UNIVERSITY OF SOUTHAMPTON

Faculty Of Science.

CHEMISTRY.

SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF PHYLLANTHOCIN.

Master Of Philosophy

By Andrew John King.

Dedicated to
my parents and family.

ACKNOWLEDGEMENTS .

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ABREVIATIONS.

Cat.	Catalytic
DBU	1,8-Diazabicyclo [5.4.0] undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethylazodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethyl aminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
EDTA	Ethylenediaminetetraacetic acid
h.	Hour
HMPA	Hexamethylphosphoramide
I.R.	Infra-red
LDA	Lithium Diisopropylamine
MCPBA	*m*-Chloroperbenzoic acid
MEM	2-Methoxyethoxymethyl
mins.	Minutes
MOM	Methoxymethyl
N.M.R.	Nuclear Magnetic Resonance
PCC	Pyridinium Chlorochromate
PhH	Benzene
PMB	*p*-Methoxybenzoyl
PPTS	Pyridinium *para*-Toluenesulphonic acid
Py	Pyridine
R.T.	Room Temperature
TBAF	Tetrabutylammonium flouride
TBDMS / TBS	Tertiary-butylmethylsilyl
TBDPS	Tertiary-butyldiphenylsilyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TFAA	Tetrafluoroacetic acid

TIPS	Triisopropylsilyl
t.l.c	Thin Layer Chromatography
T.M.	Target molecule
p-TsOH	*p*-Toluene sulphonic acid

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ABSTRACT.

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SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF PHYLLANTHOCIN.

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(+)-Phyllanthocin is a sesquiterpenoid aglycone derived from phyllanthoside, the parent disaccharide which is under advanced clinical evaluation in the United States for treatment of tumors of the breast and colon. In Chapter 1 of this thesis a review of the six syntheses of phyllanthocin reported to date is presented as well as an account of Smith's synthesis of the disaccharide phyllanthose and its union with phyllanthocin to give phyllanthoside.

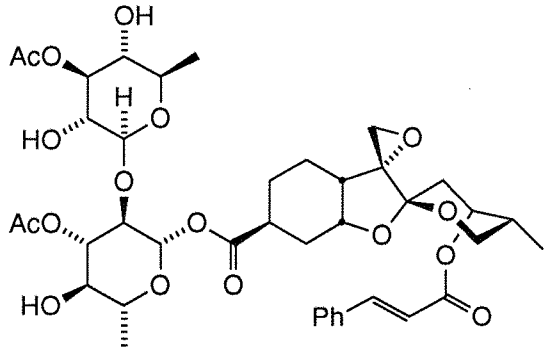
Chapter 2 summarises progress directed toward a synthesis of phyllanthocin in which the key step involves the alkylation of Faller's η^4-cyclohexadiene-Mo$(CO)_2$Cp complex by the sodium enolate of a homochiral β-ketotetrahydropyranone. Oxidative cyclofunctionalisation of the resultant η^3-allyl Mo-complex generates a tetrahydrobenzofuran which incorporates rings A and B of phyllanthocin. Preliminary model experiments which convert a tetrahydrobenzofuran to the spiroacetal framework of phyllanthocin are described.

CONTENTS.

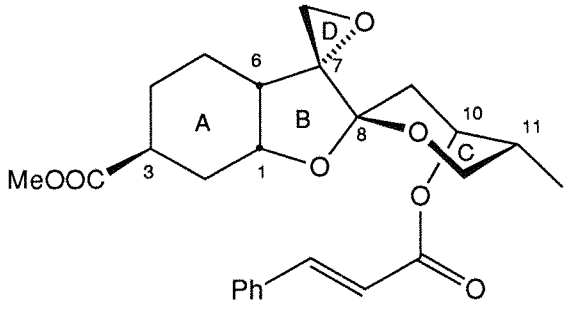
CHAPTER 1

I. INTRODUCTION

With many of the millions of different species of higher plants becoming extinct as each decade passes, it is surprising to find that less than 5% have received even superficial examination as sources of medicinal compounds [1]. The *Euphorbiaceae* family has 600 species [2] ranging from the free floating aquatics to trees with a long history of human medicinal applications. In 1977 Kupchan[3], in collaboration with the U.S. National Cancer Institute (NCI) exploratory program and the U.S. Department of Agriculture, isolated the antineoplastic glycoside phyllanthoside (**1**) from the roots of a Central American tree *Phyllanthus acuminatus,* of the *Euphorbiaceae* genus. Methanolysis of phyllanthoside afforded a crystalline aglycone, phyllanthocin (**2**). Pettit and co-workers[4,5] have now completed a detailed investigation of this Costa Rican tree and have isolated from 1.56 metric tons of chipped stems 216 g of phyllanthoside along with three new antineoplastic glycosides, phyllanthostatins I, II, II, the first two of which have in common with phyllanthoside the phyllanthocin aglycone. All structures have been confirmed by high field NMR spectroscopy and most by single crystal X-ray analysis.



(+) - PHYLLANTHOSIDE (1)



(+) - PHYLLANTHOCIN (2)

Phyllanthoside[2] was found to inhibit the growth of P-388 lymphocytic leukemia (PS system), murine B16 melanoma and carcinoma of the nasophyarynx (KB system). Phyllanthoside is now in advanced preliminary clinical trials in

the U.S. owing to its selective cyctotoxicity at very low doses toward solid tumours of the breast and colon. It has been shown[2,5] that a, 7-8 mg/kg dose of phyllanthocin will increase lifespan by 40-50% in patients suffering from P-388 lymphocytic leukemia and a dose of 16-24 mg/kg will increase the lifespan by 90-105% in patients suffering from B-16 melanoma. In addition phyllanthostatin I, phyllanthoside and phyllanthocin[6] have been shown to exhibit antiviral activity in humans and domestic animals. All three compounds were effective in cell culture studies with *Herpes simplex*, vesicular stomatitis, and Coxsackie viruses. The aglycone phyllanthocin (**2**) retains none of the anti-tumour activity of phyllanthoside which undergoes rapid metabolic degradation.

The structure of the bisabolane sesquiterpene aglycone phyllanthocin (**2**) was determined by single crystal X-ray diffraction[3], and the exact configuration of its seven asymmetric centres distributed about the tetracyclic skeleton were confirmed. An interesting feature of the structure included the unusual folded conformation of the cinnamate ester residue which was found to be almost parallel to the carbomethoxy on C-3 of the cyclohexane ring. This is contrary to the theories of conformational analysis put forward by Barton[7] in support of Cram's[8] and Prelog's[9] rules favouring an extended conformation based only on steric constraints. A recent review[10] put forward evidence of a weak CH/π interaction which could explain the folded conformation.

