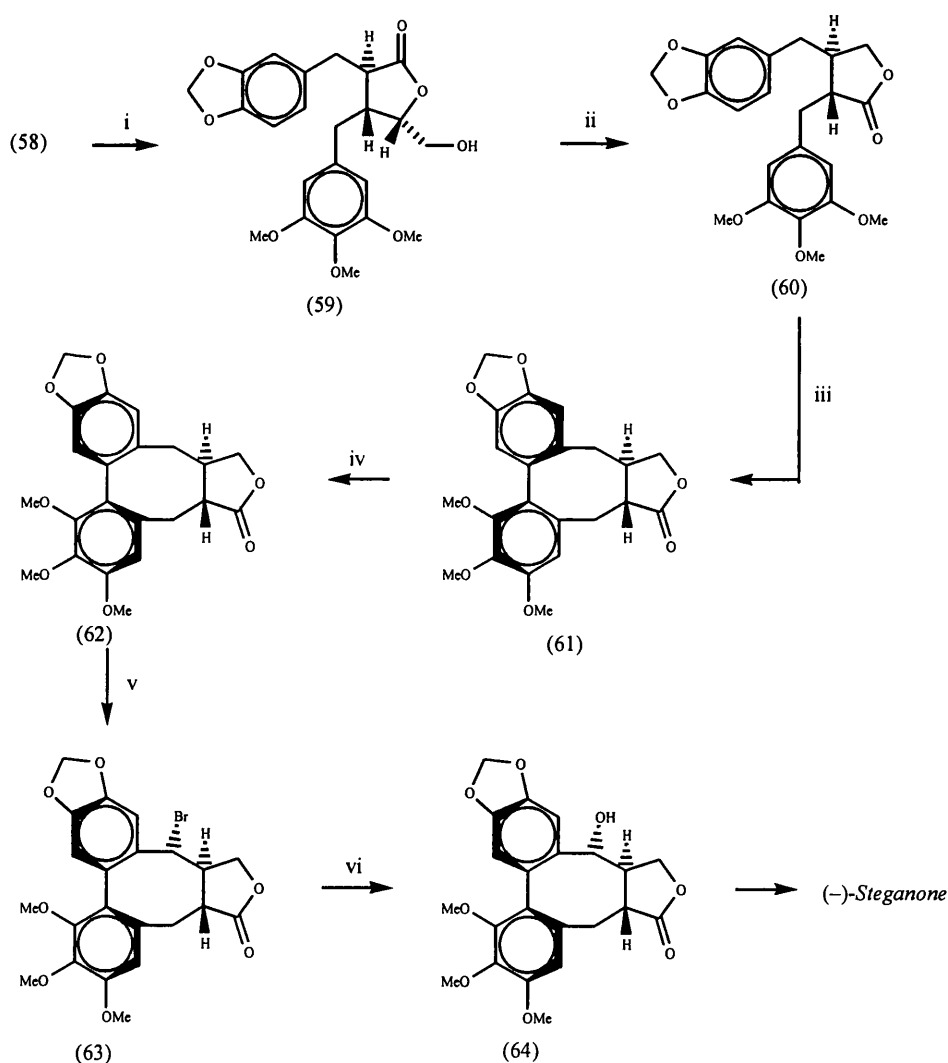
Scheme 18 continued: Reagents and Conditions
i) Raney® Ni, EtOH, reflux, 12 h, 28%; ii) a) LiAlH$_4$, THF, − 78 °C, 1 h, then rt, 1 h, 97%; b) NaIO$_4$, t-BuOH, rt, 50 min, 85%; c) CrO$_3$/pyridine, CH$_2$Cl$_2$, rt, 80 min, 95%; iii) VOF$_3$, CF$_3$CO$_2$H, CH$_2$Cl$_2$, −40 °C, 5 h, 64%; iv) (61) at 215 °C, then 195 °C, 3.5 h, 39%; v) NBS, BPO, CCl$_4$, reflux, 2 h, 97%; vi) H$_2$O$_2$-THF, 0 °C, 24 h, 85%; vii) PCC, NaOAc, CH$_2$Cl$_2$, 25 °C, 3 h, 81%.

This study was of interest since comparison of the optical rotation of the synthetic lignans with those of natural samples revealed them to be equal in magnitude but opposite in sign, which led to a revision of Kupchan's[3] original stereochemical assignment.

1.6.3 *Routes Involving the Use of Chiral Oxazolines*

Elegant studies conducted by the Meyers research group,[27] highlighted the utility of chiral aryl oxazolines for the syntheses of enantiomerically enriched lignans belonging to both the dibenzocyclooctadiene and aryltetralin series.[27, 28, 29]

1.6.3.1 The Meyers Synthesis of (–)-Steganone

In 1987 Meyers and co-workers revealed their own contribution to deliver enantioselective (–)-steganone.[27] In contrast to any other previously published enantioselective approaches the unique and potentially high risk feature of this approach was the early construction, in enantiomerically pure/enriched form, of the biaryl unit, containing all of the requisite functional groups in addition to the proper substituents to prevent racemisation by simple aryl-aryl bond rotation around the central axis.

The upper aryl portion (65) was prepared from readily available piperonal in two steps involving bromination and acetalisation. The lower aryl portion (66) was furnished from commercially available 3,4,5-trimethoxybenzoic acid by a series of

well-precedented steps and using the beautiful oxazoline chiral auxiliary developed by the Meyer's group.[27] Using the entrainment method,[30] the Grignard reagent of the aryl bromide (65) was generated. The key coupling reaction furnished the biaryl coupling products (67 and 68) in high yield as a 7:1 diastereomeric mixture (Scheme 19). Although at this juncture assignment of the major diastereomer to (67) and the minor to (68) was purely arbitrary, this assumption proved to be correct as the synthesis reached its final target.[27]
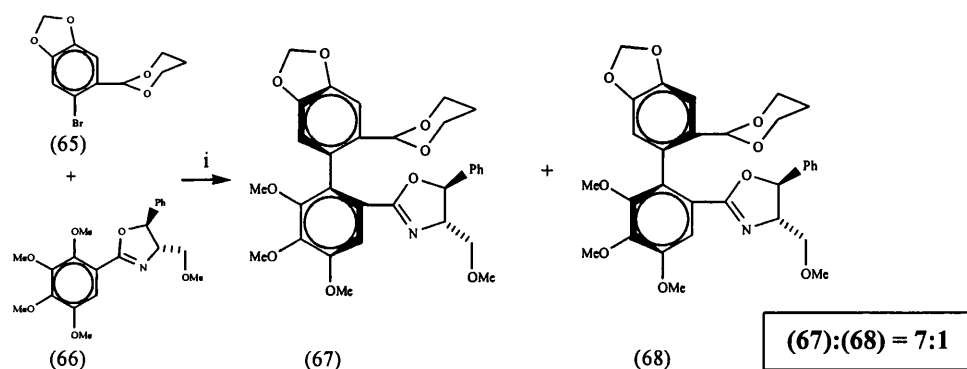
Scheme 19: Reagents and Conditions
i) (65), Mg, THF, reflux, add 1,2-dibromoethane, reflux 1 h, then add (66), reflux, o/n, (67) 65% and (68) 9%.

In order to elaborate the biaryl (67) to the eight-membered ring and aware of the potential dangers the acetal functionality was unmasked at low temperature, immediately treating the resultant aldehyde with methylmagnesium bromide to afford a diastereomeric mixture of the secondary alcohols (70a and 70b) (Scheme 19 continued).
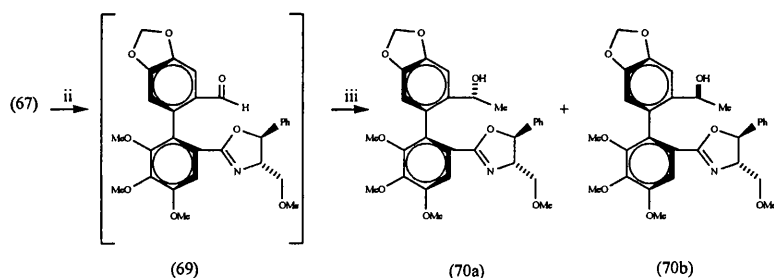
Scheme 19 continued: Reagents and Conditions
ii) 3 N hydrochloric acid, THF, −5 °C, 2.5 h; iii) MeMgBr, THF, −78 °C, 1 h, (70a) 47% and (70b) 45%.

It had previously been observed that even this single sp^2 substituent (aldehyde) *ortho* to the biaryl linkage led to aryl-aryl bond rotation and hence racemisation. The secondary alcohols (70) that were generated in high yield existed as a 1:1 diastereomeric mixture and were found to be completely stable to aryl-aryl bond rotation even when heated under reflux in toluene. The authors belief that the bulky oxazoline at the other *ortho*-position would contribute to raising the barrier to bond rotation, thus allowing the aldehyde (69) to have a reasonable half-life, was therefore proven.

The mixture of secondary alcohols were then protected as their allyl ethers (Scheme 20). The oxazoline was then removed, again under the mildest possible conditions, by treatment with sodium bisulphate-water in THF. Isolation of (71) in an acidic medium was found to be imperative since selection of neutral or alkaline conditions during the work-up resulted in hydrolysis to the amide. Reduction with lithium aluminum hydride generated the primary alcohol (72), which was immediately transformed into the brominated compound and then directly converted to the malonate ester (73). Rhodium-catalyzed isomerization followed by hydrolytic cleavage of the resultant enol ether catalysed by mercuric chloride-mercuric oxide then led to the deprotected alcohol which was oxidised to the methyl ketone and then brominated using Ziegler's method. The α-bromo ketone was then treated with potassium *tert*-butoxide to furnish the cyclic ketone and the remainder of the synthesis was completed using the Ziegler approach.[15]

(70)

(71)

(72)

(73)

(74)

(75)

(–)-Steganone
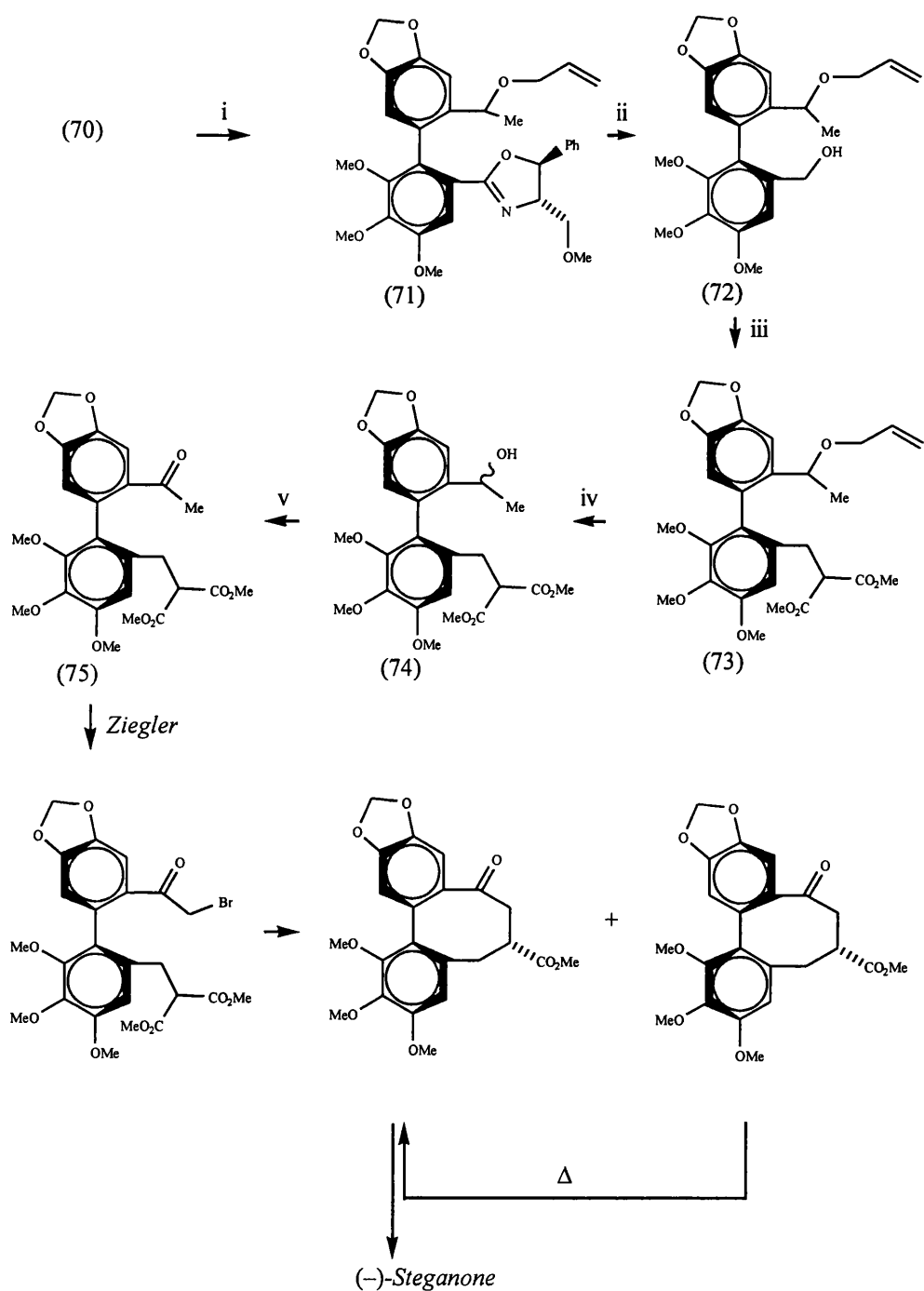
Scheme 20: Reagents and Conditions
i) NaH, THF, 25 °C, 30 min, then add allyl iodide, THF, 25 °C, 18 h, 85%; ii) a) NaHSO$_4$.H$_2$O, THF, 25 °C, 3 h, H$_2$O, 25 °C, 48 h; b) LiAlH$_4$, THF, 0 °C, crude used in next step; iii) a) NBS, PPh$_3$, CH$_2$Cl$_2$, 0 °C, 1.5 h, 73% (crude); b) Na, dimethyl malonate, MeOH, 25 °C, 1 h, 61% overall from (ii); iv) a) diazabicyclo[2.2.2]octane, (Ph$_3$P)$_3$RhCl, 10% aq EtOH, reflux, 3 h; b) HgCl$_2$, HgO, 10% aq acetone, 10% aq EtOH, 25 °C, 18 h, 83% over 2 steps; v) PCC, NaOAc, CH$_2$Cl$_2$, 25 °C, 2 h, crude (75) used in next step.

45

Although extremely adventurous this synthesis is somewhat low yielding on the final steps, and it was also discovered that the sample of (−)-steganone prepared had an enantiomeric excess of only 80-84% which the authors felt was encountered at the α-bromination stage.

1.6.3.2 The Uemura Formal Synthesis of (−)-Steganone

Uemura and co-workers also considered the malonate ester intermediate (73) envisaged by Meyers[27] in their synthesis of (−)-steganone, as a valuable intermediate.[31] A Suzuki coupling of the planar chiral (arene)-chromium tricarbonyl complex (76) and the aryl boronic acid (77) generate the biaryl (78). Elaboration of (78) in a further seven steps led to the malonate ester (73) (Scheme 21).
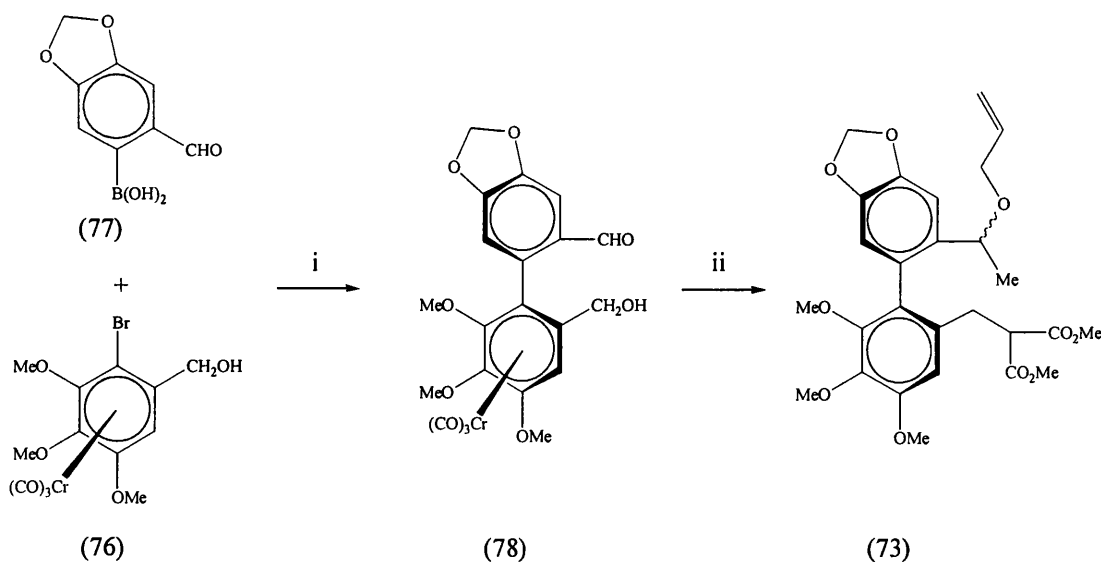
Scheme 21: Reagents and Conditions
i) Pd(PPh₃)₄, aq Na₂CO₃, MeOH, reflux, 1 h, 67%; ii) a) t-BuMe₂SiCl, imidazole, CH₂Cl₂, 87%; b) MeLi, diethyl ether, −78 °C, 95%; c) allyl bromide, NaH, THF, DMF, 63%; d) hν, O₂, diethyl ether, 90%; e) n-Bu₄NF, THF, 98%; f) CBr₄, PPh₃, CH₂Cl₂, 0 °C; g) NaCH(CO₂Me)₂, MeOH.

1.6.4 Routes Involving Samarium(II) iodide Promoted Radical Coupling

1.6.4.1 The Molander Synthesis of (–)-Steganone

The fact that steganone remains a target of interest almost thirty years after its isolation is appropriately reflected by the following approach to be discussed in this subsection inasmuch as it appeared in the literature[32] during the preparation of the present introductory section.

The route taken by Molander and co-workers, features for the first time a samarium(II) iodide promoted 8-endo ketyl–olefin radical coupling to install, in a single transformation, the 8,5 ring system of steganone (Scheme 22).[32]
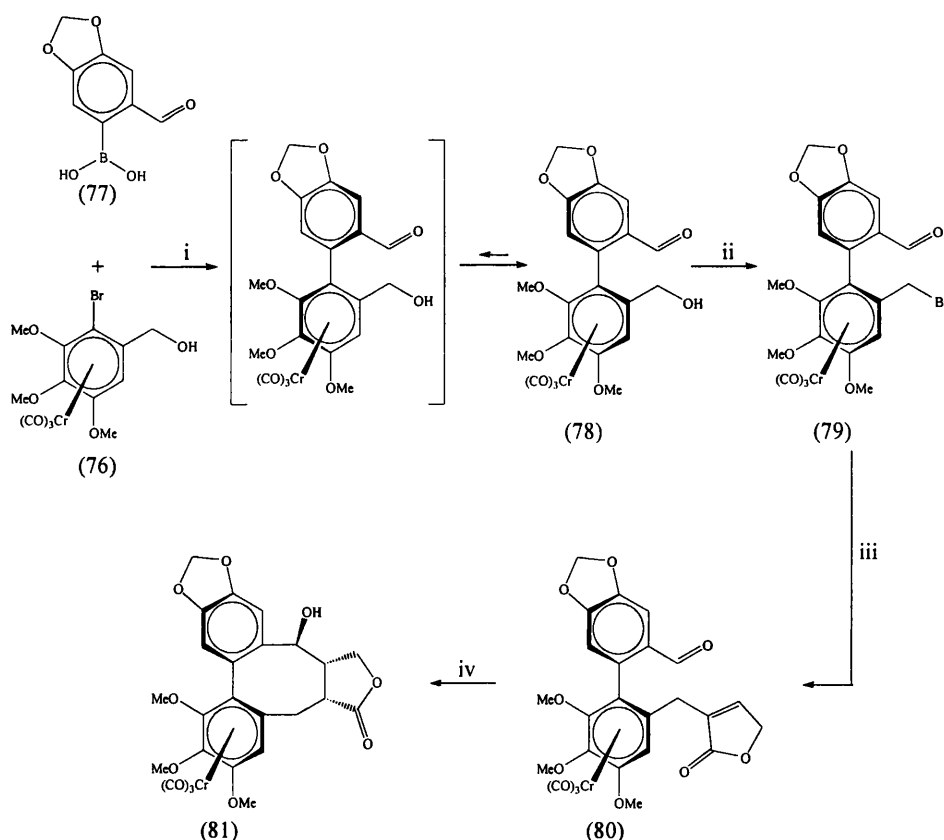
Scheme 22: Reagents and Conditions
i) Pd(PPh₃)₄, Na₂CO₃, MeOH, H₂O, 72% crude mass; ii) MsCl, Et₃NHBr, 96%; iii) 3-(tributylstannyl)-(5H)-furan-2-one, Pd₂(dba)₃, AsPh₃, THF, reflux, 91%; iv) SmI₂, t-BuOH, THF/HMPA, 0 °C, 73%.

The synthetic route commenced from the enantiopure biaryl (78), encountered previously in the work by Uemura[31] et al. The alcohol (78) was firstly converted to the corresponding benzylic bromide (79), and then to the desired substituted furanone (80) by a palladium-catalysed coupling with a stannylated butenolide in the presence of the weakly coordinating $AsPh_3$ ligand, in a commendable yield. The SmI_2-promoted 8-endo ketyl-olefin cyclisation then generated, as a single diastereomer, the chromium-complexed isopicrosteganol (81) in good yield. The cyclisation was thought to occur via two sequential electron transfer steps to generate a samarium(III) enolate.[32] Oxidation of (81) using, PCC buffered with NaOAc in CH_2Cl_2 accomplished the deprotection/decomplexation reaction and the simultaneous oxidation of the secondary carbinol to the corresponding ketone (82) (Scheme 23).
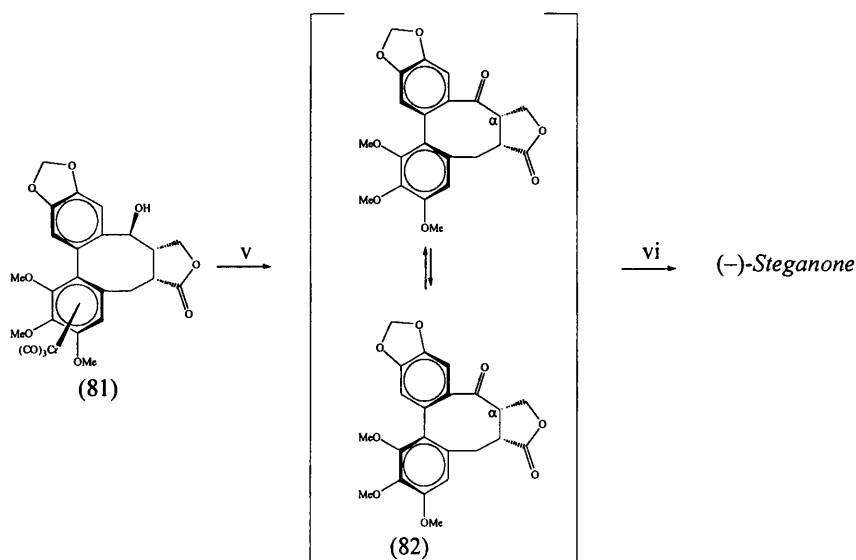
Scheme 23: **Reagents and Conditions**
v) PCC, NaOAc, CH_2Cl_2, 85%; vi) DBU, THF, reflux, 82%.

Equilibration of the stereocentre α to the ketone carbonyl of enantiopure (82) was achieved by refluxing (82) in DBU/THF to afford (–)-steganone from enantiopure picrosteganone (82) in high yield and with an optical purity >99%.[32]

1.6.5 *Resolution - The Classical Approach*

The traditional sequence for resolution of a racemic mixture involves the three steps of formation of diastereomers, their separation, and a final regeneration. Whilst it is often discounted in the modern academic world of efficient asymmetric synthesis it should however be noted that the use of a chiral auxiliary also requires three steps in order to achieve its objective. Casual inspection of the current literature on total asymmetric synthesis also serves to convince that a disproportionately large number of steps are often required to prepare a single enantiomer as opposed to the racemate.

It is therefore fitting perhaps, that in this final selection, the last synthetic route to (–)-steganone has proven to be the most efficient.

1.6.5 1 The Raphael Synthesis of (–)-Steganone

In the first instance, prior to embarking on their asymmetric route to steganone, Raphael *et al.,* focused on improving their existing strategy for the racemic natural product.[33] In particular, the original photochemical process which was developed to deliver the substituted 9-(pyrrolidin-1-yl)phenanthrene (15) involved a photolysis in liquid ammonia and this key intermediate was not amenable to large scale preparation of (15). In order to obviate this drawback, a new procedure suitable for scaling up purposes was devised, and this method was then applied in the enantioselective synthesis of (–)-steganone.[34]

The synthesis commenced with the coupling of methylenedioxyphenylzinc chloride (83) and N-cyclohexyl-2-iodo-3,4,5-trimethoxybenzylideneamine (84) in the presence of a nickel(0) catalyst, to generate after the hydrolytic work-up the biphenyl aldehyde (85) in a commendable yield (Scheme 24).[34]
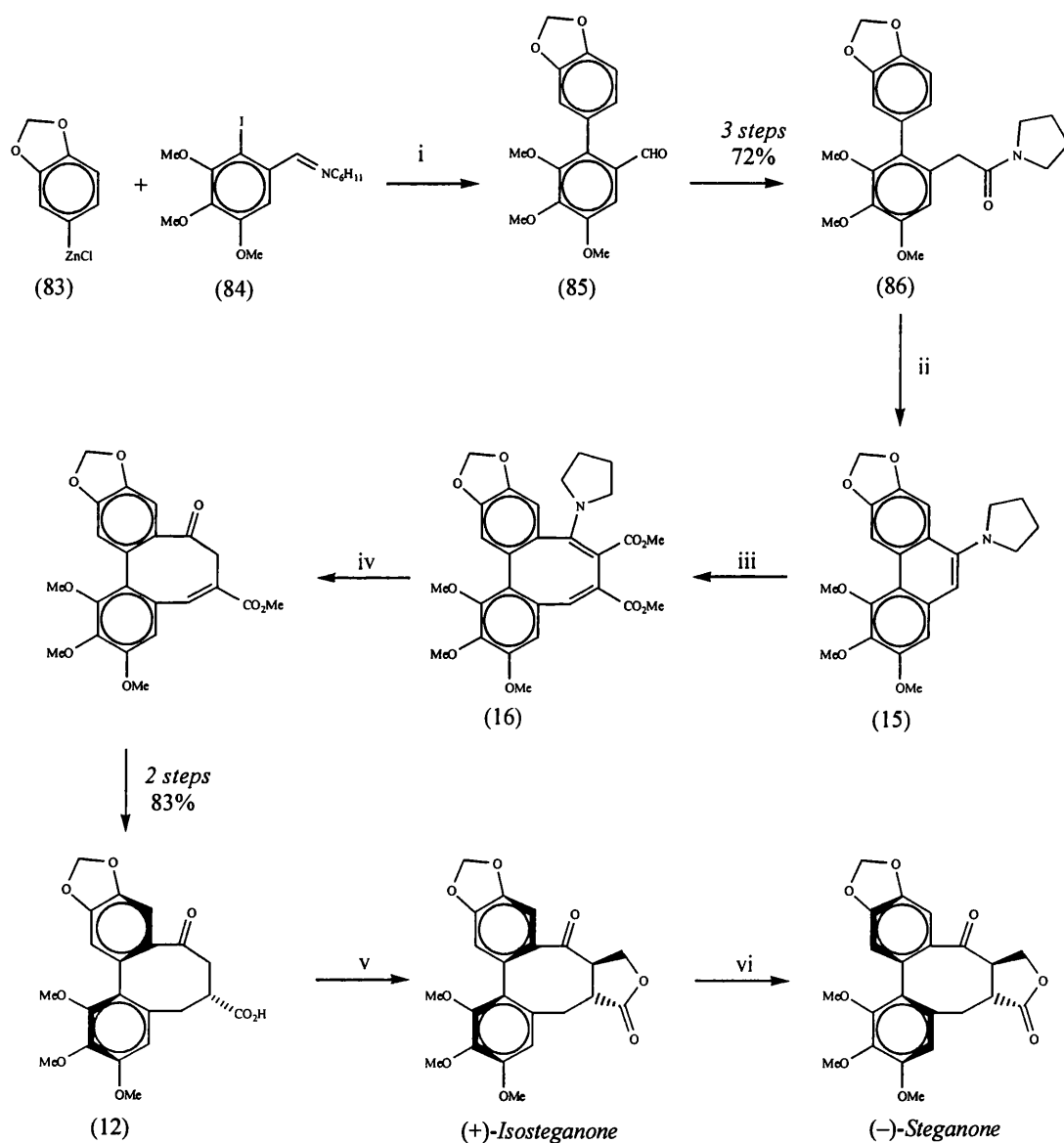
Scheme 24: Reagents and Conditions
i) a) Ni, −20 °C, 4 h; b) 2 N hydrochloric acid, CH₂Cl₂, reflux, 1.5 h, 82% over 2 steps; ii) POCl₃, CHCl₃, 5 h, 94%; iii) dimethyl but-2-ynedioate, 1,4-dioxan, reflux, 44 h, 89%; iv) 5% hydrochloric acid, MeOH, 12 h, 95%; v) a) 37% aq formaldehyde, 5% aq KOH, 25 °C, 1 h; b) Jones reagent, acetone, 0 °C, 36% over 2 steps; vi) xylene, reflux, 1 h, 92%.

Until that time nickel(0)-mediated couplings were primarily considered to suit symmetrical couplings and furthermore had been shown to be ineffective when two *ortho*-substituents flanked the reactive carbon sites. The authors attributed the success of their particular nickel(0)-mediated coupling to the chelating ability of the imine group of (84), which was thought to stabilise the transient arylnickel intermediate.[34] The acyl pyrrolidine (86) was then generated from the aldehyde (85) by a three-step sequence and then subjected to a phosphoryl chloride mediated cyclisation which furnished the phenanthrene derivative (15) in a high yield. The familiar ring expansion with dimethyl but-2-ynedioate then furnished the dibenzocyclooctadiene (16) in excellent yield and this was then converted to the standard racemic oxo-acid (12). Resolution of the oxo-acid (12) was performed through conversion into the salts derived from (–)-(*S*)-2-amino-3-phenylpropan-1-ol.[34] The (+)-enantiomer of the oxo-acid (12) underwent the two-step sequence involving base catalysed condensation with formaldehyde and Jones oxidation to produce (+)-isosteganone, which was finally thermally rearranged to the atropisomeric (–)-steganone.[34]

The Raphael-Larson approach to (–)-steganone is noteworthy for a number of reasons. Despite the need for late resolution, the natural product was delivered in sixteen-steps from readily available 2-iodo-3,4,5-trimethoxybenzaldehyde alcohol in a handsome yield of 10%, which essentially equals that of the racemic synthesis of Kende. Additionally, the recognition of the inherent biaryl chirality of the molecule previously undetected by Kende, represented a significant advance in the study of bisbenzocyclooctadiene lignan lactones. To date, the Raphael approach to steganone

remains unchallenged as the most efficient synthesis of enantiomerically pure (–)-steganone.

1.7 Chronology and Overview of the Synthetic Routes to Steganone

It is both interesting and instructive at this stage to highlight a few selected observations from the variety of highly efficient and creative routes which have evolved over almost three decades. These are shown in Table 1.

Total Syntheses Year	Research Group	Method of Biaryl Coupling	Oxo-acid (12) intermediate	Chiral Synthesis
1976	Kende[8]	Non-phenolic oxidative	Yes	No
1976	Raphael[10]	Photochemical ring closure	Yes	No
1977	Raphael[11]	Modified Ullmann type	Yes	Yes
1978	Krow[13]	Photochemical ring closure	Yes	No
1980	Ziegler[15]	Modified Ullmann type	Yes	No
1980	Robin[24]	Ullmann coupling	Yes	Yes
1981	Ghera[14]	Photochemical ring closure	Yes	No
1984	Koga[26]	Non-phenolic oxidative	No	Yes
1985	Magnus[12]	Non-phenolic oxidative	Yes	No
1987	Meyers[27]	Grignard coupling	Yes	Yes
2000	Molander[32]	Suzuki coupling	No	Yes
Formal Syntheses				
1993	Narasimhan[17]	Free radical coupling	Synthesis leads to (12)	No
1995	Uemura[31]	Suzuki coupling	Synthesis leads to (12)	Yes

Table 1: Published Syntheses of Steganone

The first and perhaps self-evident statement is that every single synthesis has used a coupling reaction to forge the σ-bond between the two aromatic rings. More unusual perhaps is the fact that of the thirteen synthetic approaches (including the formal syntheses) all except the routes of Uemura,[31] Narasimhan,[16,17] and Molander[32] have used either a modified Ullmann coupling or non-phenolic oxidative coupling reagent to establish the biaryl bond. Most surprising of all is that the oxo-acid (12) has served as a common intermediate in no less than nine of the routes especially since the subsequent steps involving introduction of the hydroxymethyl group and lactonisation proceed in a uniformly low yield, typically around 17%. It is even ironic to note that the Koga route which featured the use of a pre-formed γ-lactone, then required its programmed destruction. To date, the Molander route is the only one which avoids this problem. Of the five total and one formal route to a single enantiomer, that by Raphael is by far the most efficient in terms of overall yield (10%) and even more as for the racemic series (23%).
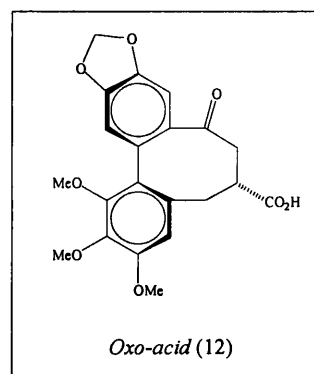
Oxo-acid (12)

Given that closer scrutiny of these syntheses reveals considerable overlap and convergence we therefore considered that there was further opportunity for alternative strategies. The approach within our own group forms the prelude to the following section.

Chapter 2

Results and Discussion

2.1 Introduction: The Cobalt-Mediated [2+2+2] Cycloaddition Strategy for the Construction of Steganone Analogues

The foregoing introductory section has hopefully highlighted the wide variety of synthetic routes to steganone which have evolved over almost three decades, and which have culminated in effective routes to this intriguing molecule with significant biological activity. It is nevertheless very surprising, as revealed by the comparative analysis, that the vast majority of routes had converged on the oxo-acid (12) which then required the low yielding and often variable formaldehyde condensation sequence for elaboration to the *trans*-fused γ-lactone moiety (Scheme 25).
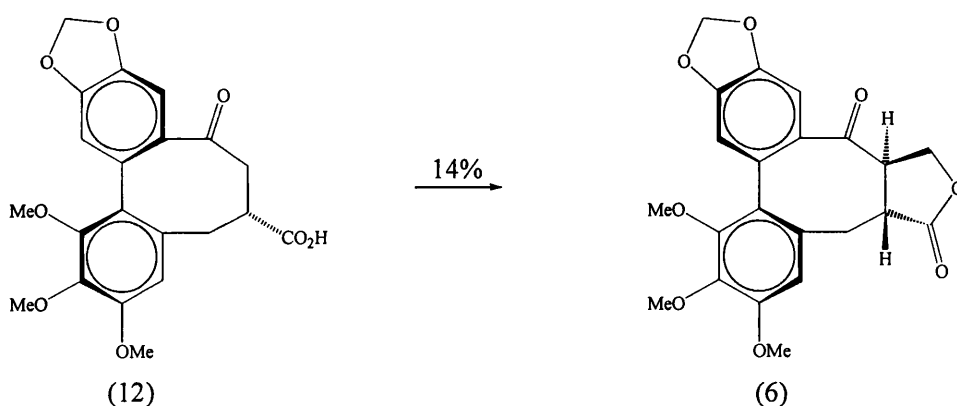
Scheme 25: Conversion of Oxo-Acid (12) to Steganone (6)

Furthermore, and perhaps less surprising is the fact that every single synthesis required, at some stage, the coupling of the two intact aromatic rings to form the biaryl unit. This appears to be a mandatory operation.

Finally, careful examination of the published routes reveals that on most occasions a linear sequence is involved.

With these thoughts in mind, and given that the properties of steganone (6) itself are well known, the primary objective, initiated within our own group in 1992, was to develop a highly convergent and chemically versatile route which would allow access to a host of steganone analogues for use in structure activity studies.

2.2 A Novel Retrosynthetic Strategy Towards Racemic Analogues of Steganone

The retrosynthetic design initiated by Motherwell and Ujjainwalla in 1992 utilised an entirely novel disconnection previously unexploited in this area for concomitant construction of both the northern aryl ring and the fully functionalised eight-membered cyclooctadiene unit.[35] The key element of the synthetic strategy involved the use of the tethered diyne (88) in a cobalt-mediated [2+2+2] cycloaddition, thereby avoiding any form of biaryl coupling and enabling the potential for construction of a series of functionalised aryl rings A and simultaneous ring closure of the functionalised eight-membered carbocyclic ring (Scheme 26).[35] The formation of an eight-membered ring in such reactions was unprecedented at that time.
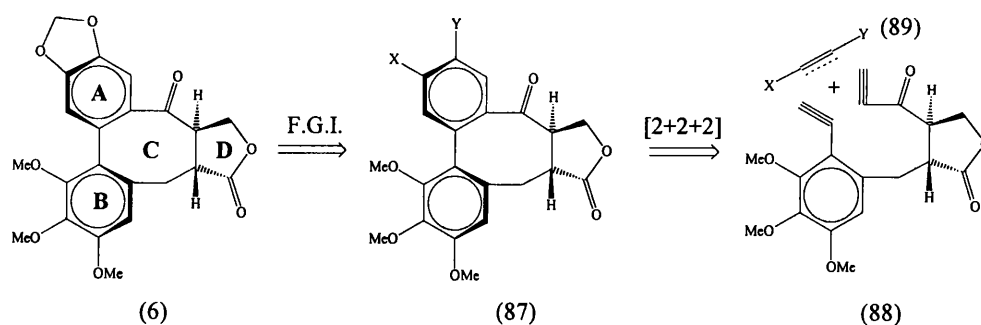
Scheme 26: The Motherwell–Ujjainwalla Retrosynthesis of Steganone (6)

Although installation of the ring-A methylenedioxy unit of steganone itself could be problematic and somewhat restrict the choice of the 2π-component, it was considered that the use of a variety of 2π-addends (89) in the cobalt-mediated [2+2+2] cycloaddition, and further elaboration of the generated functionalised northern aryl unit, could potentially allow access to a range of steganone analogues.[35]

A concise and convergent approach to the tethered diyne precursor (90) was also envisaged (Scheme 27).[35] The required *trans* stereochemistry round the γ-lactone would be derived by a sterically controlled alkylation of the lactone enolate from (94) with the benzylic bromide (92). The benzylic bromide or left hand coupling fragment (92) was then derived from the Raphael intermediate (93),[34] while the γ-lactone or right hand coupling fragment (94) was to be elaborated from paraconic acid (95).[35] Furthermore, the selection of a series of the benzylic bromides as alkylation partners would then enable further variation in the generation of a wide variety of analogues.

Left hand coupling fragment   Right hand coupling fragment

Scheme 27

(92)   (94)

(93)   (95)
Raphael intermediate   *(±)-Paraconic acid*
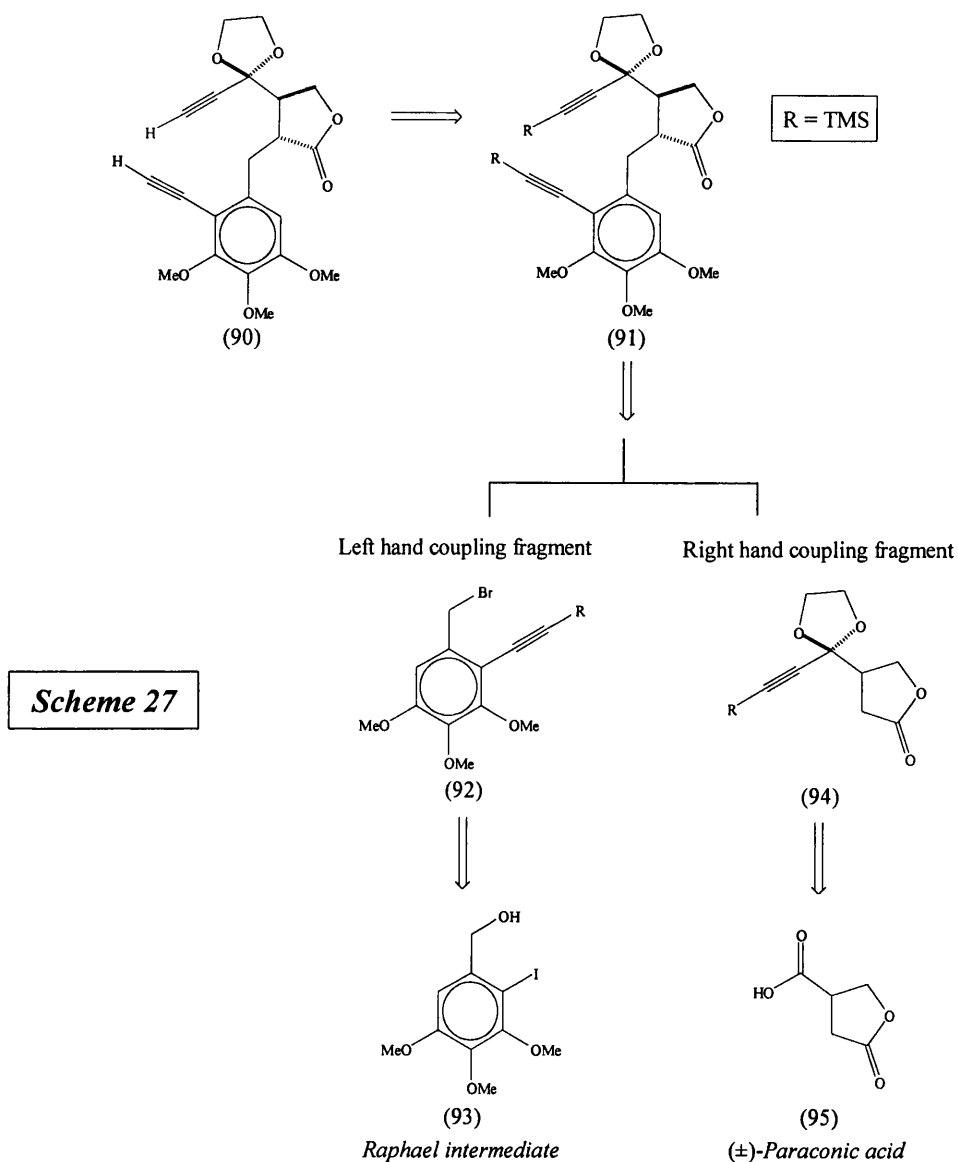
2.3 Previous Work Within the Group

Racemic paraconic acid (95), the cornerstone of the synthesis of the right hand

coupling fragment, was readily accessible from diethyl succinate (96) in a moderate

yield, by a 4-step sequence entailing Claisen condensation, hydrogenation, thermal

lactonisation and saponification. A further three steps involving palladium-catalysed

coupling of the derived acid chloride with Me₃SiC≡CSnMe₃ followed by ketalisation

of the resultant ynone, then furnished the γ-lactone (94). Commencing from readily available 3,4,5-trimethoxybenzaldehyde (97), the benzylic bromide (92) was prepared in high overall yield by a series of well-precedented steps, involving iodination, borohydride reduction, a palladium catalysed coupling reaction of the resultant iodoarene with $Me_3SiC≡CH$, followed by the final transformation to the benzylic bromide (92) via the PPh_3-CB_4 protocol.[35] The entire carbon skeleton of the tethered diyne (90) was then assembled via the stereoselective anionic coupling of the left and right hand fragments (Scheme 28). These steps will be discussed in greater detail at a later stage.
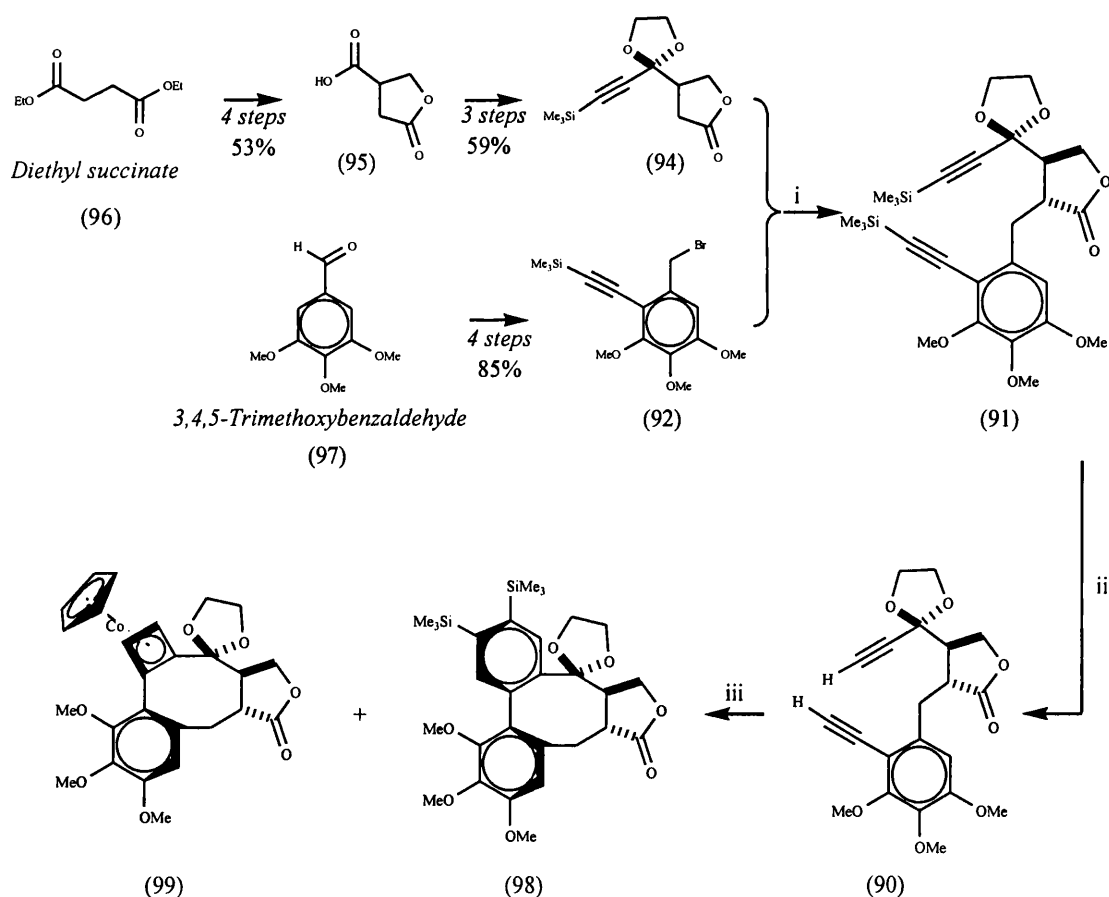
Scheme 28: Reagents and Conditions

i) (94), LDA, –78 °C, 30 min, then (92) at –35 °C, –35 to 25 °C, o/n, 80%; ii) K_2CO_3, MeOH, 25 °C, o/n, 95%; iii) BTMSA (100), reflux, addition of (90) in THF and $CpCo(CO)_2$ in THF over 9 h, hv (300 W tungsten lamp), 14% (98) and 56% (99).

The alkylation of the lithium enolate constituted the key step of the convergent synthetic route.[35] It proceeded smoothly through prior generation of the lithium enolate at −78 °C in THF, followed by quenching with the benzylic bromide (92) at −35 °C, furnishing the required diyne (91) as a single diastereoisomer in a commendable yield of 80%. Global desilylation of the acetylenic groups then followed, delivering the tethered diyne (90) in nine steps and proceeding with an efficient 30% overall yield from diethyl succinate (96). The standard irradiation conditions developed by Vollhardt[36] were then employed to perform the crucial CpCo(CO)$_2$-mediated [2+2+2] cycloaddition step, using the parent diyne (90) and bis(trimethylsilyl)acetylene (100) as the third acetylenic component. In the event however, the desired biaryl (98) was isolated in only 14% yield and the cobaltacyclobutadiene complex (99) was the major product (56%). Fortunately, nOe experiments conducted on the biaryl (98) concluded that it was indeed the correct atropisomer which corresponded to the natural series.[35]

In summary, Motherwell and Ujjainwalla demonstrated for the first time, the viability of using a tethered deca-1,9-diyne (90) in a cobalt-mediated [2+2+2] cyclobenzannulation strategy for construction of the steganone core in a highly convergent and efficient manner. The cycloadduct (98) delivered was potentially equipped for elaboration to steganone itself and to a range of analogues. In comparison to many of the previously published routes, this approach circumvented the frequently applied thermal isomerisation to generate the correct atropisomer.[35]

Following on from this pioneering study by Ujjainwalla, attempts to extent and refine this approach within the group were continued by Bradley,[39] who initially

focused on refining the route and especially on improving the yield of the desired biaryl (98) in the cobalt-mediated [2+2+2] cycloaddition.