Ring B of the tetrahydrobenzofuran ring system has two spiro centres, with all four of its carbons being stereogenic. The C-7 spiro epoxide has an *endo*-orientated oxygen relative to the *cis*- fused C7-C8 bicyclic subunit and it was the construction of this spiroacetal moiety that generated our synthetic interest in this molecule.

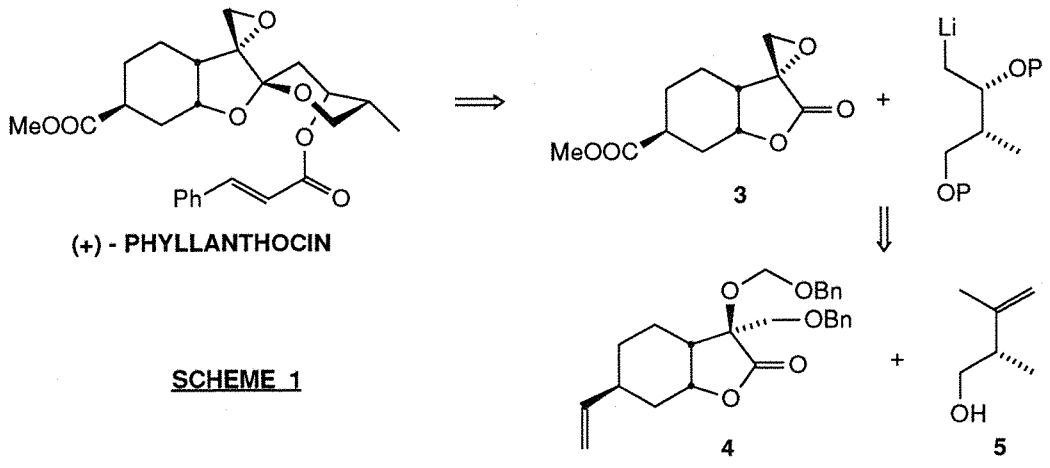
II. PREVIOUS SYNTHETIC ROUTES

Six syntheses of phyllanthocin have been reported to date and these will be surveyed in the order in which they were published.

II.1 *The Collum Strategy*

The first total synthesis of (+)-phyllanthocin was reported in 1984 by McGuirk and Collum[11] whose convergent synthetic strategy is outlined in

Scheme 1. (*S*)-(-)-Perilla aldehyde (Scheme 2) was converted to the corresponding diastereoisomeric cyanohydrins which were protected as the benzyloxymethyl ethers **7**. The cyanohydrin derivatives **7** were then subjected to a thexylborane-mediated double hydroboration - oxidation[12] which achieved a highly stereocontrolled introduction of the annular hydroxyl group because of differential rates of hydroboration of the two alkene functions. The side chain double bond underwent rapid hydroboration and the resultant borane then directed the second intramolecular hydroboration leading to a bicyclic borane which, on oxidation, afforded the diol **8**.

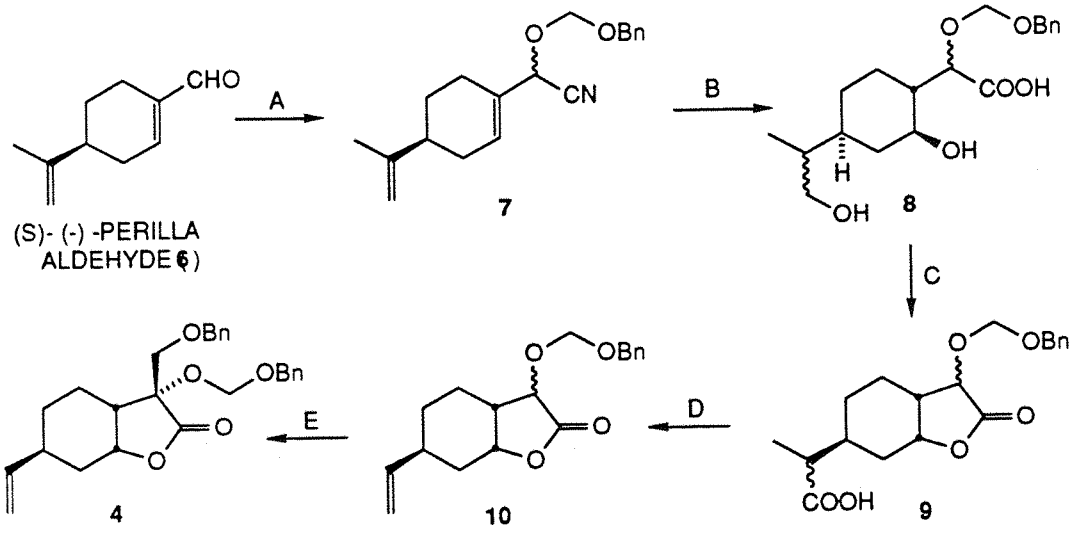


SCHEME 1

After hydrolysis of the nitrile in **8** to the carboxylic acid, an intramolecular Mitsunobu reaction[13] proceeded with complete inversion of stereochemistry at the alcoholic centre resulting in a *cis*-fused tetrahydrofuranone. The remaining primary hydroxyl function in the side chain was then oxidised to the carboxylic acid using chromic acid. The carboxyl group was removed by an oxidative decarboxylation using lead tetra-acetate in the presence of cupric salts[14] to give the alkene **10** as a readily separable mixture of epimers. Interestingly, the decarboxylation was free of regioisomeric purities.

With the removal of the carboxyl group, only 2 diastereoisomers remained corresponding to the epimers at C-7. Fortunately, the stereochemistry at C-7 was of no consequence since it was destroyed in the next step by conversion of **10** to the lithium enolate which was then alkylated selectively from the *exo*-face of the bicyclic system to give the

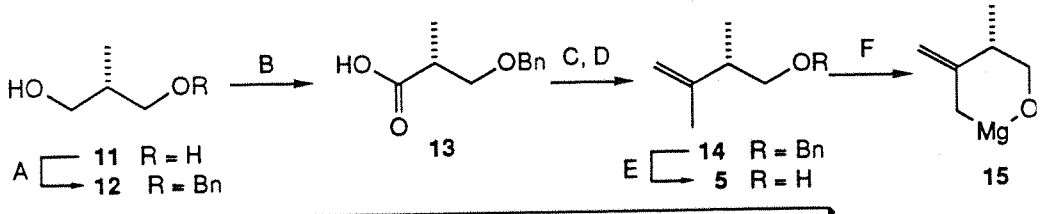
crystalline product **4** in 17.5% overall yield.



SCHEME 2 Experimental conditions and yields

A (i) KCN/HOAc, Et_2O, 25°C (95%); (ii) $PhCH_2OCH_2Cl$, py, 60°C (51%)
B (i) Thexylborane, THF, -40°C, H_2O/NaOAc (83%); (ii)KOH, Ethanol, 100°C, (95%)
C (i) EtOOCN=NCOOEt, PPh_3, THF, -20 °C; (ii)Jones reagent, acetone, 0°C (81%)
D $Pb(OAc)_4$, $Cu(OAc)_2$, py, PhH, 80°C
E $PhCH_2OCH_2Cl$, THF, HMPA, -60°C

The fragment required to append the C-ring was prepared in enantiomerically pure form from the the homochiral alcohol **11** as shown in Scheme 3. The key step in this sequence was the selective metallation of the allylic methyl group in intermediate **5** using Schlosser's base (*t*-BuOK,

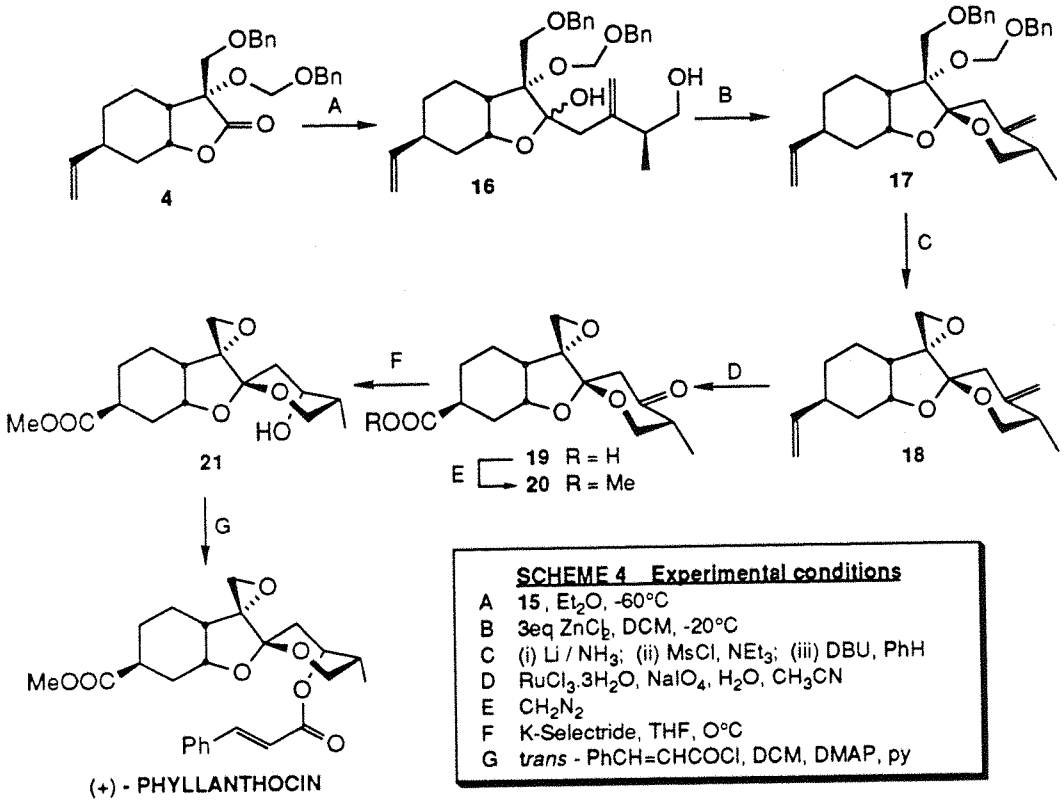


SCHEME 3 Experimental conditions and yields

A NaH, BnBr, DMF, RT
B Jones reagent, acetone
C (i) 1.5eq $(COCl)_2$, PhH; (ii) 3eq $MeCuLi$, Et_2O, -78°C (75-80%)
D $Ph_3P=CH_2$, THF
E Li, NH_3 (55-60% 2 steps)
F (i) *t*-BuOK, *n*-BuLi,hexane, 0°C; (ii) $MgBr_2$, THF

n-BuLi/hexane, 0°C) to give a lithium dianion which was converted to the magnesiocycle **15** on treatment with magnesium chloride. Reaction of the

tetrahydrofuranone **4** with magnesiocycle **15** then led to the diastereoisomeric adducts **16** which cyclised with a very high level of stereocontrol on treatment with zinc chloride to produce the spiroacetal ring in **17** in 69% overall yield from the tetrahydrofuranone. The ratio of diastereoisomers at the anomeric centre was 48:1.



SCHEME 4 Experimental conditions

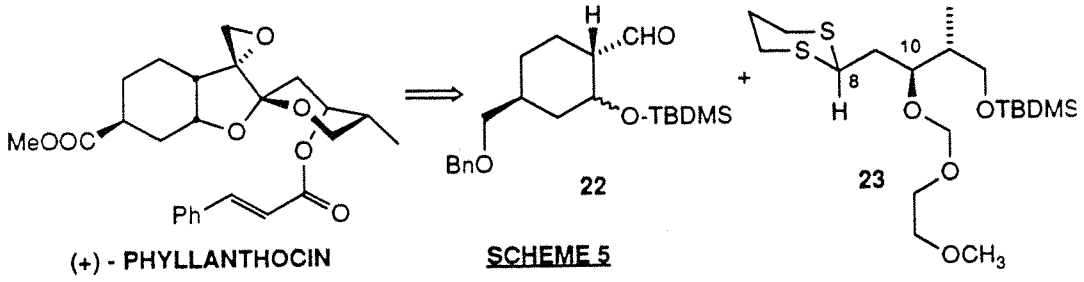
A	**15**, Et_2O, -60°C
B	3eq $ZnCl_2$, DCM, -20°C
C	(i) Li / NH_3; (ii) MsCl, NEt_3; (iii) DBU, PhH
D	$RuCl_3.3H_2O$, $NaIO_4$, H_2O, CH_3CN
E	CH_2N_2
F	K-Selectride, THF, O°C
G	*trans* - PhCH=CHCOCl, DCM, DMAP, py

The spiroepoxide **18** was formed in three steps using standard reactions. Reductive debenzylation of **16** followed by selective mesylation of the primary hydroxyl group and treatment with DBU afforded **18** in 82% overall yield. The two alkenic moieties of **18** were oxidised using Sharpless' catalytic ruthenium tetroxide methodology[15] to provide a rapid and mild route to the keto-acid **19**.