As we have seen, the partially optimised conditions of the crucial CpCo(CO)$_2$-mediated [2+2+2] cycloaddition step of the tethered deca-1,9-diyne (90) and BTMSA (100), developed by Ujjainwalla[35] delivered the undesired cobaltcyclobutadiene complex (99) as the major product but failed to provide a high yield of the desired biaryl (98).[35] Nevertheless, the formation of (99) was encouraging as it confirmed both the viability of the eight-membered ring closure and also the *trans* stereochemistry around the γ-lactone.

Consideration of the CpCo(CO)$_2$-mediated co-cyclisation of the tethered diyne (90) and BTMSA (100), led to the postulate that the rearrangement of the cobaltacyclopentadiene complex (101) to the cobaltcyclobutadiene complex (99) was preferred over the co-ordination of a molecule of BTMSA (100) and subsequent formation of the biaryl cycloadduct (98) (Scheme 29). Formation of complexes similar to the isolated cobaltcyclobutadiene complex (99) are well documented in the literature[37,38] and generally considered to arise when either co-ordination or insertion of the third 2π-alkyne component has proven problematic.

However, despite exhaustive experimentation to improve the yield of the desired biaryl (98), Bradley met with limited success.[39] Employing the conditions previously utilised in the group[35] and replacing THF, the co-solvent, by acetonitrile, saw the yield of the biaryl cycloadduct (98) improve by a further 5%. The differing abilities of THF and acetonitrile to act as ligands for cobalt was thought to contribute directly to this improved yield.[39] Acetonitrile, especially because of its π-acceptor

character, was thought to facilitate displacement of the carbon monoxide ligands on CpCo(CO)$_2$ more readily than the previously employed THF.
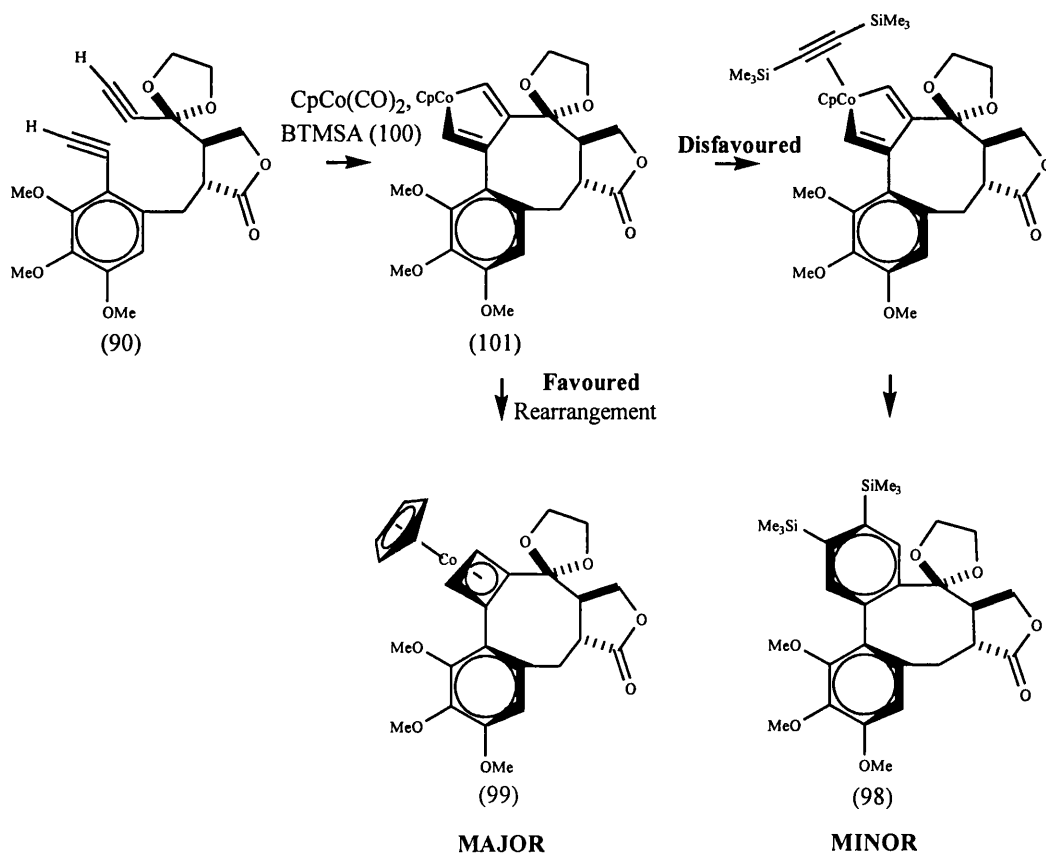
Scheme 29

To date, this transformation of the tethered diyne (90) *via* a cobalt-mediated [2+2+2] cycloaddition to deliver the biaryl (98) in a yield of 19%, represents the most successful metal mediated cycloaddition of a tethered deca-1,9-diyne with any 2π addend.[40]

With this established route to the biaryl (98) in hand, it was then appropriate to demonstrate the utility of the existing methodology towards the synthesis of

steganone analogues. Deprotection of the ketal (98) with wet formic acid delivered

the parent ketone (102) in a moderate yield (Scheme 30).

(98)

(102)   (103)   (104)
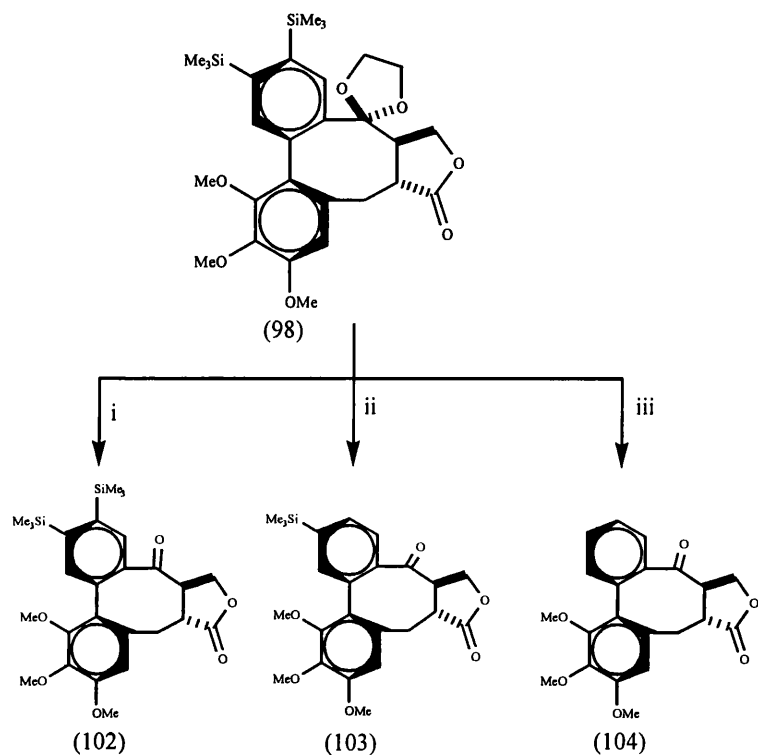
Scheme 30: **Reagents and Conditions**
i) HCO$_2$H, 20 °C, 24 h, 54%; ii) CF$_3$CO$_2$H, 20 °C, 12 h, 73%; iii)
CF$_3$CO$_2$H, reflux, 12 h, 51%.

Deprotection accompanied by selective mono- or di-protodesilylation was also

performed in a single step by treatment of the biaryl (98) with TFA either at room

temperature or at reflux. In this fashion, a further two racemic steganone analogues

were thus obtained. (Scheme 30).[39]

2.4 Objectives of the Present Work

Within the framework of the existing route which had evolved within the group, it was nevertheless clear that several desirable objectives had yet to be achieved. The first of these, which is almost mandatory for any modern effort in synthetic organic chemistry, lay in the possibility of developing a route to chiral steganone analogues, and the various approaches which have been adopted form the second part of this chapter.

Since the most obvious solution to the problem of an asymmetric synthesis lay in the possibility of using the existing route and incorporating the correct enantiomer of paraconic acid as a key building block, it was decided, in the first instance, to work in the racemic series with a view to improving and understanding some of the more problematic steps and hence streamlining this approach. The first objective in this respect lay in our concerns around the use of the ynone (105) as the key intermediate. As might be anticipated, ynone (105) had proven to be somewhat sensitive and prone to decomposition, presumably by polymerisation. Of even greater importance was the fact that it required the use of highly toxic trimethyltin chloride to prepare the stannylated alkyne for the palladium catalysed coupling reaction, and that this very reagent was then produced again as the by-product of the coupling reaction. Approaches which obviated the use of tin reagents and / or of the fragile ynone (105) *per se*, were therefore of interest.
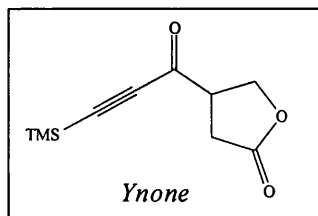
Ynone

The second objective within the racemic series, lay, yet again, in attempting to improve the low yielding, but absolutely essential cobalt-mediated [2+2+2] cycloaddition of the tethered diyne (90) with the third alkyne component.

2.5 Further Investigations of the Cobalt-Mediated [2+2+2] Cycloaddition Approach

2.5.1 *Synthesis of the Right Hand Coupling Fragment (94)*

In pursuit of our objectives we therefore commenced on the synthesis of racemic paraconic acid (95) (Scheme 31).[39]
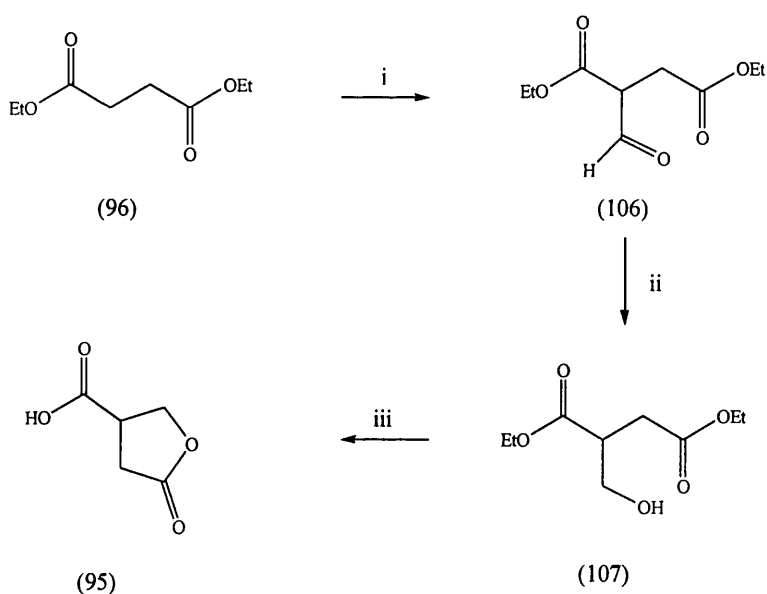
Scheme 31: **Reagents and Conditions**
i) Ethyl formate, Na, (1 mol%) EtOH, Et$_2$O, rt, 16 h, 44%; ii) NaBH$_4$, MeOH, 0 °C, 5 h, 80%; iii) 2.75 N NaOH reflux, 1.5 h, then passage through Amberlite® IR-120 H$^+$ ion exchange resin, 55%.

Thus, the crossed Claisen condensation of diethyl succinate (96) with ethyl formate in the presence of sodium and of 1 mol% of ethanol in diethyl ether afforded formyl succinate diethyl ester (106) isolated in a yield of 44%. The ^{1}H NMR indicated that this diester existed as a 1:1 mixture of its keto and enol forms. Our yield was some 15% lower than the reported value,[39] presumably due to ester hydrolysis on acidic work-up. Saponification of the diester was reported to be a highly facile process,[35] especially in the event of the pH of the aqueous phase dropping below pH 3, and this may have occurred if the rapid acid washes in the work–up were conducted slowly. In the original literature procedure,[39] the second step required a high pressure (150 atm) hydrogenation of (106) over a Raney® nickel catalyst, and this was the method which had been used by Ujjainwalla.[35] However, since the apparatus available was only suitable for batches of 10 g, this reduction step was subsequently replaced by a simple borohydride reduction protocol developed by Bradley,[39] which was reported to furnish the alcohol (107) albeit, in only 40% yield. Whilst the experimental details proved to be perfectly reproducible, we were particularly gratified to discover that a minor modification to the work-up procedure, *viz.* evaporation of only two thirds of the solvent prior to acidification contributed to improving the isolated yield to 80%. A non-regioselective saponification was then performed by refluxing the primary alcohol (107) in a solution of 2.75 *N* sodium hydroxide, closely followed by the addition of Amberlite® IR-120 H$^+$ ion exchange resin which promoted lactonisation to afford the crude acid. On distillation at 200 °C (0.2 mmHg) racemic paraconic acid (95) was obtained in 55% yield and in an overall yield of 19% from readily available diethyl succinate (96). Subjection of the extremely viscous crude paraconic acid mixture to distillation under the

aforementioned temperature and pressure led us to suspect that some thermal degradation of the acid was occurring during distillation. Thus, we attempted to purify the crude acid by recrystallisation. Once generated, the crude mixture was subjected to soxhlet extraction utilising DCM for 48 h. Dichloromethane emerged as the most suitable solvent for this purpose from trials involving chloroform, diethyl ether, methanol, and THF. The DCM extracts were dried, evaporated under reduced pressure and recrystallisation was then attempted of the resulting solid, by utilising a number of solvent systems. Efforts to facilitate the recrystallisation were however unsuccessful and we were therefore obliged to distil the crude acid for future use.

Racemic paraconic acid (95) was then elaborated to the desired ketal (94) firstly, via the earlier route developed within the group (Scheme 32).[39]
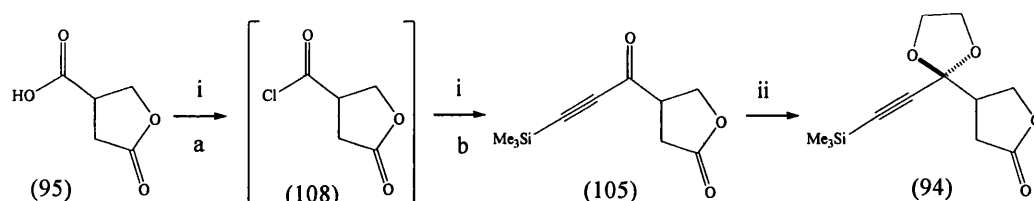
Scheme 32: **Reagents and Conditions**
i) a) $(COCl)_2$, DMF (cat.), DCM, rt, 100%; b) $Me_3SiC\equiv CSnMe_3$ (109), (2 mol%) $Pd(PPh_3)_2Cl_2$, $ClCH_2CH_2Cl$, 50 °C, 16 h, 64%; ii) $HOCH_2CH_2OH$, PPTS (cat.), benzene, reflux, 12 h, 88%.

Thus, the acid (95) was transformed to the corresponding acid chloride (108) in quantitative yield by the classical method involving treatment with oxalyl chloride in the presence of dimethylformamide as catalyst in DCM at room temperature. The resultant acid chloride, because of its sensitivity to water was either used immediately on preparation, or, stored under an inert atmosphere at +2 °C. In an attempt to ascertain its stability, by monitoring any changes in its ^1H nmr, we

discovered that the derived acid chloride (108) remained stable for over a week. The palladium-catalysed coupling of (108) with the alkynylstannane, $Me_3SiC\equiv CSnMe_3$ (109) proceeded as expected to deliver the desired ynone (105) in a yield of 64%.

The mechanism of this interesting coupling reaction[41] is shown in Scheme 33.

$(Ph_3P)_2PdCl_2$

A

$Pd(PPh_3)_2$

B

R—(O)—C≡C—TMS

R—(O)—Cl

R—(O)—Pd(PPh_3)_2—C≡C—TMS

D

R—(O)—Pd(PPh_3)_2Cl

C

Me_3SnCl

Me_3Sn——≡——TMS
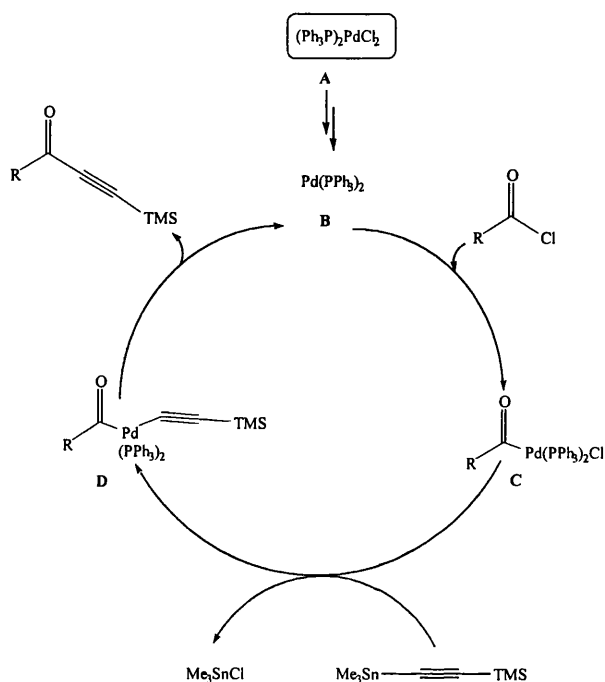
Scheme 33

The catalytic cycle commences with the generation of the active catalyst bis(triphenylphosphine)palladium(0) (B) from bis(triphenylphosphine)palladium(II) chloride (A). The active species (B) then undergoes oxidative addition of the acid chloride to give the acylchloropalladium complex (C). A transmetallation reaction between (C) and the alkynylstannane (109) yields an acylalkynylpalladium(II) species (D), which undergoes reductive elimination of the ynone and regenerates B. The product (D) of the transmetallation reaction has not been isolated, which has led to the presumption that the reductive elimination reaction is faster than transmetallation.[41]

The required unsymmetrical alkyne, $Me_3SiC{\equiv}CSnMe_3$ (109), which was required for the above coupling reaction, was prepared by treatment of (trimethysilyl)acetylene with *n*-butyllithium followed by subsequent quenching of the resulting acetylide anion with trimethyltin chloride. A slight excess of this anion (1.1 equivalents of the anion for every 1 equivalent of trimethyltin chloride) was selected to minimise potential problems associated with the purification of $Me_3SiC{\equiv}CSnMe_3$(109), and especially those that could arise due to contamination from trimethyltin chloride residues (Equation 2).

$$Me_3Si{-}{\equiv}{-}H \xrightarrow{\quad i \quad} Me_3Si{-}{\equiv}{-}SnMe_3$$

(109)
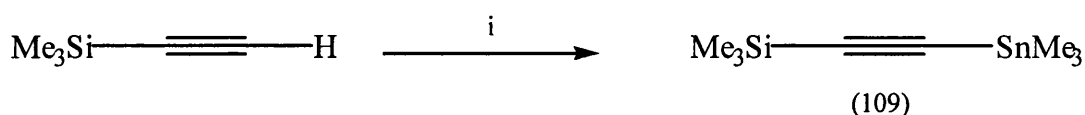
Equation 2: Reagents and Conditions
i) *n*-BuLi, Me_3SnCl, THF, 0 °C, 67%.

The reaction conditions under which alkynyl ketones are generated are also known to promote their self-reaction.[42] Standing at room temperature alone transforms alkynyl ketones to highly viscous syrups, presumably due to oligomerisation and / or polymerisation, as suggested by Logue and Teng.[42] Thus, once generated, it was essential to immediately protect our "rather" unstable ynone (105). Despite its reported instability at room temperature, (105) proved to be robust under an inert atmosphere at a temperature of +2 °C for up to 2 weeks, as monitored by ^{1}H nmr. Ketalisation of the ynone (105) was readily achieved by refluxing (105) in benzene, with ethylene glycol and PPTS as a catalyst. The ketal (94) was isolated in a yield of 88%, the overall yield being 11% from diethyl succinate.

2.5.2 Investigations into Alternative Routes for the Synthesis of the Ynone (105)

Although the improved sequence above provided a concise and highly efficient route to multigram quantities of the required ynone (105), the shortcoming of this approach was the necessity to employ trimethyltin chloride in the preparation of $Me_3SiC{\equiv}CSnMe_3$ (109). Trimethyltin chloride is well known to be exceptionally toxic.[43] Moreover, the use of trimethyltin chloride on a large scale, and its regeneration in the subsequent coupling, clearly poses as an unattractive feature in an otherwise appealing approach. Accordingly, our attention was promptly focused on alternative routes for elaboration of racemic paraconic acid to the ynone (105).

An extensive search of the literature revealed a number of approaches which have been used for the preparation of alkynyl ketones.[44] Ujjainwalla, prior to the successful palladium coupling for ynone (105), had investigated the utilisation of Grignard reagents with acid chlorides,[45] Weinreb amide technology[46] and Friedel-Crafts acylation reactions[47] as alternative possible avenues to (105).[35]

We focused on a method described by Yamaguchi and co-workers.[48] These authors utilised one of the most efficient approaches to generate alkynyl ketones,[44] which involved acylation of metal acetylides by esters (Scheme 34) and is reputed to avoid the over alkylation problem encountered in the reaction of Grignard reagents with acid chlorides. Although the authors did not cite the use of lithium (trimethylsilyl)acetylide as a nucleophilic source and did not mention the use of γ-lactones as acylating agents, the strikingly low reaction time of *ca.* 30 min persuaded us to investigate the applicability of generating our desired ynone (105) *via* the

Yamaguchi method. In retrospect, given that the γ-lactone is probably the more reactive "cyclic ester", this selection was a rather unwise choice.
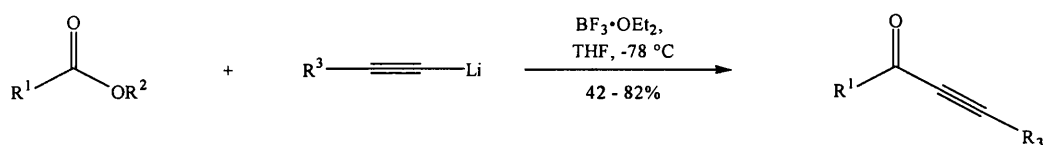
$$\text{Scheme 34}$$

Whilst initial attempts to esterify paraconic acid (95) either under standard conditions using methanol / sulphuric acid (catalytic) technology,[49] or with the methanol / boron trifluoride etherate protocol[50] both failed, the simple functional group interconversion of the racemic acid (95) *via* esterification of the resultant acid chloride, afforded the methyl ester (110) in 49% overall yield over 2 steps (Scheme 35).
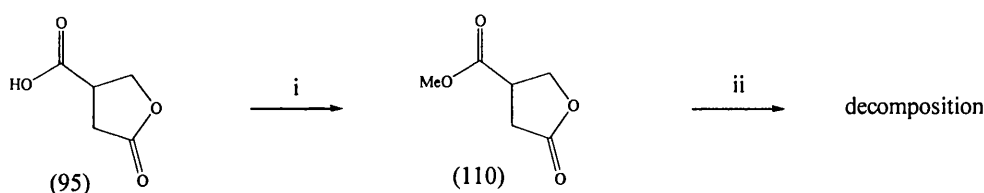
Scheme 35: **Reagents and Conditions**
i) a) (COCl)$_2$, DMF (cat.), DCM, rt, 1 h; b) MeOH, pyridine, (1.5 eq.), 0 °C, 1 h, over 2 steps 49%; ii) Lithium (trimethylsilyl)acetylide, BF$_3$•OEt$_2$ THF, −78 °C, 30 min.

The attempted acylation of lithium (trimethylsilyl)acetylide was then performed by the successive addition of the methyl ester (110), followed by 2 equivalents of distilled boron trifluoride etherate to 1 equivalent of freshly prepared lithium (trimethylsilyl)acetylide at −78 °C in THF (Scheme 35). In the event however, the reaction was not clean on tlc and co-spotting against a previously

prepared sample of the ynone (105) confirmed the absence of a compound with an identical retention factor (R_f) to (105).

Further recourse to the literature revealed an interesting approach to alkynyl ketones reported by Midland and Nguyen.[51] Having transformed racemic paraconic acid (95) to the acid chloride (108), the acylation was attempted by subsequent treatment of (108) in THF/HMPA (10%) at low temperature with freshly prepared lithium (trimethylsilyl)acetylide, under conditions employed by Midland and Nguyen.[51] In a separate attempt, utilising conditions described by Terashima et al.,[52] the acid chloride (108) was treated with magnesium (trimethylsilyl)acetylide at a low temperature. The required organomagnesium reagent was prepared by treating (trimethylsilyl)acetylene with ethylmagnesium bromide. Both reactions proceeded extremely poorly, and gave complex mixtures from which the desired ynone (105) was isolated with an exceptionally low yield of 5% (Scheme 36).

(95) (108) (105)
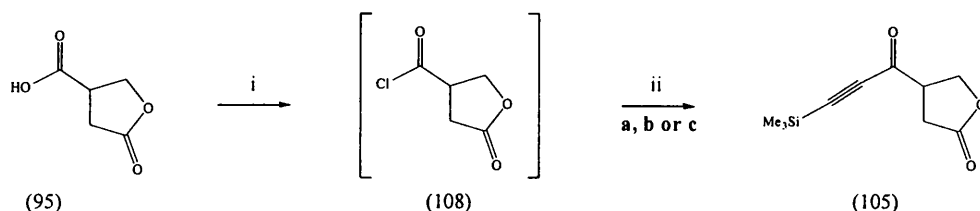
Scheme 36: Reagents and conditions
i) (COCl)$_2$, DMF (cat.), DCM, rt, 1 h,100%; ii) a) Lithium (trimethylsilyl)acetylide, CuCl (cat.), THF/HMPA (10%), −78 °C, 5%; b) Magnesium (trimethylsilyl)acetylide, THF/HMPA (10%), −78 °C, 5%; c) Me$_3$SiC≡CZnCl, (10 mol%) Pd(PPh$_3$)$_4$, THF, 26 °C, 12 h, 45%.

Finally, we decided to examine a method developed in 1983 by Negishi and co-workers[53] who described a convenient and generalised route to ketones via the cross-coupling reaction of organozinc reagents with acyl chlorides catalysed by palladium-phosphine complexes (Equation 3).[53]

$$R^1ZnX \quad + \quad R^2COCl \quad \xrightarrow{\quad i \quad} \quad R^1COR^2$$

<div style="border:1px solid black; padding:5px; display:inline-block;">

Equation 3: **Reagents and Conditions**
i) (5 mol%) Pd(PPh$_3$)$_4$, THF, 25 °C.

</div>

Contrary to the expectations of the Negishi research group,[53] the direct reaction of organozinc reagents and acid chlorides failed to provide the desired ketones in high yield. However, by performing the reaction in the presence of 5 mol% of tetrakis(triphenylphosphine)palladium(0) in THF at 25 °C, the Japanese group reported that dramatically improved yields of the desired products could be obtained. The authors described the scope of the palladium catalysed cross-coupling reaction as very broad with respect to the partners involved. We were accordingly compelled to investigate the applicability of the Negishi reaction, to deliver our ynone (105).

The required alkynylzinc chloride was available *via* the established method by Carpita and Rossi[54] and involved a transmetallation reaction of freshly prepared lithium (trimethylsilyl)acetylide with dry zinc chloride at low temperature, to form the required alkynylzinc chloride. Dropwise addition of alkynylzinc chloride to a mixture of (108) and 10 mol% Pd(PPh$_3$)$_4$ in THF at 26 °C afforded the ynone (105) in a very gratifying, but moderate yield of 45% (Scheme 36).

Our objective of eliminating further use of the stannylated alkyne, Me$_3$SiC$\equiv$CSnMe$_3$ in the palladium-catalysed coupling with the acid chloride (108) was therefore successfully accomplished.

Whilst a direct comparison of the two palladium-catalysed coupling methods from the acid chloride to the ynone (105) clearly indicates that the original stannane method gives a superior yield, the organozinc reagent is certainly the more practical and less dangerous method for large scale work, and at this stage, the current route proceeding to (105) holds a marginal lead of 2% over that which was originally employed (Scheme 37).
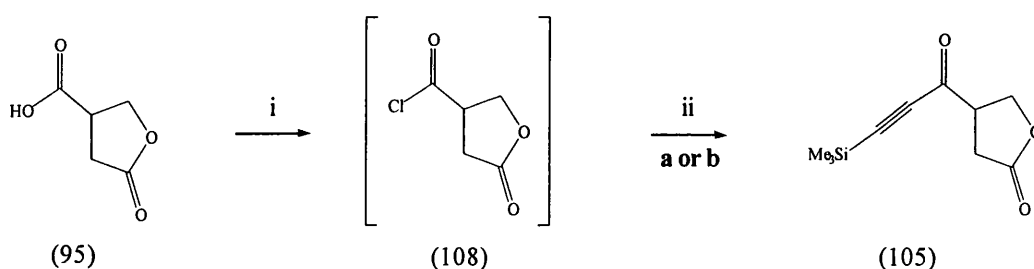
Scheme 37: Reagents and conditions
i) (COCl)$_2$, DMF (cat.), DCM, rt,100%; ii) a) i) n-BuLi, Me$_3$SiC≡CH, THF, 0 °C, add Me$_3$SnCl, THF, 0 °C, 67% (109); ii) (108), (2 mol%) Pd(PPh$_3$)$_2$Cl$_2$, ClCH$_2$CH$_2$Cl, add (109), 50 °C, 64%; ii) b) Me$_3$SiC≡CZnCl, (10 mol%) Pd(PPh$_3$)$_4$, THF, 26 °C, 12 h, 45%.

2.5.3 Synthesis of the Left Hand Coupling Fragment (92)

In contrast to the difficulties experienced with the ynone (105), the benzylic bromide (92) was obtained in a very straightforward fashion by the established route used within the group (Scheme 38).[39]

(97)   i   (111)   ii   (93)

iii

(92)   iv   (112)
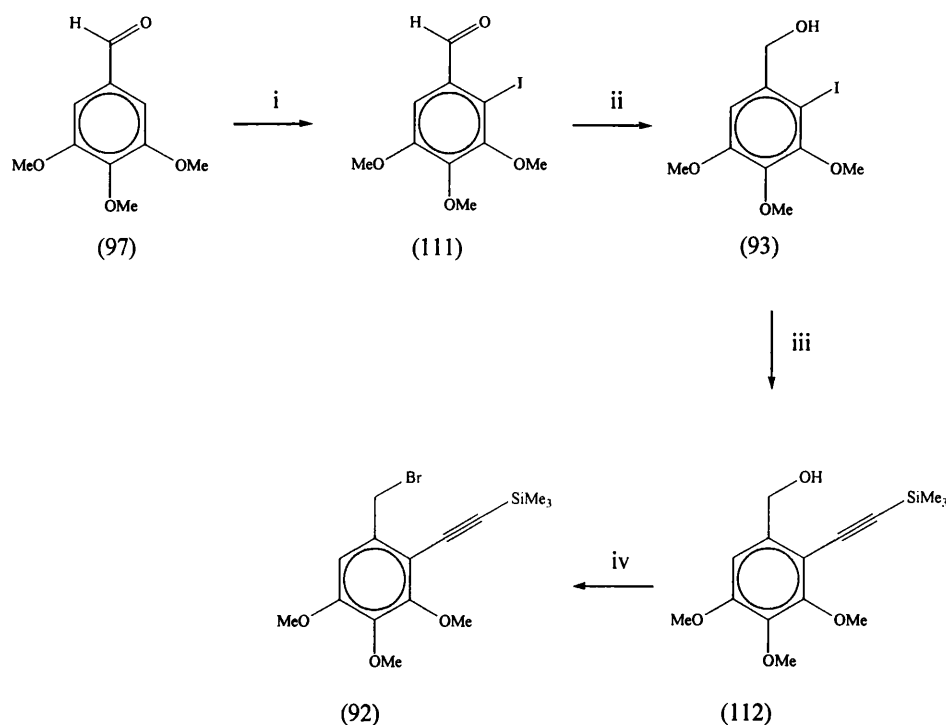
Scheme 38: **Reagents and Conditions**
i) I_2, $Ag(O_2CCF_3)$, DCM, rt, 15 h, 91%; ii) $NaBH_4$, MeOH, 0 °C, 4 h, 79%; iii) $Me_3SiC\equiv CH$, (7.6 mol%) $Pd(PPh_3)_2Cl_2$, (15 mol%) CuI, Et_3N, 50 °C, 3 h, 88%; iv) CBr_4, PPh_3, Et_2O, 24 h, 83%.

Electrophilic iodination of readily available 3,4,5-trimethoxybenzaldehyde (97) with iodine and silver trifluoroacetate in DCM and subsequent borohydride reduction of the resultant iodoarene (111), gave the benzylic alcohol (93) with an overall yield of 72% over 2 steps. A Stephens-Castro[55] palladium catalysed coupling reaction of (93) and (trimethylsilyl)acetylene, furnished the highly functionalised aryl acetylene (112) and the required conversion of benzylic alcohol (112) to benzylic bromide (92) was then achieved in high yield using the excellent triphenylphosphine-tetrabromomethane methodology. The overall yield of this sequence was 53% from 3,4,5-trimethoxybenzaldehyde.

2.5.4 Coupling of the Lactone (94) and Benzylic Bromide (92). Preparation of the Parent Diyne (91)

With the left and right hand coupling fragments in hand the alkylation of the γ-lactone enolate from (94) with the benzylic bromide (92) was then successfully repeated.
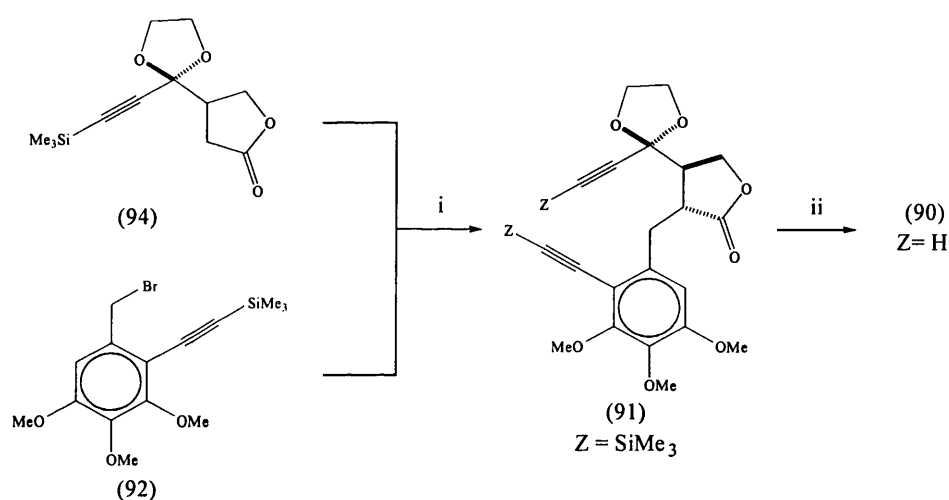
Scheme 39: **Reagents and Conditions**
i) (94), LDA (1.0 eq), –78 °C, THF, then added (92) at –35 °C,
1 h, –35 °C, 73%; ii) K₂CO₃ (cat.), MeOH, rt, 6 h, 90%.

Thus, the lactone enolate was generated as described,[39] at –78 °C in THF and quenched by the subsequent addition of benzylic bromide in THF at the more elevated temperature of –35 °C (Scheme 39). As previously reported, this alkylation was completely stereoselective giving (91) as a single diastereoisomer, which was isolated in a yield of 73% along with recovered benzylic bromide (21%). A global desilylation was performed by stirring the diyne (91) with potassium carbonate as a

basic catalyst in methanol at ambient temperature to furnish the tethered diyne (90)

in 90% yield, and in an overall yield of 8% from diethyl succinate.

At this stage, the significantly improved yield in the borohydride reduction step

and the introduction of a stannane free coupling had combined to provide a route to

the diyne (91) which was more suitable for larger scale work. Nevertheless, the

instability of the alkynyl ketone (105) even under an inert atmosphere at "low"

temperature (−2 °C) still remained as a source of concern. We were therefore keen to

investigate further alternative approaches to the diyne (91) which bypassed the direct

intermediacy of ynone (105).

2.5.5 An Alternative Retrosynthetic Analysis towards the Parent Diyne (91)

Our first thoughts around this approach are summarised in the retrosynthetic

analysis shown in Scheme 40.

Paraconic acid

(91)　　　　　　　(113)

Left hand coupling
fragment
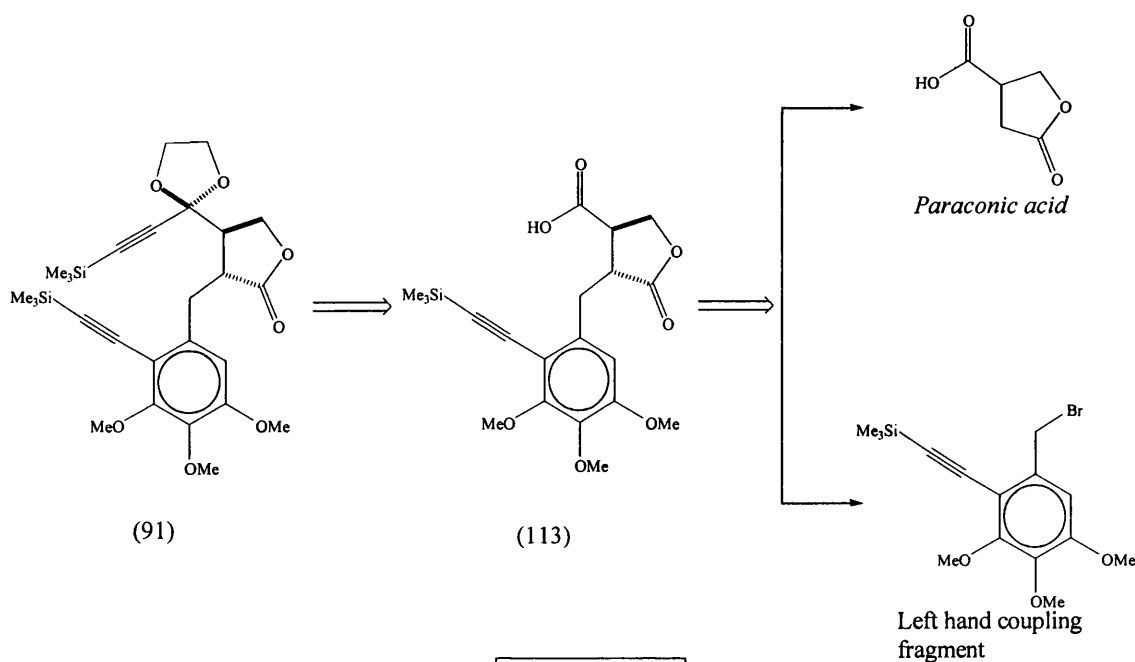
Scheme 40

In this alternative disconnection, we envisaged that *trans* diastereoselective alkylation of the dianion of paraconic acid with our benzylic bromide (92) would furnish a more robust higher molecular weight lactone acid (113), which could then be elaborated to the diyne by the same sequence of reactions which had been successfully used for paraconic acid itself.

To this end, the simple model study shown in Scheme 41 below was undertaken.

Since a careful examination of the available literature shed no light on the comparable acidity of the protons at α- and β- positions of the monolithium salt of paraconic acid we decided to test our hypothesis that the lactone enolate could be formed by treating

paraconic acid (95) with two equivalents of lithium diisopropylamide to generate the dianion (114) and then to trap the resultant species with 2 equivalents of readily available benzyl bromide (116).
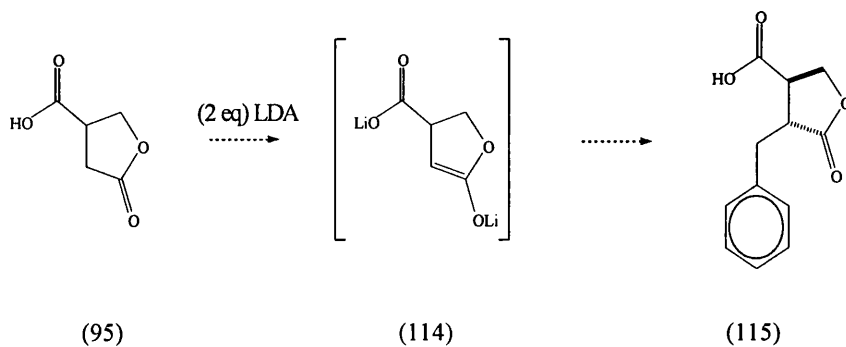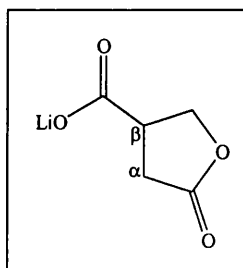
	(2 eq) LDA		
(95)		(114)	(115)

Scheme 41

With this objective in mind paraconic acid (95) was treated with two equivalents of freshly prepared lithium diisopropylamide in THF (Equation 4, and Table 2).

(95)   (115)
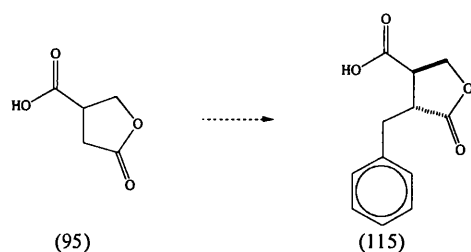
Equation 4

Entry	Reagents and Conditions	Yield of (115)(%)
1	i) (2 eq) LDA, THF, −35 °C and added (2 eq) benzyl bromide (116), −35 °C, 1 h	0
2	i) (2 eq) LDA, (10%) THF/DMPU, −35 °C then DMPU (1 eq); and added (2 eq) benzyl bromide (116), −35 °C, 1 h	0
3	i) (2 eq) LDA, (10%) THF/HMPA, −35 °C then HMPA (1 eq); and added (2 eq) benzyl bromide (116), −35 °C, 1 h	0

Table 2

As the temperature was lowered, at −20 °C formation of a solid was immediately apparent. In order to effect the coupling, under Entry 1 we employed the conditions utilised in the stereoselective coupling of the right (94) and the left hand fragments (92) for the synthesis of the diyne (91). The temperature was therefore lowered to −35 °C, two equivalents of benzyl bromide (116) were then added, and the mixture was stirred at −35 °C for 1 h. No coupled products were isolated after the work-up, and 95% of the benzyl bromide was recovered. In Entries 2 and 3, the

coupling reaction was repeated utilising THF/DMPU and THF/HMPA under the conditions described in Entry 1. These attempts also failed to generate any coupled products and we were forced to conclude that the lack of solubility of the "generated dianion" may have rendered the reaction with benzyl bromide unsuccessful.

In order to circumvent the difficulties faced due to the lack of solubility of the "dianion", we then decided to protect the carboxylic acid group of paraconic acid by a masking group which would tolerate the basic conditions required for enolate anion formation. We believed that the γ-lactone enolate would be formed in preference to the exocyclic ester enolate, by analogy with the increased acidity of cyclopentanone over a simple acyclic ketone.[56]

Firstly, we focused on protecting the acid functionality as its trimethylsilyl ester.[57] Paraconic acid (95) was refluxed in a solution of *N,O*-bis(trimethylsilyl)acetamide (BSA) for 6 h to afford the trimethylsilyl ester (117), isolated with a yield of 60% (Equation 5).

(95)   i   (117)
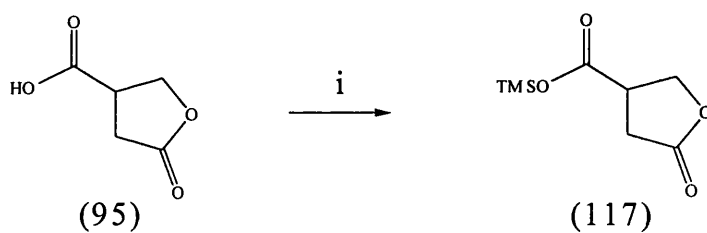
Equation 5: Reagents and Conditions
i) BSA, reflux, 6 h, 60%.

With (117) in hand, we commenced our alkylation study (Equation 6, and Table 3). Unfortunately as shown in Table 3, under both Entries 1 and 2, and in similar fashion to our previous efforts in coupling paraconic acid (95) and benzyl bromide, a solid precipitated prior to reaching the temperature of −35 °C.

(117)   (118)
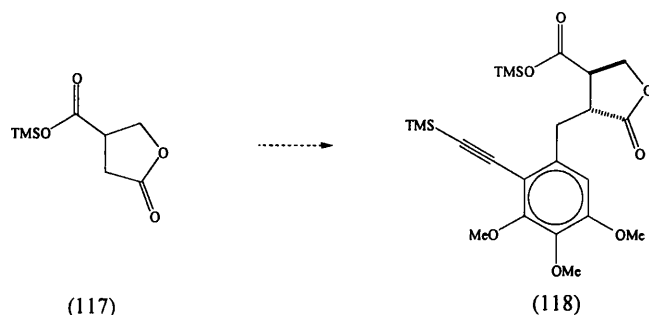
Equation 6

Entry	Reagents and Conditions	Yield of (118)(%)
1	i) (1 eq) LDA, THF, –35 °C and added (1 eq) benzylic bromide (92), –35 °C, 1 h	0
2	i) (1 eq) LDA, (10%) THF/DMPU, –35 °C then (1 eq) DMPU and added (1 eq) benzylic bromide (92), –35 °C, 1 h	0
3	i) (1 eq) LDA, (10%) THF/HMPA, –35 °C then (1 eq) HMPA and added (1 eq) benzylic bromide (92), –35 °C, 1 h	0

Table 3

In Entry 3 the reaction was repeated with HMPA. Although the reaction mixture appeared as a cloudy suspension, once again, no coupled product was isolated. In all three attempts ~95% of the benzylic bromide fragment (92) was recovered after the work-up.

In a second tactic, we decided to employ the orthoester methodology developed by Corey during his studies in the prostaglandin and leukotriene area.[58]

Thus, the required oxetane (119) was prepared, by refluxing readily available 2-hydroxymethyl-2-methyl-1,3-propanediol (120) with diethyl carbonate, potassium

81

hydroxide (catalytic) and ethanol for 16 h and was isolated with a yield of 29% (Equation 7).[59,60]
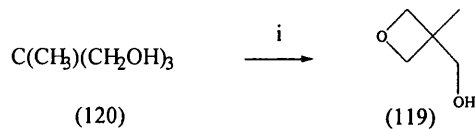
Equation 7: Reagents and Conditions
i) $(EtO)_2CO$, (2 mol%) KOH, EtOH (1 mL), reflux, 16 h, 29%.

Although the reaction was only performed once, the yield was some 10% lower than the value reported in the literature,[59] presumably due to side reactions which take place, under the reaction conditions (Scheme 42).

Scheme 42

(119)
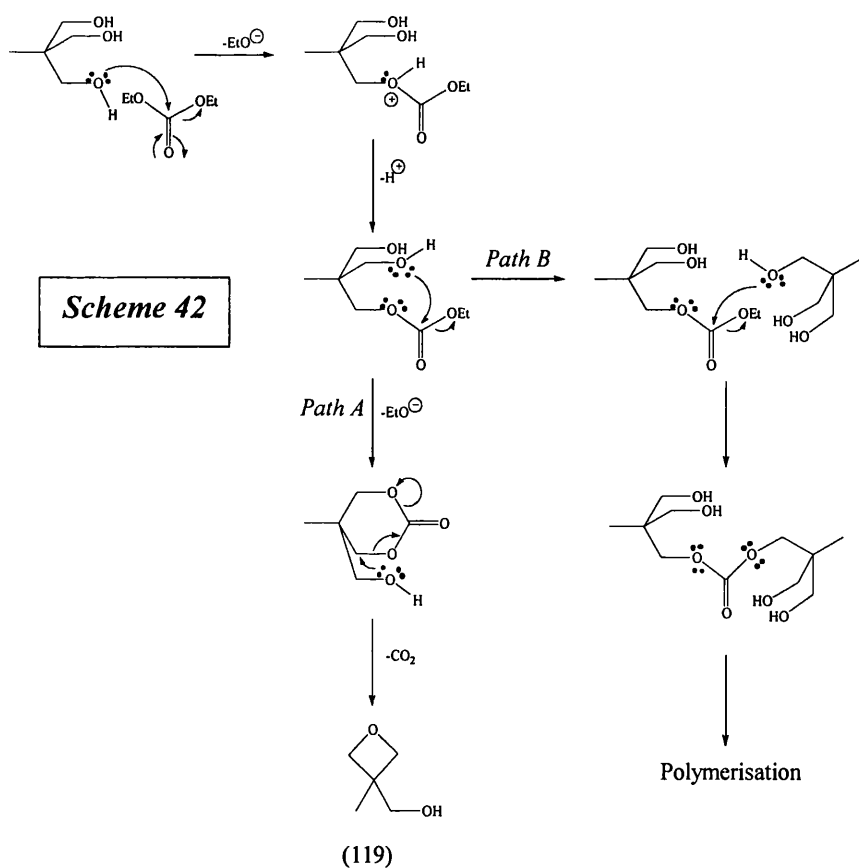
Under standard conditions paraconic acid (95) was subjected to esterification and the oxetane ester (121) was isolated with a yield of 79%. Treatment of the ester

82

(121) with boron trifluoride etherate in DCM at 0 °C for 2 h then generated the ortho

ester (122) in a yield of 81% (Scheme 43).