To complete the synthesis, the acid **19** was esterified by diazomethane and the resulting keto ester **20** reduced with high chemo- and diastereoselectivity by equatorial delivery of hydride from the hindered reducing agent K-Selectride to provide the axial alcohol **21** in 42% yield from **18**. Finally, esterification of **21** with *trans*-cinnamoyl chloride gave (+)-phyllanthocin.

II.2 *The Williams strategy*

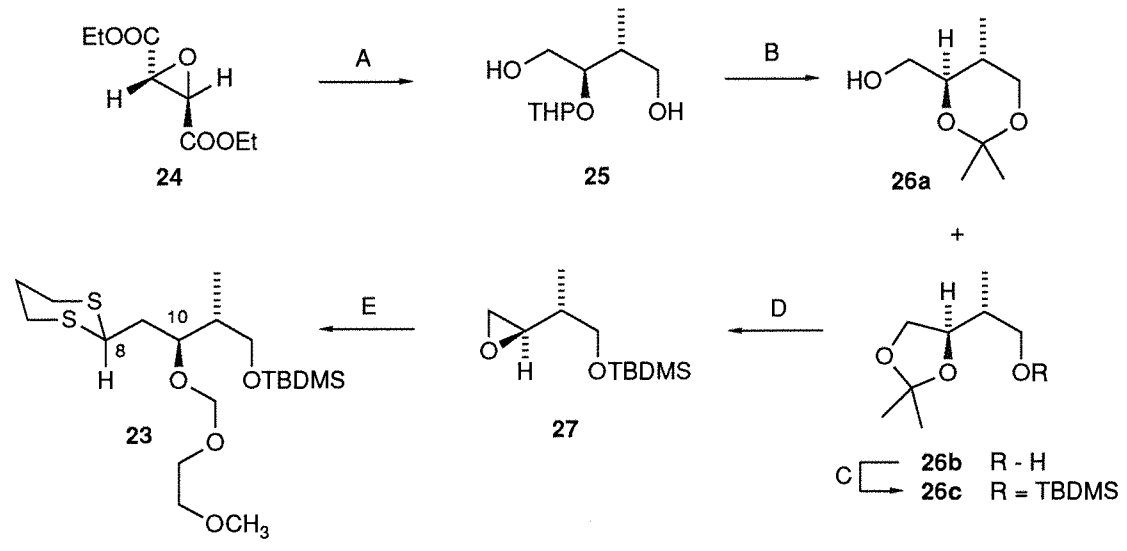
Williams and Sit reported a highly convergent synthesis of (+)-phyllanthocin[16] from two principal fragments: cyclohexane carboxaldehyde **22** and the dithiane **23** which serves as an acyl anion equivalent (Scheme 5). The homochiral 1,3 - dithiane **23** was synthesised from (+) - tartaric acid *via* the oxiran **24** as outlined in Scheme 6. Lithium dimethylcuprate was used to open the epoxide **24** to give the alcohol **25** which incorporated the two stereogenic centres at C-10 and C-11 of phyllanthocin. The hydroxyl function was protected as the THP ether and the two ester functions reduced to the diol **25**.



SCHEME 5

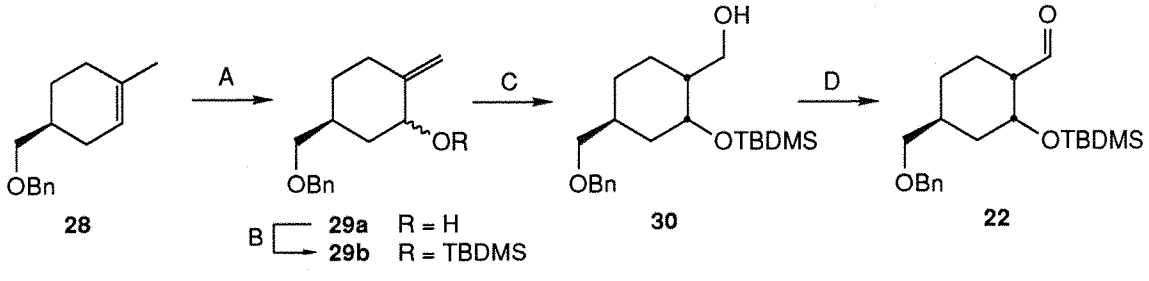
Removal of the tetrahydropyranyl group *via* acid-catalysed methanolysis provided a water-soluble triol which was not purifed further but immediately treated with acetone and *p*-toluenesulphonic acid to provide a mixture of the 1,3-dioxan **26a** and the the 1,3-dioxolan **26b** in the ratio 1:5 respectively. After protection of the sole remaining hydroxyl function in the mixture **26a** and **26b** as the corresponding *t*-butyldimethylsilyl ethers, the diastereoisomers were separated by column chromatography to provide pure **26b**. Selective hydrolysis of acetonide **26b** proved problematic due to the concomitant removal of the TBDMS group in an acidic medium. However treatment of **26b** with excess 1,2-ethandithiol achieved selective removal of the acetonide to unmask the diol function which was converted to the oxiran **27** in the usual way. Finally, nucleophilic cleavage of the oxiran by 2-lithio-1,3-dithian followed by protection of the resultant alcohol as the MEM-ether gave the desired fragment **23a**.

The A-ring fragment **22** with its three stereogenic centres was prepared



SCHEME 6 Experimental conditions and yields

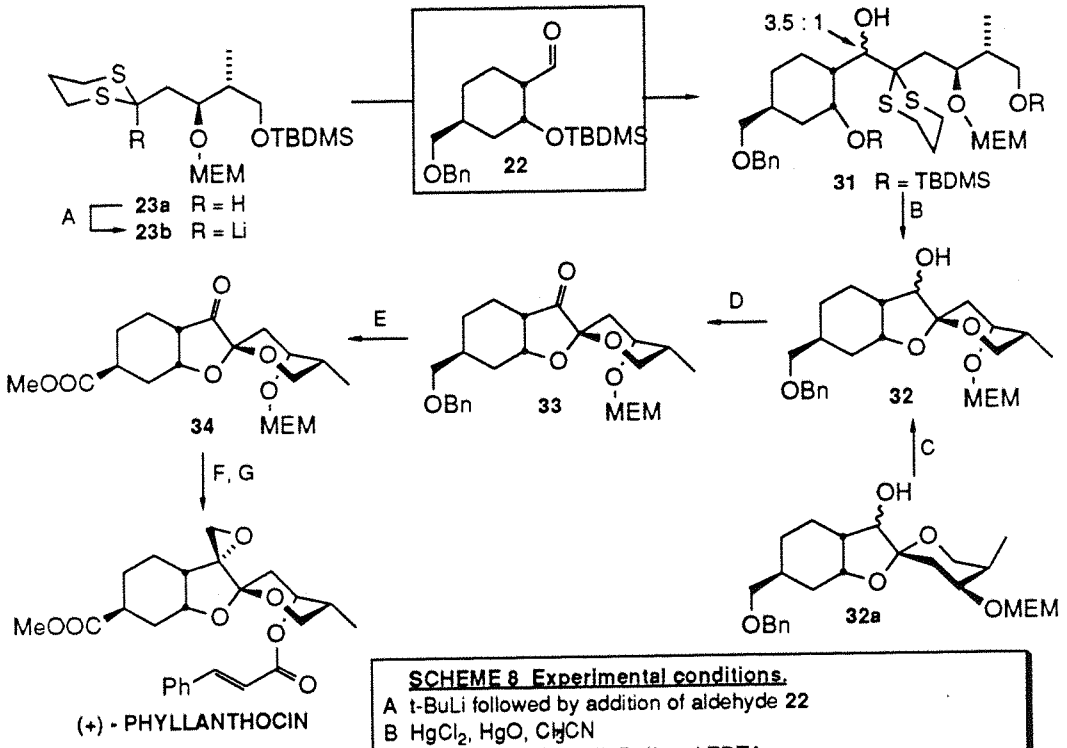
A (i) $LiMe_2Cu$, Et_2O, -78°C; (ii) Dihydropyran, *p* -TsOH; (iii) $LiAlH_4$
B (i) *p* - TsOH, CH_3OH, 22°C; (ii) acetone, *p* - TsOH
C (i) t-$BuMe_2SiCl$, DMAP, DCM, 22°C, 2 h; (ii) separate
D (i) Ethanethiol (7eq), $CHCl_3$, *p* - TsOH; (ii) TsCl, Et_3N, DCM; (iii) NaH, THF (76% overall from **26b**)
E (i) 2-lithio-1,3-dithiane, THF, -25°C, 95%; (ii) MEM-Cl, DMAP, di-isopropylethylamine ,40 h, 95%



SCHEME 7 Experimental conditions and yields

A (i) MCPBA, DCM, 10°C -> RT 89%; (ii) Li 2,6-dimethylpiperidide, Et_2O, 50°C, 2 h, 90%
B t-$BuMe_2SiCl$, DMF, DMAP, 22°C, 18 h 100%
C Borane, THF, 22°C, H_2O_2, NaOH
D PCC

as shown in Scheme 7. The homochiral benzyl ether **28** was epoxidised with *m*-chloroperbenzoic acid efficiently but the stereocontrol was poor. A 1:1 mixture of diastereoisomers was obtained which were then subjected to base-induced epoxide opening using lithium 2,6-dimethylpiperidide to afford the exocyclic allylic alcohols **29a** as a 1:1 mixture of isomers. The epoxide cleavage was highly regioselective for the generation of the exocyclic alkene; only 6% of the endocyclic allylic alcohols was obtained. After the formation of the TBDMS ethers, the axial and equatorial isomers **29b** were separated by using column chromatography. Hydroboration of the axial TBDMS ether **29b** occurred with only modest stereoselectivity (*ca.* 2:1) to give preferentially alcohol **30** in 65% yield. The required aldehyde **22** was obtained by PCC oxidation of the primary alcohol **30**.



SCHEME 8 Experimental conditions.
A t-BuLi followed by addition of aldehyde **22**
B $HgCl_2$, HgO, CH_3CN
C (i) $Mg(OCOC_5)_2$; (ii) Buffered EDTA
D Jones oxidation
E (i) H_2, 5% Pd/C, CH_3OH; (ii) Jones oxidation; (iii) diazomethane
F (i) $ZnBr_2$, DCM, 22°C, 8 h; (ii) Dimethylsulphoxonium methylide
G Cinnamoyl chloride, DCM, DMAP, 40°C, 2 h.

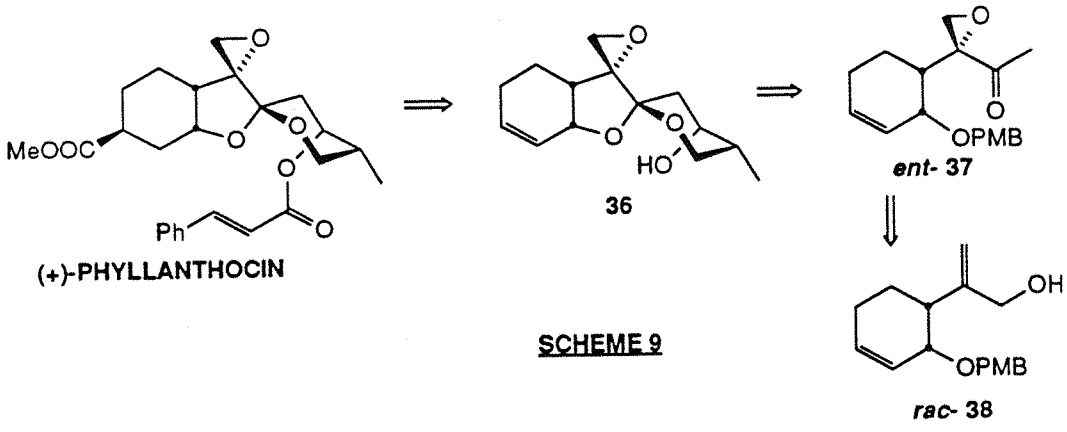
The union of fragments **22** and **23a** was achieved by condensing the lithio derivative **23b** with the aldehyde function of **22** to generate a separable mixture of two diastereoisomers. The silyl protecting group was removed by TBAF under acidic conditions to afford the triols **31a,b**

(Scheme 8).

Hydrolysis of the dithiane moiety afforded a 3:1 mixture of spiroacetals **32a** and **32b** as well as the deprotected keto triol which was removed by chromatography. Addition of a protic acid rapidly formed the spiroacetals in good yield, but these kinetic conditions favoured the formation of the unnatural isomer **32a**. All was not lost however, as the configuration of the C-8 spiro centre of the unnatural isomer, could be isomerized by treatment with a Lewis acid such as $ZnBr_2$ with concomitant loss of the MEM protecting group. Williams and Sit found that magnesium trifluoroacetate[17] was the reagent of choice to isomerise **32a** to **32b**. The selectivity of this Lewis acid results from the formation of a stable chelation complex between the C-ring axial hydroxyl function and the B-ring tetrahydrofuran oxygen in **32b** which could then be freed of the magnesium ion by sequestration using EDTA. In this way the required spiroacetal **32b**, contaminated with only trace amounts of the unnatural spiroacetal configuration **32a**), could be obtained. Oxidation of the secondary alcohol provided the required ketone **33**.