(119)   (121)   (122)
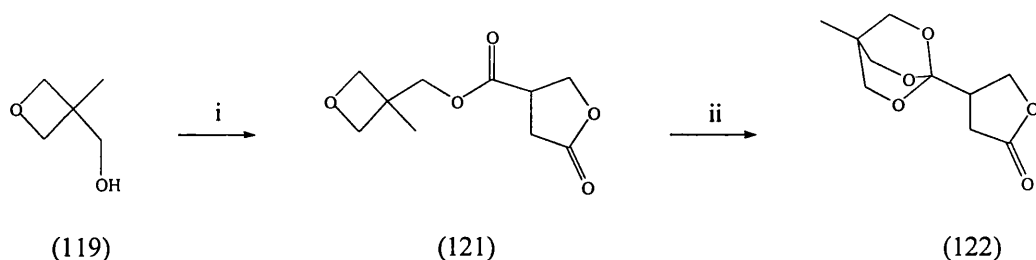
Scheme 43: Reagents and Conditions
i) Pyridine, 0 °C, added to (108), DCM, 0 °C, 3 h, 79%; ii) BF₃•OEt₂, DCM, 0 °C, 2 h,
then at rt for 15 h, 81%.

With the ortho ester (122) in hand we commenced on the synthesis of the

protected γ-butyrolactone (123) (Equation 8 and Table 4).

(122)   Equation 8   (123)
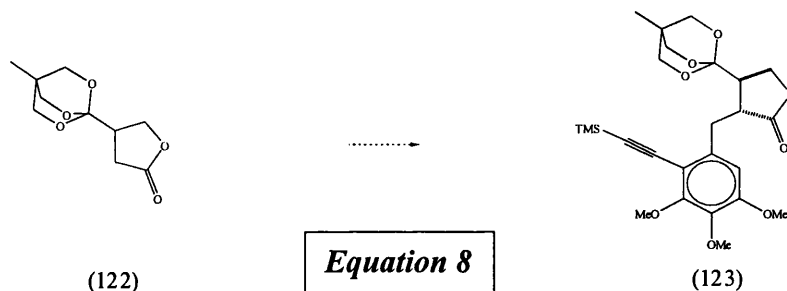
Entry	Reagents and Conditions	Yield of (123)(%)
1	i) (1 eq) LDA, THF, -78 °C, then raised to –35 °C and added (1 eq) benzylic bromide fragment (92), –35 °C, 1 h	0
2	i) (1 eq) LDA, (10%) THF/HMPA, –35 °C then HMPA (1 eq) then added (1 eq) benzylic bromide fragment (92), –35 °C, 1 h	0
3	i) (1 eq) LDA, THF, (1 eq) HMPA, –5 to –10 °C then added (1 eq) benzylic bromide fragment (92), –5 to –10 °C, 1 h	0

Table 4

Coupling of the ortho ester protected paraconic acid with the key benzylic bromide fragment (92) was attempted as detailed in Entry 1 (Table 4), under the conditions employed to perform the stereoselective coupling of the right and left hand fragments (94 and 92) in the synthesis of diyne (91). In Entry 2, the reaction was repeated in a mixture of THF/HMPA to improve the solubility of the ortho ester (122). As the solubility of the ortho ester (122) in THF was found to be problematic at temperatures below −12 °C, the coupling reaction was finally repeated at temperatures between −5 - −10 °C with HMPA (1 equivalent) as demonstrated under Entry 3. The desired monoyne (123) was sadly not isolated, it was therefore decided to discontinue this alternative disconnection approach.

2.5.6 *Attempted Improvements to the Cobalt Catalysed [2+2+2] Cycloaddition Reaction*

With the development of the more practical and equally efficient "tin free" route to the diyne (91), it was then possible to return to the most problematic step of the synthesis, *viz.*, the crucial cobalt-mediated [2+2+2] cycloaddition step.

This was considered to be an especially daunting task, particularly in view of the fact that very considerable effort had already been devoted within the group to this key reaction. The reproducible yield of 19% using BTMSA (100) as the third 2π addend had only been achieved after long and careful experimentation,[39] and the production of the cobalt cyclobutadiene complex (99) as the major product was a source of considerable concern and frustration to all involved (Scheme 44).

Furthermore, as noted by the present investigator, careful positioning of the light source which also controlled the temperature was also necessary for the success of this step.

(90)   (98)   (99)
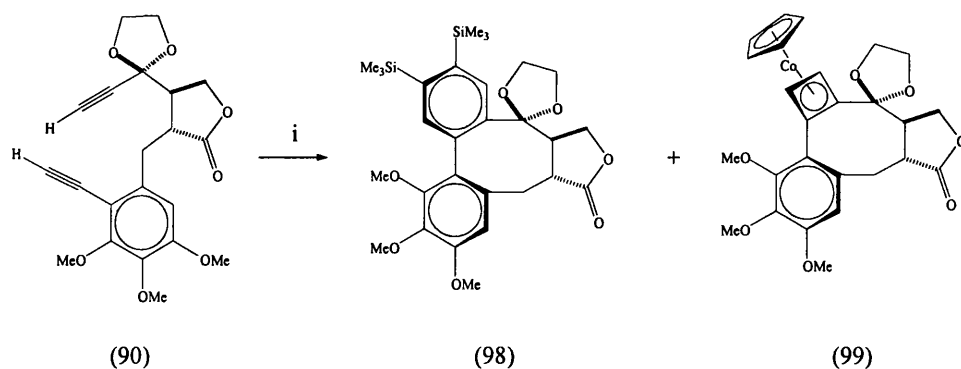
Scheme 44: **Reagents and Conditions**
i) Addition of (90) and CpCo(CO)$_2$ over 9 h, to a solution of CpCo(CO)$_2$ in BTMSA (100)/acetonitrile, reflux, hv (300 W tungsten lamp), 8 h, 19% (98) and 35% (99).

It should also be noted that previous studies within the group had, in addition, focused on the use of other metals such as rhodium,[39] and nickel[39] which are also known to promote [2+2+2] cycloaddition, as well as a variety of ingenious tethering strategies[39] to deliver the third alkyne component in intramolecular fashion. All of these efforts however had been to no avail.

The essential root of the problem was considered to arise because of steric problems associated with the coordination of the third alkyne component, which is of course necessary for the subsequent insertion and reductive elimination steps to give the desired aromatic ring. Thus, as shown in Scheme 45, the cobalt cyclobutadiene complex (99) can form from either the initial diyne complex (124) or more probably, by a rearrangement of the metallacyclopentadiene (101). This pathway is not unknown in Vollhardt chemistry[61] and could certainly compete favourably in a

sterically congested environment where the cyclopentadienyl ring and the functionalised eight-membered ring combine to thwart the approach of bis(trimethylsilyl)acetylene.
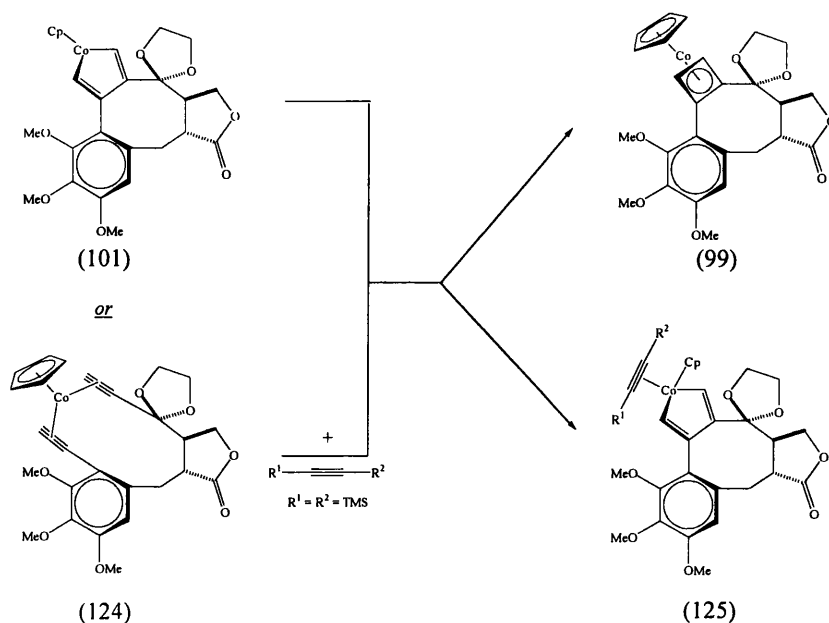
Scheme 45

We were however encouraged and inspired to continue the cobalt studies because of a personal communication from Professor Barry Trost[62] in which he revealed that a cobalt species generated by *in situ* reduction of tris(acetylacetonato)cobalt(III) (Co(acac)$_3$) (126) with triisobutylaluminum in the presence of triphenylphosphine as a coordinating ligand could be used as a catalyst for [2+2+2] cycloaddition of three alkyne components. Although his own programme was still at an embryonic stage, Professor Trost kindly provided the experimental conditions for the transformation shown in Scheme 46.[62]

(127)   (128)   (129)
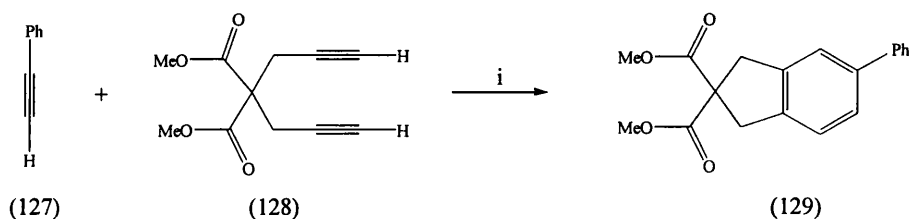
Scheme 46: **Reagents and Conditions**
i) (5 mol%) Co(acac)$_3$ (126)/(25 mol%) (i-Bu)$_3$Al /(20 mol%) PPh$_3$, benzene, rt, 59%.

From a formal standpoint, this reaction is similar in concept to a system developed by Lyons for the homo-Diels-Alder reaction of norbornadiene (130) with monosubstituted alkynes (Equation 9 and Table 5).[63-65] In this instance the low valent cobalt complex was formed by reducing tris(acetylacetonato)cobalt(III) (Co(acac)$_3$) (126) with diethylaluminum chloride (DEAC) in the presence of the bidentate ligand bis(1,2-diphenylphosphino)ethane (DIPHOS).

(130)   +   RC≡CH $\xrightarrow[\substack{DEAC,\\DIPHOS,\\benzene, rt}]{[Co(acac)_3],}$ (131)   *Equation 9*
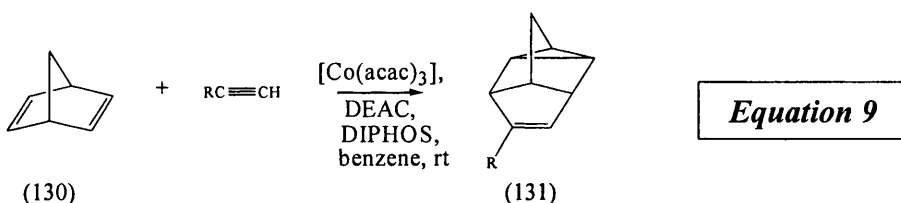
Entry	R	Reaction Temperature (°C)	Norbornadiene converted (%)	Selectivity of (131) (%)
1	H	45	49	90
2	Ph	35	20	86
3	Me	62	95	16
4	Et	62	50	25

Table 5

More recently, Lautens and co-workers[66,67] have gone one step further by demonstrating that the selection of the chiral phosphines, *S,S*-chiraphos and *R*-prophos lead to a highly enantioselective variant of the above reaction (Equation 10).

$$+ \equiv CR \xrightarrow[\substack{Et_2AlCl, \\ \text{chiral phosphine ligand,} \\ \text{benzene}}]{Co(acac)_3,}$$

(130)   (132)

| * = stereo centre |
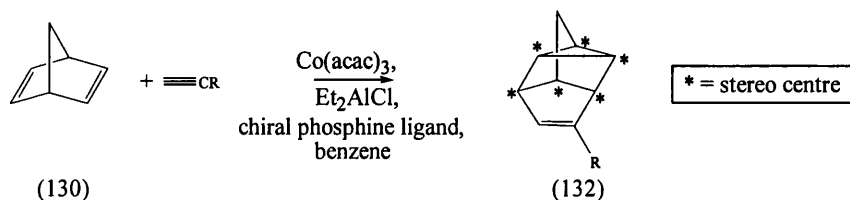
Equation 10

The [2+2+2] cycloaddition of alkynes to norbornadiene has also been studied by Lyons[63-65] who has speculated that the mechanism may involve the intermediacy of a metallacycle followed by coordination of the alkyne to give (133), insertion and then reductive elimination as shown in Scheme 47.

(130)   (133)   *Insertion*

Reductive elimination | -M

(134)
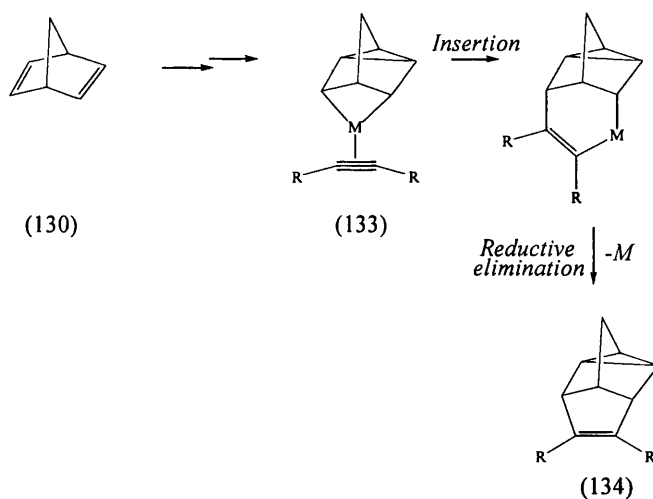
Scheme 47

Since such a mechanistic sequence can also be advanced in Vollhardt's chemistry, we felt that the [2+2+2] cycloaddition mediated by the Trost[62] catalyst for three-alkynes would provide a unifying theme.

We were particularly attracted to the application of the Trost catalytic system for the key cycloaddition step in our approach to steganone analogues for several reasons. Thus, in the first instance, we considered that the absence of the cyclopentadienyl (Cp) cap which is present in the Vollhardt system but not in the Trost catalyst could well lead to a sterically less congested intermediate which would facilitate coordination and insertion of the third alkyne component. Secondly, the absence of carbon monoxide ligands from the Trost catalyst could well explain the fact that this catalyst system operates at a much lower temperature than that of Vollhardt[38] where loss of carbon monoxide ligands is certainly not a facile process. Since the rearrangement of a cobalt metallacyclopentadiene to a cyclobutadiene complex has generally occurred at higher temperatures,[35] lower operating temperature should also favour our desired [2+2+2] cycloaddition over the undesired competing reaction.

Given that the only example available to us was that involving the reaction of the symmetrical propargyl malonate derivative with phenylacetylene (Equation 11),[62] we elected to carry out a preliminary study in order to reproduce this reaction and also to examine a range of alkynes as the third 2π-component.

(128)   (129)
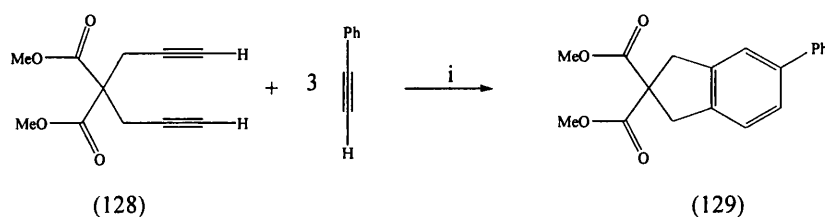
Equation 11: Reagents and Conditions
i) (5 mol%) Co(acac)$_3$/(25 mol%) (i-Bu)$_3$Al/(20 mol%) PPh$_3$, benzene, rt, 59%.

The required diyne (128) was readily prepared by double alkylation of dimethyl malonate with propargyl bromide as shown in Equation 12.[68]

(128)

Equation 12: Reagents and Conditions
i) (2 eq) Na, (2 eq) (80 wt.%) propargyl bromide, MeOH, rt, 1 h, 85%.

Two methods[69-71] were then examined for the preparation of tris(acetylacetonato)cobalt(III) (126) and these are shown in Scheme 48. Of these, the second[71] using cobalt carbonate as the source proved to be much more straightforward and was therefore preferred.

Method 1 $[Co(NO_3)_2 \cdot 6H_2O]$ $\xrightarrow{\text{i}}$ $\{Na_3[Co(CO_3)_3] \cdot 3H_2O\}$ $\xrightarrow{\text{ii}}$ $Co(acac)_3$

(135)   (126)

Method 2 $CoCO_3$ $\xrightarrow{\text{i}}$ $Co(acac)_3$

(126)

Scheme 48: Reagents and Conditions
Method 1: i) (30%) H_2O_2, $NaHCO_3$, 0 °C, 2 h, 79%; ii) 2,4-pentanedione, $(CH_3)_2CO/H_2O$ (3:2), (70%) HNO_3, reflux, 30 min, 20%, (overall yield 16% over two steps). Method 2: i) 2,4-Pentanedione, heat to 90 °C then added (30%) H_2O_2, 1 h, 70%.

The stage was accordingly set to examine a range of alkynes with the model diyne (128) using the Trost catalyst system and the results of this study are shown in Equation 13 and Table 6. It should be noted that all experiments preserved the ratio used by Trost to generate the low valent cobalt catalyst viz. $Co(acac)_3$:PPh_3:(i-Bu)$_3$Al: – 1:4:5.

MeO ... O ... ≡ H + R‖R' → MeO ... O ... R / R'   **Equation 13**

(128)

Entry	R	R'	Catalyst (mol%)	Temp. (°C)	Product	Yield (%)
1	Ph	H	5	22	—	0
2	Ph	H	12.5	22	R = Ph R' = H (129)	61
3	CH_2OH	H	12.5	22	—	0
4	CH_2OTBD-MS (136)	H	12.5	32	Complex Mixture (137)	—
5	TMS	H	12.5	32	R = $SiMe_3$ R' = H (138)	59
6	CH_2OTMS (139)	CH_2OTMS	12.5	32	—	0
7	TMS	TMS	12.5	32	—	0

Table 6

Examination of the results in the Table 6 reveals that, in our hands the use of only 5 mol% of the catalyst system was unsuccessful (Entry 1). However, by increasing the quantity of catalyst to 12.5 mol% we were then able to reproduce the

result reported by Professor Trost. At a later stage (Entries 4 – 7), it was found that a temperature of 32 °C gave more uniformly consistent results. Although propargyl alcohol (Entry 3) and its *tert*-butyldimethylsilyl ether (Entry 4) failed to give any evidence of the desired aromatic products, it was very encouraging to note that (trimethylsilyl)acetylene was a very good 2π-addend in this reaction (Entry 5). Attempted use of the di-substituted acetylenes in Entries 6 and 7 failed, however, to give any evidence for formation of the desired products.

Armed with this knowledge we then returned to the use of our precious diyne (90) for the construction of steganone analogues (Equation 14 and Table 7). To our extreme disappointment however, even with the selection of those monosubstituted alkynes which had worked well in the model study and in spite of attempting to use increased loadings of catalyst, all of our efforts were uniformly unsuccessful.

Equation 14

(90)
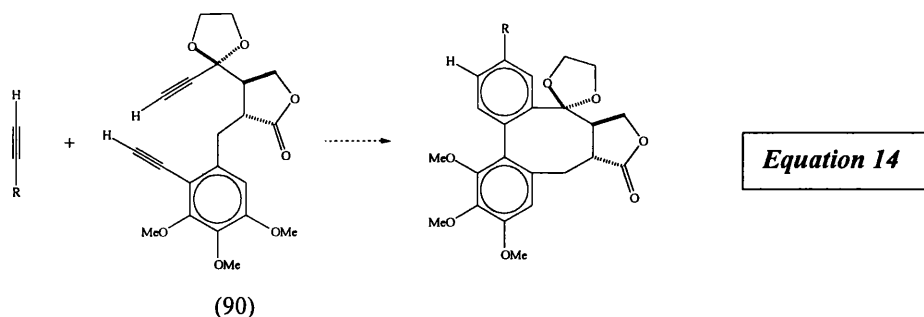
Entry	R	Reaction Conditions Catalyst (mol%), Temp. (32 °C)	Yield (%)
1	Ph	12.5	0
2	Ph	15.0	0
3	Ph	17.5	0
4	Ph	20.0	0
5	Ph	22.5	0

Table 7

Entry	R	Reaction Conditions Catalyst (mol%), Temp. (32 °C)	Yield (%)
1	TMS	12.5	0
2	TMS	15.0	0
3	TMS	17.5	0
4	TMS	20.0	0
5	TMS	22.5	0

Table 7 continued

The key [2+2+2] cycloaddition step using the tethered diyne (90) therefore remains to this day as the single step in which we have failed to achieve a very good yield in this highly convergent route to steganone analogues.

2.6 Synthetic Approaches Directed Towards Chiral Analogues of Steganone

2.6.1 *Introduction*

In the preceding sections we have described the work which was undertaken with a view towards optimisation of the route developed within the group towards racemic analogues of steganone. Such an approach was taken, not only because it provided valuable training experience in the manipulation of the intermediates involved, but also because we considered that the selection of (*R*)-(+)-paraconic acid (140) as the chiral right hand fragment would provide an expedient entry into steganone analogues of the correct absolute configuration found in the natural

product itself. In particular, as shown in Scheme 49, we reasoned that the steps involved in both the transformation of the acid to the key ynone (141) and in the subsequent coupling and [2+2+2] cycloaddition would hold little danger of racemisation. The fact that the natural twist of the atropisomeric biaryl unit was formed in the cobalt-mediated [2+2+2] cycloaddition was considered to be an additional bonus.

(140)
(R)-(+)-Paraconic acid

(141)
Key ynone

(142)
Right hand coupling fragment

(93)
Raphael intermediate

(92)
Left hand coupling fragment

(143)

R = TMS

(+)-Steganone
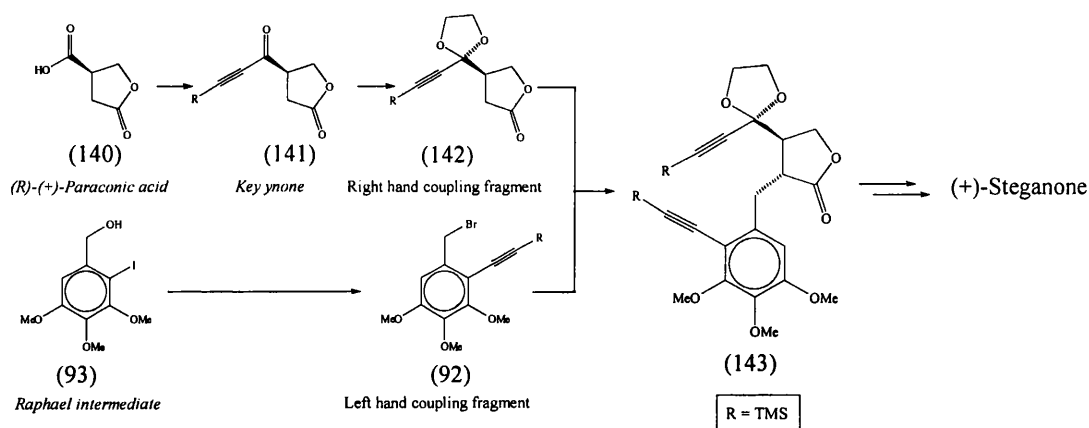
Scheme 49

Thus, while the various steps in the racemic route were examined and modified, a contemporaneous study was initiated towards the preparation of multigram quantities of (R)-(+)-paraconic acid (140) in the hope that successful fusion of these two efforts would culminate in a concise route to chiral analogues of (+)-steganone.

2.6.2 *Existing Literature Approaches to Enantiopure Forms of Paraconic Acid*

It was therefore appropriate at this stage to make a careful examination of the existing literature devoted to the preparation of enantiopure forms of paraconic acid. To our initial surprise, even though (R)-(+)-paraconic acid (140) was the cornerstone of our synthetic approach, we discovered that methods for the preparation of the enantiomer, (S)-(−)-paraconic acid (144), were much more common. This fact was a direct consequence of its popularity as a starting material for the synthesis of (3R)-(−)-A-factor (145), a natural product which was isolated from *Streptomyces griseus* in 1976, by Khokhlov and co-workers[72,73] and then shown to be an autoregulator of cytodifferentiation,[74,75] inducing the production of streptomycin in these strains of bacteria.

In essence, and also in chronological terms, the different strategies which have been used can be categorised into three types, those

(3R)-(−)-A-Factor (145)
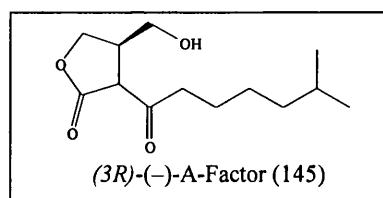
using classical resolution, those involving an enzyme-mediated step, and those which require enantiospecific synthesis using either a chiral auxiliary or a chiral reagent. Each of these are discussed in turn.

2.6.2.1 Resolution

As we have see in the Raphael route to (−)-steganone,[34] the classical method of optical resolution should never be dismissed. In the case of paraconic acid, this was

first achieved in 1965 by Tocanne and Asselineau,[76] through repeated crystallisation of the diastereoisomeric salts formed by reaction with either enantiomer of α-phenylethylamine. This approach was also adopted by Mori[77a] in 1981, who prepared (S)-(–)-paraconic acid (144) through salt formation either with the alkaloid brucine, or with (R)-(+)-α-phenylethylamine, and also revised[78] the absolute configuration of the enantiomers of paraconic acid which had been misassigned by Tocanne and Asselineau. Close scrutiny of the experimental sections in the papers from both the French and the Japanese research groups reveals however, that this resolution is very inefficient. Thus, because of the necessity for at least five crystallisations of the salts, 45 g of racemic paraconic acid is required to produce 0.8 g of the single enantiomer, representing a "yield" of some 2%. For this reason, the resolution approach was rejected.

2.6.2.2 Enzyme-Mediated Routes to (R)-(+)- and (S)-(–)-Paraconic Acid

The use of an enzymatic step in a synthetic sequence has grown spectacularly over the last twenty years, and within this area, the idea of using an enzyme as a catalyst for the transformation of a prochiral substrate into a single enantiomer has proven to be especially useful.[79,80] This was the approach taken by Mori and Chiba[81] in 1989 in their ongoing studies towards the synthesis of (3R)-(–)-A-factor, and is in fact the only published route which can specifically provide the (R)-(+)-enantiomer of paraconic acid. The essence of their synthetic plan is encapsulated in Scheme 50 below and hinges on the ability of an enzyme to achieve either enantioselective

esterification of a prochiral diol (146) or enantioselective hydrolysis of a prochiral

diacetate (147) to afford the differentiated intermediates (A) as key building blocks.

Asymmetric Esterification   **Asymmetric Hydrolysis**

(146)

or

(147)

or

R = Benzyl or allyl   (A)

(148)   (140)

(R)-(+)-Paraconic acid
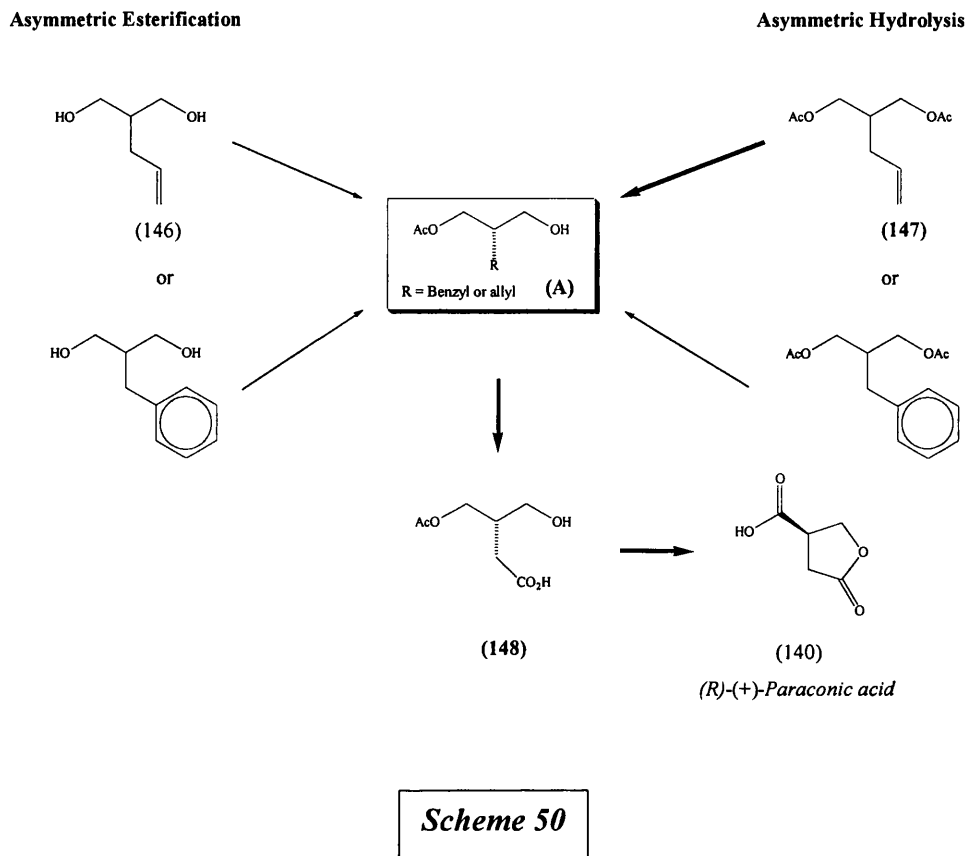
Scheme 50

The allyl or benzyl groups in (A) can then serve as latent functionality since,

on subsequent oxidative cleavage, the necessary carboxylic acid function for lactone

formation is unmasked.

In the event, as implied by the bold arrows in Scheme 50, the most efficient

route to (R)-(+)-paraconic acid (140) itself was found to involve the lipase MY

mediated asymmetric hydrolysis of the prochiral diacetate (147) which proceeded

with an enantiomeric excess of 89% and a modest yield of 35%. This was then

converted in three steps via the acid (148) to provide crude (R)-(+)-paraconic acid

with an overall yield of 39% from the key intermediate (A, R = allyl). Unfortunately,

since (R)-(+)-paraconic acid was not necessary for the authors work related to (3R)-

(−)-*A*-factor (145), no further attempt was made to purify this product. Nevertheless, this approach was selected for future study and this approach will be discussed in detail at a later stage.

2.6.2.3 Asymmetric Synthesis of (*S*)-(−)-Paraconic Acid (144) and Related Potential

Precursors Using a Chiral Auxiliary or a Chiral Reagent

The popularity of (*3R*)-(−)-A-factor (145) as a synthetic target has spawned several asymmetric routes towards this molecule,[77,78,80-84] several of which require the four step sequence from (*S*)-(−)-paraconic acid (144) for completion. Even although this was the "wrong" enantiomer for our own synthetic work, it was of course of interest to examine these with a view to modification and hence development of our own route to (*R*)-(+)-paraconic acid (140). The synthetic routes outlined below illustrate the modern approach to asymmetric synthesis, either through the use of a chiral reagent, or through selection of a chiral auxiliary.

Thus, the first steps of the synthesis of optically active A-factor developed by Parsons[82] are shown in Scheme 51 and rely on the use of the Corey oxazaborolidine[85] to install the necessary chiral centre in (153). The transformation of (153) to (154) then proceeds through a Johnson–Claisen rearrangement as the key step. The beauty of this approach lies in the subsequent steps of differentiated lactonisation to give either (155) or (156), both of which were subsequently transformed into the *A*-factor.

Clearly, for our own purposes, deprotection of (155) followed by oxidation would provide (*R*)-(+)-paraconic acid (140).

(149)

i

(150)

ii

(151)

HO H
(153)

iv

O
(152)

OTBDMS

iii

(154)

v

OTBDMS

O
O

vi

OTBDMS

(155)

O
O

(3S)-(+)-A-Factor

vii

(156)

O
O

(3R)-(–)-A-Factor
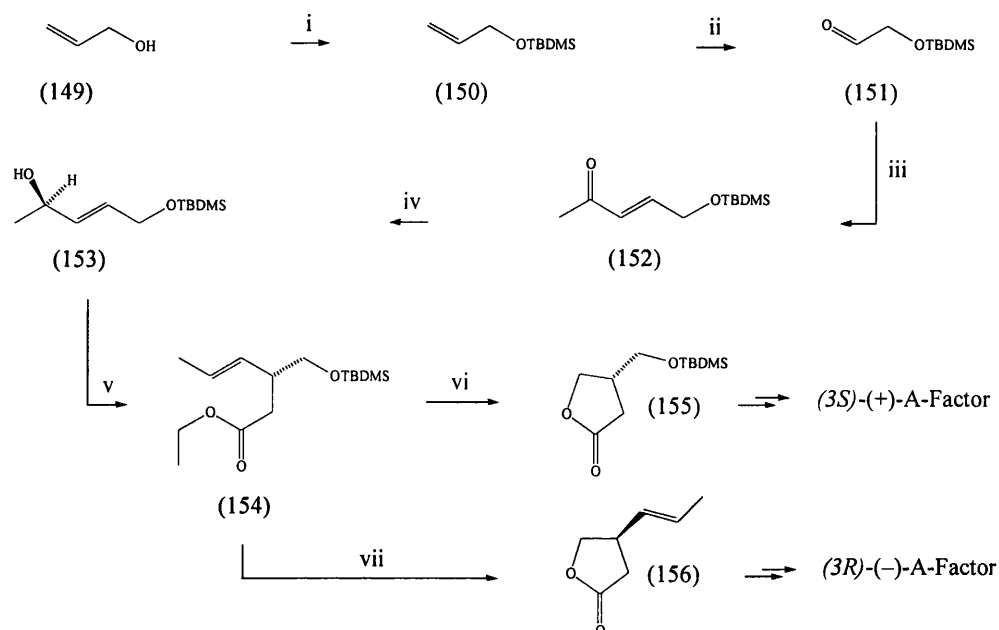
Scheme 51: Reagents and Conditions
i) TBDMSCl, TEA, DMAP, CH$_2$Cl$_2$; ii) O$_3$, CH$_2$Cl$_2$, PPh$_3$, 90% over steps i and ii; iii) K$_2$CO$_3$, diethyl(2-oxopropyl)phosphonate, H$_2$O, 80%; iv) (0.6 eq) BH$_3$•THF, (0.05 eq) oxazaborolidine, THF, 80% (84% ee); v) triethyl orthoacetate, (0.01 eq) hexanoic acid, 138 °C, 75%; vi) O$_3$, CH$_2$Cl$_2$, NaBH$_4$, EtOH, 60%; vii) conc. HCl (trace), (20:1) THF/H$_2$O, 80%.

From a purist viewpoint, our only concern with this route lay in the low overall

yield and in the fact that the CBS reduction[85] proceeded in only 84% ee to give

(153), and thus, at some stage, further purification, probably by classical resolution,

would be required to furnish pure (R)-(+)-paraconic acid. Accordingly, we directed

our attention to syntheses which involved the use of a chiral auxiliary, and which,

through separation of diastereomers at some stage, would allow us to obtain optically

pure product.

Within this vein, (*S*)-(−)-paraconic acid (144) has been prepared by Senanayake[86] as shown in Scheme 52. Once again, as in the enzyme-mediated route developed by Mori and Chiba,[81] the benzyl or allyl group serves as latent functionality for the introduction of a carboxylic acid.

(157)   (158)   (144)
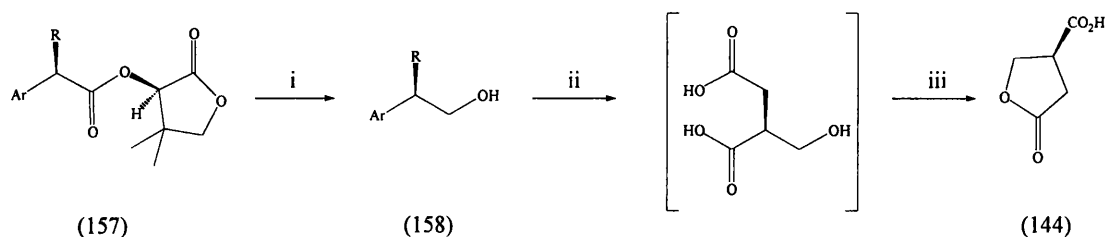
R = Benzyl or allyl

Scheme 52: **Reagents and Conditions**
i) LiAlH$_4$; ii) RuCl$_3$, NaIO$_4$, CCl$_4$, CH$_3$CN, H$_2$O; iii) 1 *N* HCl, 61% (>88% ee).

Since the same group had shown in earlier work[86] that the use of (*S*)-(−)-ethyl lactate instead of (*R*)-(−)-pantolactone as the chiral auxiliary could furnish the alternate diastereoisomer (159), (Scheme 53), a chiral route to our desired enantiomer was clearly possible.

(159)
or

(157)
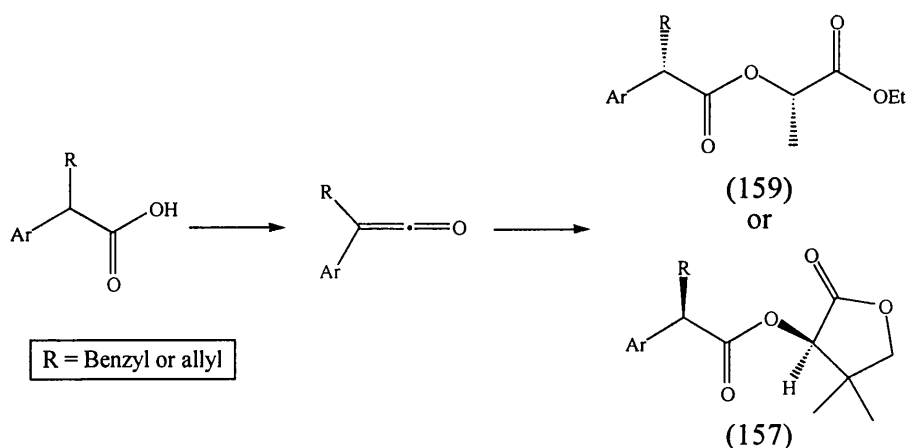
R = Benzyl or allyl

Scheme 53

100

It is not perhaps surprising that the remaining two routes feature the use of the popular Evans oxazolidinone as the chiral auxiliary.[83, 84, 87]

Thus, in their sequential aldol-lactonisation strategy for the synthesis of enantiopure (–)-roccellaric acid, (–)-protolichesterinic acid and (–)-methylenolactocin, Sibi and co-workers[87] developed the route shown in Scheme 54.

X_C = Chiral auxilliary

(160)   (161)

$R = n\text{-}C_{13}H_{27}$
or
$R = n\text{-}C_5H_{11}$

(–)-Protolichesterinic Acid,
$R = n\text{-}C_{13}H_{27}$

Or

(–)-Methylenolactocin Acid,
$R = n\text{-}C_5H_{11}$

(163)

(162)

(–)-Roccellaric Acid, $R = n\text{-}C_{13}H_{27}$
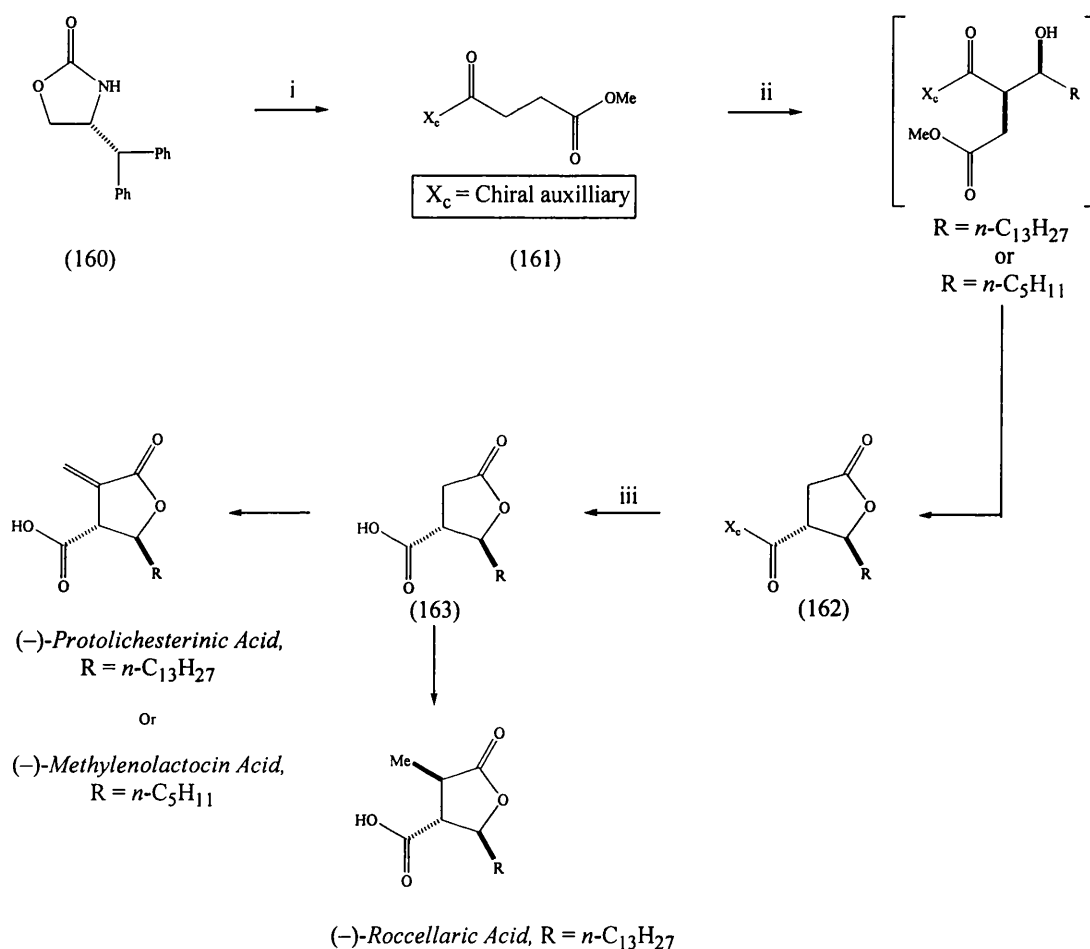
Scheme 54: **Reagents and Conditions**
i) n-BuLi, $ClCOCH_2CH_2CO_2CH_3$, –78 °C, THF, 97%; ii) a) Bu_2BOTf, TEA, CH_2Cl_2, 0 °C; b) RCHO, –78 °C to 0 °C, 55 – 82%; iii) LiOH, H_2O_2, THF, H_2O, 0 °C, 81 - 85%.

Although these authors did not prepare (S)-(–)-paraconic acid, the possibility of selecting the correct oxazolidinone and using formaldehyde (R = H) as the aldehyde should, in principle, deliver our required enantiomer of paraconic acid. We

were intrigued by the spontaneous chemoselective lactonisation step in this sequence which offered possibilities for rigorous purification of the lactone intermediate (162). The formal resemblance to the succinate method used in our racemic synthesis was also apparent and an encouraging feature.

The route to enantiopure (S)-(−)-paraconic acid (144) developed by Rawlings and first communicated in 1995 also uses the Evans oxazolidinone (164) derived from D-valine (Scheme 55).[83] In this instance, N-acylation with dihydrocinnamoyl chloride followed by alkylation of the Z-titanium enolate with benzyl chloromethyl ether sets the required stereocentre in intermediate (166).[83] Hydrogenolysis of the benzyl group followed by acetylation then provided intermediate (167) for oxidation of the aromatic ring with ruthenium(VIII) oxide to give (168). Removal of the chiral auxiliary with lithium hydroperoxide followed by hydrolysis of the acetate was then reported to furnish (S)-(−)-paraconic acid (144), with the overall yield for these last two steps being reported as 40%. The selection of L-valine as the chiral auxiliary should therefore automatically guarantee the synthesis of (R)-(+)-paraconic acid (140).

Scheme 55: Reagents and Conditions
i) n-BuLi, dihydrocinnamoyl chloride, 90%; ii) TiCl₄, (i-Pr)₂NEt, BnOCH₂Cl, 65%; iii) a) H₂/Pd/C; b) Ac₂O, pyridine, 90% over steps a and b; iv) RuCl₃, H₅IO₆, 65%; v) LiOH/H₂O₂ then 6 N hydrochloric acid, 40%.
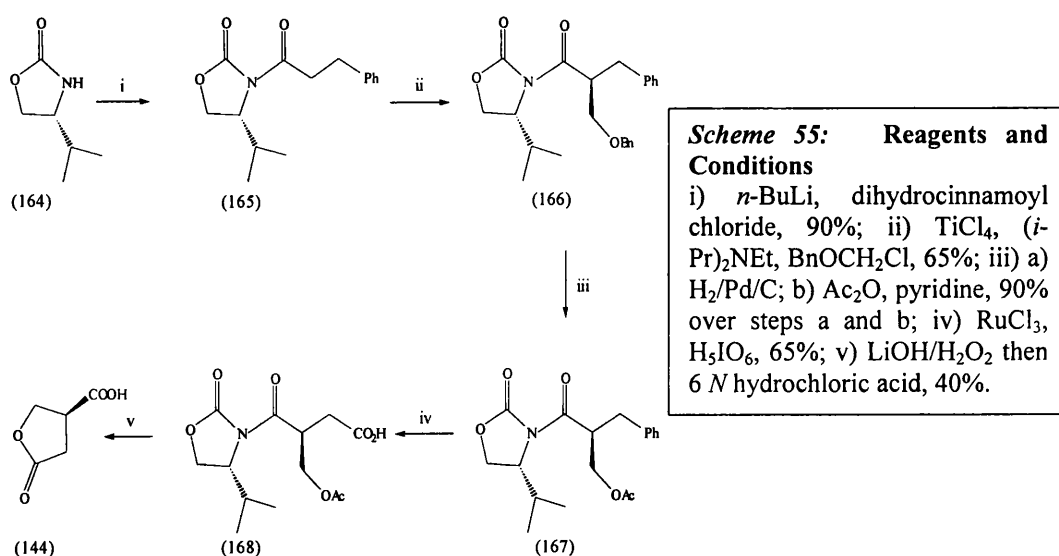
2.6.3 Synthesis of (R)-(+)-Paraconic Acid (140)

2.6.3.1 Enzyme-Mediated Route to (R)-(+)-Paraconic Acid

After careful consideration of the above routes in terms of length, overall efficiency, and optical purity, we selected, in the first instance, to adopt the sequence involving the enzyme-mediated transformations described by Mori and Chiba.[81]

The entire route used by Mori and Chiba[81] is set out in the Scheme 56.