Three simple steps (catalytic debenzylation, Jones oxidation, esterification) converted **33** to the ester **34**. After removal of the MEM protected group in **34** with zinc bromide, the spirocyclic oxiran was introduced stereoselectively (30:1) using dimethylsulphoxonium methylide. Finally esterification of the free hydroxyl group with cinnamoyl chloride provided (+)-phyllanthocin.

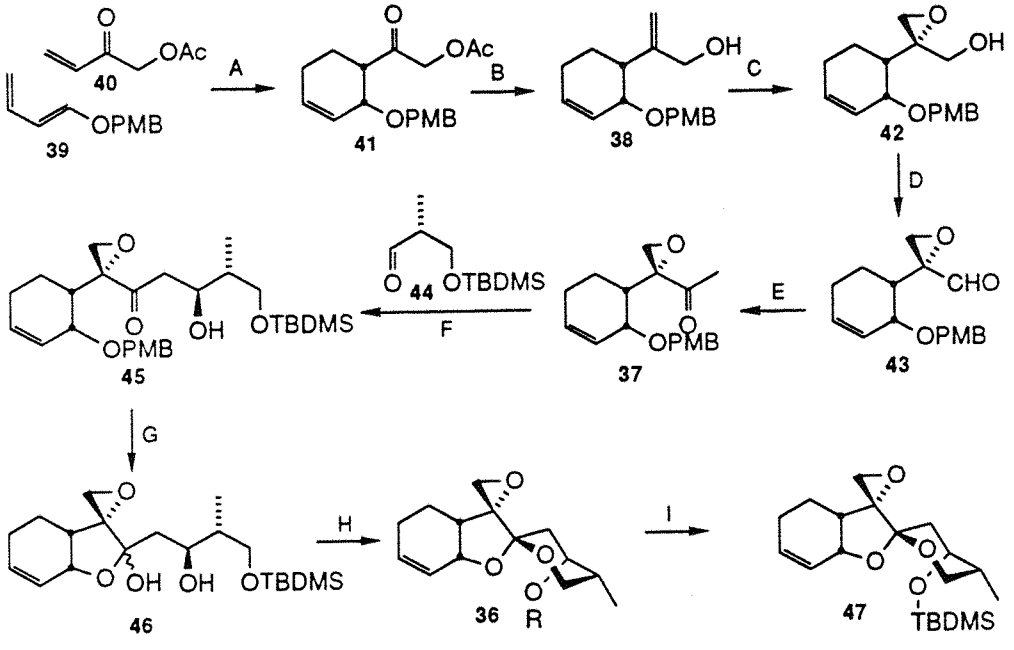
II.3 *The Burke Strategy*



(+)-PHYLLANTHOCIN **36** ***ent*- 37** ***rac*- 38**

SCHEME 9

Burke and co-workers have recently published full experimental details of their 17-step synthesis of (+)-phyllanthocin which was first published in 1985[18, 19]. Their strategy, outlined in Scheme 9, includes the use of a Sharpless epoxidation to introduce the oxiran function in **37** as well as secure a homochiral intermediate from the racemic allylic alcohol **38**. A particularly elegant feature was the use of a Rh(I)-catalysed hydroformylation reaction on the A-ring cyclohexene to introduce the carbomethoxy group at C-3.



SCHEME 10 Experimental conditions and yields

A	Heat (69%)
B	(i) $Ph_3P{=}CH_2$, THF, -100°C; (ii) K_2CO_3, MeOH, 25°C (61%)
C	*t*BuOOH, (+)-Diethyl tartrate, Ti (O-*t*Bu)$_4$, DCM, -23°C, 5.5 h (95%)
D	Swern oxidation
E	(i) MeLi (5eq), THF, -78°C, 6 min; (ii) Swern oxidation (71%)
F	LDA, THF, -78°C, 1 h, Aldehyde**44**, 10 min. (65%)
G	DDQ, DCM, H_2O (19:1), 25°C, 1 h (94%)
H	5% HF, CH_3CN, 25°C, 10 min (95%)
I	*t*-BuMe_2SiOTf, 2,6-lutidine, DCM, 0°C, 10 min

The synthesis began (Scheme 10) with a Diels-Alder reaction between acetoxymethyl vinyl ketone **40** and the *p*-methoxybenzyl-substituted butadiene **39** which gave the A-ring cyclohexene derivative **41** as a 3.7:1 mixture of isomers (only the major isomer shown). A Wittig methylenation

followed by methanolysis of the acetate gave the the allylic alcohol **38** in 61% yield.

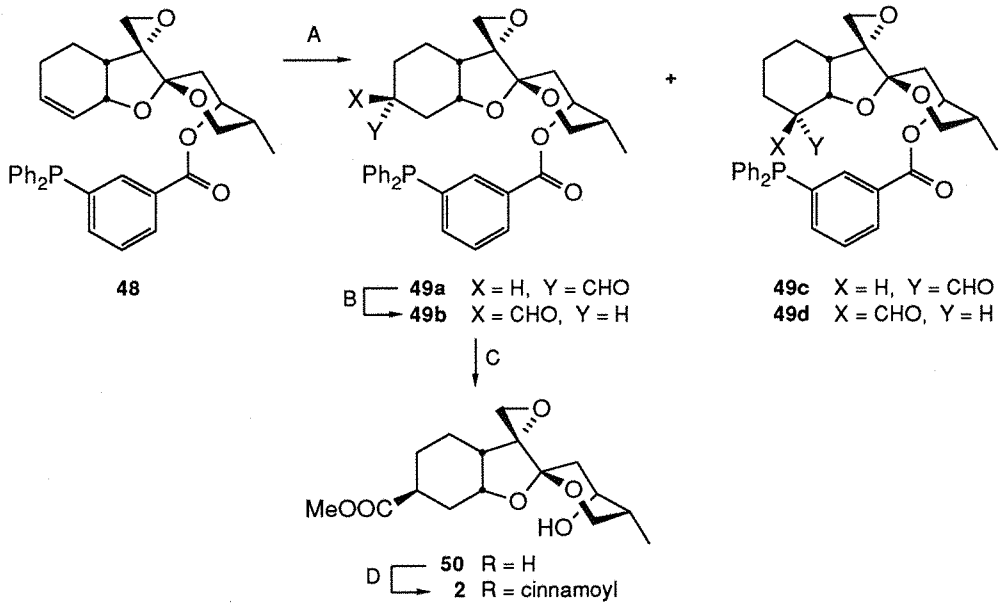
Application of the Sharpless epoxidation[15] to the allylic alcohol **38** was attempted in two modes. Kinetic resolution failed in that the rate differential for the epoxidation of the enantiomers of **38** was insufficient. However, epoxidation to complete consumption of **38** with L-(+)-diethyl tartrate/$Ti(O\text{-}t\text{-}Bu)_4$/*t*-BuOOH gave diastereoisomeric epoxides in a combined yield of 95% from which the desired crystalline epoxide **37**(≥ 95% ee) was easily isolated by column chromatography. The epoxy alcohol **37** was then converted in two simple steps[20] to the epoxyketone **43**.