(169) → i → (146) → ii → (147) → iii

(172) ← v ← (171) ← iv ← (170)
(S)-(–)-Monoacetate

↓ vi

(140)
(R)-(+)-Paraconic acid
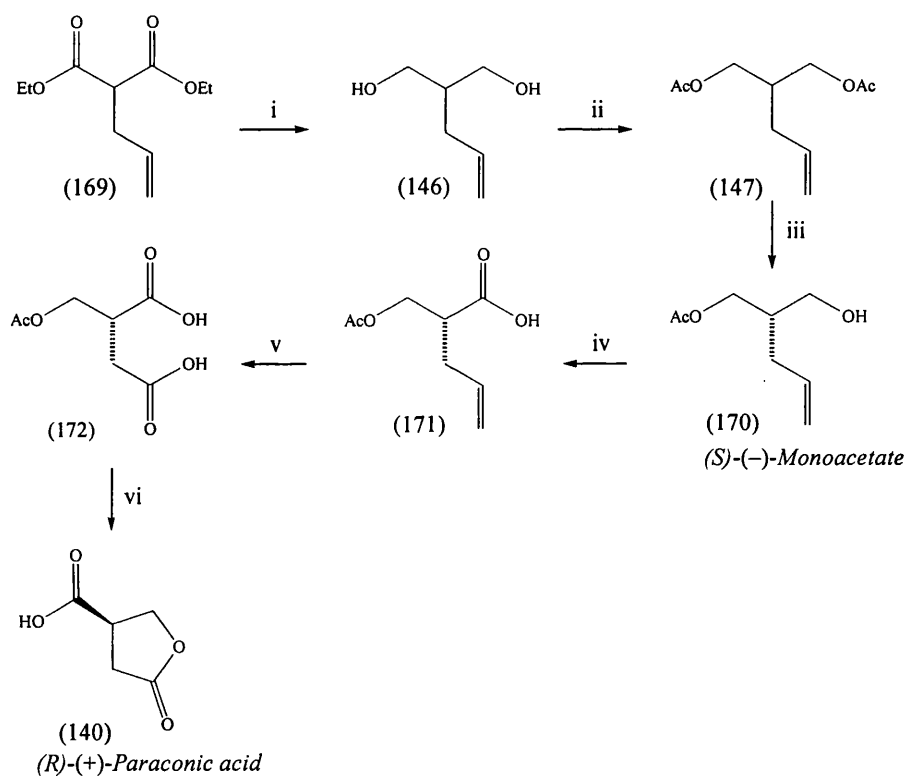
Scheme 56: Reagents and Conditions
i) LiAlH₄, Et₂O, 0 °C, 1 h, 90%; ii) Ac₂O, pyridine, DMAP, 22 °C, 12 h, 87%; iii) lipase from *Candida cylindracea* (Fluka), 30% phosphate buffer (pH = 6.95)-acetone, triton® X-100, 3 h, 82% (ee), 42%; iv) 2.26 *N* Jones reagent, acetone, rt, 12 h, 76% crude (171); v) RuO₂, NaIO₄, (1:1:1.5) CCl₄/CH₃CN/H₂O, rt, 12 h; vi) 6 *N* hydrochloric acid, rt, 48 h, 2% overall yield from (170).

Thus, lithium aluminum hydride reduction of readily available diethyl allylmalonate (169) followed by a global acetylation of the diol (146), using the

acetic anhydride/TEA/DMAP method furnished the prochiral diacetate (147) with an

overall yield of 65% over two steps. At a later stage, this was improved to 78% over

the two steps by applying the standard acetylation methodology with acetic

anhydride/pyridine/DMAP at room temperature. With (147) in hand we were

therefore ready to embark on the key step, the enzymatic hydrolysis of the prochiral

diacetate (147). Out of a variety of lipases screened for the enzymatic hydrolysis,

lipase MY was reported by Mori and Chiba to deliver (170) with the optimal

enantiomeric excess.[81] However, due to the unavailability of lipase MY we were

obliged to employ the lipase from *Candida cylindracea* which also has an excellent

reputation for use in stereoselective ester hydrolysis.[88] This enzyme has been used by

Ramos Tombo and co-workers for enantioselective hydrolysis of a range of prochiral

diacetates with enantiomeric excesses ranging from 61% - >95%.[89] In fact, the very

transformation which we wished to employ had been used by Sells and Nair in their

approach to *cis*- and *trans*-dideoxynucleosides (Scheme 57) *via* the (*S*)-(−)-

monoacetate (170) which was formed with an enantiomeric excess of 98.7%.[90]

dideoxynucleosides
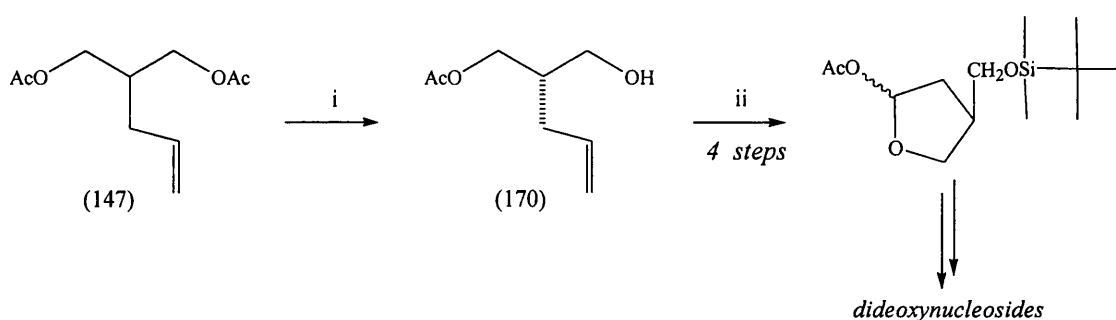
Scheme 57: **Reagents and Conditions**
i) Lipase from *Candida cylindracea* (Sigma, Type VII), 30% aq acetone, triton® X-100, 1.0 *N* NaOH (pH=6.95-7.00), 7.5 h, 98.7% (ee), 50%; ii) a) *tert*-butyldimethylsilyl chloride, imidazole, 99%; b) NaOMe, MeOH, then 1 *N* hydrochloric acid, 97%; c) NaIO₄, OsO₄, H₂O, 0 °C, then NaHSO₄, 98%; d) CH₃CN, molecular sieves, TEA, DMAP, Ac₂O, 78%.

Sells and Nair reported that the *Candida cylindracea*-mediated asymmetric hydrolysis furnished the desired monoacetate (170) with optimal enantioselectivity when the hydrolysis was conducted in a 30% aqueous-acetone medium, with a carefully maintained pH of 6.95 - 7.00.[90] As the reaction progressed, the action of the hydrolase generated (170), and, of course, acetic acid as the by-product which lowered the pH.

In view of the fact that there was no previous in house expertise of enzyme-mediated transformations within the group, we therefore initiated a systematic study using the lipase from *Candida cylindracea* (Equation 15 and Table 8). Each entry was conducted as a batch of three separate experiments, and each experiment was performed on 15.2 mmol of (147).

The hydrolysis was first performed under the conditions previously described by Sells and Nair.[90] In Entry 1 the pH of the medium was maintained at 7.00 ± 0.01 by the addition of a solution of 1 *N* sodium hydroxide. As an automated addition-pH controller was not available, we decided to perform the asymmetric hydrolysis using a phosphate buffer (pH 7.00 ± 0.1)-acetone medium, thereby eliminating the inconvenience of a lengthy manual addition of base. The enantioselectivity of this hydrolase is reportedly optimal in 30% aqueous-acetone medium over the conventional phosphate buffer (pH 7.00).[81] With this in mind, we decided to use a 30% phosphate buffer (pH 7.00 ± 0.01)-acetone medium in the lipase-mediated hydrolysis. To our knowledge the utility of a phosphate buffer (pH 7.00)-acetone medium has not been documented in the literature. Under these conditions described above, Entries 2 and 3 were performed. For each of our 15.2 mmol scale reactions, a volume of 200 mL of the phosphate buffer (pH 7.00 ± 0.1) was required.

Diacetate (147)   →   unconsumed (147)   +   Monoacetate (170)   +   Diol (146)
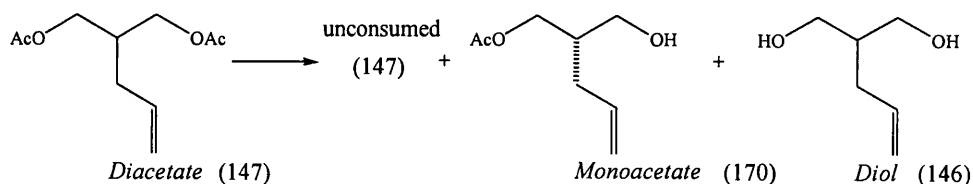
Equation 15

Entry	Reaction Temp. (°C) Time (h)	Ratio (147):(170):(146)	pH of the medium	(S)-(−)-Monoacetate (170) $[\alpha]_D$ (c=1.21,CHCl₃) ee (%), yield (%)
1	27 7.5	4:1:2	1N Sodium hydroxide pH 7.00 ± 0.01	−5.27 66 14
2	27 3.0	2:1:-	Buffer standard solution[a] pH 7.00 ± 0.1	−5.43 68 33
3	27 6.0	-:2:1	Buffer standard solution[a] pH 7.00 ± 0.1	−4.07 51 67
4	27 3.0	1:1:-	Sodium phosphate buffer[b] pH 6.95	−6.54 82 42
5	27 6.0	-:1:1	Sodium phosphate buffer[b] pH 6.95	−4.31 54 55

[a]Commercially purchased from Fluka; [b]prepared as described by Maniatis.[91]

Table 8: Lipase from *Candida cylindracea*-mediated asymmetric hydrolysis

At a later stage, and in anticipation of adopting the Mori-Chiba route towards a multigram scale synthesis of (R)-(+)-paraconic acid (140), large volumes of the phosphate buffer would be required and a convenient procedure described by Maniatis[91] for preparation of a sodium phosphate buffer of pH 6.95 was used.

Thus, the asymmetric hydrolysis of (147) was repeated in Entries 4 and 5 utilising this freshly prepared sodium phosphate buffer (pH 6.95). The enantiomeric excess of (S)-(−)-monoacetate (170) reported above was calculated on the basis of the specific optical rotation ($[\alpha]_D^{22.5}$ = −7.98°; c=1.21, CHCl₃) reported by Mori and

106

Chiba.[81] As can be seen from Entry 5, and in accordance with published literature, extending the reaction times led to a dramatic decrease in the enantiomeric excess. Thus, in our hands the most successful set of conditions are those described in Entry 4, with an ee of 82% and 42% yield. Despite this, the reproducibility of the reaction and the observed enantiomeric excesses was somewhat variable for reasons which are not clearly understood. This can be clearly seen from the three "identical" experiments shown below in Table 9.

Entry	Reaction Temp (°C) Time (h)	Ratio (147):(170):(146)	pH of the medium	(S)-(−)-Monoacetate (170) $[\alpha]_D$ (c=1.21,CHCl$_3$) ee (%), yield (%)
4	27 3.0	1:1:-	Sodium phosphate buffer[a] pH 6.95	-6.54 82 42
6	27 3.0	4:4:1	Sodium phosphate buffer[a] pH 6.95	-5.35 67 48
7	27 3.0	1.5:2.5:1	Sodium phosphate buffer[a] pH 6.95	-4.07 51 49

[a]prepared as described by Maniatis.[91]

Table 9: Lipase from *Candida cylindracea*-mediated asymmetric hydrolysis

We were fully aware that this would result in the production of batches of (R)-(+)-paraconic acid (140) of differing enantiomeric purity. However, in such an event the traditional method of optical resolution could in principle be used to enrich the optical purity of (140).

The enantiomeric excesses of the (S)-(−)-monoacetate (170) reported by Chiba and Mori were calculated on the basis of the specific optical rotation for the (R)-(+)-monoacetate ($[\alpha]_D^{22}$ = +13.6°, c=0.96 CHCl$_3$).[81] It is apparent however that there may be some confusion in the literature since surprisingly, the value which they

quoted was reported by Kishi *et al.* in their synthesis of the right half of monensin (Scheme 58) to correspond to the monobenzyl ether (173).[92]

Scheme 58
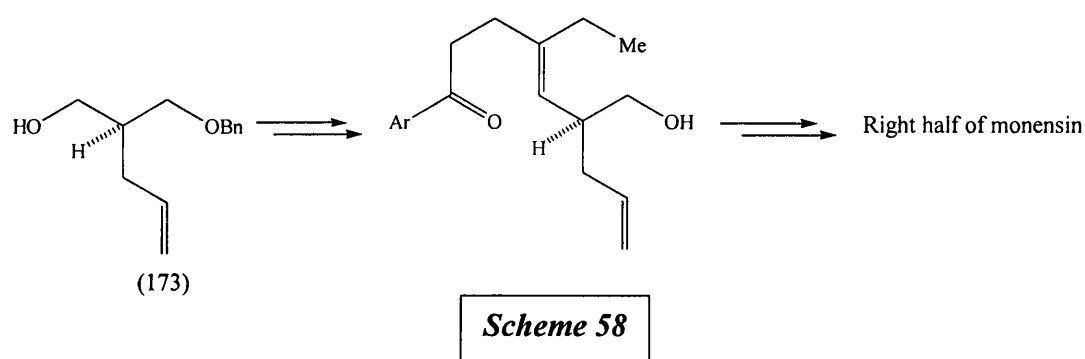
A thorough search of the literature shed no further light on the specific optical rotation of (*S*)-(–)-monoacetate (170). We therefore attempted to determine its enantiomeric excess utilising the nmr shift reagent, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [Eu(hfc)$_3$]. However, this too proved unsuccessful. Fortunately the undetermined enantiomeric excess posed no serious setback. Although we were fully aware that preparation of the Mosher ester[93] and / or correlation of the monoacetate (170) with the monobenzyl ether (173) reported by Kishi *et al.*[92] would enable us to determine the "genuine" enantiomeric excess, we decided at this stage to continue and complete the synthesis of (*R*)-(+)-paraconic acid (140) and to determine its optical purity.

Thus, Jones oxidation of the monoalcohol (170) afforded the monoacid (171) as a viscous pale reddish oil which was isolated in a yield of 76%. The polarity of the acid functionality hindered purification of the monoacid (171) by flash column chromatography. However, the appearance of the additional C=O stretch at 1777cm^{-1} and the broad hydrogen bonded hydroxyl stretch at 3519 cm^{-1} in the i.r of the monoacid (171), confirmed the presence of the acid functionality. The monoacid was

then subjected to further oxidation by the ruthenium dioxide and sodium periodate method[94] and attempts were then made to extract the diacid (172) from the aqueous medium as described by Mori and Chiba.[81] Somewhat surprisingly, according to these authors, the procedure involved saturating the aqueous layer with sodium chloride and then using DCM as the extracting solvent. The DCM extracts were dried and evaporated. However no (R)-(+)-paraconic acid was detected by ^{1}H nmr. Our attempts were repeated, sadly to no avail. The high polarity of the diacid (172) obviously prevented its extraction from the salted aqueous layer by the organic solvent. (Ether, THF and ethyl acetate were also employed as extracting solvents). Presumably the partition coefficient of the diacid (172) favoured the salted aqueous medium. The aqueous layer was therefore freeze dried and the resultant crude residue was subjected to lactonisation by treatment with 6 N hydrochloric acid at room temperature for 48 h. It was encouraging to note that the ^{1}H nmr of the crude residue contained the necessary signals corresponding to paraconic acid as well as acetic acid, thus confirming that lactonisation had indeed occurred. In our hands however, the crude (R)-(+)-paraconic acid (140) was produced in only 2% overall yield from the (S)-(−)-monoacetate (170), as opposed to the 39% obtained by Chiba and Mori, which was also as we have previously stated, not further purified.

Although the above enzyme-mediated route represents the only formal approach to (R)-(+)-paraconic acid (140) in the literature, we were very concerned by the capricious and irreproducible nature of the lipase hydrolysis step. This, when later in conjunction with the apparent confusion over correlated $[\alpha]_D$ values, the unusual extraction method for a polar diacid (172), and the fact that the sample

obtained by Chiba and Mori was never fully purified caused us to question the validity of continuing such an approach.

Accordingly at this stage, we decided to adopt a different strategy, and to base our route to (R)-(+)-paraconic acid (140) on those which had been successfully used for the (S)-(−)-enantiomer, which as we have seen, has often featured in syntheses of (3R)-(−)-A-factor (145).

2.6.3.2 Chiral Auxiliary Based Routes to (R)-(+)-Paraconic Acid

Consideration of the established asymmetric syntheses of (S)-(−)-paraconic acid (144) and related congeners suggested to us that the selection of an Evans' chiral oxazolidinone as the auxiliary would allow us to investigate and modify two of the routes which had been developed, viz., that developed by Sibi et al.[87] towards (−)-roccellaric acid (Scheme 54, p. 101) and that used by Crawforth and Rawlings[83] for (S)-(−)-paraconic acid itself (Scheme 55, p. 102).

We were initially attracted towards the approach taken by Sibi[87] purely and simply because of our familiarity with the racemic route to paraconic acid using diethyl succinate.

Thus, as shown in Scheme 59 we reasoned that the oxazolidinone (174) derived from L-valine (175) could be deprotonated and reacted with 3-carbomethoxypropionyl chloride to give the chiral succinate analogue (176). Although reaction of the boron enolate derived from acyloxazolidinone (176) with some form of formaldehyde under standard aldol conditions could in principle lead directly to the γ-lactone (179), we were aware that the reactivity of paraformaldehyde

polymer, or 1,3,5-trioxan could be problematic and that the generation and handling of solutions of monomeric formaldehyde by depolymerisation was a delicate operation. For this reason, we decided to explore the chiral variant of the racemic route involving formylation in the hope that the subsequent reduction would be highly diastereoselective. The removal of the chiral auxiliary would then complete the synthesis.
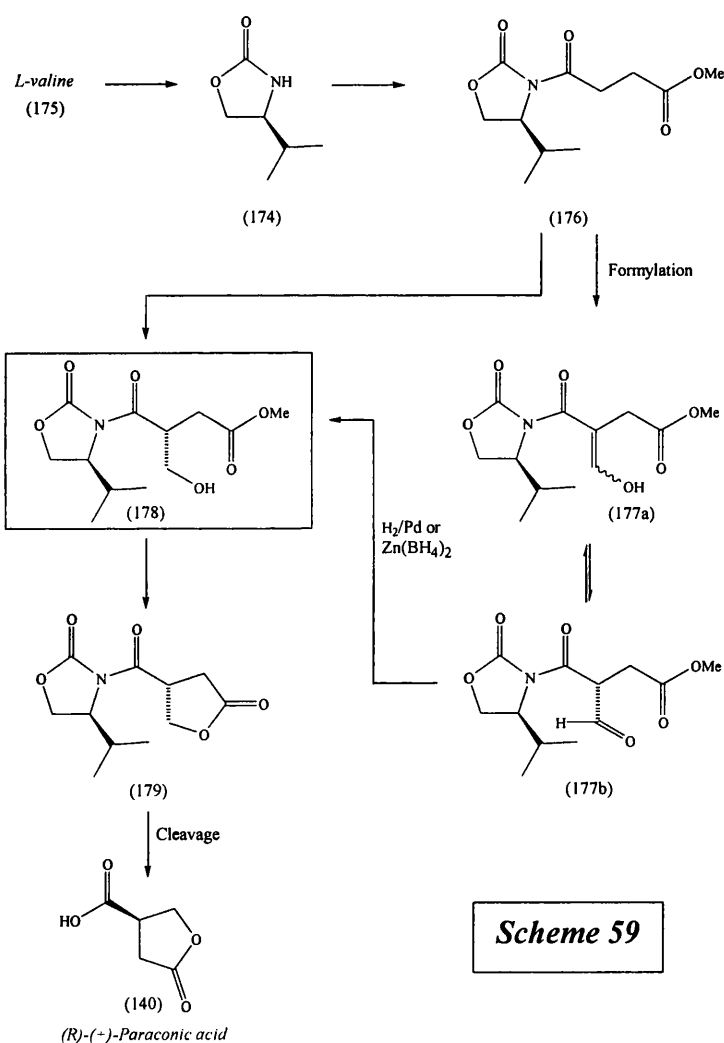
Scheme 59

The required (S)-(+)-4-isopropyloxazolidin-2-one (174) was available *via* a well-established route (Scheme 60).[95,96]

(175)   (180)   (174)

Scheme 60: Reagents and Conditions
i) NaBH$_4$, I$_2$, THF, 0 °C, for 3 h then reflux, 16 h, 81%; ii) (10 mol%) K$_2$CO$_3$, (EtO)$_2$CO, 120 °C, 3.5 h, 68%.

Thus, diborane reduction of L-valine (175) afforded the alcohol in an isolated yield of 81%. The L-valinol (180) was then cyclised by Evan's diethyl carbonate procedure[96] to furnish the chiral oxazolidinone (174) and the crude product was recrystallised twice to furnish the desired product in 68% yield, and with an overall yield of 55%.

The acylation of the chiral oxazolidinone (174) was performed under standard conditions by treating the oxazolidinone (174) with n-butyllithium and quenching the resultant anion with commercially available 3-(carbomethoxy)propionyl chloride. The product oxazolidinone (176) was formed in 90% yield (Scheme 61) as a viscous oil.

(174)   (176)

Scheme 61: Reagents and Conditions
i) n-BuLi, ClC(O)CH$_2$CH$_2$CO$_2$Me, THF, -78 °C, 3 h, 90%.

Ager and co-workers have reported that *N*-acylation of a variety of chiral oxazolidinones can be conducted at room temperature with TEA and DMAP (catalytic) using either the acid chloride or the anhydride.[97] As this procedure circumvented the use of *n*-butyllithium, it was also attempted, but, in this instance failed to afford any of the *N*-acyloxazolidinone.

The stage was then set for the introduction of the formyl group, which to the best of our knowledge has not been attempted using Evans type auxiliaries. Based on the use of the standard stereoselective boron enolate methodology for aldol reactions[98-101] which had been used by Sibi[87] for his closely related *N*-acyloxazolidinone, we elected to examine the reactivity of the dibutylboron enolate using ethyl formate and formyl acetic anhydride as the electrophilic partners (Scheme 62).

(176)

i, ii
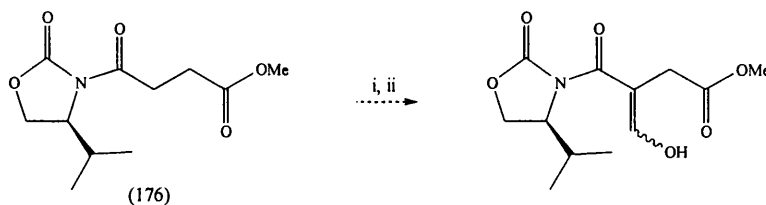
Scheme 62   Reagents and Conditions
i) *n*-Bu₂BOTf, DCM, TEA, –78 °C; ii) add ethyl formate or acetic formic anhydride in DCM at –78 °C, 30 min.

In both reactions however, the starting *N*-acyloxazolidinone (176) was recovered in greater than 90% yield.

Frustrated by this apparent lack of reactivity, we then decided, as shown in Scheme 63 to examine the use of benzyl chloromethyl ether as a protected formaldehyde equivalent in a diastereoselective *C*-alkylation reaction using the titanium enolate conditions which have also been well described by Evans.[102-104] The

necessary titanium enolates were generated by reaction with titanium tetrachloride

using either triethylamine or diisopropylethylamine as the base.
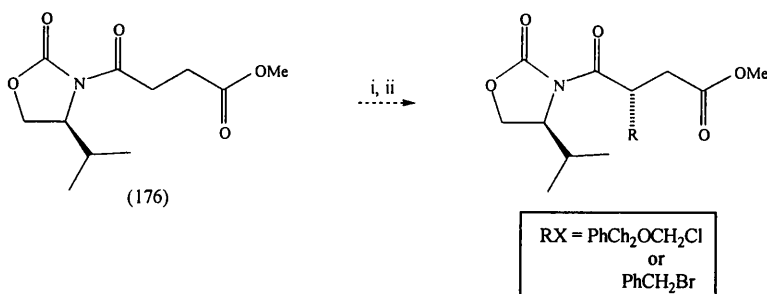
Scheme 63: **Reagents and Conditions**
i) TiCl$_4$, DCM, −78 °C/0 °C, then add base, 20 min; ii) RX, −78 °C/0 °C, 1h.

The results of this study are shown in Table 10.

Entry	Reagents and Conditions	Yield (%)
1	TiCl$_4$, TEA, benzyl chloromethyl ether, DCM, −78 °C	0
2	TiCl$_4$, TEA, benzyl bromide, DCM, −78 °C	0
3	TiCl$_4$, DIPEA, benzyl chloromethyl ether, DCM, 0 °C	0
4	TiCl$_4$, DIPEA, benzyl bromide, DCM, 0 °C	0

Table 10

To our chagrin, no evidence whatsoever was adduced for the formation of an

alkylated product using either benzyl chloromethyl ether or even benzyl bromide as a

test electrophile. Given the wealth of successful alkylations performed on titanium

enolates of N-acyloxazolidinones, we can only conclude that the remote

carbomethoxy group in the present case plays a destructive role.

As we were unable to achieve either a boron enolate mediated C-acylation or a

titanium enolate driven C-alkylation of our chiral succinate equivalent, we therefore

turned, albeit reluctantly, to reproduce the mirror image of the synthesis reported by

Crawforth and Rawlings.[83]

Even although the communication by Crawforth and Rawlings did not provide

any full experimental details, the first five steps as shown in Scheme 64 proceeded

without incident and our yields were comparable and even in some instances superior

to those reported for the enantiomeric series.
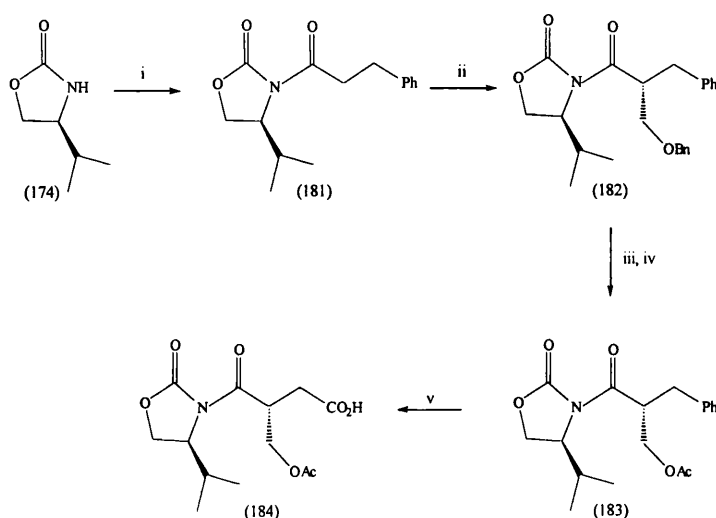
Scheme 64: **Reagents and Conditions**
i) *n*-BuLi, dihydrocinnamoyl chloride, THF, 0 °C, 79%; ii) TiCl$_4$, TEA, BnOCH$_2$Cl, 0 °C, 16 h, 68%; iii) H$_2$ (10%) Pd/C, EtOH, rt, 16 h, alcohol (182a) 85%; (iv) Ac$_2$O, pyridine, DMAP, rt, 16 h, 90%; iv) RuCl$_3$, H$_5$IO$_6$, CCl$_4$:CH$_3$CN:H$_2$O (1:1:2), 77%.

In principle, all that remained to complete the synthesis of (*R*)-(+)-paraconic

acid (140) was the removal of the chiral auxiliary using the lithium hydroperoxide

protocol[105] and to achieve hydrolysis of the intermediate acetate (185) and

concomitant lactonisation by treatment with 6 *N* hydrochloric acid as shown in the

Scheme 65.

Scheme 65: Reagents and Conditions
i) 30% aq THF, LiOH / 30 wt.% H₂O₂, 0 –
+4 °C, rt, 16 h, then 6 N hydrochloric acid.
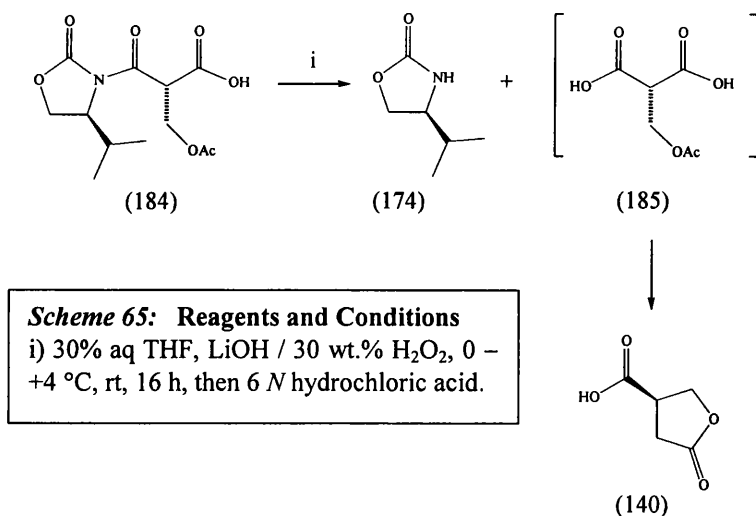
In our hands, after cleavage of the N-acyloxazolidinone (184) with lithium

hydroperoxide, it was possible to recover the chiral auxiliary derived from L-valine

(174) in an encouraging 72% yield. Treatment of the aqueous layer containing the

dicarboxylic acid (185) with 6 N hydrochloric acid at room temperature for 48 h

followed by freeze drying, Soxhlet extraction with dichloromethane for 48 h, and

removal of solvent then provided a crude solid which was distilled at 200 °C (0.2

mmHg). In this fashion (R)-(+)-paraconic acid was isolated in 17% yield and in high

optical purity, as evidenced by comparison of our specific rotation ([α]$_D$ = +56.7° (c

= 0.50, MeOH)) with that in the literature for the S-enantiomer ([α]$_D$ = –59.6° (c =

0.61, MeOH)). On a second occasion, repetition of this sequence gave (R)-(+)-

paraconic acid in 15% yield.

We were disappointed by the isolated yield of the acid, especially since the

chiral auxiliary had been recovered in 72% yield. This implied that the subsequent

step involving acid catalysed hydrolysis of the acetate and lactonisation was failing

to produce the optimal yield. Our own yield did not bear comparison with that of

116

40% reported by Crawforth and Rawlings[83] for the synthesis of (S)-(−)-paraconic acid (144).

In order to improve the yield of the final hydrolysis and lactonisation steps, we then decided to employ an alternative protecting group strategy. Important criteria in selecting these protecting groups included the necessity that they should be even more labile to acidic hydrolysis than the acetate, and that they should also resist oxidation by ruthenium tetroxide. Four different groups were accordingly selected for study (Equation 16 and Table 11).[106]

P = Protecting Group

Equation 16
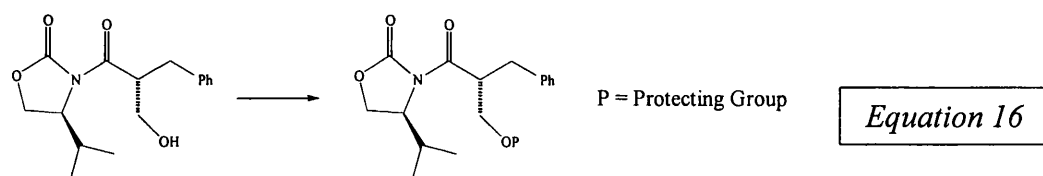
Entry	Protecting Group (P)	Reagents and Conditions	Yield (%)
1	THP (186)	Dihydropyran, amberlyst®-15, Et₂O, rt, 12 h	75
2	TBDMS (187)	TBDMSCl, imidazole, THF, rt, 12 h	100
3	Bz (188)	Benzoyl chloride, pyridine, DCM, rt, 24 h	100
4	COCl₃ (189)	Trichloroacetic anhydride, pyridine, DCM, rt, 12 h	90

Table 11

Unfortunately, the THP group (186) did not survive the oxidation step using ruthenium tetroxide whilst the TBDMS (187), trichloroacetate (189) and benzoate (188) groups, although stable to oxidation, proved difficult to drive to completion even when further portions of catalyst were added. Efforts to process crude mixtures

through the final hydrolysis and lactonisation steps using these varied protecting groups were singularly unsuccessful.

The final "sting in the tail" of this tale came after completion of our own study when Crawforth and Rawlings published their full paper on the synthesis of (S)-(–)-paraconic acid (144) in 1998.[84] Very close examination of the experimental section of this paper revealed that cleavage of 13.6 mmol (4.1g) of the N-acyloxazolidinone enantiomer of (184) had furnished 220 mg of (S)-(–)-paraconic acid (144). The correct arithmetic for this step corresponds to a yield of 12%, and not in fact to a yield of 40% reported both in the communication[83] and in the full paper![84] In the final analysis, our own hydrolysis and lactonisation steps were 5% better than that in the literature.

2.6.4 Conclusion

In summary, a considerable amount of time was devoted in an effort to obtain (R)-(+)-paraconic acid (140) in multigram quantities. Of the three strategies investigated, the lipase-mediated route was plagued in particular by the irreproducibility of the enantioselective hydrolysis of the prochiral diester and the relatively low yields in the subsequent steps, as well as some curious inconsistencies. Of the two routes which involved the use of the Evans oxazolidinone derived from L-valine, the chiral succinate proved to be resistant to the introduction of the new chiral centre whether by formylation or even more surprisingly by alkylation. Thus in the final analysis, the approach adopted by Crawforth and Rawlings proved to be the most successful. However, even with an "improved" yield over that "reported" in the

literature, this route to chiral (R)-(+)-paraconic acid (140) proceeded in only 7% overall yield from the N-acyloxazolidinone (181), and was clearly inefficient for our purposes.

With this background in mind, we therefore set out to devise an entirely different route to chiral steganone analogues.

2.7 A Novel Convergent Approach to Chiral Steganone Analogues *via* a Tandem Michael Addition / α-Alkylation Sequence

2.7.1 *Introduction and Objectives of the Present Work*

Throughout our studies, even although the steganone core was the focus of our attention, we were aware that it was only one member of the relatively large class of lignan lactones, and that many different and highly ingenious synthetic strategies had been developed over the years.

In particular, we were intrigued by a series of papers from Pelter, Ward and their collaborators[107-110] in which the conjugate addition of the acyl anion equivalent derived from arylbis(phenylthio)methane (190) to butenolide (191) could be followed by trapping of the resultant γ-lactone enolate (192) by a benzyl halide or an aromatic aldehyde to provide adducts containing the basic lignan skeleton. This elegant and highly convergent approach which guarantees the necessary *trans*-fusion around the γ-lactone ring, can be exemplified by the key step in this group's versatile synthesis of lignans related to podophyllotoxin[107-109] as summarised in Scheme 66.

(190)   (191)   (192)
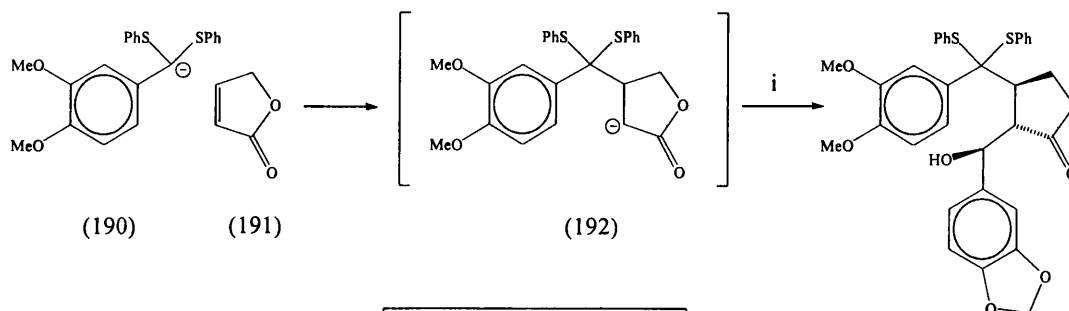
Scheme 66: Reagents
i) Piperonal.

As we have seen, a similar approach was taken by Koga[26] using a chiral

butenolide (56) in his asymmetric route to steganone (Section 1.6.2.1).

Of equal interest to us, in terms of a chiral acyl anion equivalent, was the

recent work by the Enders group on the use of enantiopure metalated α-amino

nitriles[111-115] derived from (S,S)-(+)-2,2-dimethyl-5-methylamino-4-phenyl-1,3-

dioxan (193) as the chiral auxiliary. The power of this methodology is readily

exemplified as shown in Scheme 67, which reveals that a highly diastereo- and

enantioselective synthesis of 2-substituted 3-aroylcyclohexanones (194) is possible

by a tandem Michael addition / α-alkylation sequence using cyclohexanone[112]

(193)

(194)
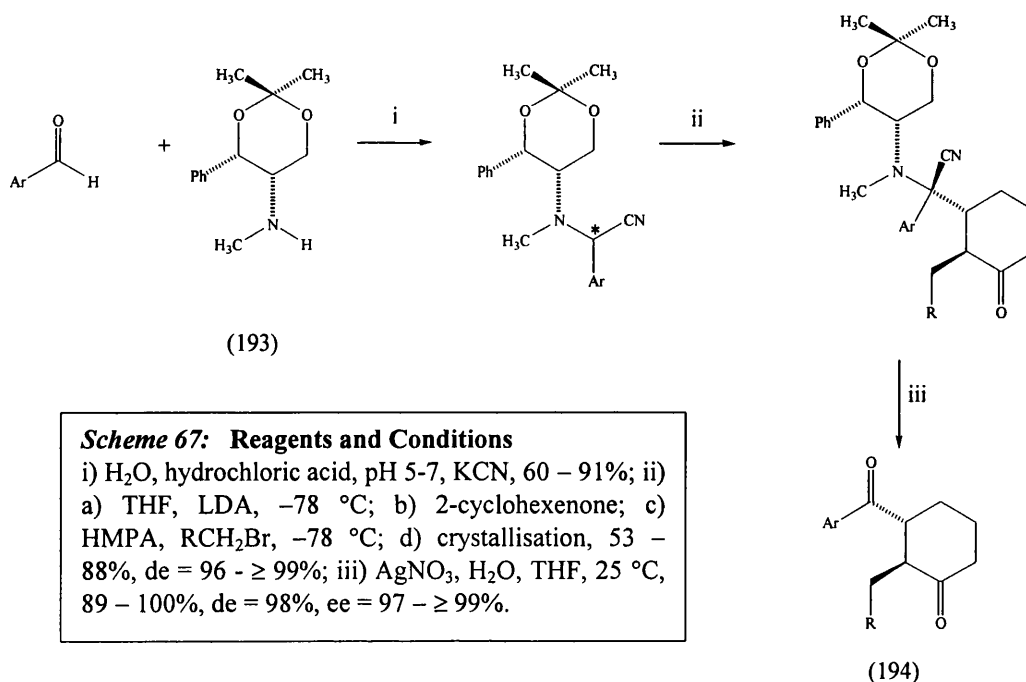
Scheme 67: Reagents and Conditions
i) H$_2$O, hydrochloric acid, pH 5-7, KCN, 60 – 91%; ii)
a) THF, LDA, –78 °C; b) 2-cyclohexenone; c)
HMPA, RCH$_2$Br, –78 °C; d) crystallisation, 53 –
88%, de = 96 - ≥ 99%; iii) AgNO$_3$, H$_2$O, THF, 25 °C,
89 – 100%, de = 98%, ee = 97 – ≥ 99%.

The combination of the Enders chiral acyl anion equivalent as the carbanion with the tandem Michael addition / α-alkylation sequence using butenolide (191) developed by Pelter and Ward[107-109] suggested to us that a new and highly attractive strategy for steganone analogues should be possible. Moreover, as shown by the retrosynthetic analysis in Scheme 68, it was also possible to retain the potentially versatile use of the cobalt-mediated [2+2+2] cycloaddition chemistry.
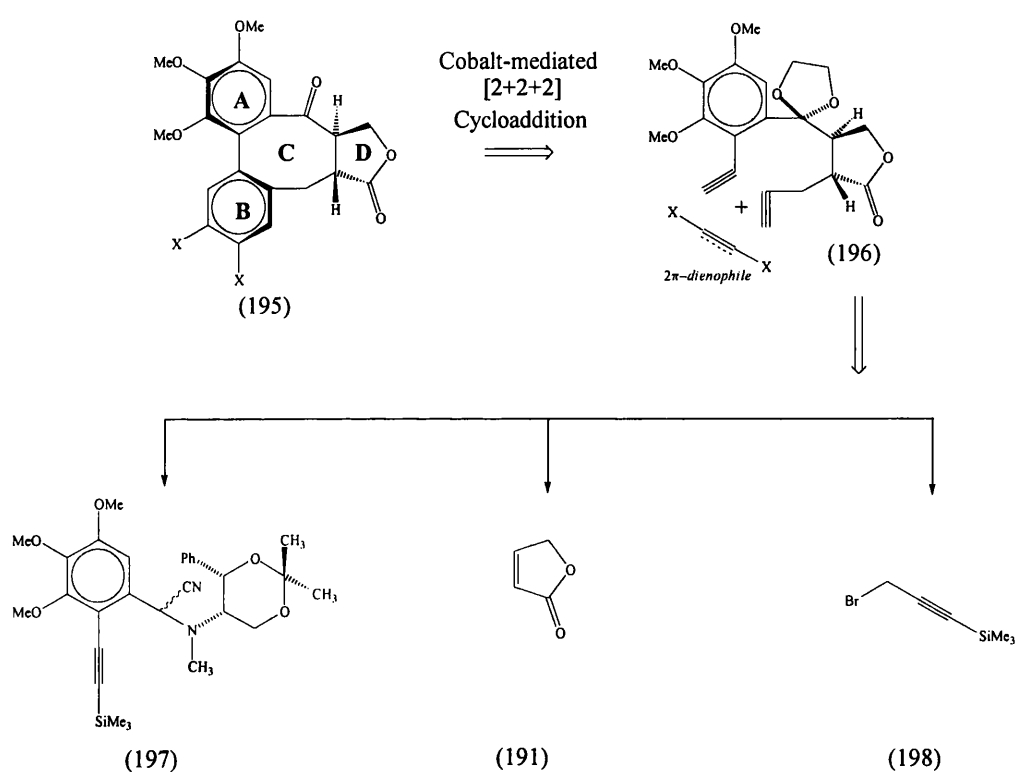
Scheme 68

Examination of the above scheme reveals that, in essence, this approach has transposed the northern and southern aromatic rings inasmuch as it is now ring B which is constructed by the metal-mediated cycloaddition. Our optimistic hope of course was that the steric constraints involved in the use of the new diyne fragment derived from (196) would be less demanding than in the original route to racemic steganone. Although a wide variety of intact aromatic aldehydes could have been

selected for the northern ring A component, we elected in the first instance to use the trimethoxy derivative shown in the unnatural analogue (195), for the simple reason that the derived benzylic alcohol (112) was already available to us from the studies on the racemic route. Of the remaining two components required for the tandem Michael addition / α-alkylation sequence, both 3-bromo-1-(trimethylsilyl)-1-propyne (198) and γ-crotonolactone or 2(5H)-furanone (191) were commercially available. In view of the high purchasing cost of the latter however, we decided to prepare it *via* a well established procedure[116] involving dehydrobromination of α-bromo-γ-butyrolactone (199) (Equation 17).

(199)   (191)
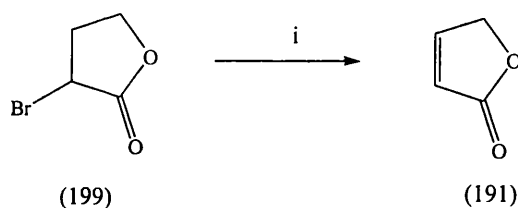
Equation 17: Reagents and Conditions
i) TEA, ether, reflux, 17 h, 69%.

Thus, dropwise addition of triethylamine to a refluxing solution of (199) in ether for 12 h afforded the butenolide (191) isolated in a yield of 69%. In a recent communication by Nasman and Pensar,[117] the use of DIPEA as the base in toluene at 70 °C for 1 h was reported to give improved yields in this reaction. These authors had performed the reaction on a 96 g scale, and, in view of the simplicity of the reaction conditions, we were encouraged to repeat it. In our hands however, when the reaction was repeated on a 12 g scale, the yield dropped to 55%.

The situation with respect to the highly functionalised aromatic acetylenic aldehyde (200) is summarised in Scheme 69.

(111) → (200)

(93) → (112)
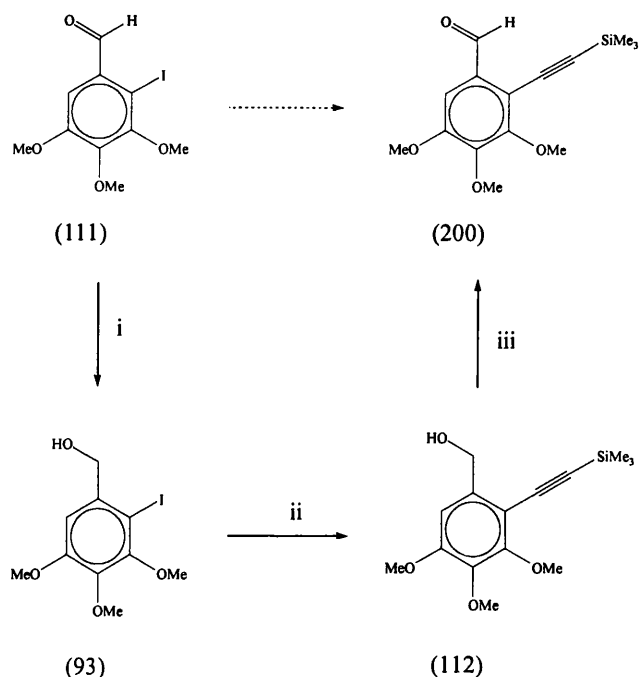
Scheme 69: Reagents and Conditions
i) NaBH$_4$, MeOH, 0 °C, 79%; iii) (5 mol%) Pd(OAc)$_2$, (20 mol%) PPh$_3$, (5 mol%)
CuI, DIPA, 50 °C, 79%; iv) PDC, DCM, rt, 6 h, 96%.

In the first instance, a sample of (200) was simply prepared in high yield by
PDC oxidation of a batch of the benzylic alcohol (112) which had been employed for
the southern aromatic ring in the racemic route. To our surprise however, attempts to
achieve the direct coupling of 2-iodo-3,4,5-trimethoxybenzaldehyde (111) with
(trimethylsilyl)acetylene to give (200) using the Pd(PPh$_3$)$_2$Cl$_2$
bis(triphenylphosphine)palladium(II) chloride, copper(I) iodide and TEA
methodology were uniformly unsuccessful. Since the presence of electron
withdrawing groups on the aryl ring is generally considered to facilitate the
palladium catalysed coupling reaction,[118,119] this result was unexpected.

(PPh₃)₂PdCl₂

$HC{\equiv}CR$

CuI catalyst / Et₂NH

$R = TMS$

[NEt₂H₂]Cl

$(PPh_3)_2Pd{-\!\!-}(C{\equiv}CR)_2$

$RC{\equiv}CC{\equiv}CR$

Pd(PPh₃)₂

A

$R'C{\equiv}CR$

R'X

$R'I \;=\;$

$(PPh_3)_2Pd\!\!\overset{R'}{\underset{C{\equiv}CR}{\big\langle}}$

$(PPh_3)_2Pd\!\!\overset{R'}{\underset{X}{\big\langle}}$

[NEt₂H₂]Cl

$HC{\equiv}CR$

CuI catalyst / Et₂NH
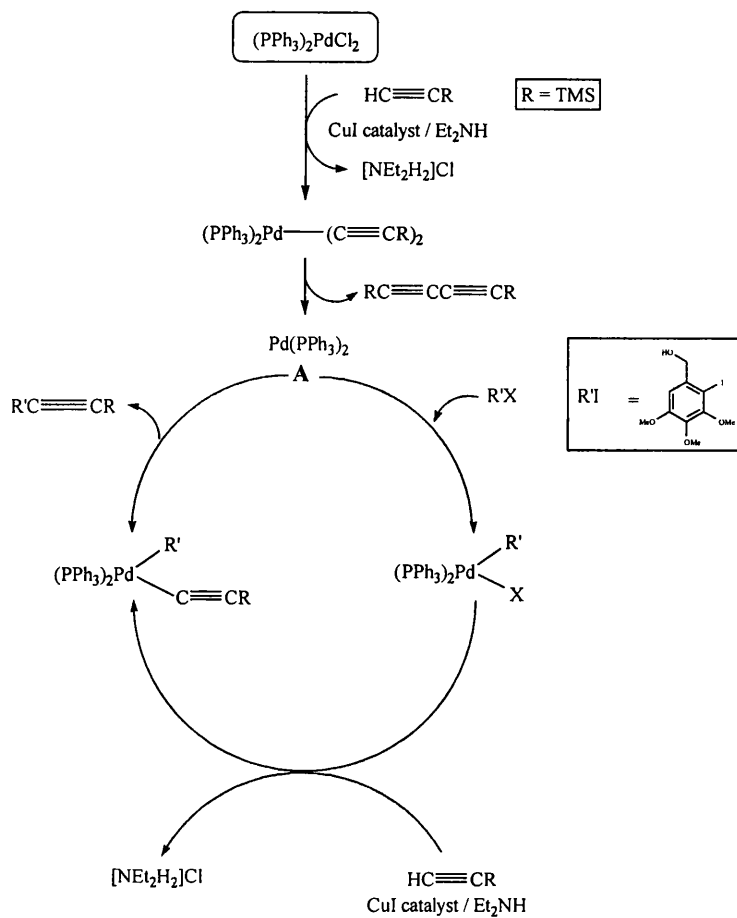
Scheme 70

The mechanism of this reaction is generally considered to proceed by reduction of bis(triphenylphosphine)palladium(II) chloride to a palladium(0) (**A**) species through coupling of two molecules of the alkyne in the presence of the cuprous salt and the amine. Oxidative addition of the aromatic iodide to the palladium(0) species thus generated is reported to be a facile process.[118a] The arylpalladium(II) iodide so formed then reacts with an acetylide anion to yield an unstable aryl(σ-ethynyl) palladium(II) intermediate which undergoes reductive elimination of the product arylacetylene with concomitant regeneration of the palladium(0) species to maintain

the catalytic cycle. The detailed mechanism of the oxidative addition step has variously been discussed in terms of nucleophilic aromatic substitution, electron transfer, or of a three centre nature (Scheme 70).[118b]

At a later stage, when we wished to bring through further batches of aldehyde (112), we were concerned to find that this reaction was somewhat capricious, probably because of the variable quality of the commercial samples of bis(triphenylphosphine)palladium(II) dichloride. This problem was eventually solved by *in situ* generation of palladium(0) using palladium(II) acetate, triphenylphosphine, copper(I) iodide and DIPA as described by Gibb,[200] and coupling proceeded routinely in 79% yield.

2.7.1.1 Synthesis of the Enders Chiral Auxiliary (193)

The next step in our synthetic sequence required formation of the α-amino nitrile (197) (Scheme 68, p. 121) from the aldehyde and the Enders chiral auxiliary (*S,S*)-(+)-2,2-dimethyl-5-methylamino-4-phenyl-1,3-dioxan (193) (Scheme 67, p. 120). When this present synthetic strategy was initiated, (193) was considered to be commercially available from Acros Organics. On enquiry however, we found that it was no longer available, and we were therefore obliged to prepare it. Examination of the literature revealed that the four step route shown in Scheme 71 had been followed, involving initial protection of (1*S,2S*)-(+)-2-amino-1-phenyl-1,3,- propanediol (201) as its hydrobromide salt (202) followed by conversion to the 1,3- dioxane derivative (203) and introduction of the methylamino group *via* the formamide (204) and subsequent lithium aluminum hydride reduction (Scheme 71).

OH OH   → i →   OH OH   → ii →

Ph''''''   Ph''''''

NH₂   NH₃Br ⊕ ⊖

(201)   (202)   (203)

(193)   ← iv ←   (204)
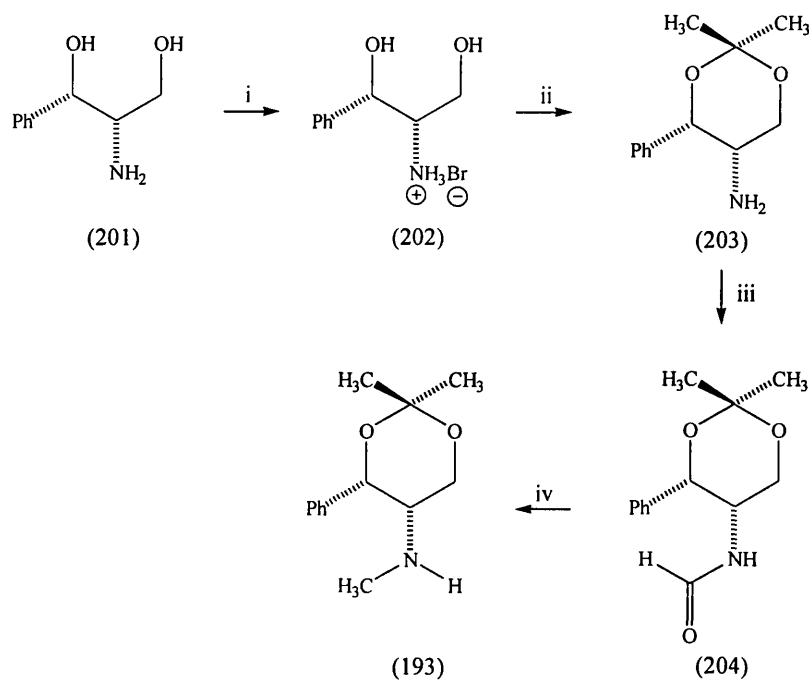
Scheme 71: **Reagents and Conditions**
i) (1 eq) HBr, 100%; ii) reference 121; iii) a) methyl formate, reflux, b) crystallisation; iv) LiAlH₄, THF, reflux, 84% over steps iii) and iv).

The last two steps however, were only described in a footnote by Enders with reference to a doctoral thesis[115] whilst the preparation of the intermediate 1,3-dioxan (203) had been reported by Weinges and co-workers.[121,122]

Thus, the hydrobromide salt (202) was formed in quantitative yield by treatment of the amine (201) with one equivalent of hydrogen bromide. The general conditions reported by Weinges and co-workers for the formation of the 1,3-dioxan derivative (203) were not unusual, and involved treatment of the salt (202) with two equivalents of phosphorus pentoxide in acetone at room temperature for 12 h. Whilst the phosphorous pentoxide can certainly function as a dehydrating agent, it was clear to us that the proton which is necessary to catalyse formation of 1,3-dioxan

derivative can only come either from hydrobromide salt or through the presence of adventitious water which would lead to the formation of phosphoric acid. Sadly, in spite of repeated attempts in the presence and absence of some additional water, the ^{1}H nmr of the crude reaction mixture failed to reveal the expected singlets between 1.5 - 2.0 δ corresponding to the incorporation of the *gem*-dimethyl group in (203). The crude "yield" in reactions was always in excess of 100% and we therefore considered that we were plagued by problems of self condensation of acetone which also made isolation of any product extremely difficult.

Several of the other variants which we tried, all of which were uniformly unsuccessful are collected in Table 12 below.

Entry	Reagents and Conditions	Literature Reference
1	(2 eq) P_2O_5, acetone, rt, 12 h.	Weinges[121]
2	(2 eq) P_2O_5, acetone, H_2O (1 mL), rt, 12 h.	–
3	I_2, acetone, rt, 16 h.	Kartha[123]
4	PPTS (cat.), acetone, rt, 16 h.	–
5	$(MeO)_2C(CH_3)_2$, PPTS (cat.), acetone, rt, 12 h	–
6	$(MeO)_2C(CH_3)_2$, (1.1 eq) PPTS, DMF, 40 °C	Kitamura[124]
7	$(MeO)_2C(CH_3)_2$, (2 eq) P_2O_5, rt, 72 h – 7 days	–

Table 12

Thus far, all of our attempts to furnish the acetonide (203) were unsuccessful. Since the formation of a 1,3-dioxan derivative with acetone necessarily leads to steric

hindrance because of the introduction of an axial methyl group, we decided to use the alternative optically active (2*R*,4*S*,5*S*)-(+)-5-amino-2,4-diphenyl-1,3-dioxan (205) to provide our much needed chiral auxiliary (206). Weinges and co-workers had also reported the synthesis of this optically active 1,3-dioxan (205) *via* the cyclisation of N-protected 1,3-propanediol (202) with benzaldehyde and isolated the required chiral 1,3-dioxane (205) in a yield of 87% (Scheme 72).[121]
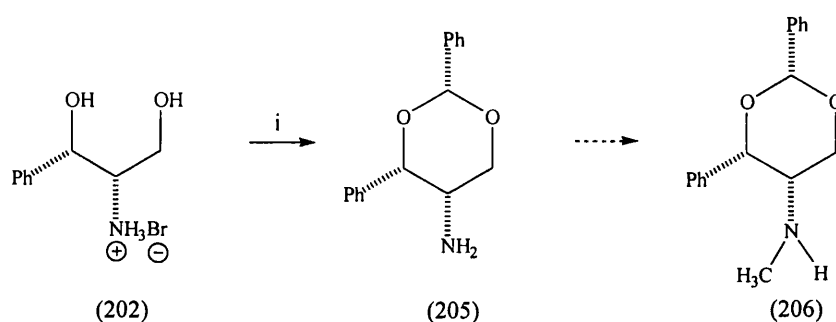
Scheme 72: Reagents and Conditions
i) Benzaldehyde, (2 eq) P_2O_2, rt, 16 h, 87%.

We therefore attempted to prepare (2*R*,4*S*,5*S*)-(+)-5-amino-2,4-diphenyl-1,3-dioxane (205) as described by Weinges *et al.*[120,121] by treatment of the hydrobromide salt (202) with two equivalents of phosphorus pentoxide in the presence of an excess of benzaldehyde at room temperature for 16 h under the described conditions. Surprisingly under these conditions we isolated the derived imine (207) in 82% yield (Scheme 73).
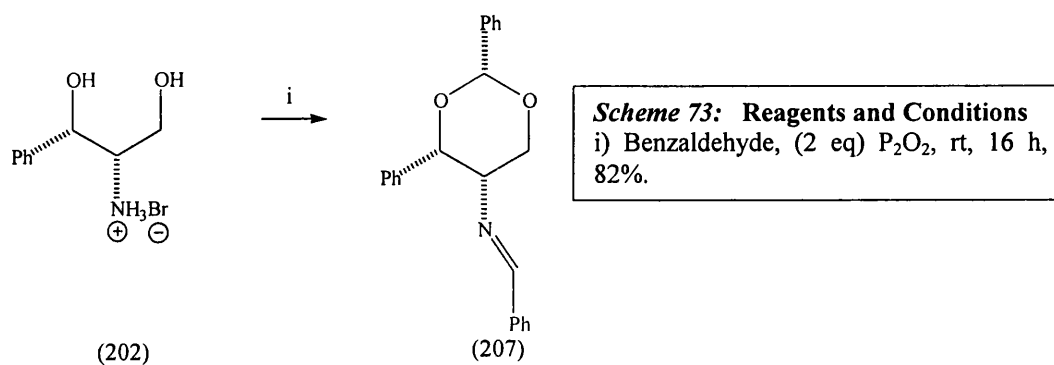
Scheme 73: Reagents and Conditions
i) Benzaldehyde, (2 eq) P_2O_2, rt, 16 h, 82%.

We were initially surprised since Weinges and co-workers did not mention the formation or the isolation of imine (207) *via* their procedure.[121] In their described method of cyclisation, the amine was regenerated and the excess of benzaldehyde was removed by steam distillation. Clearly however, during the course of our distillation, imine hydrolysis did not occur.

We also attempted to generate (2*R*,4*S*,5*S*)-(+)-5-amino-2,4-diphenyl-1,3-dioxane (205) by cyclising the hydrobromide (202), with only 1 equivalent of benzaldehyde using 2 equivalents of phosphorus pentoxide and a number of different solvent systems including acetonitrile, benzene and DCM. Disappointingly, all of these reactions failed to generate the required chiral 1,3-dioxane (205) owing partly to the insolubility of the *N*-protected 1,3-propanediol (202) in the solvents studied, and this line of investigation was discontinued.

We reasoned that the low solubility of the primary amine salt (202) in most organic solvents was partly responsible for its lack of reactivity. Therefore, we decided to focus on alternative and useful protecting groups with the criteria that they should preferentially mask the primary amine functionality in the presence of alcohol functionality.

Our first candidate was the formamide (208) (Scheme 74), since we were aware that this derivative was eventually prepared for reduction by lithium aluminum hydride. Moreover, we were aware that, even if formate esters of the diol were produced, these could be easily transesterified by methanol in the presence of a formamide.

(201)   (208)
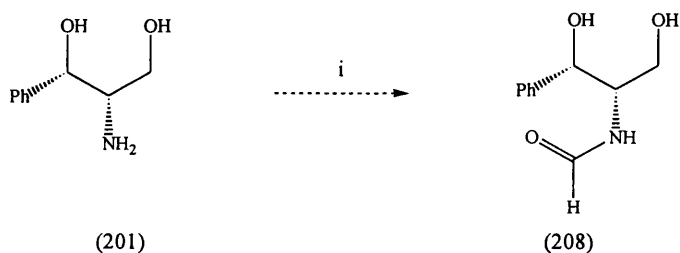
Scheme 74: Reagents and Conditions
i) Ethyl formate, reflux.

Unfortunately, our attempts to *N*-formylate the primary amine functionality by refluxing (1*S*,2*S*)-(+)-2-amino-1,3-propanediol (201) either in neat or mixed ethyl formate-acetonitrile systems were to no avail.

We also attempted to utilise the popular, 9-fluorenylmethyoxycarbonyl amino-protecting group (FMOC).[125]

Under the conditions described by Carpino and Han, using FMOCCl, and sodium bicarbonate (10%) in dioxane, the primary amine functionality was indeed protected.[125] The FMOC derivative however was only an intermediate and subsequent nucleophilic attack on the carbamate function (209) by the two hydroxyl groups (*via* routes 1 or 2) generated a mixture of oxazolidinones as shown in Scheme 75.

(201)   (209)   (210)   (211)
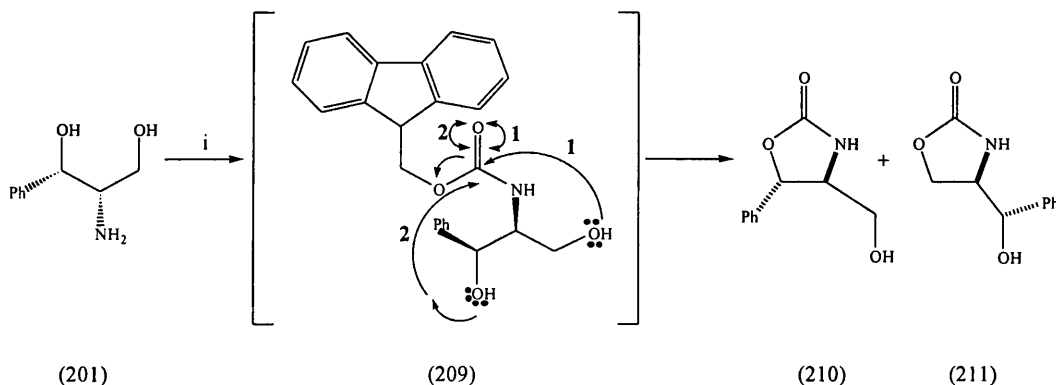
Scheme 75: Reagents and Conditions
i) FMOCCl, (10%) NaHCO₃, 1,4-dioxane.

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Finally, simple practical considerations won the day and the cyclisation of the hydrobromide salt (202) was attempted again using 1,3-propanediol (202), 1.1 equivalents of 2,2-dimethoxypropane, and a substoichiometric quantity of PPTS in 1,4-dioxane as the crucial solvent. The reaction was performed at room temperature (*ca.* 24 °C) for 12 h. It was the solubility of (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (201) in dioxane, as revealed in the process of protecting the amine (201) with the FMOC group, which prompted us to repeat the cyclisation reaction. To our delight, the expected 1,3-dioxane (203) was finally isolated in a yield of 52% in a reaction which was clean by tlc. The subsequent *N*-formylation of the (4*S*,5*S*)-(+)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxane (203) was performed by refluxing the substrate in ethyl formate to afford the *N*-formyl 1,3-dioxane (204) in quantitative yield and this was used without further purification. The final lithium aluminum hydride reduction of the *N*-formyl 1,3-dioxane (204) then furnished the Enders chiral auxiliary (193) in an isolated yield of 79% (Scheme 76) and with an overall yield of 41% from commercially available (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (201).

(202)   (203)   (204)   (193)
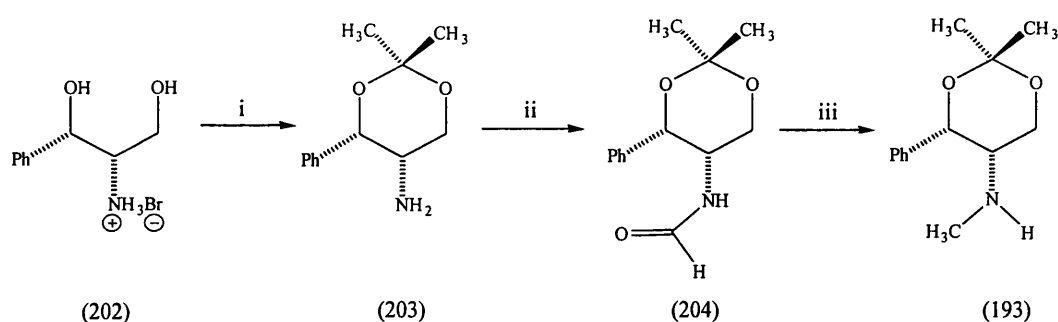
Scheme 76: **Reagents and Conditions**
i). (CH₃)₂C(OMe)₂, 1,4-dioxane, PPTS (cat.), rt, 12 h, 52%: ii) ethyl formate, reflux, 16 h, 100%; iii) LiAlH₄, Et₂O, 0 °C, 4 h then rt for 16 h, 79%.

2.7.1.2 Attempted Synthesis of the Diyne Fragment (197)

With the precious chiral auxiliary (193) and the elaborated aldehyde (200) in hand, we then embarked on the preparation of the α-amino nitrile (197) (Scheme 77).

(193)   (200) R = SiMe₃
         (212) R = H

(197)

Scheme 77

Under the conditions described by Enders and co-workers for the synthesis of α-amino nitriles,[111-115] the chiral auxiliary (193) and the elaborated aldehyde (200) were treated with potassium cyanide in aqueous methanol (10%) at room temperature (*ca.* 22 °C) and the pH of the medium was carefully maintained between 4 and 5.[111-115] Under these conditions the expected α-amino nitrile (197) was not generated, the chiral auxiliary (193) was recovered intact and the only product was terminal alkyne (212). Although a number of methods are available to perform desilylation of protected alkynes we were unaware that potassium cyanide in methanol (*ca.* 22 °C) could also actively promote this reaction. In the hope that the palladium catalysed coupling reaction could be performed after the formation of the α-amino nitrile, the

reaction was then repeated with 2-iodo-3,4,5-trimethoxybenzaldehyde (111) and the chiral auxiliary (193) under the same conditions described by Enders et al.[111-115]

However, once again, no coupling product was isolated. Aidhen and Narasimhan synthesis of α-morpholinoacetonitrile, the advanced precursor in Raphael's synthesis of steganone (6),[17] prompted us to repeat the coupling reaction under conditions described by Narasimhan. The aldehyde (111) and chiral auxiliary (193) were also treated under the conditions described by Narasimhan and Aidhen[17] using potassium cyanide, and 1 equivalent of hydrochloric acid in aqueous methanol (10%). The mixture was refluxed for 12 h. This reaction was also repeated with a higher percentage of methanol (50%) to improve the solubility of 2-iodo-3,4,5-trimethoxybenzaldehyde (111). Sadly, no α-amino nitrile product was isolated in any of these attempts.

Originally when we planned our approach to the diyne precursor (196), the presence of a flanking substituent *ortho*- to the aldehyde functionality in the aromatic ring was not foreseen to introduce any problems. In retrospect however, it is clear that the 109° angle of approach of the amine to the aldehydic carbonyl can suffer from severe steric congestion (Scheme 78).

Scheme 78

133
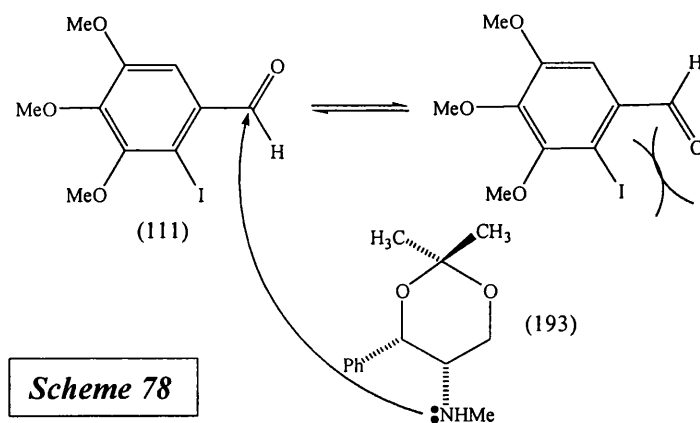
Indeed, a careful search of the literature prior to embarking on the synthesis of the α-amino nitrile (197) revealed no examples from the Enders group in which the chiral auxiliary (193) was successfully reacted with an ortho substituted aromatic aldehyde. We accordingly decided to replaced the iodine atom by the sterically less demanding bromo-substituent using 2-bromo-3,4,5-trimethoxybenzaldehyde (213) as the aldehyde component which was simply prepared by the addition of a solution of bromine in carbon tetrachloride to a refluxing solution of the aldehyde (97) in carbon tetrachloride and isolated in a yield of 60%.[126] The synthesis of the Enders α-amino nitrile (214) was then attempted under the conditions previously described for the iodo-derivative (Scheme 79 and Table 13), but no evidence was adduced once again for formation of the desired product.

(193)   (213)   (214)
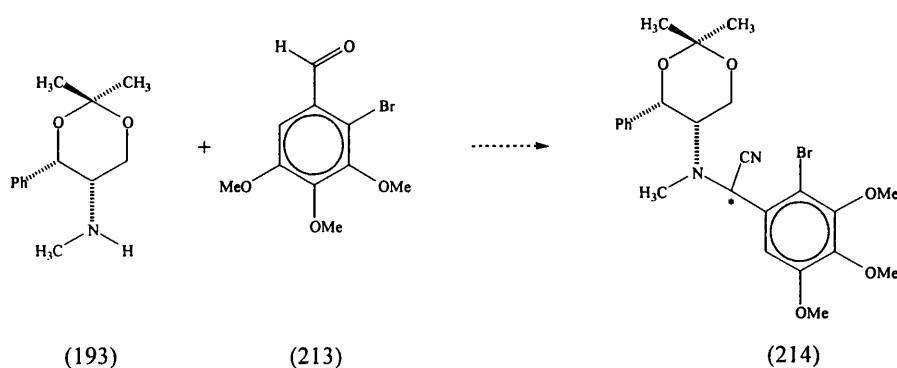
Scheme 79

Entry	Reagents and Conditions	Yield (%)
1	KCN, aq methanol (10%), pH 4-5, reflux, 12 h	0
2	KCN, aq methanol (10%), pH 6, reflux, 12 h	0
3	KCN, aq methanol (50%), pH 6, reflux 12 h	0

Table 13

In the formation of the α-amino nitrile, the first step of the mechanism is the

formation of the carbinolamine (215) followed by loss of water to give the iminium

salt. This then reacts with the cyanide to give the α-amino nitrile (Scheme 80).[127]

(213)   (193)   (215)

**Scheme 80**
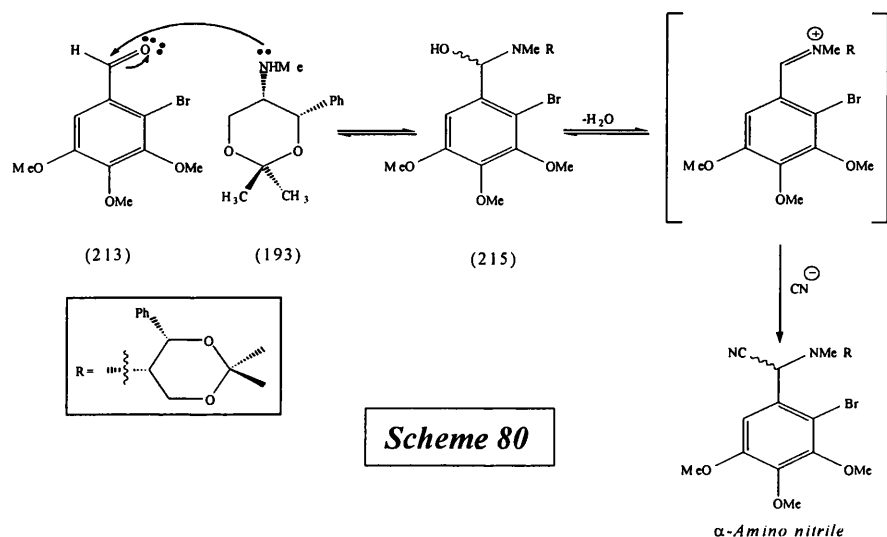
α-Amino nitrile

It is clear that the conditions under which our reactions were performed did

not favour the formation of the iminium salt and we therefore attempted to generate

the α-amino nitrile *via* a further number of alternative approaches as shown in Table

14.

Entry	Reactions and Conditions	Yield (%)
1	Aryl bromide (213), chiral auxiliary (193), KCN, 4 Å molecular sieves, DCM, rt, 12 h	0
2	Aryl bromide (213), chiral auxiliary (193), KCN, NaHSO₃, MeOH (50%), rt, 12 h	0
3	Aryl bromide (213), chiral auxiliary (193), KCN, 18-crown-6, MeCN, rt, 12 h	0
4	i) Aryl bromide (213), chiral auxiliary (193), 4Å molecular sieves, DCM, rt, 12 h; ii) TMSCN, DCM, rt, 5 h	0

Table 14

A range of α,β-unsaturated aldehydes were reported to be converted to the corresponding imines by Roelofsen and van Bekkum by treating the aldehyde with primary amines in the presence of 4Å molecular sieves in DCM.[128] Removal of any water generated in the formation of the iminium salt should favour the equilibrium to the right. This approach was attempted in Entry 1. α-Amino nitriles have also been generated in quantitative yield by treating aldehydes or ketones with potassium cyanide in an aqueous solution of sodium bisulphate as reported by De Kimpe *et al.*[129] This approach was attempted in Entry 2. The use of 18-crown-6 to produce "naked" cyanide anions which act as strong nucleophiles was also attempted in Entry 3.[130] We finally adopted an approach used by Ojima *et al.*,[131] involving the 1,2-addition of (trimethylsilyl) cyanide (Entry 4). This approach was also unsuccessful.

Of the range of aromatic aldehydes employed by Enders *et al.*, the reaction of piperonal with the chiral auxiliary (193) afforded the corresponding α-amino nitrile (216) in a yield of 79%.[111-115]

| *Piperonal* | (193) | (216) |
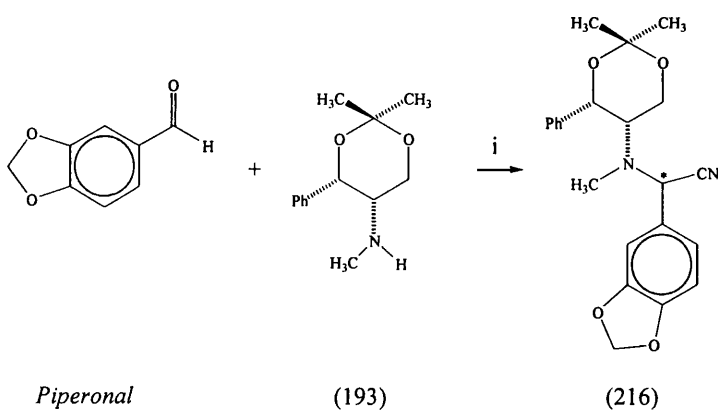
Equation 17: Reagents and Conditions
i). KCN, hydrochloric acid, H$_2$O, pH 4-5, 79%.

Thus we also decided to examine the reactivity of 6-bromopiperonal (217) in the synthesis of the α-amino nitrile. This substrate would of course provide the true northern aromatic ring of steganone (6). 6-Bromopiperonal (217) was simply prepared by the dropwise addition of bromine to a mixture of piperonal in acetic acid and isolated in a yield of 75% (Scheme 81).[27]

(217)
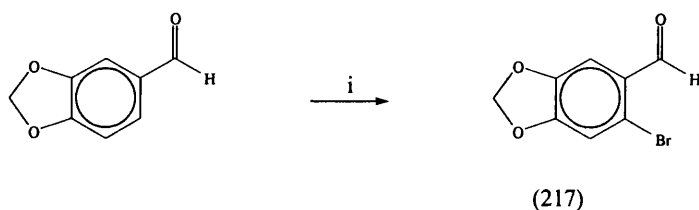
Scheme 81: **Reagents and Conditions**
i). Br_2, acetic acid, rt, 18 h, 75%.

Unfortunately, all of our attempts to procure the α-amino nitrile under the conditions indicated in Table 15 were unsuccessful.

Entry	Reaction and Conditions	Reference
1	KCN, aq. methanol (10%), pH 4-5, rt, 12 h	Enders[111-115]
2	KCN, aq. methanol (10%), pH 6, reflux, 12 h	Narasimhan[17]
3	KCN, aq. methanol (50%), pH 6, reflux, 12 h	Narasimhan[17]

Table 15

In summary, to the best of our knowledge, there are no reported examples in which the Enders chiral auxiliary (193) and an aromatic aldehyde flanked by an ortho-substituent have been reacted to form the corresponding α-amino nitrile. We

can only assume that the failure of the above reactions is firmly routed in the sterically hindered nature of the secondary amine (193), and that the presence of even a single substituent *ortho-* to the aldehyde functionality on the aromatic ring effectively precludes α-amino nitrile formation. This contention is also supported by the chemistry developed in the following section.

2.7.2 *Studies Directed via the α-Morpholinonitrile Approach*

Whilst the preparation of the Enders chiral auxiliary (193) and the efforts to obtain the *ortho* functionalised aromatic α-amino nitriles as described above were in hand, we also decided to follow through the racemic variant of this approach with a view to defining suitable experimental conditions for the key tandem Michael addition / α-alkylation reaction with the butenolide (191).

This decision was taken after examination of the early steps of the Aidhen and Narasimhan formal synthesis of steganone (6) which were published in these authors full paper.[17]

Thus, as shown in Scheme 82, the functionalised biaryl ketones (218) had been assembled using the α-morpholino nitrile (219) derived from 6-bromopiperonal (217).
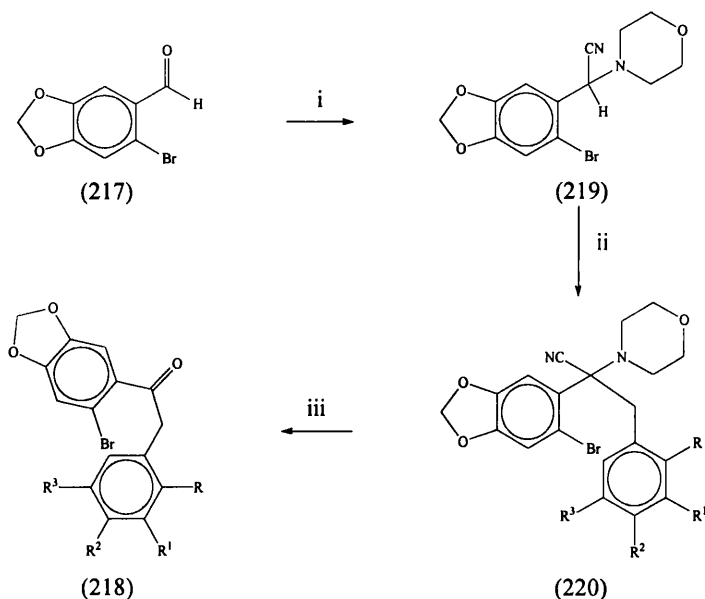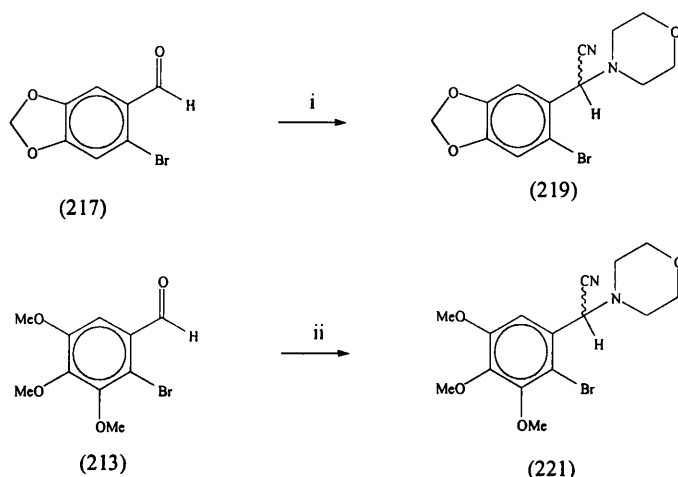
Scheme 82: Reagents and Conditions
i) Morpholine, (10%) aq methanol, 6 N hydrochloric acid, KCN, reflux, 3.5 h, 92%; ii)
a) (1 eq) NaH, DMF; b) substituted benzyl chloride, DMF; iii) crude from step b), 6 N
hydrochloric acid, 70 – 80%.

The very fact that α-(2-bromo-4,5-methylenedioxyphenyl)-α-morpholinonitrile

(219) could in fact be prepared lends added credence, in retrospect, to the idea that

the Enders chiral auxiliary (193) is too hindered to react in its own right as the amine

component.

We therefore set out to reproduce the preparation of (219). Thus, 6-

bromopiperonal (217) was refluxed in a mixture of morpholine (1.1 equivalents)

hydrochloric acid (1.1 equivalents), aqueous methanol (10%) and potassium cyanide

for 12 h. The derived product (219) was isolated in a yield of 54%.[17] The reaction

was then repeated and the percentage of methanol increased to 50%, to effectively

improve the solubility of the aldehyde derivative (217).[132] This simple alteration

improved the isolated yield of (219) to 89%. In similar fashion, 2-bromo-3,4,5-

trimethoxybenzaldehyde (213) was refluxed in a mixture of morpholine (1.1

equivalent) hydrochloric acid (1.1 equivalent), aqueous methanol (50%) and potassium cyanide for 12 h to afford the corresponding α-morpholinonitrile (221) isolated in a yield of 77% (Scheme 83).


(217) → i → (219)

(213) → ii → (221)

Scheme 83: Reagents and Conditions
i) Morpholine, (50%) aq methanol, 6 N hydrochloric acid, KCN, reflux, 48 h, 89%; ii) morpholine, (50%) aq methanol, 6 N hydrochloric acid, KCN, reflux, 48 h, 77%.

With these substrates in hand, we then set out to introduce the necessary alkyne unit. Elaboration of both of the α-morpholinonitriles (219 and 221) *via* the Stephens-Castro methodology[55] using bis(triphenylphosphine)palladium(II) chloride, (trimethylsilyl)acetylene and copper(I) iodide in TEA at 50 °C failed. The failure was in part due to partial solubility of the α-morpholinonitrile substrates (219 and 221) in TEA. Diethylamine has also been employed in such alkynylation reactions and can act as a replacement for TEA as both base and solvent.[118a] Disappointingly, both substrates (219 and 221) were insoluble in diethylamine. Further efforts were made using TEA (2 equivalents) in three different solvents, DCM, THF and benzene. However, the required products were not formed under these conditions.

Further examination of the literature revealed a very interesting paper by Hobbs who had reported the transformation of a variety of iodonucleosides to their corresponding alkynylamino nucleosides which were subsequently used for enzymatic or chemical labelling of all four bases of DNA (Scheme 84).[134]


(222)   (223)

X = NH$_2$
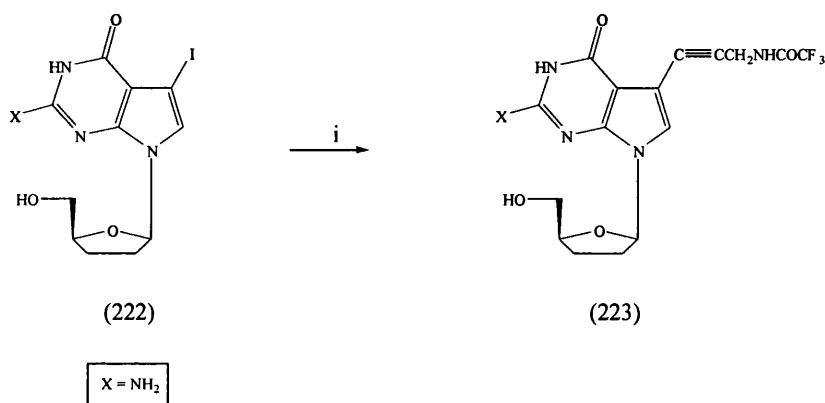
Scheme 84: Reagents and Conditions
i) (3 eq) HC≡CCH$_2$NHCOCF$_3$, (10 mol%) (Ph$_3$P)$_4$Pd, (5 mol%) CuI, TEA, DMF (10 mL), rt, 4 h, 78%.

We noted that Hobbs had also attempted to perform the alkynylation by employing bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide with the appropriate terminal alkyne in TEA and that these conditions had also failed to generate the required product, owing, in part, to the insolubility of the iodonucleoside in TEA.[134] Further work however, had revealed that treatment of the iodonucleosides with tetrakis(triphenylphosphine)palladium(0), copper(I) iodide and the terminal alkyne in DMF successfully furnished the alkynylamino nucleosides with commendable yields. Hobbs attributed the success of this coupling reaction as primarily due to the profound influence of the solvent DMF, and also to the change of palladium(0) source.[134]

We were encouraged by these observations and therefore decided to apply modified reaction conditions to the case of our α-morpholinonitriles (219) and (221). Thus the palladium(0) catalyst was generated *in situ* from palladium acetate and triphenylphosphine in triethylamine, and five equivalents of (trimethylsilyl)ethyne in DMF as solvent at 50 °C. The ratio of palladium acetate to triphenylphosphine 1:≅2. To our delight, as shown in Scheme 85, when a solution of α-morpholino nitrile (219) in DMF was added dropwise to the preformed palladium(0) species and the reaction mixture was then heated at 50 °C for 48 h, the desired arylalkyne (224) was isolated in 69% yield.

(219) i (224)
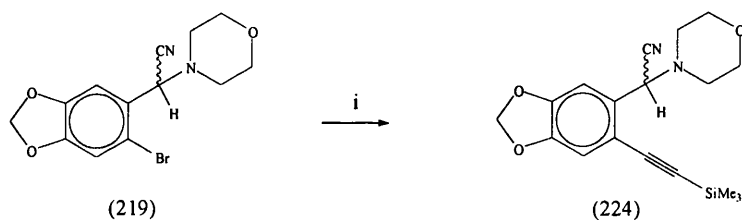
Scheme 85: Reagents and Conditions
i) Pd(OAc)₂, PPh₃, TEA, (trimethylsilyl)ethyne, DMF, 50 °C, 48 h, 69%.

Unfortunately, in the case of the sterically more congested trimethoxy derivative (221), even although the reaction time was extended to seven days, it could not be driven to completion and this problem was exacerbated by the fact that the starting material and product had identical R_f values and these were isolated as an inseparable mixture (Scheme 86). At the present time, evidence for product formation comes from ^{1}H nmr spectrum which exhibits signals at 6.97 (Ar*H*), 5.07

(NC*H*), 3.85 (OC*H*₃), 3.77 (OC*H*₃), 3.74 (OC*H*₃), 3.58 (C*H*₂OC*H*₂), 2.59

(C*H*₂NC*H*₂), 0.27 (Si*Me*₃) corresponding to the derived product (225) in Scheme 86.

(221)   (225)   +   *Starting material*
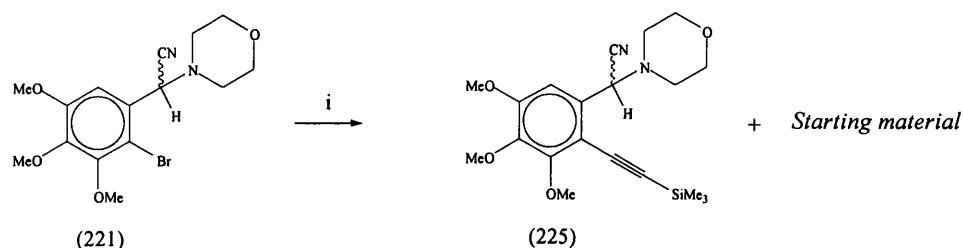
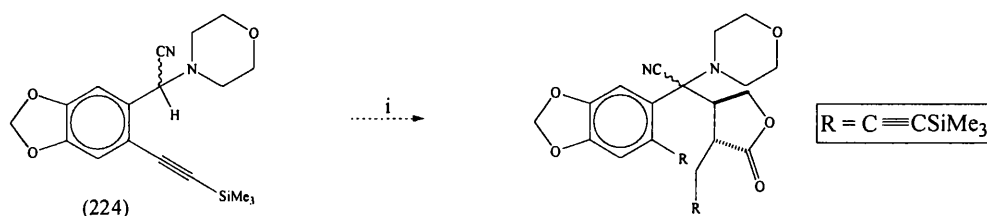**Scheme 86: Reagents and Conditions**
i) Pd(OAc)₂, PPh₃, TEA, (trimethylsilyl)ethyne, DMF, 50 °C, 48 h – 7 days,
mixture of (221) and (225).

With the three components for the tandem Michael addition / α-alkylation step

now available, our efforts were directed towards this crucial step (Scheme 87).

(224) $R = C \equiv CSiMe_3$

Scheme 87: Reagents and Conditions
i) (1.0 eq) LDA, THF, –78 °C, then at –35 °C added butenolide (191), 1 h, then
added 3-bromo-1-(trimethylsilyl)-1-propyne (198).

Our first efforts were based on our familiarity with the generation of the γ-

lactone enolate from (94) and its alkylation with the benzylic bromide (92) which

was used for the stereoselective formation of the diyne (91) in the original racemic

route (Scheme 27, p. 58). Thus the α-morpholinonitrile (224) was treated with 1

equivalent of freshly prepared lithium diisopropylamide at –78 °C, whereupon the

reaction mixture acquired a deep red colouration.[17] The temperature of the reaction was then elevated to −35 °C and 1 equivalent of butenolide (191) was added slowly followed by the addition of 3-bromo-1-(trimethylsilyl)-1-propyne (198). Both in this reaction, and in a subsequent attempt, the starting α-morpholinonitrile (224) was recovered in 95% yield.

Efforts were also made to carry out the reaction using 1.1 equivalents of sodium hydride in DMF at room temperature as described by Narasimhan[17] *vide supra* (Equation 1, p. 34) but these were similarly unrewarding.

Further perusal of the literature then revealed that a very similar type of reaction had been carried out by Ishibashi and co-workers in their synthesis of podophyllotoxin derivatives (Scheme 88).[135,136] It was of particular interest to note that this group had used a reasonably congested *O*-ethoxyethyl cyanohydrin and that the addition of two equivalents of HMPA was also considered to be very important in order to achieve high yields of product in the tandem sequence.

(226)   (227)   (228)

(229)

Scheme 88: Reagents and Conditions
i) a) (1.0 eq) LDA, THF, −78 °C, then added butenolide (191),
2 h, 57%.
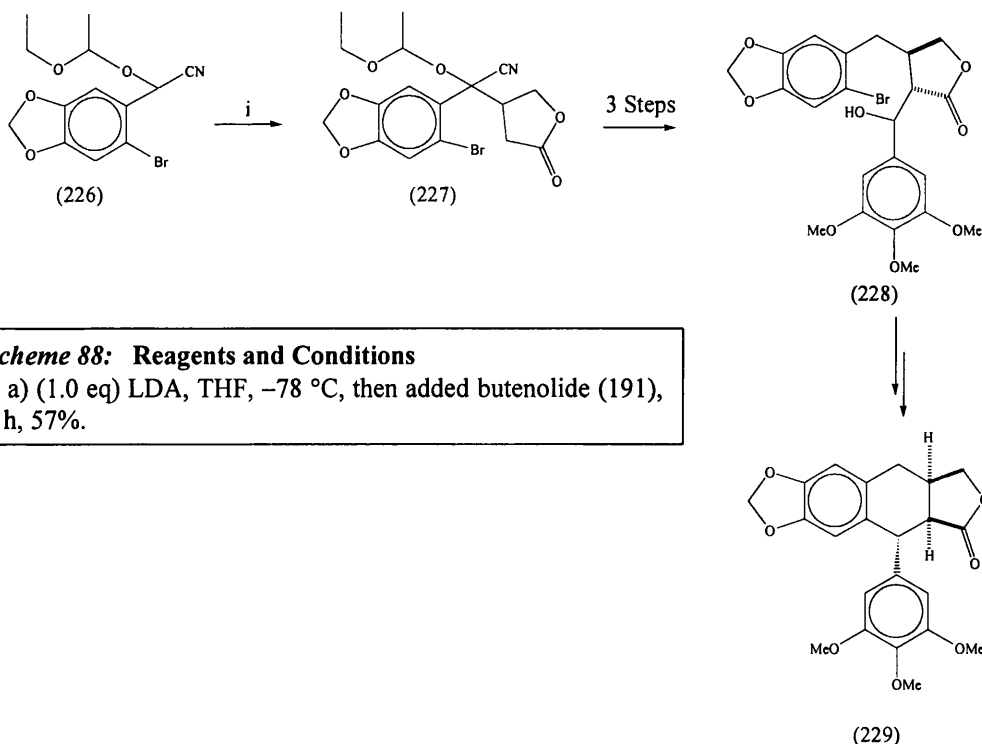
In terms of literature analogy it is also pertinent to note that the tandem sequence developed by Enders *vide supra* (Scheme 67, p 120) also requires the addition of HMPA for a successful outcome.

Accordingly, the α-morpholinonitrile (224) was treated with 1 equivalent of lithium diisopropylamide and 2 equivalents of HMPA at −78 °C. The temperature of the reaction was then raised to −35 °C and 1 equivalent of butenolide (191) was added. Work-up of the reaction at this stage led to the formation of no less than six closely running spots on analytical tlc, and subsequent chromatography allowed the recovery of some unreacted α-amino nitrile (224) (24%). There was no evidence however, for the formation of the desired Michael adduct, and, with some 76% of the starting α-morpholinonitrile (224) unaccounted for, it was essential to try and determine the stability range of the acyl anion equivalent formed on deprotonation.

Thus, the α-aminonitrile (224) was treated with 1 equivalent of lithium diisopropylamide in the presence of two equivalents of HMPA at −78 °C, and the temperature was then raised to −35 °C and stirring was continued for one hour, prior to quenching the reaction mixture with ammonium chloride. Under these conditions, the starting α-morpholinonitrile (224) was recovered in 92% yield, thereby confirming that the anion was indeed sufficiently stable at this temperature.

From the foregoing attempts to achieve the tandem Michael addition / α-alkylation approach to a novel diyne precursor (196), it is clear that we have reached a stage which is often encountered in anionic chemistry where there is a delicate balance between carbanion generation, stability and reactivity, and this is especially true in tandem or cascade sequences. It may still be that there are a series of temperature windows through which the various carbanions can be controlled to yield the desired product. The indication at this moment is that it is the instability of the γ-

lactone enolate at -35 °C which is problematic. Unfortunately, at this stage, because of time constraints, further experimental work in this direction was not possible.

2.8 Summary and Perspectives

The work described in this thesis leads to the speculation that many new and improved reactions are still required for organic synthesis.

While some improvements were made in the racemic route to steganone analogues, a need still exists for an alternative to the cobalt chemistry developed by Vollhardt, particularly in terms of developing more labile ligands than carbon monoxide and also in terms of devising an active catalyst which can operate effectively in more hindered environments.

In terms of asymmetric synthesis, even although we were able to improve on the yield obtained by Crawforth and Rawlings, it is clear that the number of steps required to a relatively small chiral fragment can often be considerable. In terms of paraconic acid itself, an interesting approach would be to examine the copper catalysed addition of an aryl or vinyl group to butenolide in the presence of chiral catalysts and to complete the synthesis by simple ozonolysis. Another alternative could be to explore the asymmetric conjugate addition of cyanide anion.

For the chiral acyl anion equivalent it is also necessary to develop a less sterically demanding amine component in the α-amino nitrile such as perhaps the enantiomers of 2,5-dimethylpyrolidine.

The tandem Michael addition / α-alkylation approach, although thus far to be achieved is beginning to show some signs of promise inasmuch as the problem seems

to reside in the stability of the γ-lactone enolate at the temperatures which have been investigated thus far.

As always, in organic synthesis, for every problem encountered, it is always possible to suggest a variety of alternative strategies and tactics. The only remaining requirements are time and perseverance.

Chapter 3

Experimental

3.1 General Procedures

Infrared spectra were recorded in wavenumbers (cm^{-1}) on a Perkin Elmer 1605 FT-IR spectrometer using sodium chloride plates or a potassium bromide disc as appropriate. ^{1}H NMR spectra were recorded at ambient temperature, at 400 MHz on a Varian VXR 400 or a Bruker AMX 400, or at 300 or 500 MHz on a Bruker, AMX 300 or ADVANCE 500 respectively. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AMX 300. Unless otherwise stated all, NMR spectra were run in CDCl$_3$. Chemical shifts are expressed in parts per million (δ) relative to the internal reference: the residual peak, i.e. CHCl$_3$ (δ_H=7.27) and the CDCl$_3$ triplet (δ_C=77.0). Coupling constants (J) were measured in Hertz (Hz). Optical rotations were measured using a PolAAr 2000 at ambient temperature (*ca.* 22 °C). Measurements were made in the solvent specified in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded by FAB on a VG ZAB–SE double focusing instrument. Melting points were recorded on a Reichert hot stage melting point apparatus and are uncorrected.

Analytical thin layer chromatography (tlc) was performed on aluminium-backed plates (Merck Kieselgel 60 F$_{254}$). Compounds were visualised using ultraviolet light (254 nm), anisaldehyde, 2,4-dinitrophenylhydrazine, iodine vapour, ninhydrin, alkaline potassium permanganate(VII) or vanillin as appropriate. Preparative column chromatography was performed at low positive pressure using Merck Kieselgel 60 (230-400 mesh).

"Petrol" refers to petroleum–ether (b.p. 40-60 °C). Diethyl ether, referred to as ether and THF were distilled immediately prior to use from sodium benzophenone ketyl under an atmosphere of nitrogen. Dichloromethane was distilled from calcium

hydride, benzene and toluene from sodium wire under an atmosphere of nitrogen. Diethylamine, DIPA, DIPEA, and TEA were distilled from potassium hydroxide pellets and stored over potassium hydroxide pellets. Pyridine was distilled from potassium hydroxide pellets and stored over type 4Å molecular sieves. Acetone was dried with anhydrous calcium sulphate, distilled, and stored over type 4Å molecular sieves. Other reagents were purified using literature procedures,[137] or were used as purchased.