Appendage of the carbons which eventually make up the C-ring was achieved by means of a diastereoselective aldol reaction between the lithium enolate of **37** and the homochiral aldehyde **44**. The aldol reaction[21] furnished a 3.6:1 mixture of diastereoisomers in 83% yield from which the desired *anti*-isomer **45** was easily isolated by column chromatography. After oxidative removal of the *p*-methoxybenzyl protecting group a mixture of hemiacetals **46** was obtained which cyclised under thermodynamic control on treatment with 5% aqueous HF in acetonitrile to give the desired spiroacetal **36** in 91% yield. These results stand in contrast to the poor diastereoselectivity in the spiroacetalisation reaction promoted by protic acids previously studied by Williams and Sit (*vide supra*).

The principal task remaining was the introduction of the carbomethoxy group at C-3. After protection of the C-10 axial hydroxyl function as the *t*-butyldimethylsilyl ether **47**, regioselective functionalisation of the cyclohexene subunit was attempted. Unfortunately, **47** was inert to the usual methods for effecting hydrometalation/formylation (e.g., hydrozirconation with Schwartz's reagent $[(Cp)_2Zr(H)Cl]$ or 9-BBN). Regioselective hydroformylation was eventually achieved using a Rh(I) catalyst but adequate regiocontrol (C-3 *vs* C-4) was secured only after extensive investigation revealed the importance of a suitable phosphine tethered to the C-10 hydroxyl function as shown in Scheme 11.

The tethered phosphine **48** was prepared in 88% *via* DCC coupling with the appropriate phosphine carboxylic acid (Scheme 11). On hydroformylation at elevated temperature and pressure, a mixture of C-formyl products were obtained in the ratio **49a: 49b: 49c: 49d** = 7.7 : 0.3 : 1 : 1. Thus, the formyl group was delivered selectively to the C-3 position

with the *endo*stereochemistry which is a consequence of an *intramolecular* hydroformylation. The position of the phosphine on the tether was found to be critical for the desired regiocontrol.



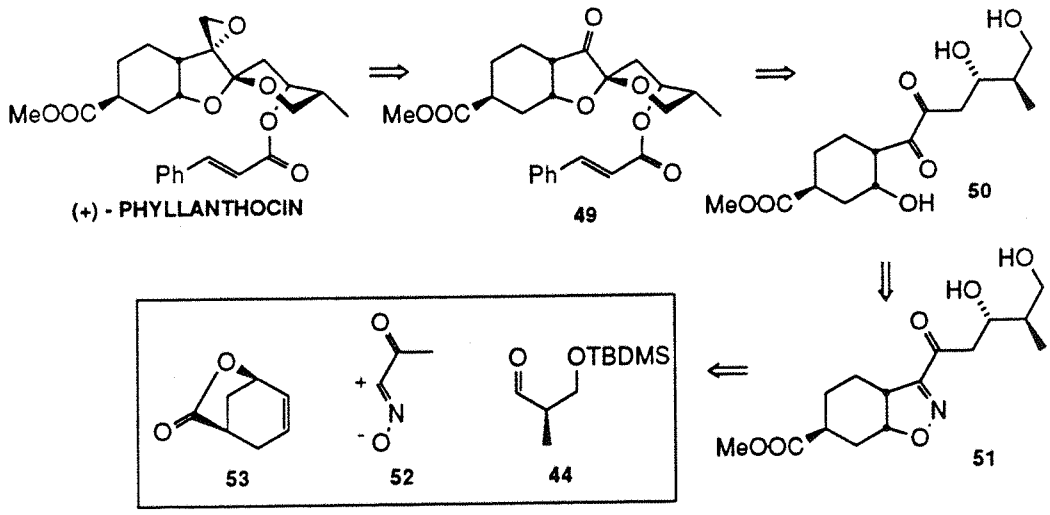
SCHEME 11 Experimental conditions and yields

A 8 mol % [(COD) $RhOAc]_2$, PhH, 1:1 CO/H_2 (710 psi), 85°C, 3 h (77%)
B NaOMe, MeOH, 25°C, 2 h (73%)
C (i) H_2CrO_4, acetone, 0°C, 10 min; (ii) NaOH, MeOH, 75°C; (iii) CH_2N_2, Et_2O, 0-> 25°C (84%)
D Cinnamoyl chloride, DMAP, DCM (82%)

To complete the synthesis, Burke and co-workers first epimerised the *endo*-formyl derivative **49a** to the thermodynamically preferred *exo* compound **49b**. The aldehyde **49a** was then converted to the ester in the usual way and the phosphine tether removed by hydrolysis to give **50**. Finally, esterification of the free C-10 hydroxyl function in **50** with cinnamoyl chloride gave (+)-phyllanthocin.

II.4 *The Martin Strategy*

Martin and coworkers[22] accomplished a total synthesis of (+)-phyllanthocin using a strategy (Scheme 12) which features a stereo- and regioselective dipolar cycloaddition of a nitrile oxide followed by unmasking of the resultant isoxazoline to provide a key β-hydroxy ketone. Their synthesis began (Scheme 13) with the known homochiral lactone **57** which underwent dipolar cycloaddition in refluxing toluene with the