[2+2+2] cycloaddition reactions involving irradiation were carried out with a 500 W tungsten lamp placed at a distance of 15 cm from the filament of the bulb to the centre of the reaction vessel. Slow addition of solutions was achieved by use of a mechanically driven syringe-pump.

All glassware was flame-dried under a stream of nitrogen immediately prior to use. Unless otherwise stated all reactions were carried out under a nitrogen atmosphere.

3.2 Preparation of individual compounds

Preparation of Diethyl-2-methanoylbutan-1,4-dioate (106)

(106a)   (106b)
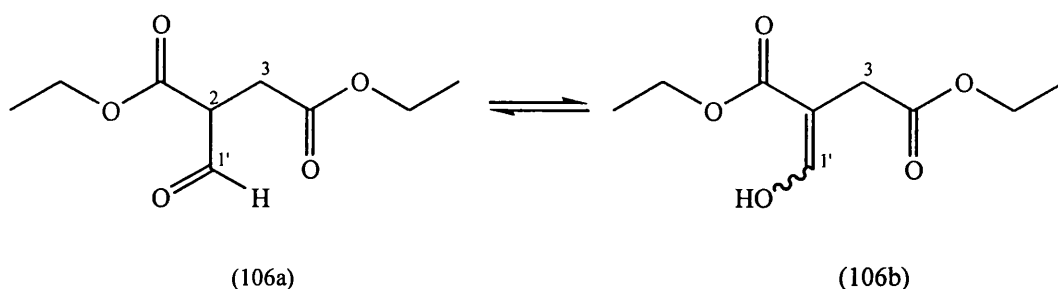
Finely cut sodium (8.46 g, 368 mmol) was added to a solution of diethyl succinate

(48.16 g, 277 mmol) and ethyl formate (31.18 g, 421 mmol) in ether (500 mL). After

the addition of ethanol (0.5 mL) the mixture was stirred mechanically at ambient

temperature for 16 h. Water (500 mL) was added to the resulting viscous orange

mixture and the stirring was continued until the dissolution of the suspended solids.

After separation, the aqueous layer was acidified with 1.0 N hydrochloric acid and

extracted with ether (3 × 250 mL). All organic extracts were combined, washed with

sat. aq $NaHCO_3$ (750 mL), brine (750 mL), dried ($MgSO_4$) and evaporated under

reduced pressure to obtain a viscous oil. On distillation (98-101 °C, 1.5 mmHg) (lit[39]

135-138 °C, 14 mmHg) (106) (24.58 g, 44%) was obtained as a colourless oil; NMR

(400 MHz, $CDCl_3$) indicated a 1:1 mixture of keto (106a) and enol (106b) forms δ_H

9.94 (<1H, s, H-1' of (106a)), 7.09 (<1H, d, J=12.7, H-1' of (106b)), 4.28 (<2H, q,

J=7.1, ethyl CH_2 of (106a) or (106b)), 4.24 (<2H, q, J=7.1, ethyl CH_2 of (106a) or

(106b)), 4.15 (<2H, q, J=7.1, ethyl CH_2 of (106a) or (106b)), 4.14 (<2H, q, J=7.1,

ethyl CH_2 of (106a) or (106b)), 3.80 (<1H, m, H-2 of (106a)), 3.07(<2H, s, H-3 of

(106b)), 2.94 (<1H, dd, J=17.5, 6.1, H-3 of (106a)), 2.87 (<1H, dd, J=17.4, 6.2, H-3

of (106a)), 1.28 (13H, 2 × CH_3 of (106a), 2 × CH_3 of (106b) and OH of (106b)); ν_{max} (NaCl, film) 3339 (w, O-H), 2984 (w), 1736 (s, C=O), 1673 (s, C=O), 1373 (m), 1179 (vs), 1099 (s), 1030 (s) cm^{-1}; *m/z* (FAB) 203 (MH$^+$, 81%), 157 (100%), 129 (70%); Found: [M+H]$^+$, 203.0910. C$_9$H$_{15}$O$_5$ requires *M*, 203.0919.

*Preparation of Diethyl-2-hydroxymethylbutan-1,4-dioate (107)*
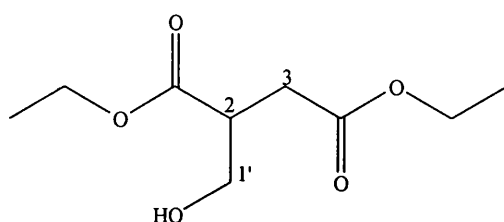
(107)

Sodium borohydride (1.49 g, 39 mmol) was added portion-wise to a stirred solution of (106) (20 g, 99 mmol) in methanol (490 mL) at 0 °C, over a period of 30 min. The mixture was stirred at this temperature for 5 h and allowed to warm to ambient temperature. Approximately two thirds of the solvent was removed under reduced pressure and 1.0 *N* hydrochloric acid (500 mL) was added. The aqueous mixture was extracted with DCM (3 × 500 mL), the organic extracts were combined, washed with sat. aq NaHCO$_3$ (500 mL), brine (500 mL), dried (MgSO$_4$) and evaporated under reduced pressure to obtain a viscous oil. On distillation the alcohol (107) (16.08g, 80%) (106-108 °C, 0.6 mmHg) (lit[39] 153-155 °C, 17 mmHg) was obtained as a colourless oil; NMR (400 MHz, CDCl$_3$) δ_H 4.13 (4H, m, 2 × ethyl CH_2), 3.83 (2H, m, H-1'), 3.01 (1H, m, H-2), 2.71 (1H, dd, J=16.7, 7.1, H-3), 2.61 (1H, dd, J=16.7, 6.6, H-3), 1.26 (6H, m, 2 × CH_3); ν_{max} (NaCl, film) 3522 (br m, O-H), 2984 (m), 1785 (m, C=O), 1733 (s, C=O), 1375 (m), 1175 (s), 1028 (m) cm^{-1}; *m/z* (FAB) 205

(MH$^+$, 37%), 191 (99%), 177 (48%), 159 (93%), 145 (100%), 127 (42%), 113 (14%); Found: [M+H]$^+$, 205.1090. $C_9H_{17}O_5$ requires M, 205.1076.

Preparation of Paraconic acid (95)
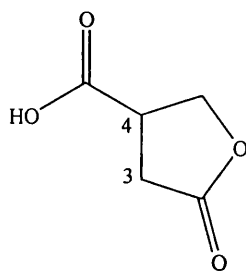
(95)

A solution of 2.75 N sodium hydroxide (40 mL) was added over a period of 1 h to a refluxing solution of the alcohol (107) (6.27 g, 31 mmol) in ethanol (13 mL). Refluxing was continued for a further 30 min. After the solution was allowed to cool to ambient temperature, Amberlite$^{®}$ IR-120 ion exchange resin was added until the solution was acidic (pH 2-3). The mixture was filtered, and the Amberlite$^{®}$ resin was washed with distilled water until the washings were neutral. The filtrate and washings were combined, concentrated under reduced pressure and purified by short path distillation (200 °C, 0.2 mmHg) to give the acid (95) (2.21 g, 55%) as a colourless oil that solidified upon standing to give a white solid, m.p. 58-60 °C (lit[39] 60-63 °C); NMR (300 MHz, CDCl$_3$) δ_H 10.02 (1H, s, CO$_2$H), 4.53 (2H, m, H-5), 3.53 (1H, m, H-4), 2.92 (1H, dd, J=18.0, 6.8, H-3), 2.81 (1H, dd, J=18.0, 9.6, H-3); ν_{max} (KBr) 3462 (s), 3004 (br s, OH), 1774 (br s, C=O), 1386 (m), 1195 (s), 1032 (s), 671 (m) cm^{-1}; m/z (FAB) 131 (MH$^+$, 100%), 113 (22%); Found: [M+H]$^+$, 131.0342. $C_5H_7O_4$ requires M, 131.0344.

Preparation of [(Trimethylsilyl)ethynyl]trimethylstannane (109)

$$Me_3Si \overbrace{\hspace{3cm}}^{\equiv} SnMe_3$$
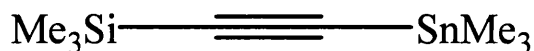
(109)

A 2.47 *M* solution of *n*-butyllithium in hexanes (21 mL, 51 mmol) was added

dropwise over 1 h to a stirred solution of (trimethylsilyl)acetylene (4.93 g, 50 mmol)

in THF (30 mL) at 0 °C. Stirring was continued for a further 30 min, followed by the

dropwise addition of a solution of trimethyltin chloride (10 g, 50 mmol) in THF (5

mL). After stirring for 1 h at 0 °C, the solution was allowed to reach ambient

temperature, and stirred overnight. The reaction mixture was poured into ice water

(100 mL) and extracted with DCM (3 × 100 mL). The combined organic extracts

were washed with brine (300 mL), dried ($MgSO_4$) and evaporated under reduced

pressure. The viscous oil was purified, by short path distillation (59 °C, 10 mmHg) to

give (109) (8.77 g, 67%) as a colourless liquid, that solidified upon standing to give

colourless solid, m.p. 40-42 °C (lit[138] 41-44 °C); NMR (300 MHz, $CDCl_3$) δ_H 0.30

(9H, s, Sn*Me*$_3$), 0.18 (9H, s, Si*Me*$_3$); ν_{max} (NaCl, film) 2957 (s), 2369 (w), 2083

(alkyne, w), 1405 (w), 1247 (s), 847 (s), 784 (s), 696 (s) cm^{-1}.

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

(105)
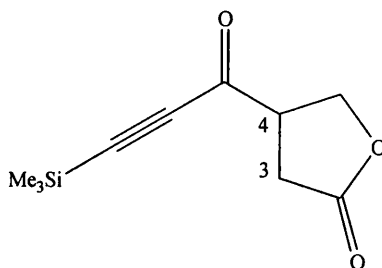
(105)

Method A

Oxalyl chloride (0.5 mL, 5.77 mmol) was added to a stirred suspension of the acid (95) (0.50 g, 3.85 mmol) in DCM (5 mL) followed by DMF (3 drops). After the paraconic acid had dissolved and the effervescence had subsided (*ca.* 1 h) the solvent was removed under high vacuum. The residue was then dissolved in 1,2-dichloroethane (5 mL) and bis(triphenylphosphine)palladium(II) chloride (53 mg, 0.075 mmol) added. To this a solution of [(trimethylsilyl)ethynyl]trimethylstannane (109) (1.20 g, 4.60 mmol) in 1,2-dichloroethane (2 mL) was added dropwise and the resulting mixture was stirred at 50 °C for 16 h. After cooling to ambient temperature and filtering through a pad of Celite®, the solution was poured into water (10 mL). On separation of the layers, the aqueous layer was extracted with DCM (3 × 10 mL). The organic extracts were combined, washed with brine (30 mL), dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, DCM as eluent) to give the ynone (105) (0.52 g, 64%) as a viscous reddish oil[39]; NMR (300 MHz, CDCl₃) δ_H 4.50 (1H, dd, J=9.7, 6.0, H-5), 4.43 (1H, dd, J=9.7, 8.2, H-5), 3.48 (1H, m, H-4), 2.88 (1H, dd, J=18.0, 6.5, H-3),

2.68 (1H, dd, J=18.1, 9.8, H-3), 0.18 (9H, s, SiMe₃); ν_{max} (NaCl, film) 2964 (m),

2151 (w, alkyne), 1783 (s, lactone C=O), 1678 (s, ynone C=O), 1477 (w), 1377 (w),

1415 (w), 1253 (s), 1173 (s), 1126 (s), 1034 (m), 853 (s), 764 (s) cm⁻¹; m/z (FAB)

211 (MH⁺, 100%), 195 (42%), 167 (33%), 137 (26%), 125 (65%); Found: [M+H]⁺,

211.0779. $C_{10}H_{15}O_3Si$ requires M, 211.0790.

Method B

A 2.94 M solution of n-butyllithium in hexanes (2 mL, 5.88 mmol) was added

dropwise to a stirred solution of (trimethylsilyl)acetylene (0.83 mL, 5.87 mmol) in

THF (10 mL) at 0 °C. Stirring was continued for a further 30 min, followed by the

dropwise addition of a 0.71 M solution of zinc chloride in THF (8.20 mL, 5.82

mmol) at 0 °C. The mixture was stirred at room temperature for 10 min and used

immediately.[54]

Oxalyl chloride (0.57 mL, 6.53 mmol) was added to a stirred suspension of the acid

(95) (0.76 g, 5.87 mmol) in DCM (8 mL) followed by DMF (1 drop). Once the

paraconic acid had dissolved and the effervescence had subsided (ca. 1 h) the solvent

was removed under high vacuum. The residue was dissolved in THF (8 mL) and

tetrakis(triphenylphosphine)palladium(0) (0.68 g, 0.59 mmol) added. The solution of

[(trimethylsilyl)ethynyl]zinc chloride (prepared above) was added dropwise and the

resulting mixture was stirred at 26 °C for 12 h. The mixture was filtered through a

pad of Celite® which was washed with ether (10 mL). The combined filtrate and

washings were washed with water (15 mL), sat. aq NaHCO₃ (15 mL), brine (15 mL)

dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by

flash column chromatography (silica, DCM as eluent) to give the ynone (105) (0.56

g, 45%) as a yellow oil.[39]

Preparation of 4,5-Dihydro-4-[2-[(trimethylsilyl)ethynyl]-1,3-dioxolan-2-yl]-2(3H)-

furanone (94)
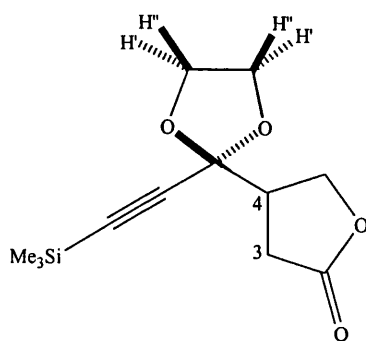
(94)

A mixture of the ynone (105) (1.25 g, 5.95 mmol), pyridinium *p*-toluenesulfonate

(0.27 g, 1.07 mmol) in benzene (30 mL), and ethylene glycol (15 mL, 268 mmol)

was heated under reflux for 12 h with azeotropic removal of water. The solution was

allowed to cool to ambient temperature and poured into sat. aq $NaHCO_3$ (30 mL).

The aqueous and organic phases were separated and the aqueous phase extracted

with ether (2 × 30 mL). The combined organic extracts were washed with brine (60

mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was

purified by flash column chromatography (silica, DCM as eluent) to give the acetal

(94) (1.33 g, 88%) as a pale yellow solid, m.p. 64-65 °C (lit[39] 61.5-64.5 °C); NMR

(300 MHz, $CDCl_3$) δ_H 4.41 (2H, d, J=6.4, 2 × H-5), 4.14 (2H, m, 2 × H' or 2 × H"),

4.02 (2H, m, 2 × H' or 2 × H"), 3.00 (1H, m, H-4), 2.69 (1H, dd, J=17.3, 6.3, H-3),

2.68 (1H, dd, J=17.3, 9.3, H-3), 0.19 (9H, s, Si*Me₃*); v_{max} (KBr) 2958 (m), 2902 (m),

2357 (w, alkyne), 2161 (w), 1770 (s, C=O), 1252 (m), 1175 (w), 1098 (m), 854 (s),

756 (m) cm^{-1}; m/z (FAB) 255 (MH$^+$, 23%), 239 (31%), 169 (100%), 157 (31%), 125

(43%); Found: [M+H]$^+$, 255.1045. $C_{12}H_{19}O_4Si$ requires M, 255.1053.

Preparation of 4,5-Dihydro-4-[(methoxy)carbonyl]-2(3H)-furanone (110)
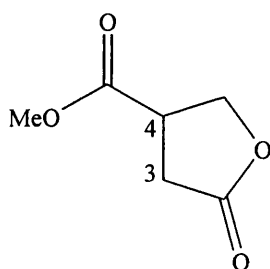

(110)

Oxalyl chloride (0.8 mL, 9.20 mmol) was added to a stirred suspension of the acid

(95) (1.00 g, 7.69 mmol) in DCM (5 mL). DMF (2 drops) was added to this mixture

and once all the paraconic acid had dissolved and the effervescence had subsided (*ca.*

1 h), the solvent was evaporated under high vacuum. The residue was dissolved in

DCM (5 mL), DMAP (0.02 g, 0.16 mmol) added and the mixture was cooled to 0 °C.

Dry methanol (1 mL) followed by pyridine (1 mL) was added dropwise and the

stirring continued at 0 °C for a further 30 min. The reaction mixture was allowed to

reach ambient temperature, diluted with DCM (10 mL), washed with sat. aq copper

sulphate (2 × 15 mL), sat. aq NaHCO$_3$ (15 mL), and brine (15 mL). The organic

extracts were dried (MgSO$_4$) and evaporated under reduced pressure. The viscous oil

was purified by flash column chromatography (silica, 50% ethyl acetate in ether as

eluent) to give the *methyl ester* (110) (0.54 g, 49%) as a colourless oil; NMR (300

MHz, CDCl$_3$) δ_H 4.50 (2H, m, 2 × H-5), 3.78 (3H, s, O*Me*), 3.48 (1H, m, H-4), 2.90

(1H, dd, J=17.7, 7.4, H-3), 2.77 (1H, dd, J=17.9, 9.6, H-3); NMR (75 MHz, CDCl$_3$)

δ_C 172.55, 68.91, 52.61, 39.71, 30.72; ν_{max} (NaCl, film) 3538 (w), 2958 (m), 1782 (s,

C=O), 1736 (s, C=O), 1440 (s), 1362 (s), 1174 (s), 1022 (s), 940 (m), 839 (m) cm^{-1};

m/z (FAB) 145 (MH$^+$, 100%), 137 (37%), 127 (16%), 113 (20%), 107 (16%); Found:

[M+H]$^+$, 145.0503. C$_6$H$_9$O$_4$ requires M, 145.0501.

*Preparation of 2-Iodo-3,4,5-trimethoxybenzaldehyde (111)*
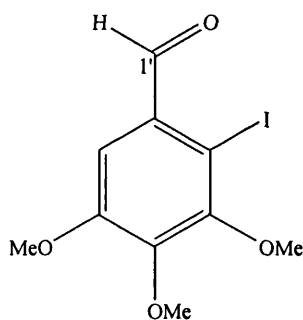
(111)

Silver trifluoroacetate (18.82 g, 85 mmol) was added to a solution of 3,4,5-trimethoxybenzaldehyde (16.70 g, 85 mmol) in DCM (300 mL). A solution of iodine

(23.80 g, 94 mmol) in DCM (400 mL) was added dropwise to this mixture over a

period of 6 h, stirring was continued at ambient temperature for 15 h. The solution

was then filtered through a pad of Celite® which was washed with DCM (50 mL).

The combined filtrate and washings were washed with 1.0 M aq sodium thiosulfate

solution (2 × 500 mL), sat. aq NaHCO$_3$ (500 mL) and brine (500 mL), dried

(MgSO$_4$) and evaporated under reduced pressure. The residue was purified by flash

column chromatography (silica, 30% ether in petrol as eluent) to give the iodide

(111) (24.89 g, 91%) as yellow needles, m.p. 62-64 °C (lit[34] 66-66.5 °C); NMR (300

MHz, CDCl$_3$) δ_H 10.05 (1H, s, H-1'), 7.35 (1H, s, Ar*H*), 3.97 (3H, s, O*Me*), 3.92 (3H,

s, O*Me*), 3.90 (3H, s, O*Me*); ν$_{max}$ (KBr) 2939 (m), 2846 (m), 1684 (s, C=O), 1559

(s), 1458 (m), 1364 (s), 1325(s), 1153 (s), 1103 (s), 991 (s) cm^{-1}; *m/z* (FAB) 323

(MH$^+$, 100%), 307 (19%), 196 (25%); Found: [M+H]$^+$, 322.9789. C$_{10}$H$_{12}$O$_4$I requires

M, 322.9780.

*Preparation of 2-Iodo-3,4,5-trimethoxybenzyl alcohol (93)*
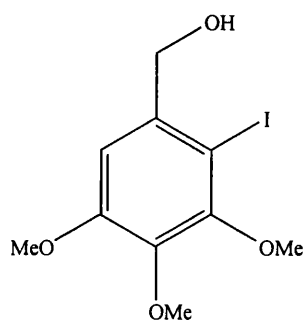
(93)

Sodium borohydride (2.91 g, 77 mmol) was added portion-wise over 1 h to a stirred

solution of the iodide (111) (22.38 g, 70 mmol) in methanol (300 mL) at 0 °C. The

solution was stirred at this temperature for a further 3 h and left at –2 °C for 12 h.

The solution was allowed to warm to ambient temperature and the solvent was

removed under reduced pressure. The residue was acidified with 2.0 *N* hydrochloric

acid (150 mL) and extracted with ether (3 × 300 mL). The combined organic extracts

were washed with sat. aq NaHCO$_3$ (900 mL), brine (900 mL), dried (MgSO$_4$) and

evaporated under reduced pressure. The crude product was purified by flash column

chromatography (silica, 50% ether in petrol as eluent) to give the alcohol (93) (17.79

g, 79%) as white needles, m.p. 55-56 °C (lit[39] 57-58 °C); NMR (300 MHz, CDCl$_3$) δ$_H$

6.92 (1H, s, Ar*H*), 4.65 (2H, s, C*H$_2$*), 3.88 (6H, s, 2 × O*Me*), 3.87 (3H, s, O*Me*), 2.21

(1H, s, OH); ν_{max} (KBr) 3279 (s, O-H), 2939 (m), 1565 (s), 1481 (s), 1391 (s), 1324 (s), 1191 (s), 1158 (s), 1104 (s), 1004 (s), 924 (w) cm^{-1}; m/z (FAB) 324 (M$^+$, 73%), 307 (100%); Found: M$^+$, 323.9863. C$_{10}$H$_{13}$O$_4$I requires M, 323.9859.

Preparation of 2-[(Trimethylsilyl)ethynyl]-3,4,5-trimethoxybenzyl alcohol (112)
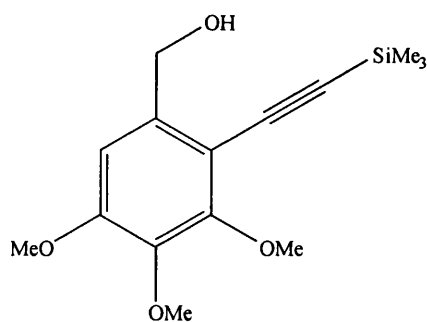

(112)

(Trimethylsilyl)acetylene (1.3 mL, 9.2 mmol) was added dropwise to a stirred suspension of the alcohol (93) (2.00 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 TEA (12 mL). The reaction mixture was warmed to 50 °C and stirred at this temperature for 3 h. After cooling to ambient temperature the reaction mixture was poured into water (25 mL) and extracted with ether (3 × 25 mL). The combined ether extracts was washed with brine (75 mL), dried (MgSO$_4$) and evaporated 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 (112) (1.60 g, 88%) as a pale brown solid, m.p. 69-72 °C (lit[139] 71-73 °C); NMR (300 MHz, CDCl$_3$) δ_H 6.76 (1H, s, ArH), 4.73 (2H, d, J=6.2, CH_2), 3.97 (3H, s, OMe), 3.89 (3H, s, OMe), 3.85 (3H, s, OMe), 2.20 (1H, t, J=6.2, OH), 0.27 (9H, s,

SiMe_3); v_{max} (KBr) 3463 (m, O-H), 2942 (m), 2147 (s, alkyne), 1594 (s), 1488 (s),

1404 (m), 1325 (m), 1250 (m), 1130 (s), 1043 (m), 1020 (m), 860 (m), 841 (s) cm^{-1};

m/z (FAB) 294 (M$^+$, 87%), 277 (100%), 115 (37%); Found: M$^+$, 294.1277.

$C_{15}H_{22}O_4Si$ requires M, 294.1287.

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

(92)

(92)
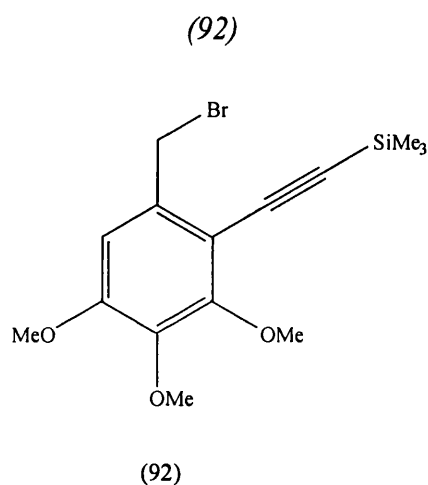
Carbon tetrabromide (4.14 g, 12.6 mmol) was added to a stirred solution of the

alcohol (112) (1.60 g, 5.4 mmol) and triphenylphosphine (3.31 g, 12.6 mmol) in

ether (50 mL). After stirring at ambient temperature for 24 h, the mixture was filtered

through a pad of silica, which was washed with ether (50 mL). The filtrate and

washings were combined and evaporated under reduced pressure. The residue was

purified by flash column chromatography (silica, 20% ether in petrol as eluent) to

give the bromide (92) (1.60 g, 83%) as a buff solid, m.p. 56-58 °C (lit[39] 57-58 °C);

NMR (300 MHz, CDCl$_3$) δ_H 6.73 (1H, s, ArH), 4.63 (2H, s, CH_2), 3.98 (3H, s, OMe),

3.89 (3H, s, OMe), 3.87 (3H, s, OMe), 0.30 (9H, s, SiMe_3); v_{max} (KBr) 2938 (m),

2146 (s, alkyne), 1593 (m), 1453 (m), 1404 (m), 1334 (s), 1243 (s), 1124 (s), 1067

(s), 843 (s) cm^{-1}; m/z (FAB) 357 (MH$^+$, 11%), 277 (100%), 205 (37%); Found: [M+H]$^+$, 357.0531. C$_{15}$H$_{22}$O$_3$^{79}BrSi requires M, 357.0522.

Preparation of (3R*,4R*)-4,5-Dihydro-3-[[3,4,5-trimethoxy-2-
[(trimethylsilyl)ethynyl]phenyl]methyl]-4-[2-[(trimethylsilyl)ethynyl]-1,3-dioxolan-
2-yl]-2(3H)-furanone (91)

(91)
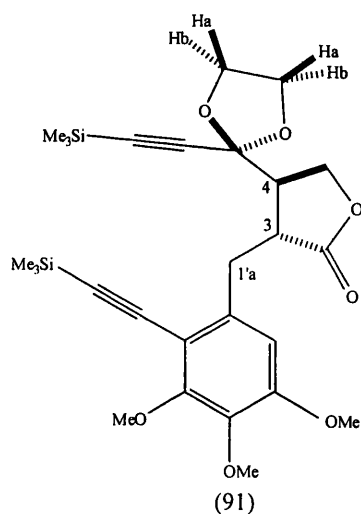
A freshly prepared solution of 1.01 M lithium diisopropylamide in THF/hexanes (2.1 mL, 2.12 mmol) was added dropwise to a solution of the acetal (94) (0.52 g, 2.05 mmol) in THF (10 mL) at −78 °C. After the mixture was stirred at −78 °C for 30 min, the temperature was allowed to rise to −35 °C and a solution of the bromide (92) (0.73 g, 2.05 mmol) in THF (10 mL) was added dropwise. Stirring was continued at −35 °C for 1 h, and the solution was allowed to reach ambient temperature and stirred for a further 12 h. The reaction mixture was quenched with sat. aq ammonium chloride (25 mL) extracted with ether (3 × 25 mL) and the combined extracts were washed with brine (75 mL), dried (MgSO$_4$) and evaporated 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) the recovered

bromide (92) (0.15 g, 21%), and (91) (0.79 g, 73%) as buff needles, m.p. 108-110 °C

(lit[39] 109.5-110 °C); NMR (300 MHz, CDCl$_3$) δ_H 6.60 (1H, s, ArH), 4.40 (1H, dd,

J=9.7, 2.3, H-5), 4.05 (3H, m, H-5, 2 × Ha or 2 × Hb), 3.95 (3H, s, OMe), 3.88 (2H,

m, 2 × Ha or 2 × Hb), 3.86 (6H, s, 2 × OMe), 3.32 (1H, dd, J=17.1, 8.2, H-1'a), 3.11

(2H, m, H-1'a and H-3), 2.95 (1H, dt, J=7.7, 2.3, H-4), 0.27 (9H, s, SiMe_3), 0.16 (9H,

s, SiMe_3); ν_{max} (KBr) 2152 (m, alkyne), 1763 (s, C=O), 1594 (m), 1490 (m), 1377

(m), 1249 (m), 1178 (m), 1121 (m), 1071 (m), 1014 (m), 843 (m) cm^{-1}; m/z (FAB)

531 (MH$^+$, 57%), 397 (34%), 277 (52%), 169 (51%), 125 (100%); Found: [M+H]$^+$,

531.2221. C$_{27}$H$_{39}$O$_7$Si$_2$ requires M, 531.2234.

Preparation of (3R*,4R*)-4,5-Dihydro-3-[[3,4,5-trimethoxy-2-

*ethynyl]phenyl]methyl]-4-[2-ethynyl-1,3-dioxolan-2-yl]-2(3H)-furanone (90)*
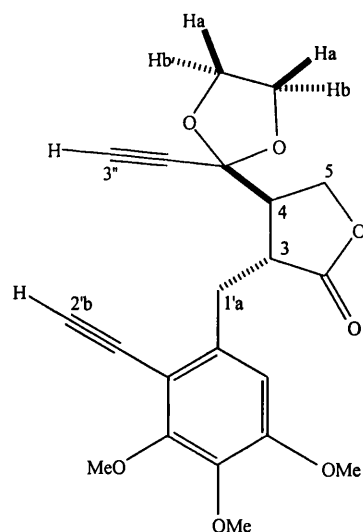
(90)

Anhydrous potassium carbonate (10 mg, 0.072 mmol) was added to a stirred solution

of the (91) (0.34 g, 0.64 mmol) in methanol (5 mL) and the stirring continued at

ambient temperature for 6 h. The reaction mixture was poured into water (10 mL) and extracted with DCM (3 × 10 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 80% ether in petrol as eluent) to give the diyne (90) (0.22 g, 90%) as buff needles, m.p. 89-91 °C (lit[39] 90.5-94.5 °C); NMR (300 MHz, $CDCl_3$) δ_H 6.63 (1H, s, ArH), 4.39 (1H, dd, J=10.0, 3.3, H-5), 4.14 (1H, dd, J=10.0, 7.9, H-5), 4.08 (2H, m, 2 × Ha or 2 × Hb), 3.97 (5H, m, 2 × Ha or 2 × Hb and OMe), 3.86 (6H, s, 2 × OMe), 3.48 (1H, m, H-2'b), 3.33 (1H, m, H-1'a), 3.18 (2H, m, H-1'a and H-3), 2.91 (1H, dt, J=8.0, 3.2, H-4), 2.45 (1H, s, H-3"); v_{max} (KBr) 3280 (s), 2927 (m), 2162 (w, alkyne), 1767 (s, C=O), 1595 (m), 1486 (w), 1404 (m), 1128 (s), 1029 (m) cm^{-1}; m/z (FAB) 387 (MH^+, 100%), 205 (46%), 154 (51%), 136 (50%), 115 (49%); Found: $[M+H]^+$, 387.1438. $C_{21}H_{23}O_7$ requires M, 387.1444.

Attempted Coupling of Paraconic acid (95) and benzyl bromide

(95)

i) (2 eq) LDA , THF/HMPA (10%), then (1 eq) HMPA , −35 °C

ii) (2 eq) Benzyl bromide , −35 °C, 1 h
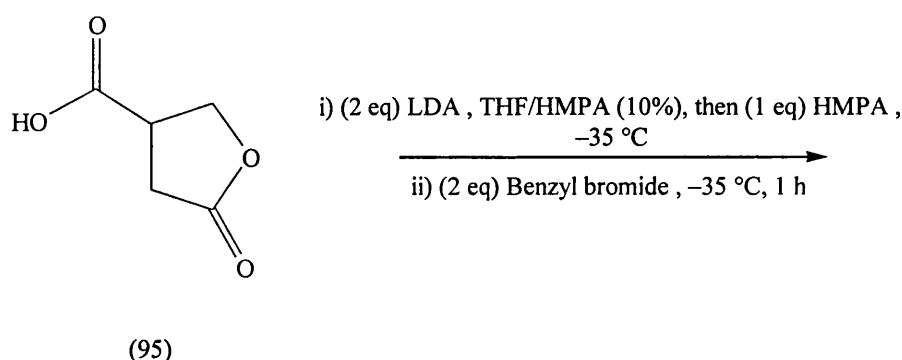
A freshly prepared solution of 1.27 M lithium diisopropylamide in THF/hexanes (15.2 mL, 19.30 mmol) was added dropwise to a solution of paraconic acid (95) (1.25g, 9.62 mmol) in THF/HMPA (10%) (10 mL) at −35 °C. A yellow suspension

formed immediately. HMPA (1.70 mL, 9.77 mmol) was added dropwise and the temperature was maintained at –35 °C. A solution of benzyl bromide (2.30 mL, 19.34 mmol) in THF (10 mL) was added dropwise at –35 °C and the stirring was continued for 1 h. The solution was allowed to reach ambient temperature. It was quenched with sat. aq ammonium chloride (20 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 20% petrol in ether as eluent); the starting benzyl bromide (3.14 g, 95%) was recovered. No coupled product was isolated.

Preparation of 4,5-Dihydro-4-[(trimethylsilyl)carboxylate]-2(3H)-furanone (117)
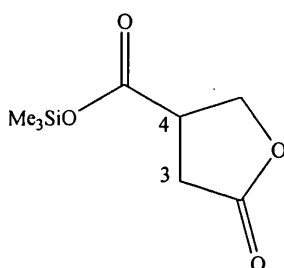

(117)

Paraconic acid (95) (2.51 g, 19.31 mmol) and *N,O*-bis(trimethylsilyl)acetamide (6.2 mL, 25.08 mmol) were heated under reflux for 6 h. After cooling to ambient temperature the reaction mixture was purified by short path distillation (125 °C, 0.08 mmHg) to give the *trimethylsilyl ester* (117) (2.35 g, 60%) as a colourless oil; NMR (300 MHz, CDCl₃) δ_H 4.48 (2H, m, 2 × H-5), 3.42 (1H, m, H-4), 2.85 (1H, dd, J=18.0, 6.8, H-3), 2.73 (1H, dd, J=18.0, 9.5, H-3), 0.31 (9H, s, Si*Me₃*); NMR (75 MHz, CDCl₃) δ_C 175.4, 171.3, 69.1, 41.1, 30.8, -0.5; v_{max} (NaCl, film) 3408 (w),

3238 (w), 2963 (m), 1784 (s, C=O), 1718 (s, C=O), 1365 (s), 1256 (s), 1210 (s), 1174 (s), 1040 (m), 1004 (m), 852 (s) cm^{-1}; *m/z* (FAB) 203 (MH$^+$, 100%), 136 (50%); Found: [M+H]$^+$, 203.0732. C$_8$H$_{15}$O$_4$Si requires *M*, 203.0740.

Attempted Coupling of 4,5-Dihydro-4-[(trimethylsilyl)carboxylate]-2(3H)-furanone

(117) and benzylic bromide (92)

i) (1 eq) LDA , THF/HMPA (10%), then (1 eq) HMPA, –35 °C

ii) (1 eq) Benzylic bromide (92) , –35 °C, 1 h

(117)
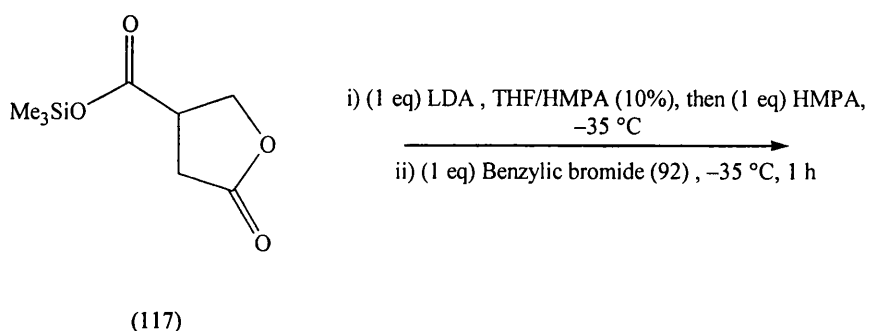
A freshly prepared solution of 1.27 *M* lithium diisopropylamide in THF/hexanes (7.6 mL, 9.62 mmol) was added dropwise to a solution of *trimethylsilyl ester* (117) (1.94 g, 9.62 mmol) in THF/HMPA (10%) (10 mL) at –35 °C. A cloudy suspension formed. HMPA (1.70 mL, 9.77 mmol) was added dropwise and the temperature was maintained at –35 °C. A solution of benzylic bromide (92) (3.42 g, 9.62 mmol) in THF (10 mL) was added dropwise at –35 °C and the stirring was continued for 1 h. The solution was allowed to reach ambient temperature. It was quenched with sat. aq ammonium chloride (20 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine (60 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 20% petrol in ether as eluent), the starting benzylic bromide (92) (3.24 g, 95%) was recovered. No coupled product was isolated.

Preparation of 3-Hydroxymethyl-3-methyloxetane (119)
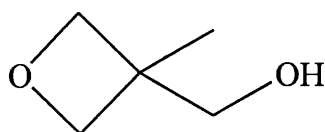
(119)

A mixture of 2-hydroxymethyl-2-methyl-1,3-propanediol (15.01 g, 125 mmol), diethylcarbonate (14.82 g, 126 mmol), potassium hydroxide (0.15 g, 2.67 mmol) and ethanol (1 mL) were heated under reflux for 16 h. The mixture was allowed to cool to ambient temperature, distilled under atmospheric pressure, ethanol (12 mL) being collected, and then at reduced pressure (112–114 °C, 20 mmHg)(lit[59,60] 120-140 °C, 50 mmHg) to give the oxetane (119) (3.65 g, 29%) as a colourless oil; NMR (300 MHz, CDCl$_3$) δ_H 4.50 (2H, d, J=5.8, 2 × CC*H*HO or 2 × CCH*H*O), 4.30 (2H, d, J=5.9, 2 × CC*H*HO or 2 × CCH*H*O), 3.57 (2H, d, J=4.8, CC*H*$_2$OH), 2.87 (1H, t, J=4.9, O*H*), 1.22 (3H, s, C*H*$_3$); ν_{max} (NaCl, film) 3409 (s, O-H), 2959 (s), 2873 (s), 1458 (w), 1384 (w), 1049 (s), 972 (s), 831 (m) cm^{-1}; *m/z* (EI) 103 (MH$^+$, 100%), 85 (32%), 15 (72%); Found: [M+H]$^+$, 103.0754. C$_5$H$_{11}$O$_2$ requires *M*, 103.0759.
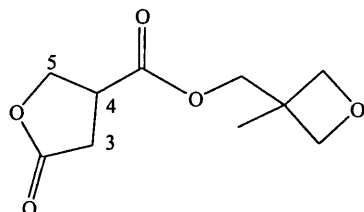
(121)

Oxalyl chloride (3.80 mL, 43.56 mmol) was added to a stirred suspension of the acid

(95) (5.06 g, 38.92 mmol) in DCM (20 mL), followed by DMF (3 drops). After the

paraconic acid had dissolved and the effervescence had subsided (*ca.* 3 h) the solvent

was removed under high vacuum. The residue was dissolved in DCM (20 mL) and

cooled to 0 °C. A mixture of the oxetane (119) (3.97 g, 38.92 mmol) in pyridine (3.2

mL) was added dropwise and the mixture was stirred at 0 °C for 3 h. It was allowed

to reach ambient temperature and washed with sat. aq copper sulphate (20 mL), sat.

aq $NaHCO_3$ (20 mL) and brine (20 mL). The organic extracts were dried ($MgSO_4$)

and evaporated under reduced pressure. The viscous oil was purified by flash column

chromatography (silica, 5% ether in ethyl acetate as eluent) to give the *oxetane ester*

(121) (6.58 g, 79%) as a colourless oil; NMR (300 MHz, $CDCl_3$) δ_H 4.56-4.38 (6H,

m, 2 × H-5, 2 × CC*H*HO and 2 × CCH*H*O), 4.24 (2H, s, C(O)OC*H*$_2$C), 3.48 (1H, m,

H-4), 2.88 (1H, dd, J=17.9, 7.0, H-3), 2.76 (1H, dd, J=17.9, 9.5, H-3), 1.32 (3H, s,

C*H*$_3$); NMR (75 MHz, $CDCl_3$) δ_C 173.1, 169.5, 77.5, 68.0, 67.2, 38.2, 37.3, 29.1,

19.2; ν_{max} (NaCl, film) 3544 (w), 3451 (w), 2964 (s), 2875 (s), 1782 (s), 1737 (s),

1459 (m), 1381 (m), 1350 (m), 1259 (m), 1220 (m), 1176 (s), 1017 (m), 978 (m), 837

(m) cm^{-1}; *m/z* (FAB), 215 (MH$^+$, 100%), 137 (20%), 113 (27%); Found: [M+H]$^+$, 215.0928. C$_{10}$H$_{15}$O$_5$ requires *M*, 215.0919.

*Preparation of 4,5-Dihydro-4-[4-methyl-2,6,7-trioxabicyclo[2.2.2]octanyl]-2(3H)-furanone (122)*
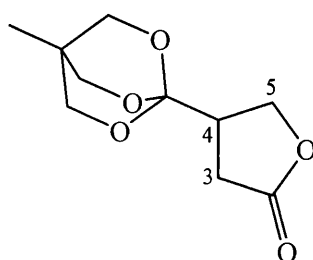
(122)

Boron trifluoride etherate (70 μL, 0.55 mmol) was added dropwise to a stirred solution of the *oxetane ester* (121) (0.47 g, 2.20 mmol) in DCM (3 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and then at ambient temperature for 15 h. The reaction mixture was quenched with TEA (40 μL) and diluted with ether (9 mL). It was filtered through a pad of Celite$^®$ that was washed with ether (3 mL). The filtrate and washings were combined, dried (MgSO$_4$) evaporated under reduced pressure and the residue was purified by flash column chromatography (silica pre-treated with TEA, 2% methanol in ether as eluent) to give the *ortho ester* (122) (0.38 g, 81%) as a white solid, m.p. 107-109 °C; NMR (300 MHz, CDCl$_3$) δ$_H$ 4.42 (1H, dd, J=9.4, 5.2, H-5), 4.28 (1H, dd, J=9.4, 8.1, H-5), 3.91 (6H, s, 3 × CC*H*$_2$O), 2.68 (2H, m, H-4 and H-3), 2.52 (1H, dd, J=17.8, 9.6, H-3), 0.82 (3H, s, C*H*$_3$); NMR (75 MHz, CDCl$_3$) δ$_C$ 177.4, 109.1, 73.2, 68.9, 41.3, 31.1, 29.8, 14.8; ν$_{max}$ (KBr) 3513 (s, br), 3419 (s, br), 2940 (m), 2884 (m), 2361 (w), 1778 (s, C=O), 1480 (m), 1402 (m), 1353 (m), 1276

(m), 1180 (s), 1097 (m), 1032 (s), 988 (s), 956 (m), 901 (m), 756 (m) cm^{-1}; m/z (FAB) 215 (MH$^+$, 100%), 136 (42%), 113 (35%); Found: [M+H]$^+$, 215.0928. C$_{10}$H$_{15}$O$_5$ requires M, 215.0919.

Preparation of Sodium tris-carbonatocobaltate(III) trihydrate (135)

$$\{Na_3[Co(CO_3)_3] \cdot 3H_2O\}$$
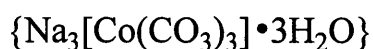
(135)

Sodium bicarbonate (14.56 g, 173.33 mmol) was dissolved in water (18 mL) and cooled to 0 °C with stirring. A solution of cobalt(II) nitrate hexahydrate (10.09 g, 34.68 mmol) in water (18 mL) was added dropwise followed by 30% hydrogen peroxide (3.5 mL). The mixture was stirred for a further 1 h at 0 °C, filtered and the precipitate washed with cold water (5 mL), ethanol (3 × 5 mL) and dry ether to give (135) (9.87 g, 79%) as an olive solid (lit[70] dec. 93 °C). Once prepared, (135) was used immediately.

Preparation of Cobalt(III) acetylacetonate (126)
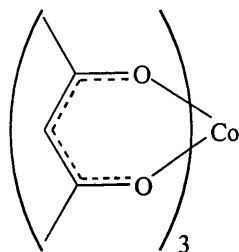
(126)

Method A

Sodium tris-carbonatocobaltate(III) trihydrate (135) (3.60 g, 9.94 mmol), acetylacetone (3.01 g, 29.31 mmol), 70% nitric acid (2 mL) in a mixture of 60% acetone in water (50 mL) was heated under reflux for 30 min. The solution was evaporated until a dark green precipitate appeared. It was then allowed to cool to ambient temperature, filtered and the crude product recrystallised (acetone and water) to give (126) (0.71 g, 20%) as dark green needles, m.p. 215-216 °C (lit[71] 213 °C); NMR (400 MHz, CDCl₃) δ_H 5.53 (1H, s, H), 2.19 (6H, s, 2 × CH_3); m/z (FAB) 357 (MH⁺, 20%), 257 (70%), 158 (100%); Found: [M+H]⁺, 357.0760. $C_{15}H_{22}CoO_6$ requires M, 357.0748.

Method B

Cobalt(II) carbonate (5.09 g, 42.80 mmol) was added to acetylacetone (39 g, 38.95 mmol) and the mixture was heated to 90 °C with stirring, followed by the dropwise addition of 30% hydrogen peroxide (20 mL) over 50 min. The mixture was stirred at 90 °C for a further 10 min and allowed to cool to ambient temperature. It was cooled further in an ice-bath and filtered. The crude solid was dissolved in hot toluene (50 mL), hexane (300 mL) was added to the warm toluene, the mixture was cooled in an ice-bath and then filtered. The solid was vacuum dried to yield (126) (10.69 g, 70%) as dark green needles, m.p. 212-214 °C (lit[71] 213 °C).

Preparation of 4,4-Bis(methoxycarbonyl)hepta-1,6-diyne (128)
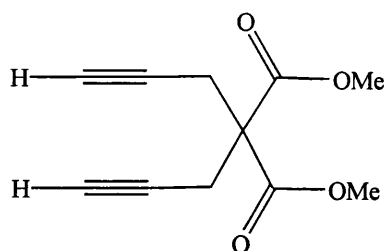
(128)

Finely cut sodium (1.65 g, 72 mmol) was added slowly to methanol (70 mL). Once the addition was complete, the solution was stirred for 30 min and then cannulated dropwise to a solution of dimethyl malonate (4.62 g, 35 mmol) in methanol (20 mL). The mixture was stirred at ambient temperature for 30 min and 80 wt.% propargyl bromide in toluene (10.86 g, 73 mmol) was added dropwise. The mixture was stirred at ambient temperature for 1 h and diluted with ether (50 mL). It was washed with water (50 mL), sat. aq NaHCO$_3$ (50 mL), brine (50 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, 50% ether in petrol as eluent) to give the diyne (128) (6.19 g, 85%) as a pale yellow solid, m.p. 84-87 °C (lit[68] 85-87 °C); NMR (400MHz, CDCl$_3$) δ_H 3.76 (6H, s, 2 × *Me*), 2.99 (4H, d, J=2.6, 2 × C*H$_2$*), 2.03 (2H, t, J=2.6, 2 × *H*C≡C); *m/z* (FAB) 209 (MH$^+$, 38%), 154 (44%), 136 (44%), 107 (28%); Found: [M+H]$^+$, 209.0807. C$_{11}$H$_{13}$O$_4$ requires *M*, 209.0814.

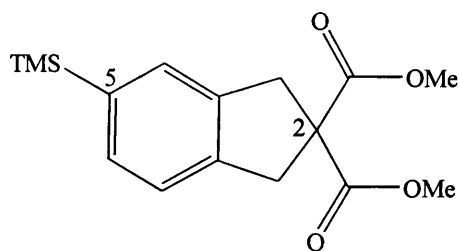*Preparation of Dimethyl-5-phenylindane-2,2-dicarboxylate (129)*
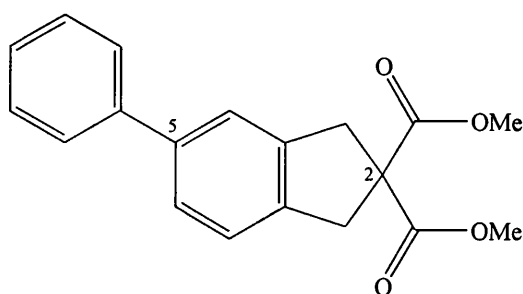
(129)

Triphenylphosphine (109 mg, 0.42 mmol) was added to a stirred solution of cobalt(III) acetylacetonate (126) (37 mg, 0.10 mmol) in benzene (2 mL). The mixture was stirred for 10 min followed by the dropwise addition of a 1.0 M solution of triisobutylaluminum in hexanes (500 μL, 0.50 mmol). A dark brown solution resulted which was stirred for 10 min followed by the addition of the diyne (128) (166 mg, 0.8 mmol) and phenylacetylene (245 mg, 2.4 mmol) in benzene (1 mL). The mixture was stirred at 22 °C for 48 h, quenched with 5% aq HCl (10 mL) and ethyl acetate (10 mL) added. The organic layer was separated and washed with sat. aq sodium carbonate (10 mL), brine (10 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, elution gradient; 10% ether in hexane to pure ether) to give the *indane* (129) (151 mg, 61%) as a reddish oil;[62] NMR (400 MHz, CDCl$_3$) δ$_H$ 7.47-6.99 (8H, m, Ar*H*), 3.62 (6H, s, 2 × *Me*), 3.52 (2H, s, 2 × H-1 or 2 × H-3), 3.50 (2H, s, 2 × H-1 or 2 × H-3); *m/z* (FAB) 311 (MH$^+$, 10%), 257 (100%), 158 (90%); Found: [M+H]$^+$, 311.5321. C$_{19}$H$_{19}$O$_4$ requires M, 311.3529.

Attempted [2+2+2] cycloaddition of 4,4-Bis(methoxycarbonyl)hepta-1,6-diyne (128)

and bis(trimethylsilyl)acetylene.

$Co(acac)_3:PPh_3:(i-Bu)_3Al$ (1:4:5), benzene, 10 min, then add BTMSA, benzene, 32 °C, 48 h

(128)
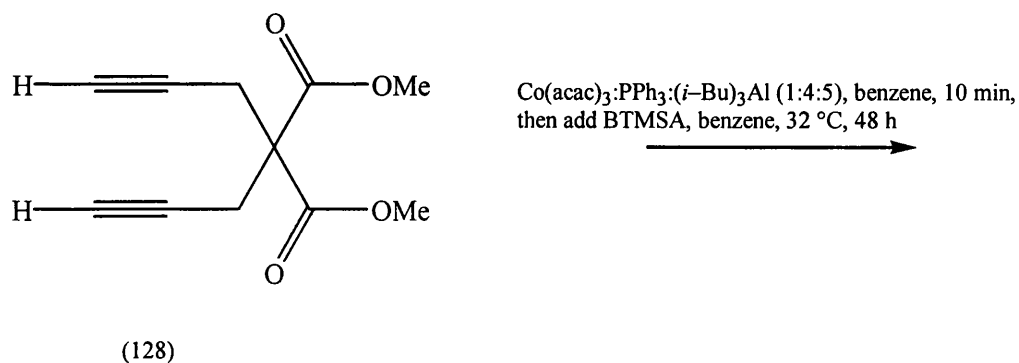
Triphenylphosphine (144 mg, 0.55 mmol) was added to a stirred solution of cobalt(III) acetylacetonate (126) (49 mg, 0.14 mmol) in benzene (2 mL). The mixture was stirred for 10 min followed by the dropwise addition of a 1.0 M solution of triisobutylaluminum in hexanes (700 µL, 0.70 mmol). The resultant dark brown solution was stirred for 10 min then the diyne (128) (233 mg, 1.12 mmol) and bis(trimethylsilyl)acetylene (573 mg, 3.36 mmol) in benzene (1 mL) were added. The mixture was stirred at 32 °C for 48 h, then quenched with 5% aq HCl (10 mL). The organic layer was separated and diluted with ethyl acetate (10 mL), washed with sat. aq sodium carbonate (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Tlc of the residue indicated five spots. The residue was purified by flash column chromatography (silica, elution gradient; 10% ether in hexane to 100% ether) to recover BTMSA (401 mg, 70%) and the diyne (128) (172 mg, 74%). No other useful products were isolated.

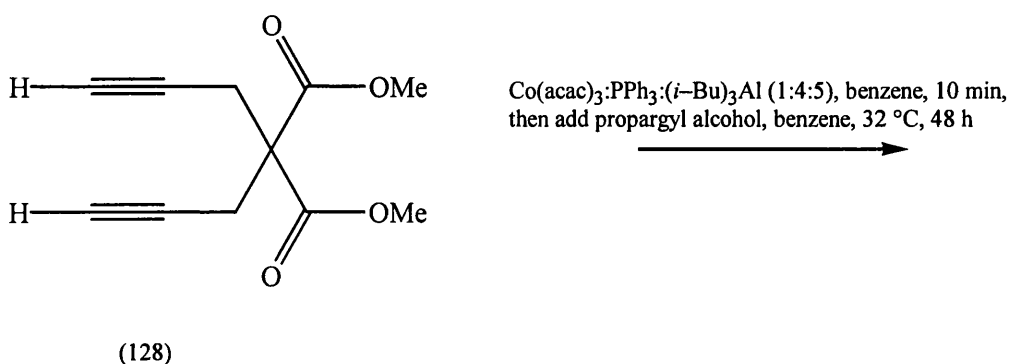*Preparation of Dimethyl-5-(trimethylsilyl)indane-2,2-dicarboxylate (138)*

(138)

Triphenylphosphine (106 mg, 0.40 mmol) was added to a stirred solution of cobalt(III) acetylacetonate (126) (37 mg, 0.10 mmol) in benzene (2 mL). The mixture was stirred for 10 min, followed by the dropwise addition of a 1.0 M solution of triisobutylaluminum in hexanes (500 μL, 50 mmol). The resultant dark brown solution was stirred for 10 min then diyne (128) (166 mg, 0.80 mmol) and (trimethylsilyl)acetylene (236 mg, 2.4 mmol) in benzene (1 mL) were added. The mixture was stirred at 32 °C for 48 h, then quenched with 5% aq HCl (10 mL). The organic was layer separated and diluted with ethyl acetate (10 mL), washed with sat. aq sodium carbonate (10 mL), brine (10 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, elution gradient; 10% ether in hexane to 100% ether) to give the *indane* (138) (144 mg, 59%) as a reddish oil; NMR (300 MHz, CDCl$_3$) δ_H 7.39-7.22 (3H, m, ArH), 3.76 (6H, s, 2 × Me), 3.64 (4H, s, 2 × CH_2), 0.27 (9H, s, SiMe_3); NMR (75 MHz, CDCl$_3$) δ_C 172.12, 140.59, 139.23, 138.02, 132.03, 129.07, 123.64, 60.05, 52.92, 40.61, 40.48, -1.04; ν_{max} (NaCl, film) 3474 (s), 2951 (m), 2897 (w), 2848 (w), 1737 (s, C=O), 1435 (s), 1272 (s), 1246 (s), 1200 (m), 1162 (m), 1070 (m), 902 (s), 841 (s), 756 (m); m/z (FAB) 307 (MH$^+$, 18%), 291 (54%), 247 (62%), 231 (49%), 173 (45%),

144 (52%), 116 (100%); Found: [M+H]$^+$, 307.1365. $C_{16}H_{23}O_4Si$ requires M,

307.1366.

Attempted [2+2+2] cycloaddition of 4,4-Bis(methoxycarbonyl)hepta-1,6-diyne (128)

and propargyl alcohol

$Co(acac)_3$:PPh_3:$(i-Bu)_3Al$ (1:4:5), benzene, 10 min,
then add propargyl alcohol, benzene, 32 °C, 48 h

(128)

Triphenylphosphine (106 mg, 0.40 mmol) was added to a stirred solution of

cobalt(III) acetylacetonate (126) (37 mg, 0.10 mmol) in benzene (2 mL). The mixture

was stirred for 10 min, then a 1.0 M solution of triisobutylaluminum in hexanes (500

μL, 0.5 mmol) was added dropwise. A dark brown solution resulted, which was

stirred for 10 min and the diyne (128) (167 mg, 0.80 mmol) and propargyl alcohol

(135 mg, 2.41 mmol) in benzene (1 mL) was then added. The mixture was stirred at

32 °C for 48 h. It was quenched with 5% aq HCl (10 mL). The organic layer was

separated and diluted with ethyl acetate (10 mL), washed with sat. aq sodium

carbonate (10 mL), brine (10 mL), dried (MgSO$_4$) and evaporated under reduced

pressure. The residue was purified by flash column chromatography (silica, 50%

ether in petrol as eluent), to recover the starting propargyl alcohol (124 mg, 92%)

and diyne (128) (152 mg, 91%). No other useful products were isolated.

Attempted [2+2+2] cycloaddition of 4,4-Bis(methoxycarbonyl)hepta-1,6-diyne (128)

and propargyloxy(tert-butyl)dimethylsilane (136)
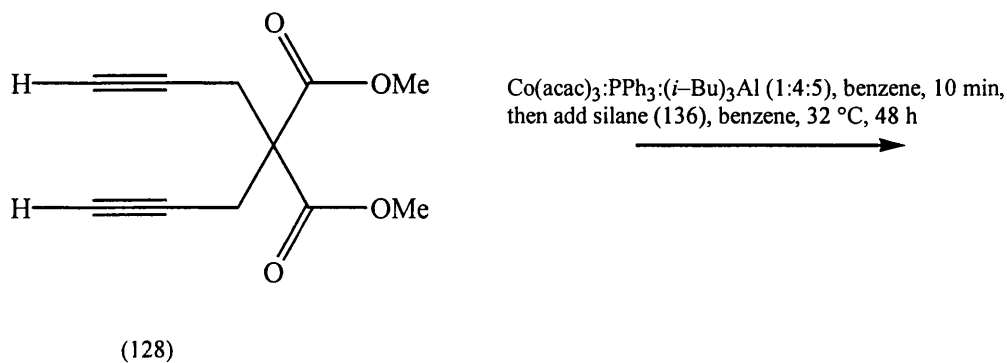
Co(acac)$_3$:PPh$_3$:(i–Bu)$_3$Al (1:4:5), benzene, 10 min,
then add silane (136), benzene, 32 °C, 48 h

(128)

Triphenylphosphine (106 mg, 0.40 mmol) was added to a stirred solution of

cobalt(III) acetylacetonate (126) (37 mg, 0.10 mmol) in benzene (2 mL). The mixture

was stirred for 10 min and a 1.0 *M* solution of triisobutylaluminum in hexanes (500

μL, 0.50 mmol) was added dropwise. A dark brown solution resulted, which was

stirred for 10 min and then the diyne (128) (167 mg, 0.80 mmol) and the silane (136)

(409 mg, 2.4 mmol) in benzene (1 mL) were added. The mixture was stirred at 32 °C

for 48 h, then quenched with 5% aq HCl (10 mL). The organic layer was separated

and diluted with ethyl acetate (10 mL), washed with sat. aq sodium carbonate (10

mL), brine (10 mL), dried (MgSO$_4$) and evaporated under reduced pressure. ^{1}H nmr

of the residue (550 mg) suggested the presence of dimethyl-5-[(*tert*-

butyldimethylsiloxy)methyl]indane-2,2-dicarbonate; NMR (400 MHz, CDCl$_3$) δ$_H$

7.16-7.13 (3H, m, Ar*H*), 4.70 (2H, s, C*H*$_2$O), 3.75 (6H, s, 2 × O*Me*), 3.60 (2H, s,

C*H*$_2$), 3.58 (2H, s, C*H*$_2$), 0.94 (9H, s, *t-Bu*), 0.10 (6H, s, Si*Me*$_2$). However, several

attempts to separate and purify the '*indane*' from the diyne (128) failed.

Attempted [2+2+2] cycloaddition of 4,4-Bis(methoxycarbonyl)hepta-1,6-diyne (128)

and 1,4-bis(trimethylsilyloxy)but-2-yne (139)

Co(acac)$_3$:PPh$_3$:(*i*–Bu)$_3$Al (1:4:5), benzene, 10 min,
then add (139), benzene, 32 °C, 48 h

(128)
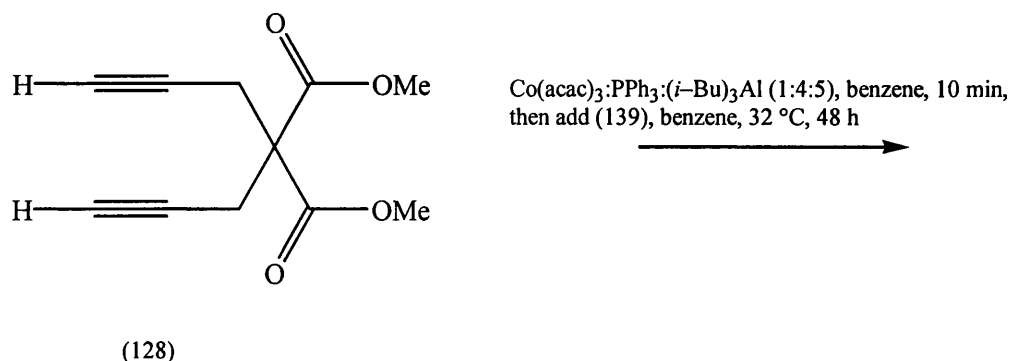
Triphenylphosphine (266 mg, 1.02 mmol) was added to a stirred solution of cobalt(III) acetylacetonate (126) (96 mg, 0.27 mmol) in benzene (2 mL). The mixture was stirred for 10 min and a 1.0 M solution of triisobutylaluminum in hexanes (1.35 mL, 1.35 mmol) was added dropwise. A dark brown solution resulted, which was stirred for 10 min and the diyne (128) (452 mg, 2.16 mmol) and the butyne (139) (1.49 g, 6.47 mmol) in benzene (1 mL) were added. The mixture was stirred at 32 °C for 48 h, then quenched with 5% aq HCl (10 mL). The organic layer was separated and diluted with ethyl acetate (10 mL), washed with sat. aq sodium carbonate (10 mL), brine (10 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 50% ether in petrol as eluent) to recover the diyne (128) (334 mg, 74%). No other useful products were isolated.

Attempted [2+2+2] cycloaddition of (3R*,4R*)-4,5-Dihydro-3-[[3,4,5-trimethoxy-2-

ethynyl]phenyl]methyl]-4-[2-ethynyl-1,3-dioxolan-2-yl]-2(3H)-furanone (90) and

(trimethylsilyl)acetylene
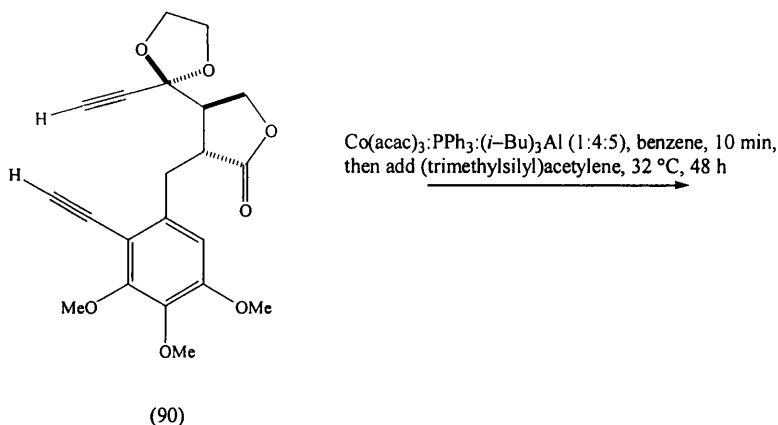
Co(acac)₃:PPh₃:(*i*–Bu)₃Al (1:4:5), benzene, 10 min,
then add (trimethylsilyl)acetylene, 32 °C, 48 h
———————————————————→

(90)

Triphenylphosphine (218 mg, 0.83 mmol) was added to a stirred solution of

cobalt(III) acetylacetonate (126) (74 mg, 0.21 mmol) in benzene (3 mL). The mixture

was stirred for 15 min then a 1.0 *M* solution of triisobutylaluminum in hexanes (1

mL, 1.0 mmol) was added dropwise. A dark brown solution resulted, which was

stirred for 10 min and diyne (90) (360 mg, 0.93 mmol) and (trimethylsilyl)acetylene

(274 mg, 2.79 mmol) in benzene (2 mL) were added. The mixture was stirred at 32

°C for 48 h. Tlc indicated the presence of starting material therefore the mixture was

stirred at 32 °C for a further 48 h, before being quenched with 5% aq HCl (3 × 10

mL). The organic layer was separated and diluted with ethyl acetate (10 mL), washed

with sat. aq sodium carbonate (10 mL), brine (10 mL), dried (MgSO₄) and

evaporated under reduced pressure. Tlc of the crude indicated four uv active spots.

The crude was purified by flash column chromatography (silica, elution gradient;

25% ether in petrol to 50% ether in petrol) (trimethylsilyl)acetylene (218 mg, 80%)

and the diyne (90) (322 mg, 89%) were recovered. No other useful products were

isolated.

Attempted [2+2+2] cycloaddition of (3R*,4R*)-4,5-Dihydro-3-[[3,4,5-trimethoxy-2-

ethynyl]phenyl]methyl]-4-[2-ethynyl-1,3-dioxolan-2-yl]-2(3H)-furanone (90) and

phenylacetylene
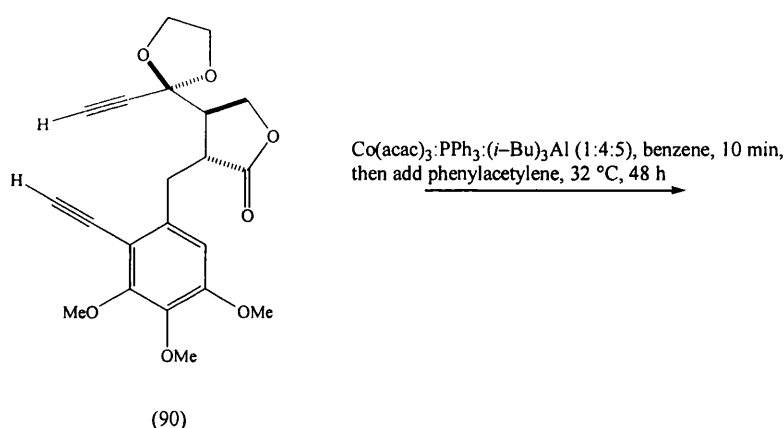
Co(acac)₃:PPh₃:(*i*–Bu)₃Al (1:4:5), benzene, 10 min,
then add phenylacetylene, 32 °C, 48 h

(90)

Triphenylphosphine (218 mg, 0.83 mmol) was added to a stirred solution of

cobalt(III) acetylacetonate (128) (74 mg, 0.21 mmol) in benzene (3 mL). The mixture

was stirred for 15 min and a 1.0 M solution of triisobutylaluminum in hexanes (1 mL,

1.0 mmol) added dropwise. A dark brown solution resulted, which was stirred for 10

min then the diyne (90) (360 mg, 0.93 mmol) and phenylacetylene (285 mg, 2.79

mmol) in benzene (2 mL) were added. The mixture was stirred at 32 °C for 48 h.

However, tlc indicated the presence of starting material, thus the mixture was stirred

at 32 °C for a further 48 h before being quenched with 5% aq HCl (3 × 10 mL). The

organic layer was separated and diluted with ethyl acetate (10 mL), washed with sat.

aq sodium carbonate (10 mL), brine (10 mL), dried (MgSO₄) and evaporated under

reduced pressure. The residue was purified by flash column chromatography (silica,

elution gradient; 25% ether in petrol to 50% ether in petrol) phenylacetylene (248 mg, 87%) and the diyne (90) (344 mg, 96%) were recovered. No other useful products were isolated.

*Preparation of 2-Allyl-1,3-propanediol (146)*

HO⌒⋀⋀OH
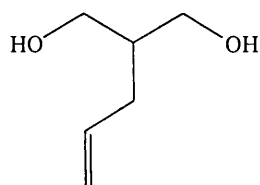
(146)

Lithium aluminum hydride (12.0 g, 316 mmol) was added to ether (400 mL) and the suspension was cooled to 0 °C with stirring. Diethyl allylmalonate (40.60 g, 203 mmol) in ether (100 mL) was added dropwise and the mixture was stirred for a further 1 h at 0 °C. It was allowed to warm to ambient temperature and stirred for 16 h. The mixture was cooled to −10 °C, wet ether (200 mL) followed by water (36 mL) was added dropwise with care. The mixture was allowed to reach ambient temperature and filtered through a pad of Celite®. The filtered cake was washed with ether (100 mL), the filtrate and washings were combined, dried (MgSO₄), evaporated under reduced pressure and then subjected to high vacuum for 10 min to remove any residual solvent to give the diol (146) (21.22 g, 90%) as a pale yellow oil;[81] NMR (400 MHz, CDCl₃) δ_H 5.78 (1H, m, C*H*=), 5.05 (2H, m, C=C*H₂*), 3.80 (2H, m, CHC*H*HOH), 3.78 (2H, m, CHCH*H*OH), 2.36 (2H, b s, OH), 2.05 (2H, m, C*H₂*C(H)=), 1.88 (1H, m, C*H*CH₂OH); ν_{max} (NaCl, film) 3359 (s, O-H), 2989 (s), 2960 (s), 2873 (s), 1650 (w, C=C), 1464 (m), 1379 (w), 1072 (m), 1039 (s, C-O), 967

(w), 953 (w) cm^{-1}; m/z (FAB) 117 (MH$^+$, 100%), 107 (10%); Found: [M+H]$^+$, 117.0913. C$_6$H$_{13}$O$_2$ requires M, 117.0916.

Preparation of 2-(Acetoxymethyl)-4-pentenyl acetate (147)
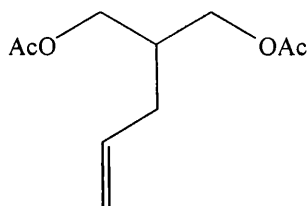

(147)

Pyridine (39.12 g, 495 mmol) was added to a solution of the diol (146) (18.44 g, 159 mmol) in DCM (800 mL). DMAP (1.50 g) was added and the mixture was stirred for 30 min. Acetic anhydride (51.94 g, 509 mmol) was added dropwise and the mixture was stirred at ambient temperature for 12 h. After dilution with ethyl acetate (500 mL), the solution was washed with aq sat. copper sulphate (3 × 500 mL), water (3 × 500 mL), sat. aq NaHCO$_3$ (2 × 500 mL) and brine (500 mL). After the organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure, the crude was distilled (71-74 °C, 0.4 mmHg) (lit[81] 84-89 °C, 0.55 mmHg) to give the diacetate (147) (27.65 g, 87%) as a colourless oil; NMR (400 MHz, CDCl$_3$) δ_H 5.80 (1H, m, CH=), 5.05 (2H, m, C=CH_2), 4.10 (4H, m, 2 × CH_2OAc), 2.12 (2H, m, CH_2C(H)=), 2.00 (6H, s, 2 × Me), 1.98 (1H, m, CHCH$_2$OAc); ν_{max} 2989 (w), 2990 (m), 1721 (s, C=O), 1641 (m, C=C), 1434 (w), 1238 (s), 972 (m) cm^{-1}; m/z (FAB) 201 (MH$^+$, 26%), 141 (100%); Found: [M+H]$^+$, 201.1120. C$_{10}$H$_{17}$O$_4$ requires M, 201.1127.

Preparation of (S)-(–)-2-(Hydroxymethyl)-4-pentenyl acetate (170)

(170)
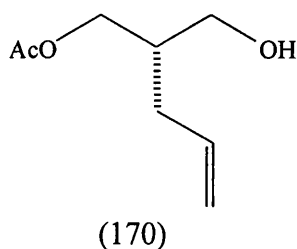
Lipase from *Candida cylindracea* (7.0 g) (Fluka) was added to a homogenised

mixture of the diacetate (147) (3.04 g, 15.2 mmol), Triton® X-100 (0.88 g), 30%

acetone (90 mL) and sodium phosphate buffer (pH 6.95) (200 mL). The mixture was

stirred vigorously while maintaining the temperature at 27 °C. The reaction was

monitored by tlc and after 3 h, ethyl acetate (150 mL) was added to quench the

reaction. The mixture was filtered through a pad of Celite®, the organic layer was

separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The

combined organic extracts were dried (MgSO$_4$) and concentrated under reduced

pressure. The crude product was purified by flash column chromatography to give

the monoacetate (170) (1.00 g, 42%) and the diacetate (147) (1.46 g, 48%), $[\alpha]_D^{23}$ =

–6.54° (c= 1.21, CHCl$_3$) (lit[81] $[\alpha]_D^{22.5}$ = –7.98° (c= 1.21, CHCl$_3$); NMR (500 MHz,

CDCl$_3$) δ_H 5.78 (1H, m, CH=C), 5.06 (2H, m, C=CH_2), 4.19 (1H, dd, J=11.2, 4.8,

CHHOAc), 4.09 (1H, dd, J=11.2, 6.6, CHHOAc), 3.61 (1H, dd, J=11.2, 4.8,

CHHOH), 3.54 (1H, dd, J=11.2, 6.3, CHHOH), 2.11 (2H, s, CH_2C(H)=), 2.07 (3H, s,

CH_3), 1.92 (1H, m, CHCH$_2$OH); ν_{max} (NaCl, film) 3467 (s, O-H), 2999 (s), 2943 (s),

2803 (s), 1725 (s, C=O), 1635 (w, C=C), 1465 (w), 1241 (s, C-O), 1039 (s, C-O),

953 (m), 876 (m) cm^{-1} m/z (FAB) 159 (MH$^+$, 69%), 154 (100%) 137 (100%) 107

(61%); Found: [M+H]$^+$, 159.1024. C$_8$H$_{15}$O$_3$ requires *M*, 159.1021.

Preparation of (R)-(–)-2-(Acetoxymethyl)-4-pentenoic acid (171)

$$
O
$$

AcO⟶⟶⟶⟶⟶⟶⟶⟶OH
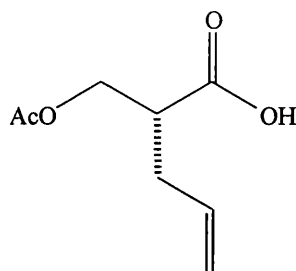
(171)

The monoacetate (170) (0.58 g, 3.67 mmol) was dissolved in acetone (15 mL) and the mixture was cooled to –5 °C with stirring. A freshly prepared solution of 2.26 N Jones reagent (4 mL, 9.04 mmol) was added dropwise and the mixture was stirred at ambient temperature for 12 h. 2-Propanol (2 mL) was added and the mixture was stirred for a further 1 h. The supernatant was decanted and the precipitate dissolved in brine (5 mL). The aqueous layer was extracted with ether (3 × 5 mL), the supernatant and the ether extracts were combined and extracted with 1 N potassium bicarbonate (3 × 10 mL). The aqueous layer was acidified with 1 N hydrochloric acid (pH 2-3), saturated with sodium chloride and extracted with ethyl acetate (2 × 5 mL). The combined organic extracts were dried (MgSO₄), evaporated under reduced pressure and then subjected to high vacuum for 10 min to give the crude acid (171) (0.48 g, 76%) as a viscous oil. The acid (171) was used without further purification, (lit[81] $[\alpha]_D^{18}$ = –7.37° (c= 1.12, CHCl₃); ν_{max} (NaCl, film) 3519 (s, COOH), 2967 (s), 2621 (s), 1777 (s, C=O), 1712 (C=O), 1465 (w), 1338(s), 1238 (s, C-O), 1039 (s, C-O), 989 (m) cm⁻¹.

Preparation of (S)-(+)-2-Amino-3-methyl-1-butanol (180)

$$CHMe_2$$

$$H_2N \overset{\displaystyle |}{\diagup} \diagdown OH$$
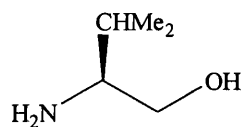
(180)

Sodium borohydride (46.99 g, 1.24 mmol) was added to a suspension of L-valine

(60.09 g, 513 mmol) in THF (1 L). The mixture was cooled to 0 °C and a solution of

iodine (130.66 g, 514 mmol) in THF (300 mL) was slowly added dropwise. During

the addition the temperature was maintained below 0 °C. Once addition was

complete, the mixture was refluxed for 16 h. After reaching ambient temperature the

mixture was cooled to 0 °C, and methanol (240 mL) was carefully added. The

mixture was concentrated under reduced pressure and the white paste that resulted

was dissolved in 20% aq potassium hydroxide (900 mL). The aqueous layer was

extracted with ether (3 × 900 mL), and the combined ether extracts were

concentrated under reduced pressure. The residual oil was distilled (62-64 °C, 3

mmHg) (lit[95] 62-67 °C, 2.5 mmHg) to yield the alcohol (180) (42.88 g, 81%) as a

colourless oil, $[\alpha]_D^{23}$ = +14.67° (neat) (lit[95] $[\alpha]_D^{20}$ = +14.6° (neat)); NMR (300 MHz,

CDCl$_3$) δ_H 3.57 (1H, dd, J=10.6, 3.8, C*H*HOH), 3.25 (1H, dd, J=10.6, 8.5, CH*H*OH),

2.54-2.41 (4H, m, O*H*, N*H*$_2$ and C*H*CH$_2$), 1.53 (1H, m, C*H*Me$_2$), 0.88 (3H, d, J=6.8,

Me), 0.86 (3H, d, J=6.7, *Me*); ν_{max} (NaCl, film) 3355 (s, O-H), 1592 (s, NH$_2$), 1468

(s), 1388 (m), 1368 (m), 1052 (s), 1019, 3282 (s), 2959 (s), 2875 (s), 929, 872 cm^{-1};

m/z (FAB) 104 (MH$^+$, 100%), 86 (3%), 72 (90%), 60 (86%); Found: [M+H]$^+$,

104.1073. C$_5$H$_{14}$NO requires *M*, 104.1075.

Preparation of (S)-(+)-4-Isopropyloxazolidin-2-one (174)
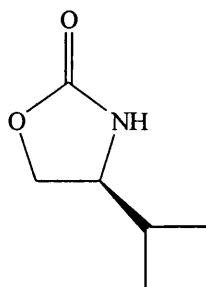
(174)

A three-necked flask equipped with a stirrer and a Vigreux column fitted with a distillation head and a receiver flask, was charged with the alcohol (180) (40.71 g, 395 mmol), anhydrous potassium carbonate (5.52 g, 40 mmol) and diethyl carbonate (92.63 g, 784 mmol). The mixture was heated at 120 °C for 3.5 h; the ethanol generated in the reaction was collected in the receiver flask that was cooled in an ice-bath. Once the cessation of the ethanol distillation took place, the yellow oil was allowed to reach ambient temperature and diluted with DCM (350 mL). The DCM extracts were washed with water (350 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The crude solid was recrystallised twice from 20% ethyl acetate in hexane to afford the oxazolidinone (174) (34.54 g, 68%) as white needles, m.p. 67-69 °C (lit[144] 71-72 °C), $[\alpha]_D^{22}$ = +14.2° (c= 7.0, CHCl$_3$) (lit[95,96] $[\alpha]_D^{20}$ = +18.0° (c= 6.0, C$_2$H$_5$OH); NMR (300 MHz, CDCl$_3$) δ_H 6.87 (1H, b s, N*H*), 4.44 (1H, dd, J=8.7, 8.7, OC*H*H), 4.10 (1H, dd, J=8.7, 6.3, OCH*H*), 3.64 (1H, m, CH$_2$C*H*N), 1.71 (1H, m, C*H*Me$_2$), 0.96 (3H, d, J=6.7, *Me*), 0.89 (3H, d, J=6.7, *Me*); v $_{max}$ (KBr) 3270 (br), 3155, 2976, 2915, 2875, 1747 (s), 1406 (s), 1362, 1328, 1246 (s), 1091 (s), 1050, 1009 (s) cm^{-1}; m/z (EI) 129 (M$^+$, 100%); Found: M$^+$, 129.0787. C$_6$H$_{11}$NO$_2$ requires *M*, 129.0790.

Preparation of (S)-(+)-3-(1-Oxo-3-carbomethoxypropyl)-4-isopropyloxazolidin-2-

one (176)
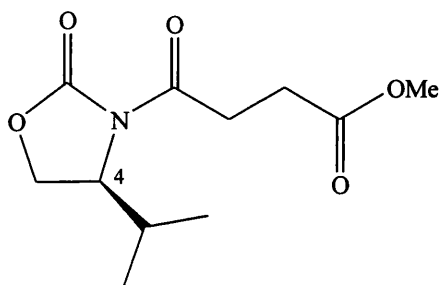
(176)

A 2.54 *M* solution of *n*-butyllithium in hexanes (6.30 mL, 16 mmol) was added dropwise over 30 min to a stirred solution of the oxazolidinone (174) (2.04 g, 15.79 mmol) in THF (100 mL) at −78 °C. Stirring was continued for a further hour followed by the dropwise addition of 3-carbomethoxypropionyl chloride (3.08 g, 20.46 mmol). After stirring for 3 h at −78 °C, the solution was allowed to reach ambient temperature and stirred overnight. It was quenched with sat. aq ammonium chloride (90 mL) and extracted with DCM (3 × 30 mL). The combined DCM extracts were washed with brine (90 mL), dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica, 1% methanol in diethyl ether as eluent) to give the *N-acyloxazolidinone* (176) (3.47 g, 90%) as a colourless oil, $[\alpha]_D^{22}$ = +12.8° (c= 1.0, CHCl₃); NMR (300 MHz, CDCl₃) δ_H 4.42 (1H, m, NC*H*CH₂), 4.35-4.25 (2H, m, NCHC*H₂*), 3.75 (3H, s, O*Me*), 3.25 (2H, m, NC(O)C*H₂*CH₂ or NC(O)CH₂C*H₂*), 2.65 (2H, m, NC(O)C*H₂*CH₂ or NC(O)CH₂C*H₂*), 2.45 (1H, m, C*H*Me₂), 0.90 (6H, m, 2 × C*H₃*); NMR (75 MHz, CDCl₃) δ_C 172.82, 171.79, 154.08, 63.56, 58.44, 51.82, 30.79, 28.36, 28.14, 17.89,

14.64; ν_{max} (NaCl, film) 3380 (w), 2962 (m), 1781 (s, C=O), 1739 (s, C=O), 1702 (s,

C=O), 1389 (w), 1366 (w), 1211 (w), 1173 (w), 1056 (w) cm^{-1}; m/z (FAB) 244

(MH$^+$, 18%), 212 (14%), 130 (18%), 115 (100%); Found: [M+H]$^+$, 244.1169.

$C_{11}H_{18}NO_5$ requires M, 244.1185.

Preparation of Acetic formic anhydride
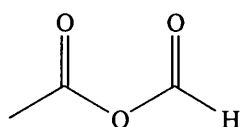
Acetyl chloride (9.83 g, 125 mmol) was added to a mixture of anhydrous sodium

formate (10 g, 147 mmol) in ether (20 mL). The mixture was stirred at 20 °C for 6 h.

then filtered and the solid was washed rapidly with anhydrous ether (8 mL). The

filtrate and washings were combined and concentrated under reduced pressure to

give the anhydride (8.01 g, 72%) as a pale-yellow oil.[141] Once prepared acetic formic

anhydride was used immediately; NMR (400 MHz, CDCl$_3$) δ_H 9.05 (1H, s, H), 2.24

(3H, s, CH_3); ν_{max} (NaCl, film) 1790 (s, C=O), 1767 (s, C=O), 1430 (w), 1376 (s),

1183 (s), 1129 (w), 1042 (s, C-O-C), 924 (s) cm^{-1}; m/z (EI) 89 (MH$^+$, 36%), 77

(36%), 66 (53%), 60 (100%); Found: [M+H]$^+$, 89.0245. $C_4H_4O_3$ requires M, 89.0239.

Preparation of Benzyl chloromethyl ether
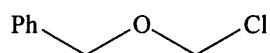
Anhydrous hydrogen chloride was bubbled through a mixture of benzyl alcohol

(146.30 g, 1.35 mmol) and 37 wt.% formaldehyde (120 g, 1.48 mmol) for 3 h.

During this period, the mixture was stirred vigorously and its temperature was maintained between 0 – +5 °C. The solution was then transferred to a separatory funnel; the organic layer was separated, dried (MgSO$_4$) and evaporated under reduced pressure. The crude was distilled (51-53 °C, 0.2 mmHg)(lit[142,143] 53-56 °C, 1.5 mmHg) to give benzyl chloromethyl ether (147.89 g, 70%) as a colourless liquid; NMR (300 MHz, CDCl$_3$) δ_H 7.39 (5H, m, Ar), 5.56 (2H, s, OCH_2Cl), 4.78 (2H, s, ArCH_2O); ν_{max} (NaCl, film) 3089 (w), 3066 (m), 3032 (s), 2950 (m), 2885 (m), 1497 (s), 1455 (s), 1386 (s), 1316 (s), 1237 (s), 1214 (m), 1118 (br, s), 1028 (m), 904 (m), 741 (s), 698 (s) cm^{-1}.

Attempted Formylation of (176) with ethyl formate

(1.1 eq) n–Bu$_2$BOTf, TEA, CH$_2$Cl$_2$, –78 °C, then add ethyl formate, –78 °C, 30 min

(176)
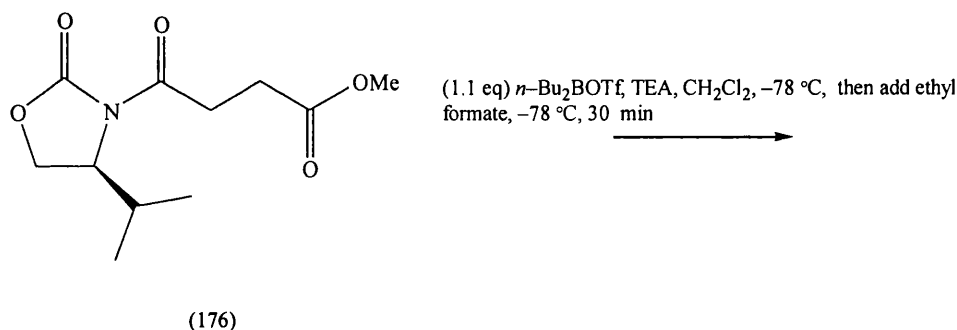
The *N-acyloxazolidinone* (176) (1.66 g, 6.82 mmol) was dissolved in DCM (15 mL) and cooled with stirring to –5 °C. A solution of 1.0 *M* dibutylboron triflate in DCM (7.5 mL, 7.5 mmol), followed by TEA (0.87 g, 8.63 mmol) was added dropwise. The solution was cooled further to –78 °C and ethyl formate (0.64 g, 8.63 mmol) was added slowly. The mixture was stirred at –78 °C for 30 min then raised to ambient temperature and stirred overnight. After the reaction mixture was quenched with (pH 7.2) aq phosphate buffer (8 mL) and methanol (22 mL), the cloudy solution that

resulted was cooled to +5 °C, (2:1) methanol: 30% aq hydrogen peroxide (22 mL) was added dropwise and the mixture stirred at this temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with ether (2 × 25 mL). The organic extracts were combined, washed with sat. aq NaHCO$_3$ (50 mL), brine (50 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica, 1% of ethanol in ether as eluent) and the starting *N-acyloxazolidinone* (176) (1.53 g, 92%) was recovered. No other useful products were isolated.

Attempted Formylation of (176) with acetic formic anhydride.

(1.1 eq) *n*–Bu$_2$BOTf, TEA, CH$_2$Cl$_2$, –78 °C, then add acetic formic anhydride, –78 °C, 30 min

(176)
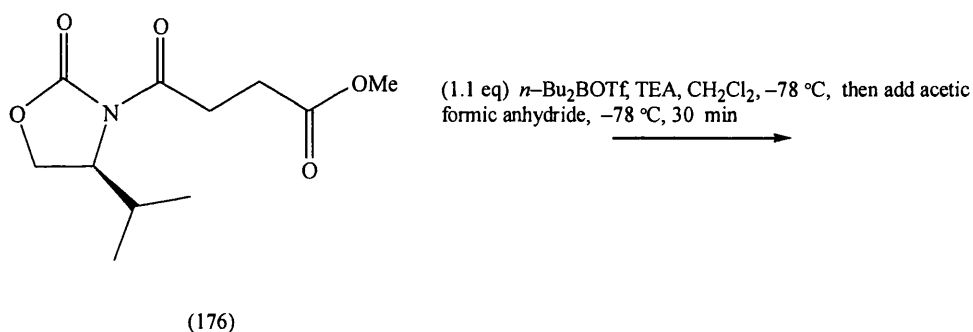
The *N-acyloxazolidinone* (176) (2.04 g, 8.39 mmol) was dissolved in DCM (15 mL) and cooled with stirring to –5 °C. A solution of 1.0 *M* dibutylboron triflate in DCM (9.0 mL, 9.0 mmol), followed by TEA (1.09 g, 10.76 mmol) was added dropwise at – 5 °C. The solution was cooled further to –78 °C and acetic formic anhydride (950 mg, 10.80 mmol) was added slowly. After stirring at –78 °C for 30 min the mixture was allowed to reach ambient temperature and stirred overnight. After quenching with (pH 7.2) aq phosphate buffer (8 mL) and methanol (22 mL), the cloudy solution that resulted was cooled to +5 °C, (2:1) methanol: 30% aq hydrogen peroxide (22

mL) was added dropwise and the mixture was stirred at this temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with ether (2 × 25 mL). The organic extracts were combined, washed with sat. aq NaHCO$_3$ (50 mL), brine (50 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica, 1% of ethanol in ether as eluent) and the starting *N*-acyloxazolidinone (176) (1.94 g, 95%) was recovered. No other useful products were isolated.
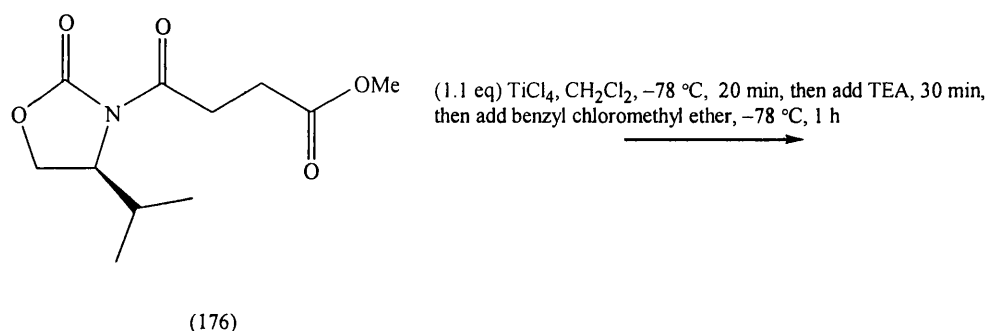
Attempted C-Alkylation of (176) with benzyl chloromethyl ether

(1.1 eq) TiCl$_4$, CH$_2$Cl$_2$, –78 °C, 20 min, then add TEA, 30 min, then add benzyl chloromethyl ether, –78 °C, 1 h

(176)

The *N*-acyloxazolidinone (176) (2.00 g, 8.22 mmol) was dissolved in DCM (30 mL) and cooled with stirring to –78 °C. Titanium(IV) chloride (1.03 mL, 9.35 mmol) was added dropwise and the mixture was stirred for 20 min. TEA (1.30 mL, 9.34 mmol) was then added dropwise and the mixture stirred at –78 °C for 30 min. Benzyl chloromethyl ether (1.37 g, 8.75 mmol) was added dropwise and the mixture stirred for 1 h, before being allowed to rise to ambient temperature and quenched with sat. aq ammonium chloride (10 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with DCM (2 × 10 mL). The organic extracts were combined, washed with brine (30 mL), dried (MgSO$_4$) and evaporated under reduced

pressure. The crude residue was purified by flash column chromatography (silica, 50% ether in petrol as eluent). The starting *N-acyloxazolidinone* (176) (1.82 g, 91%) was recovered; no other useful products were isolated.

Attempted C-Alkylation of (176) with benzyl bromide.

(1.1 eq) TiCl$_4$, CH$_2$Cl$_2$, 0 °C, 20 min, then add DIPEA
30 min, then add benzyl bromide, 0 °C, 1 h

(176)
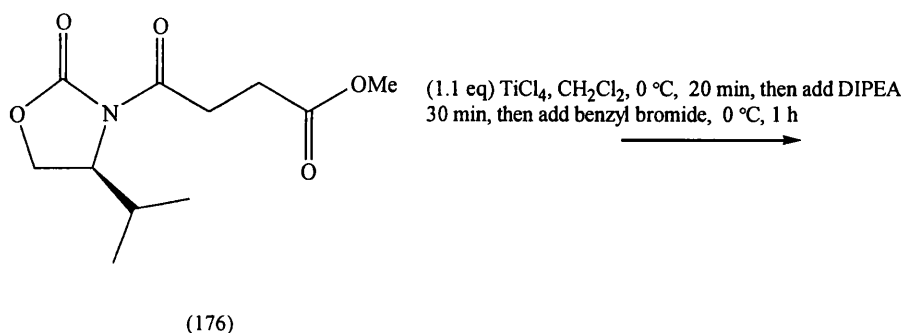
The *N-acyloxazolidinone* (176) (2.51 g, 10.32 mmol) was dissolved in DCM (30 mL) and cooled with stirring to 0 °C. A 1.0 *M* solution of titanium(IV) chloride in DCM (11 mL, 11 mmol) was added dropwise and the mixture stirred for 20 min. DIPEA (2.30 mL, 13.20 mmol) was added dropwise and the mixture stirred at 0 °C for a further 30 min. Benzyl bromide (2.0 mL, 16.81 mmol) was added dropwise and the mixture stirred at 0 °C for 1 h, then allowed to rise to ambient temperature and quenched with sat. aq ammonium chloride (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (2 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica, 5% ethyl acetate in ether). The starting benzyl bromide (2.73 g, 95%) and *N-acyloxazolidinone* (176) (2.33 g, 93%) were recovered; no other useful products were isolated.

Preparation of (S)-(+)-3-(1-Oxo-3-phenylpropyl)-4-isopropyloxazolidin-2-one (181)
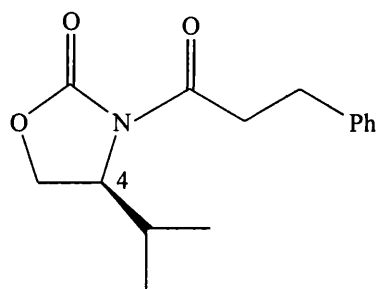

(181)

A 2.54 *M* solution of *n*-butyllithium in hexanes (82 mL, 208 mmol) was added dropwise over 20 min to a stirred solution of the *oxazolidinone* (174) (24.04 g, 186 mmol) in THF (300 ml) at −78 °C. The mixture was stirred for a further 30 min and 3-phenylpropionyl chloride (43.13 g, 257 mmol) was added dropwise and the mixture stirred for 1 h at −78 °C, allowed to rise to ambient temperature and quenched by sat. aq ammonium chloride (500 mL). The bulk of the THF and hexane was evaporated and the resulting slurry was extracted with DCM (2 × 150 mL). The organic extracts were combined, washed with sat. aq NaHCO₃ (300 mL), brine (300 mL), dried (MgSO₄) and evaporated under reduced pressure. The crude solid was recrystallised twice from 20% ethyl acetate in hexane to give the *N-acyloxazolidinone* (181) (38.41 g, 79%) as white needles, m.p. 75-77 °C, $[\alpha]_D$ = +15.58° (c= 0.9, CHCl₃); NMR (300 MHz, CDCl₃) δ_H 7.29 (5H, m, Ar*H*), 4.42 (1H, m, NC*H*CH₂), 4.23 (2H, m, OC*H₂*CH), 3.32 (2H, m, NC(O)C*H₂*CH₂ or NC(O)CH₂C*H₂*), 3.04 (2H, m, NC(O)C*H₂*CH₂ or NC(O)CH₂C*H₂*), 2.36 (1H, m, C*H*(CH₃)₂), 0.92 (3H, d, J=7.0, C*H₃*), 0.86 (3H, d, J=6.9, C*H₃*); NMR (75 MHz, CDCl₃) δ_c 172.36, 154.02, 140.45, 128.51, 128.41, 126.19, 63.36, 58.40, 37.03,

30.41, 28.35, 17.93, 14.60; v_{max} (KBr, disk) 3062 (w), 3030 (w), 2967 (m), 2926 (w),

2875 (w), 1783 (s, C=O), 1695 (s, C=O), 1489 (m), 1453 (w), 1380 (s), 1310 (s),

1210 (s), 1103 (s), 1063 (m), 1022 (m), 997 (w), 967 (w), 784 (w), 750 (m), 703 (s)

cm^{-1}; m/z (FAB) 262 (MH^+, 100%); Found: MH^+, 262.1449. $C_{15}H_{20}NO_3$ requires M,

262.1443.

Preparation of (4S,2'R)-3-[2'-Benzyloxymethyl-3'-phenylpropanoyl]-4-

isopropyloxazolidin-2-one (182)
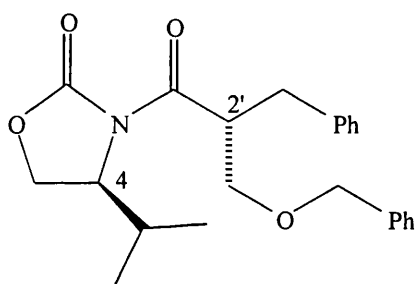
(182)

Titanium(IV) chloride (13 mL, 118.55 mmol) was added dropwise, to a stirred

solution of *N-acyloxazolidinone* (181) (27 g, 103.32 mmol) in DCM (400 mL) at –5

°C. Stirring was continued for a further 15 min, followed by the dropwise addition of

TEA (13.07 g, 129.14 mmol). The dark-red mixture was stirred for 1.5 h at –5 °C,

benzyl chloromethyl ether (32.65 g, 208.51 mmol) was added dropwise and the

mixture stirred at 0 °C for 16 h. After reaching ambient temperature, the reaction was

quenched with sat. aq ammonium chloride (400 mL). The organic and aqueous layers

were separated and the aqueous layer was extracted with DCM (2 × 400 mL). The

combined DCM extracts were washed with brine (1 L), dried (MgSO$_4$) and

evaporated under reduced pressure. The crude product was purified by flash column

chromatography (silica, 40% petrol in ether as eluent) and by recrystallisation (40:60 ethyl acetate/hexane) to give (182) (26.86 g, 68%) as a white solid, m.p. 74-75 °C, $[\alpha]_D^{23}$ = +58.6° (c= 1.22, CHCl$_3$); NMR (300 MHz, CDCl$_3$) δ_H 7.32 (10H, m, ArH), 4.57 (1H, m, NCOCH), 4.52 (2H, d, J=6.2, OCH_2Ph), 4.33 (1H, m, CH$_2$CHN), 4.11 (1H, dd, J=3.0, 9.0, CHHCHN), 4.02 (1H, dd, J=8.4, 8.9, CHHCHN), 3.82 (1H, dd, J=7.5, 9.1, CHHOBn), 3.67 (1H, dd, J=4.8, 9.2, CHHOBn), 2.98 (1H, dd, J=8.2, 13.5, CHCHHPh), 2.88 (1H, dd, J=7.3, 13.4, CHCHHPh), 2.32 (1H, m, CHMe$_2$), 0.88 (3H, d, J=7.0, Me), 0.79 (3H, d, J=6.9, Me); NMR (CDCl$_3$, 75 MHz) δ_C 174.09, 153.68, 138.58, 138.05, 129.10, 128.34, 128.25, 127.63, 127.54, 126.42, 73.02, 70.78, 63.22, 58.51, 45.10, 34.89, 28.48, 17.84, 14.65; m/z (FAB) 382 (MH$^+$, 16%), 274 (21%), 220 (16%), 130 (100%), 117 (38%); Found: [M+H]$^+$, 382.2015. C$_{23}$H$_{28}$O$_4$N requires M, 382.2018.

*Preparation of (4S,2'R)-3-[2'-Hydroxymethyl-3'-phenylpropanoyl]-4-isopropyloxazolidin-2-one (182a)*
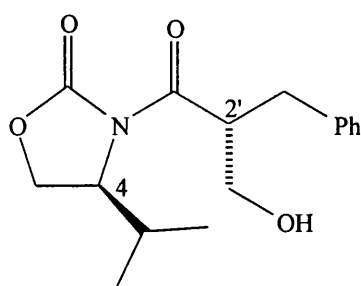
(182a)

The *N-acyloxazolidinone* (182) (22.40 g, 58.72 mmol) was added to dry ethanol (250 mL) and the mixture was stirred for 30 min. Palladium on carbon (3.13 g of 10% Pd/C) was added and the mixture was stirred vigorously under hydrogen, at ambient

temperature for 16 h. After filtration through a pad of Celite®, which was washed with ethanol (25 mL), the filtrate and washings were combined, dried (MgSO$_4$) and evaporated under reduced pressure. The crude product was recrystallised from ethyl acetate and hexane to give the *alcohol* (182a) (14.47 g, 85%) as a white solid, m.p. 83-85 °C, $[\alpha]_D^{23}$ = +116.9° (c= 0.55, CHCl$_3$); NMR (CDCl$_3$, 300 MHz) δ_H 7.28 (5H, m, Ar*H*), 4.32 (2H, m, C*H$_2$*OH), 4.18 - 4.04 (2H, m, CH$_2$C*H*N and C*H*CH$_2$OH), 3.87 (2H, m, OC*H$_2$*CHN), 3.01 (1H, dd, J=7.7, 13.4, C*H*HPh), 2.87 (1H, dd, J=7.6, 13.4, CH*H*Ph), 2.40 (2H, m, C*H*Me$_2$ and OH), 0.92 (3H, d, J=7.0, *Me*), 0.90 (3H, d, J=6.9, *Me*); NMR (CDCl$_3$, 75 MHz) δ_C 175.11, 154.03, 138.35, 129.08, 128.39, 126.47, 63.41, 63.37, 58.79, 46.91, 34.43, 28.53, 17.90, 14.68; m/z (FAB) 292 (MH$^+$, 21%), 277 (16%), 145 (34%), 130 (100%), 117 (25%); Found [M+H]$^+$, 292.1554. C$_{16}$H$_{22}$O$_4$N requires *M*, 292.1549.

Preparation of (4S,2'R)-3-[2'-Acetoxymethyl-3'-phenylpropanoyl]-4-

*isopropyloxazolidin-2-one (183)*
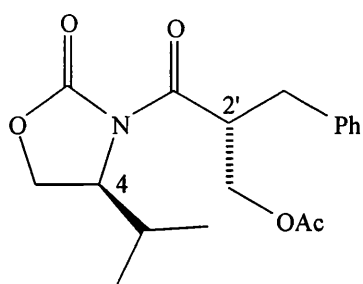
(183)

Acetic anhydride (4.26 g, 41.73 mmol) was added dropwise to a stirred mixture of the *alcohol* (182a) (10.13 g, 34.77 mmol), and DMAP (0.44 g, 3.60 mmol) in pyridine (11.3 mL). The mixture was stirred at ambient temperature for 16 h, then

diluted with DCM (150 mL), washed with sat. aq copper sulfate (2 × 150 mL), water

(2 × 150 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The crude

product was purified by flash column chromatography (silica, 2 % methanol in ether

as eluent) to give the *acetate* (183) (10.39 g, 90%) as a colourless oil, $[\alpha]_D^{23}$ = +71.8°

(c= 1.09, CHCl$_3$); NMR (300 MHz, CDCl$_3$) δ_H 7.25 (5H, m, Ar*H*), 4.56 (1H, m,

C*H*NCO), 4.33 (3H, m, C*H$_2$*OAc and C*H*CH$_2$Ph), 4.14 (1H, dd, J=2.9, 9.1,

OC*H*HCHN), 4.06 (1H, dd, J=8.4, 9.0, OCH*H*CHN), 3.00 (1H, dd, J=13.4, 7.9,

C*H*HPh), 2.91 (1H, dd, J=13.5, 7.5, CH*H*Ph), 2.25 (1H, m, C*H*Me$_2$), 2.03 (3H, s,

O*Ac*), 0.95 (3H, d, J=7.1, *Me*), 0.92 (3H, d, J=6.9, *Me*); NMR (CDCl$_3$, 75 MHz) δ_C

173.25, 170.39, 153.53, 137.62, 128.99, 128.41, 126.62, 64.44, 63.31, 58.54, 43.91,

34.99, 28.41, 20.63, 17.74, 14.62; v_{max} (NaCl, film) 2964 (m), 1778 (s, C=O), 1741

(s, C=O), 1700 (s, C=O), 1386 (m), 1302, 1228 (s), 1052 (m), 756 (w), 702 (w) cm^{-1};

m/z (FAB) 334 (MH$^+$, 10%), 274 (33%), 145 (100%), 117 (97%); Found: [M+H]$^+$,

334.1679. C$_{18}$H$_{24}$O$_5$N requires *M*, 334.1654.

Preparation of (4S,2'R)-3-[2'-Acetoxymethyl-3'-carboxypropanoyl]-4-

isopropyloxazolidin-2-one (184)
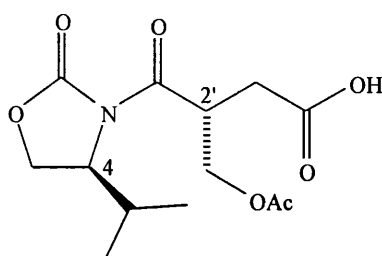
(184)

The *acetate* (183) (11.03 g, 33.08 mmol) and periodic acid (107.69 g, 472.45 mmol)

were stirred in a mixture of carbon tetrachloride (70 mL), acetonitrile (70 mL), and

water (140 mL). Ruthenium(III) chloride trihydrate (0.32 g, 1.22 mmol) was added and the mixture stirred vigorously at ambient temperature for 16 h. The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 150 mL). The organic extracts were combined, washed with brine (300 mL), dried (MgSO₄) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, elution gradient; 50% petrol in ethyl acetate to pure ethyl acetate) to give the *acid* (184) (7.64 g, 77%) as a pale yellow oil, $[\alpha]_D$ = +41.5° (c= 1.21, CHCl₃); NMR (300 MHz, CDCl₃) δ_H 9.78 (1H, b s, COO*H*), 4.45-4.23 (6H, m, OC*H₂*, C*H*N, C*H₂*OAc, C*H*CH₂COOH), 2.95 (1H, dd, J=7.5, 17.0, C*H*HCOOH), 2.53 (1H, dd, J=13.3, 17.2, C*H*HCOOH), 2.28 (1H, m, CHMe₂), 1.90 (3H, s, O*Ac*), 0.94 (3H, d, J=7.0, *Me*), 0.91 (3H, d, J=7.0, *Me*); NMR (75 MHz, CDCl₃) δ_C 177.01, 172.17, 170.60, 153.87, 63.98, 60.56, 58.58, 39.20, 32.81, 28.58, 20.65, 17.80, 14.73; v_{max} (NaCl, film) 3209-2967 (b s), 1776 (s, C=O), 1744 (s, C=O), 1700 (s, C=O), 1390 (m), 1227 (s), 1050 (s) cm⁻¹.

Preparation of (R)-(+)-Paraconic acid (140)
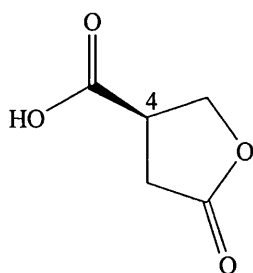
(140)

To a stirred mixture of the *acid* (184) (4.35 g, 14.44 mmol) in 30% THF in water (200 mL) at 0 °C, 30 wt.% aqueous hydrogen peroxide (10 g, 88.24 mmol) was

added dropwise. A solution of lithium hydroxide monohydrate (1.21 g, 28.8 mmol) in water (5 mL) was added dropwise to the mixture during which time the temperature was maintained between 0 - +4 °C. The mixture was stirred at ambient temperature for 16 h and quenched with sat. aq sodium sulfite (170 mL). The bulk of the tetrahydrofuran was evaporated under reduced pressure and the mixture was extracted with DCM (3 × 200 mL). The DCM extracts were combined, washed with brine (300 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, 3 % ethanol in DCM as eluent) to give the oxazolidinone (174) (1.34 g, 72 %) as a yellow solid. The aqueous layer was then acidified with 6 N hydrochloric acid and stirred at ambient temperature for 48 h. The aqueous layer was freeze dried and the crude solid extracted with DCM (soxhlet extraction for 48 h). The DCM extract was dried (MgSO$_4$) and evaporated under reduced pressure to give the crude oil which was distilled (200 °C, 0.2 mmHg) to give the acid (140) (0.32 g, 17 %) as a white solid, m.p. 54-56 °C, $[\alpha]_D^{22}$ = +56.7° (c= 0.50, MeOH)(lit[77b] for (S)-isomer $[\alpha]_D^{23}$ = −59.6° (c=0.614, MeOH)); NMR (300 MHz CDCl$_3$) δ_H 9.95 (1H, bs, COOH), 4.55 (2H, m, CH_2O), 3.45 (1H, m, H-4), 2.90-2.78 (2H, m, CH_2C(O)O); NMR (75 MHz, CDCl$_3$) δ_C 176.48, 175.87, 68.79, 39.72, 30.66; ν_{max} (KBr) 3462, 3004 (br s, O-H), 1774 (br s, O-H), 1386 (m), 1195 (s), 1032 (s), 671 (m) cm^{-1}; m/z (FAB) 130 (M+, 100%), 113 (20 %); Found: [2M+H]$^+$, 261.0602. C$_{10}$H$_{13}$O$_8$ requires M, 261.0610.

Preparation of (4S,2'R)-3-[2'–Tetrahydropyranoxymethyl-3'-phenylpropanoyl]-4-

isopropyloxazolidin-2-one (186)
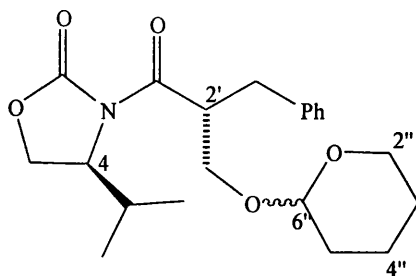
(186)

Amberlyst® 15 ion–exchange resin (5 mg) was added to a stirred solution of the alcohol (182a) (0.50 g, 1.72 mmol), dihydropyran (0.173 g, 2.06 mmol) in ether (9 mL). The mixture was stirred at ambient temperature for 12 h then filtered through a pad of Florisil®, which was washed with ether ((9 mL). The combined filtrate and washings were dried (MgSO$_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica, 3% ether in petrol as eluent) to give the ether (186) (0.48 g, 75%) as a white solid and as a mixture of diastereomers; NMR (300 MHz, CDCl$_3$) δ_H 7.21 (5H, m, ArH), 4.55 (2H, m, NCOCH and H-6"), 4.28 (1H, m, NCHCH$_2$), 4.15-3.65 (5H, m, C(O)CHCHHO, C(O)CHCHHO, H-2" and OCH_2CHN), 3.55 (1H, m, H-2"), 2.85 (2H, m, CHCH_2Ph), 2.30 (1H, m, CH(CH$_3$)$_2$), 1.80-1.60 (6H, m, 2 × H-3", 2 × H-4" and 2 × H-5"), 0.85 (6H, t, J=7.2, 2 × Me); NMR (75 MHz, CDCl$_3$) δ_C 174.0, 153.4, 138.3, 128.8, 128.1, 126.1, 98.6, 97.8, 67.9, 67.5, 62.9, 61.6, 61.2, 58.3, 44.9, 44.6, 34.9, 30.1, 28.3, 25.1, 18.8, 18.6, 17.6, 14.6; m/z (FAB) 398 (MNa$^+$, 16%), 292 (100%), 275 (52%); Found: [M+Na]$^+$, 398.1954. C$_{21}$H$_{29}$O$_5$NNa requires M, 398.1943.

Preparation of (4S,2'R)-3-[2'-tert-Butyldimethylsilyloxymethyl-3'-phenylpropanoyl]-

4-isopropyloxazolidin-2-one (187)
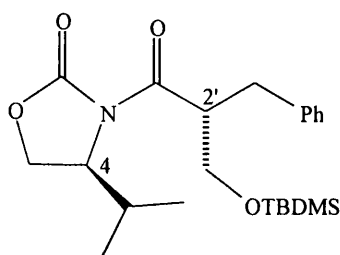
(187)

To a stirred solution of the *alcohol* (182a) (0.38 g, 1.30 mmol) and imidazole (0.11 g, 1.62 mmol) in THF (3 mL) *tert*-butyldimethylsilyl chloride (0.23 g, 1.53 mmol) was added. The mixture was stirred at ambient temperature for 12 h. Water (3 mL) was added and the organic layer separated. The aqueous layer was extracted with ether (2 × 10 mL) and the organic extracts combined, dried (MgSO$_4$) and evaporated under reduced pressure to give the *silyl ether* (187) as a white solid (0.53 g, 100%) in quantitative yield, m.p. 89-91 °C; $[\alpha]_D^{23}$= +65.1° (c=0.51, CHCl$_3$); NMR (300 MHz, CDCl$_3$) δ_H 7.25 (5H, m, Ar*H*), 4.42 (1H, m, NCOC*H*), 4.31 (1H, m, NC*H*CH$_2$), 4.10 (1H, m, C(O)CHC*H*HO), 3.97 (2H, m, C(O)CHCH*H*O and OC*H*HCHN), 3.81 (1H, m, OCH*H*CHN), 2.90 (2H, m, CHC*H$_2$*Ph), 2.31 (1H, m, C*H*(CH$_3$)$_2$), 0.90 (15H, m, 2 × *Me* and *t-Bu*Si), 0.10 (6H, s, Si*Me$_2$*); m/z (FAB) 406 (MH$^+$, 10%), 348 (100%), 219 (28%); Found: [M+H]$^+$, 406.2404. C$_{22}$H$_{36}$O$_4$NSi requires *M*, 406.2414.

Preparation of (4S,2'R)-3-[2'-Benzoyloxymethyl-3'-phenylpropanoyl]-4-

*isopropyloxazolidin-2-one (188)*
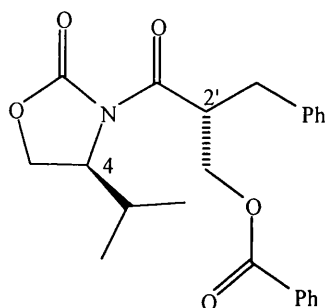
(188)

To a solution of the *alcohol* (182a) (0.45 g, 1.54 mmol) and pyridine (0.18 g, 2.31 mmol) in DCM (5 mL) benzoyl chloride (0.32 g, 2.31 mmol) was added. The mixture was stirred at ambient temperature for 24 h. Water (7 mL) was added and the organic and aqueous layers were separated and the aqueous layer extracted with ether (2 × 10 mL). The organic extracts were combined, washed with brine (30 mL), dried (MgSO$_4$) and evaporated under pressure to give the crude residue which was purified by flash column chromatography (silica, elution gradient; 10% ethyl acetate in petrol to 30% ethyl acetate in petrol) to give the *ester* (188) (0.63 g, 100%) as a white solid, m.p 105-107 °C; [α]$_D^{23}$= +89.1° (c=0.42, CHCl$_3$); NMR (300 MHz, CDCl$_3$) δ$_H$ 7.95 (2H, d, J=7.14, Ar*H*), 7.50 (1H, m, Ar*H*), 7.35 (2H, m, Ar*H*), 7.21 (5H, m, Ar*H*), 4.60 (3H, m, NCOC*H*, C(O)CHCH*H*O and OC*H*HCHN), 4.30 (1H, m, NC*H*CH$_2$), 4.08 (1H, m, C(O)CHC*H*HO), 3.95 (1H, t, J=8.1, OCH*H*CHN), 3.08 (1H, dd, J=13.3, 7.3, CHC*H*HPh), 2.90 (1H, dd, J=13.3, 7.3, CHCH*H*Ph), 2.28 (1H, m, C*H*(CH$_3$)$_2$), 0.80 (3H, d, J=7.3, C*H$_3$*), 0.75 (3H, d, J=6.9, C*H$_3$*); NMR (75 MHz, CDCl$_3$) δ$_C$ 172.8, 165.7, 153.4, 137.6, 132.8, 129.6, 129.3, 128.9, 128.3, 128.1,

126.5, 64.6, 63.1, 58.4, 44.1, 34.9, 28.6, 17.6, 14.4; *m/z* (FAB) 396 (MH$^+$, 95%), 274

(100%), 267 (76%); Found: [M+H]$^+$, 396.1830. C$_{23}$H$_{26}$O$_5$N requires *M*, 396.1811.

Preparation of (4S,2'R)-3-[2'-Trichloroacetoxymethyl-3'-phenylpropanoyl]-4-

isopropyloxazolidin-2-one (189)

(189)
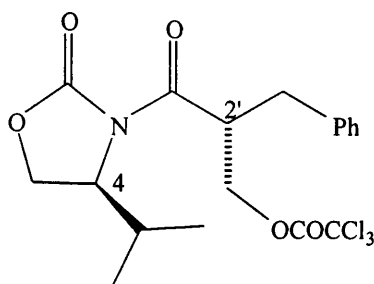
Trichloroacetic anhydride (0.41 g, 1.34 mmol) was added to a solution of the *alcohol*

(182a) (0.3 g, 1.03 mmol) and pyridine (0.10 g, 1.34 mmol) in DCM (3.5 mL). The

mixture was stirred at ambient temperature for 12 h. Water (5 mL) was added and the

layers separated. The aqueous layer was extracted with ether (10 mL) and the ether

extracts combined, washed with brine (30 mL), dried (MgSO$_4$) and evaporated under

reduced pressure. The crude product was purified by flash column chromatography

(silica, 10 % ethyl acetate in petrol as eluent) to give the *trichloroester* (189) (0.41 g,

90%) as a white solid, m.p. 87-89 °C; [α]$_D^{22}$= +70.1° (c=0.65, CHCl$_3$); NMR (300

MHz, CDCl$_3$) δ$_H$ 7.25 (5H, m, Ar*H*), 4.67 (2H, m, NCOC*H* and C(O)CHC*H*HO),

4.54 (1H, t, J=9.0, OC*H*HCHN), 4.35 (1H, m, NC*H*CH$_2$), 4.21 (1H, dd, J=9.0, 7.5,

C(O)CHCH*H*O), 4.10 (1H, t, J=9.0, OCH*H*CHN), 3.05 (1H, dd, J=13.5, 7.0,

CHC*H*HPh), 2.85 (1H, dd, J=13.5, 6.6, CHCH*H*Ph), 2.35 (1H, m, C*H*(CH$_3$)$_2$), 0.92

(3H, d, J=7.0, *CH₃*), 0.87 (3H, d, J=7.0, *CH₃*); NMR (75 MHz, CDCl₃) δ_C 172.3, 153.7, 136.7, 129.0, 128.7, 127.1, 67.2, 63.6, 58.8, 43.8, 34.8, 28.4, 17.8, 14.4.

Preparation of (1S,2S)-(+)-2-Amino-1-phenyl-1,3-propanediol-hydrobromide (202)

(202)
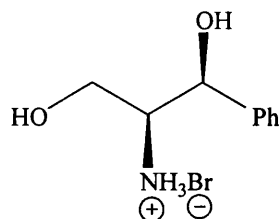
Hydrobromic acid (48 wt.% in water, 0.5 mL) was added dropwise to a stirred solution of (1S,2S)-(+)-2-amino-1-phenyl-1,3-propanediol (0.50 g, 2.99 mmol) in methanol (5 mL). The mixture was stirred at ambient temperature for 30 min and the solvent was removed under reduced pressure to give the hydrobromide (202) (0.74 g, 100%) as a pale red solid, m.p. 157-159 °C; $[\alpha]_D^{22}$= +30.1° (c=1.0, CH₃OH) (lit[121] 156-158 °C, $[\alpha]_D^{20}$= +30.4° (c=1.0, CH₃OH)); *m/z* (FAB) 168 (M⁺-Br, 100%), 154 (17%), 150 (40%), 136 (26%), 120 (28%); Found: [M-Br]⁺, 168.1027, C₉H₁₄NO₂, requires *M*, 168.1025.

Preparation of (4S,5S)-(+)-5-Amino-2,2-dimethyl-4-phenyl-1,3-dioxane (203)

H₃C　CH₃
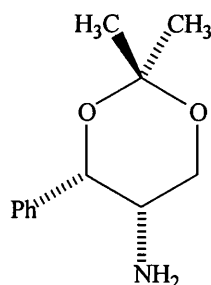
(203)

Pyridinium *p*-toluenesulfonate (0.48 g, 1.91 mmol) was added to a stirred solution of

1,4-dioxane (15 mL), 2,2-dimethoxypropane (15 mL, 122 mmol) and the

hydrobromide (202) (3.0 g, 12.10 mmol). The mixture was stirred at ambient

temperature for 12 h, it was cooled to −10 °C, basified by sat. aq potassium carbonate

and extracted with DCM (3 × 15 mL). The organic extracts were combined, dried

(MgSO₄), evaporated under reduced pressure. The residue was purified by short path

distillation (115 °C, 0.5 mmHg)(lit[121]101-103 °C, 0.1 mmHg) to give the dioxane

(203) as a colourless oil (1.30 g, 52%); $[\alpha]_D^{22}$= +55.0° (c=1.0, CHCl₃) (lit[121,122]

$[\alpha]_D^{20}$= +55.6° (c=1.0, CHCl₃)); NMR (300 MHz CDCl₃) 7.55 (5H, m, Ar*H*), 5.32

(1H, s, C*H*Ph), 4.52 (1H, dd, J=11.7, 2.3, C*H*H), 4.13 (1H, dd, J=11.7, 1.7, CH*H*),

2.98 (1H, m, C*H*NH), 2.08 (2H, bs, N*H₂*), 1.77 (3H, s, C*H₃*), 1.76 (3H, s, C*H₃*); νmax

(NaCl, film) 3358 (N-H, m), 3279 (N-H, m), 2980 (s), 2920 (m), 2870 (m), 1588 (N-

H bend, m), 1494 (w), 1454 (m), 1378 (s), 1198 (s), 1159 (w), 1129 (w), 1054 (s),

945 (w), 845 (s),740 (s), 701 (m) cm⁻¹; *m/z* (FAB) 208 (MH⁺, 66%), 150 (100%), 132

(47%), 120 (50%), 105 (78%); Found: [M+H]⁺, 208.1348. C₁₂H₁₈O₂N requires *M*,

208. 1338.

Preparation of (4S,5S)-(+)-2,2-Dimethyl-5-formylamino-4-phenyl-1,3-dioxane (204)
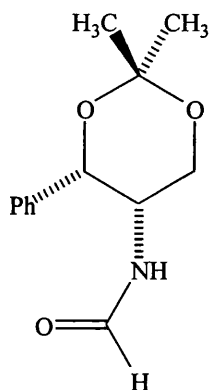
(204)

Ethyl formate (10 mL) and the dioxane (203) (0.36 g, 1.73 mmol) were heated under reflux for 16 h. The mixture was allowed to cool to ambient temperature and was evaporated under reduced pressure to give the *N*-formylate (204) (0.41 g, 100%) as a viscous syrup, which was used without further purification; NMR (CDCl$_3$, 300 MHz) δ$_H$ 7.91 (1H, s, NC(O)*H*), 7.26 (5H, m, Ar*H*), 6.12 (1H, d, J=8.3, N*H*C(O)H), 5.15 (1H, bs, C*H*Ph), 4.23 (2H, m, C*H*NH and C*H*H), 3.83 (1H, dd, J=1.6, 12.0, CH*H*), 1.52 (3H, s, C*H*$_3$), 1.49 (3H, s, C*H*$_3$); NMR (CDCl$_3$, 75 MHz) δ$_C$ 160.44, 137.95, 128.61, 128.30, 127.66, 125.87, 125.19, 99.68, 71.60, 64.58, 45.47, 29.68, 18.49; ν$_{max}$ (NaCl, film) 3061 (m), 3030 (m), 2991 (m), 2866 (m), 1657 (s, C=O), 1524 (s), 1501 (s), 1454 (s),1376 (s), 1267 (s), 1079 (s), 986 (m), 947 (m), 900 (w), 838 (w) cm^{-1}; *m/z* (FAB) 236 (MH$^+$, 17%), 178 (100%), 148 (29%), 120 (25%); Found: [M+H]$^+$, 236.1279. C$_{13}$H$_{18}$O$_3$N requires *M*, 236. 1287.

Preparation of (4S,5S)-(+)-2,2-Dimethyl-5-methylamino-4-phenyl-1,3-dioxane (193)
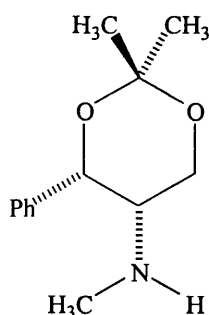

(193)

Lithium aluminum hydride (0.22 g, 5.70 mmol) was added to ether (8 mL) and the suspension was cooled to 0 °C with stirring. *N*-formylate (204) (0.67 g, 2.85 mmol) in ether (2 mL) was added dropwise and the mixture stirred at 0 °C for 4 h. The reaction mixture was allowed to warm to ambient temperature and stirred for a further 16 h. After cooling to −10 °C, wet ether (5 mL) followed by water (1 mL) were added dropwise, with care. The mixture was allowed to reach ambient temperature and filtered through a pad of Celite®. The filtered cake was washed with ether (5 mL), the filtrate and washings combined, dried (MgSO₄), and evaporated under reduced pressure. The crude oil was purified by distillation (90 °C, 0.1 mmHg)(lit[115] 77-80 °C, 0.05 mmHg) to give the dioxane (193) (0.50 g, 79%) as a colourless oil; $[\alpha]_D^{22}$= +62.0° (neat) (lit[115] $[\alpha]_D^{20}$= +61.8° (neat)); NMR (300 MHz, CDCl₃) δ_H 7.52 (5H, m, Ar*H*), 5.30 (1H, d, J=2.3, C*H*Ph), 4.22 (2H, m, C*H₂*), 2.71 (1H, m, C*H*N), 2.36 (3H, s, NH*Me*), 1.70 (3H, s, *Me*), 1.69 (3H, s, *Me*); NMR (75 MHz, CDCl₃) δ_C 139.61, 128.21, 127.19, 125.57, 99.12, 73.35, 62.02, 57.11, 34.50, 29.58, 18.76; ν_max (NaCl, film) 3349 (m), 2990 (s), 2938 (s), 2868 (s), 2799 (s), 1461 (m), 1450 (s), 1374 (s), 1269 (s), 1231 (s), 1193 (s), 1125 (s), 1072 (s), 1027 (m),

845 (s), 702 (s) cm^{-1}; *m/z* (FAB) 222 (MH$^+$, 100%), 164 (46%) 146 (18%); Found: [M+H]$^+$, 222.1489. C$_{13}$H$_{20}$O$_2$N requires *M*, 222. 1494.

Preparation of (2R,4S,5S)-(+)-5-Benzylidenamino-2,4-diphenyl-1,3-dioxane (207)
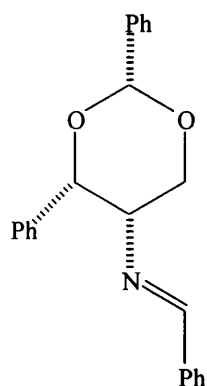
(207)

Phosphorus pentoxide (4.54 g × 2, 32 mmol) was added portion-wise to a vigorously stirred suspension of the hydrobromide salt (202) (4.0 g, 16.12 mmol) in benzaldehyde (33 mL). The mixture was stirred at ambient temperature for 16 h, then cooled to 0 °C and sat. aq potassium carbonate was added slowly until the mixture was basic (pH 12). The organic layer was separated and the aqueous layer extracted with ether (3 × 10 mL). The organic extracts were combined and dried (Na$_2$SO$_4$). The viscous crude oil was distilled under atmospheric pressure and then under reduced pressure (190 °C, 0.2 mmHg)(lit^{121} 175-176 °C, 0.2 mmHg). The product was recrystallised from *i*-propanol to give the imine (207) (4.52 g, 82%) as a white solid, m.p. 102-104 °C; [α]$_D^{22}$= +253.8° (c=1.0, CHCl$_3$) (lit^{121} m.p. 103-105 °C, [α]$_D^{20}$= +254.5° (c=1.0, CHCl$_3$)); NMR (CDCl$_3$, 300 MHz) δ$_H$ 7.86 (1H, s, CN*H*), 7.59-7.05 (15H, m, Ar*H*), 5.84 (1H, s, OC*H*O), 5.23 (1H, d, J=2.2, C*H*Ph), 4.42 (1H, dd, J=11.8, 2.2, CHC*H*HO), 4.28 (1H, dd, J=11.7, 4.3, CHCH*H*O), 3.47 (1H, m,

CHNC); m/z (FAB) 344 (MH$^+$, 40%), 238 (34%), 208 (34%), 131 (40%); Found [M+H]$^+$, 344.1647. C$_{23}$H$_{22}$O$_2$N requires M, 344.1651.

Preparation of γ–Crotonolactone (191)
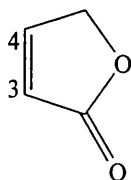
(191)

A solution of triethylamine (6.17 g, 55.61 mmol) in ether (7 mL) was added dropwise over 1 h to a refluxing solution of α-bromo-γ-butyrolactone (8.36 g. 50.67 mmol) in ether (20 mL). The mixture was refluxed for a further 16 h, then allowed to cool to ambient temperature, filtered and concentrated under reduced pressure. The resultant oil was purified by distillation (82 °C, 11 mmHg,)(lit[116] 107-109 °C, 24 mmHg) to give the butenolide (191) (2.93 g, 69%) as a colourless oil; NMR (CDCl$_3$, 300 MHz) δ_H 7.59 (1H, m, H-4), 6.17 (1H, m, H-3), 4.90 (2H, m, CH_2); ν_{max} (NaCl, film) 3630 (w), 3509 (w), 3095 (w), 1769 (s, C=O), 1733 (s, C=O), 1448 (w), 1334 (w), 1155 (m), 1091 (m), 1034 (m), 877 (m), 799 (m) cm^{-1}; m/z (FAB) 85 (MH$^+$, 100%), 77 (28%), 55 (16%); Found: 85.0293. [M+H]$^+$, C$_4$H$_5$O$_2$ requires M, 85.0290.

Preparation of 2-[(Trimethylsilyl)ethynyl]-3,4,5-trimethoxybenzaldehyde (200)
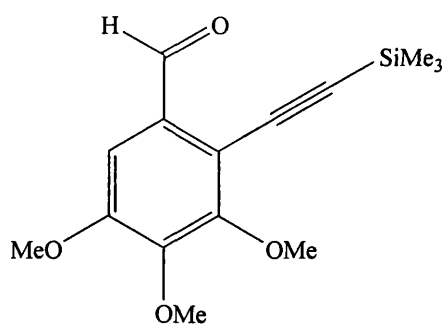
(200)

Chromium trioxide (0.031 g, 0.31 mmol) was added to a stirred solution of pyridine (0.049 g, 0.632 mmol) in DCM (2 mL) at ambient temperature. A solution of the alcohol (112) (0.150 g, 0.51 mmol) in DCM (3 mL) was added dropwise to this mixture and stirring continued at ambient temperature for 6 h. The solution was decanted, the residue washed with ether (5 mL), and the organic extracts combined and concentrated under reduced pressure. The residue was diluted with ether (5 mL) and filtered through a pad of silica, which was washed with a portion of ether (5 mL). The filtrate and washings were combined, washed with sat. aq $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the aldehyde (200) (0.14 g, 96%) as a white solid, m.p. 69-71 °C (lit[120] 70-71 °C); NMR ($CDCl_3$, 300 MHz) δ_H 10.41 (1H, s, C*H*O), 7.22 (1H, s, Ar*H*), 3.97 (3H, s, O*Me*), 3.94 (3H, s, O*Me*), 3.91 (3H, s, O*Me*), 0.27 (9H, s, Si*Me*$_3$); ν_{max} (KBr) 2944 (m), 2848 (m), 2146 (s, alkyne), 1694 (s, C=O), 1582 (s), 1488 (s), 1389 (s), 1332 (s), 1245 (s), 1202 (s), 1129 (s), 1072 (s), 1036 (s), 848 (vs), 760 (m), 648 (m) cm^{-1}; *m/z* (FAB) 293 (MH$^+$, 100%), 277 (26%), 219 (21%); Found: [M+H]$^+$, 293.1203 $C_{15}H_{21}O_4Si$ requires *M*, 293.1209.

Preparation of 6-Bromopiperonal (217)
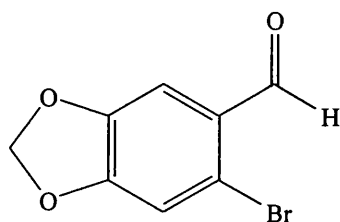
(217)

Bromine (2.10 mL, 40.98 mmol) was added dropwise to a stirred solution of piperonal (5.00 g, 33.33 mmol) in acetic acid (23 mL). The dark red solution that resulted was stirred at ambient temperature for 18 h. After filtration the crude product was recrystallised from 3% aq ethanol in ether to give the bromide (217) (5.72 g, 75%) as white needles, m.p. 128-130 °C (lit[27] 131-132 °C); NMR (300 MHz, CDCl$_3$) δ_H 10.20 (1H, s, CHO), 7.38 (1H, s, ArH), 7.08 (1H, s, ArH), 6.10 (2H, s, CH_2); v_{max} (KBr) 3053 (w), 2918 (w), 1674 (s, C=O), 1603 (s), 1489 (s), 1410 (m), 1255 (m), 1107 (s), 1029 (m), 919 (m), 973 (m) cm^{-1}; m/z (FAB) 229 (MH$^+$, 77%), 176 (33%), 154 (100%), 136 (92%), 107 (43%); Found: [M+H]$^+$, 228.9495 C$_8$H$_6$^{79}BrO$_3$ requires M, 228.9500.

Preparation of 2-Bromo-3,4,5-trimethoxybenzaldehyde (213)
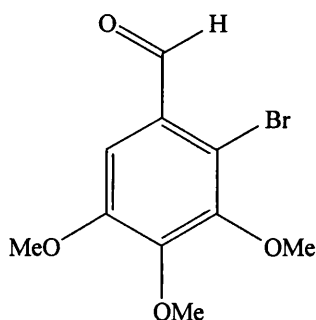
(213)

Bromine (4.0 mL, 78 mmol) was dissolved in carbon tetrachloride (35 mL) and added dropwise to a refluxing mixture of 3,4,5-trimethoxybenzaldehyde (15 g, 76.53 mmol) in carbon tetrachloride (162 mL). After refluxing for 12 h, the dark solution was cooled to ambient temperature, and washed with water (3 × 200 mL). The organic extracts were dried (MgSO$_4$) and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica, 20% DCM in petrol) to give the *bromide* (213) (12.5 g, 60%) as white needles, m.p. 102-105 °C; NMR (300 MHz, CDCl$_3$) δ_H 10.47 (1H, s CHO), 7.48 (1H, s, ArH), 4.16-4.08 (9H, m, 3 × OMe); v_{max} (KBr) 2939 (w), 2866 (w), 1692 (s, C=O), 1577 (s), 1477 (m), 1385 (s), 1331 (s), 1198 (m), 1165 (m), 1106 (m), 918 (m), 859 (m) cm^{-1}; m/z (FAB) 275 (MH$^+$, 100%), 168 (33%), 147 (19%), 136 (21%); Found [M+H]$^+$, 274.9920. C$_{10}$H$_{12}$O$_4$^{79}Br requires M, 274.9919.

Preparation of α-(2-Bromo-4,5-methylenedioxyphenyl)-α-morpholinoacetonitrile

(219)
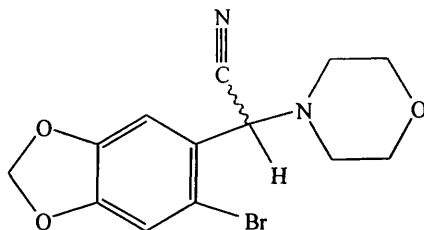
(219)

Morpholine (5.41 g, 62.10 mmol) was added to a 50% aq solution of methanol (70

mL). 6 *N* Hydrochloric acid (10.35 mL, 62.10 mmol) was added dropwise to the

stirred mixture and potassium cyanide (3.37 g, 51.75 mmol) added followed by the

bromide (217) (11.85 g, 51.97 mmol). The mixture was refluxed for 48 h, then

allowed to cool to ambient temperature, filtered, and the solid washed with water

(100 mL). The crude product was recrystallised from methanol to give the nitrile

(219) (14.97 g, 89%) as white needles, m.p. 108-110 °C (lit[17] 109-111 °C); NMR

(300 MHz, CDCl₃) δ$_H$ 7.37 (1H, s, Ar*H*), 7.35 (1H, s, Ar*H*), 6.25 (2H, s, OC*H₂*O),

5.28 (1H, s, NC*H*), 4.06 (4H, m, C*H₂*OC*H₂*), 2.89 (4H, m, C*H₂*NC*H₂*); ν$_{max}$ (KBr)

3024 (s), 2400 (s, CN), 1209 (s), 776 (s), 732 (s) cm⁻¹; *m/z* (FAB) 325 (MH⁺, 55%),

298 (89%), 240 (100%); Found [M+H]⁺, 325.0176. C₁₃H₁₄N₂O₃⁷⁹Br requires *M*,

325.0188.

Preparation of α-(2-Bromo-3,4,5-trimethoxyphenyl)-α-morpholinoacetonitrile (221)
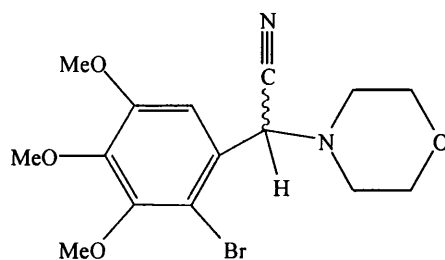
(221)

Morpholine (0.26 g, 3.01 mmol) was added to a 50% aq solution of methanol (15 mL). The mixture was stirred and 6 N hydrochloric acid (0.50 mL, 3 mmol) was added dropwise, potassium cyanide (0.17 g, 2.61 mmol) was added followed by the bromide (213) (0.69 g, 2.51 mmol). The mixture was refluxed for 48 h, then allowed to cool to ambient temperature, filtered and the solid washed with water (100 mL). The crude product was recrystallised from methanol to give the *nitrile* (221) (0.72 g, 77%) as yellow needles, m.p. 112-113 °C; NMR (300 MHz, CDCl$_3$) δ_H 7.18 (1H, s, ArH), 5.23 (1H, s, NCH), 4.11 (9H, m, 3 × OMe), 3.86 (4H, m, CH_2OCH_2), 2.81 (4H, m, CH_2NCH_2); NMR (75 MHz, CDCl$_3$) δ_C 152.42, 151.51, 143.63, 127.15, 115.13, 111.48, 108.93, 66.47, 61.81, 61.01, 60.99, 56.30, 49.64; v_{max} (KBr) 300 (s), 2989 (m), 2900 (m, CN), 1499 (s), 1357 (m), 1031 (s), 776 (s), 732 (s) cm^{-1}; m/z (FAB) 371 (MH$^+$, 20%), 344 (M-CN, 65%), 286 (100%); Found [M+H]$^+$, 371.0587. C$_{15}$H$_{20}$N$_2$O$_4$^{79}Br requires M, 371.0606.

Preparation of α-[[2-(Trimethylsilyl)ethynyl]-4,5-methylenedioxyphenyl]-α-

morpholinoacetonitrile (224)
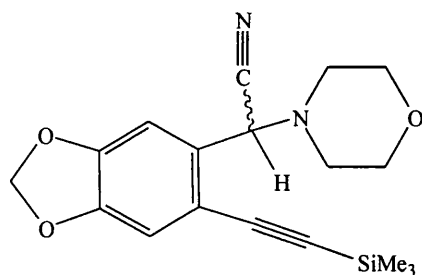
(224)

The nitrile (219) (0.90 g, 2.77 mmol) was dissolved in DMF (2 mL) and added

dropwise to a stirred suspension of palladium(II) acetate (0.17 g, 0.76 mmol), and

triphenylphosphine (0.33 g, 1.26 mmol) in TEA (8 mL). (Trimethylsilyl)acetylene

(1.39 g, 14.15 mmol) was added dropwise to the suspension, the reaction mixture

warmed to 50 °C and stirred at this temperature for 48 h. After cooling to ambient

temperature, the reaction mixture was poured into water (10 mL) and extracted with

ether (3 × 10 mL). The combined ether extracts were washed with brine (30 mL),

dried (MgSO$_4$) and evaporated under reduced pressure. The crude residue was

purified by flash column chromatography (silica, 20% ether in petrol to 50% ether in

petrol) to give (224) (0.65 g, 69%) as a pale brown solid, m.p. 123-125 °C; NMR

(300 MHz, CDCl$_3$) δ_H 7.04 (1H, s, ArH), 6.97 (1H, s, ArH), 6.03 (2H, s, OCH_2O),

5.07 (1H, s, NCH), 3.71 (4H, m, CH_2OCH_2), 2.67-2.55 (4H, m, CH_2NCH_2), 0.25

(9H, s, SiMe_3); NMR (75 MHz, CDCl$_3$) δ_C 148.17, 147.86, 129.63, 117.22, 115.79,

112.47, 108.87, 101.99, 101.71, 99.09, 66.50, 60.00, 50.10, -0.08; ν_{max} (KBr) 2939

(s), 2854 (s), 2144 (s), 1613 (m), 1481 (s), 1364 (m), 1251 (m), 1036 (m), 934 (m),

858 (m) cm^{-1}; m/z (FAB) 341 ([M-H]$^+$, 19%), 316 ([M-CN]$^+$, 100%), 256 (100%);

Found [M-H]$^+$, 341.1311. C$_{18}$H$_{21}$N$_2$O$_3$Si. requires M, 341.1321.

Preparation of α-[[2-(Trimethylsilyl)ethynyl]-3,4,5-trimethyloxyphenyl]-α-morpholinoacetonitrile (225)
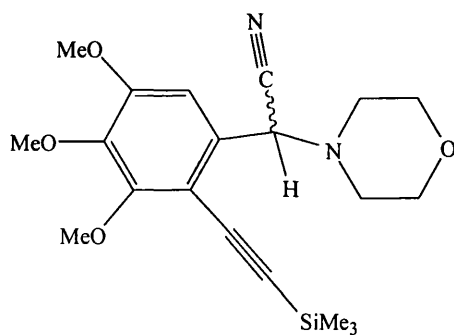

(225)

The *nitrile* (221) (0.21 g, 0.57 mmol) was dissolved in DMF (2 mL) and added dropwise to a stirred suspension of palladium(II) acetate (33 mg, 0.15 mmol), and triphenylphosphine (66 mg, 0.25 mmol) in TEA (2 mL). (Trimethylsilyl)acetylene (400 µL, 2.83 mmol) was added dropwise, the reaction mixture warmed to 50 °C and stirred at this temperature for 48 h. Stirring was continued at 50 °C for a further 7 days. After cooling to ambient temperature, the reaction mixture was poured into water (5 mL) and extracted with ether (3 × 5 mL). The combined ether extracts were washed with brine (15 mL), dried (MgSO$_4$) and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (silica, 10% ether in petrol to 80% ether in petrol) to give of the starting *nitrile* (221) and (225) as an inseparable mixture; (225) NMR (300 MHz, CDCl$_3$) δ$_H$ 6.97 (1H, s, ArH), 5.07 (1H,

s, NC*H*), 3.85 (3H, s, O*Me*), 3.77 (3H, s, O*Me*), 3.74 (3H, s, O*Me*), 3.58 (4H, m,

C*H*$_2$OC*H*$_2$), 2.49 (4H, m, C*H*$_2$NC*H*$_2$), 0.27 (9H, s, Si*Me*$_3$).

Attempted Michael addition of (224) and γ-crotonolactone (191)

(1.1 eq) LDA, HMPA, THF, −78 °C, 30 min then −35 °C
add (191), −35 °C, 1 h

(224)
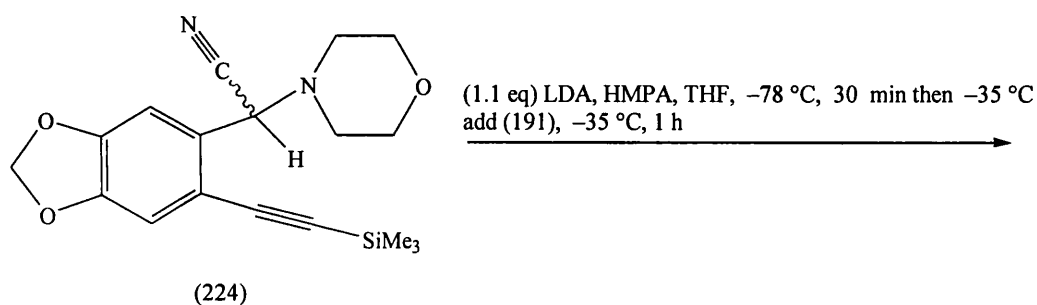
A freshly prepared solution of 1.0 *M* lithium diisopropylamide in THF/hexanes (1.2

mL, 1.2 mmol) was added dropwise to a solution of (224) (0.37 g, 1.08 mmol),

HMPA (0.42 g, 2.34 mmol) in THF (3 mL). The mixture was stirred at −78 °C for 30

min, the temperature was then allowed to rise to −35 °C and a solution of (191) (91

mg, 1.08 mmol) in THF (2 mL) was added dropwise. Stirring was continued at −35 °

C for 1h, the solution was then allowed to reach ambient temperature and stirred for

a further 12 h. The reaction mixture was quenched with sat. aq ammonium chloride

(5 mL) and extracted with ether (3 × 5 mL). The organic extracts were washed with

brine (15 mL), dried (MgSO$_4$) and evaporated under reduced pressure. Tlc of the

crude oil showed 4 spots. The residue was purified by flash column chromatography

(silica, gradient elution; 20% ether in petrol to 50% ether in petrol) to recover (224)

(0.09 g, 24%). No other useful products were isolated.

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