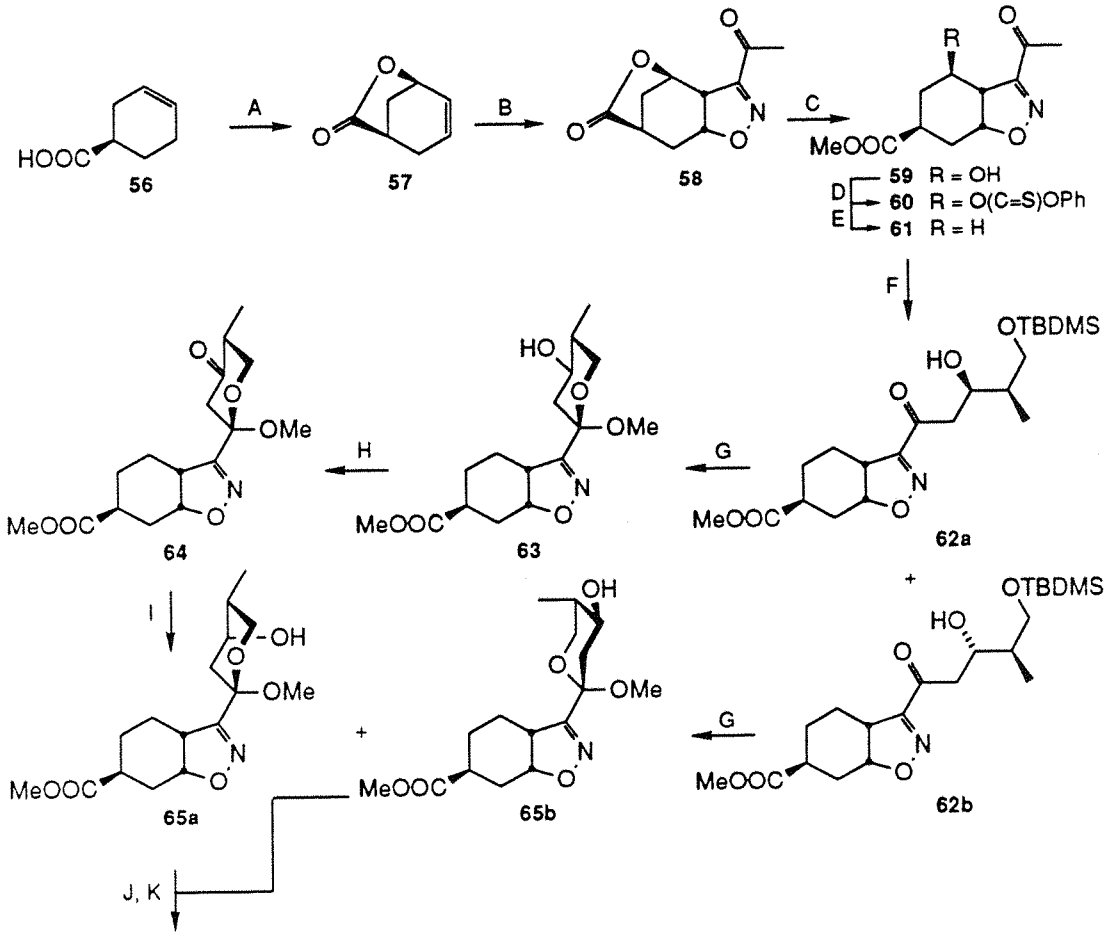


SCHEME 12

nitrile oxide **54** prepared from acetohydroximidoyl chloride to give the isoxazoline **58** (45%) along with two other diastereoisomeric adducts (20% and 15%). The lactone ring, having accomplished its intended purpose of stereochemical bias, was then opened to the hydroxy ester **59** from which the hydroxyl group was removed by radical deoxygenation of the phenylthionocarbonate ester **60** to give the isoxazoline **61** in 70% overall yield from cycloadduct **58**.

As in the synthesis of Burke and co-workers (*vide supra*), the homochiral aldehyde **44** was united to the methyl ketone in **61** *via* an aldol condensation involving the corresponding lithium enolate. Although better diastereoselectivity (9:1) could be obtained using Lewis acid-catalysed variants of the Mukaiyama directed aldol reaction, the yields were much lower (≤ 20%), perhaps as a result of competition between other heteroatoms in the substrate for the Lewis acid. The lithium enolate offered good yields (78%) of a mixture of aldol adducts **62a** and **62b** in the ratio 1.2:1 respectively.

In practical terms, the poor diastereoselectivity in the aldol reaction was of little consequence since the incorrect isomer **62a** could be converted to a useful product albeit at the expense of some additional steps. Thus, removal of the TBDMS protecting group under acidic conditions in MeOH resulted in the formation of the acetal **63** as a single isomer. The stereochemistry of the hydroxyl group in **63** was simply inverted by a two-step oxidation-reduction procedure (73%) to give **65a**. Similarly, the



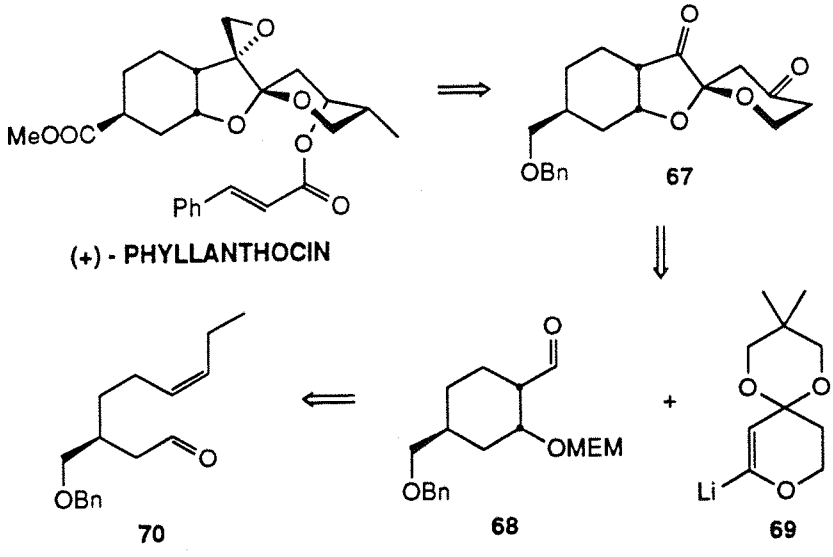
SCHEME 13 Experimental conditions and yields

A (i) I_2,; (ii) DBU (96%)
B Nitrile oxide (**54**), toluene, reflux, 18 h (45%)
C K_2CO_3, MeOH, RT, 0.5h, (85%)
D ClCSOPh (1.7eq), DMAP (2.0eq), DCM, RT, 26 h, (83%)
E Bu_3SnH (1.1eq), AIBN, PhH, reflux, 2 h (65%)
F LDA, THF, -78°C, 0.75 h; add aldehyde (**44**): **62a:62b** = 1.2:1
G 5% HF, MeOH, RT, 20 h, (70-80%)
H Py-SO_3, Me_2SO, Et_3N, RT, 0.5 h
I L-Selectride, THF, -78°C, 0.5 h, (73%)
J H_2 (55 psi) , W-2 Raney Ni, $B(OH)_3$ (3eq), MeOH(15%), RT, 20 h, (82%)
K CF_3SO_3H (5 mol %), DCM, RT, 2 h, (78%)

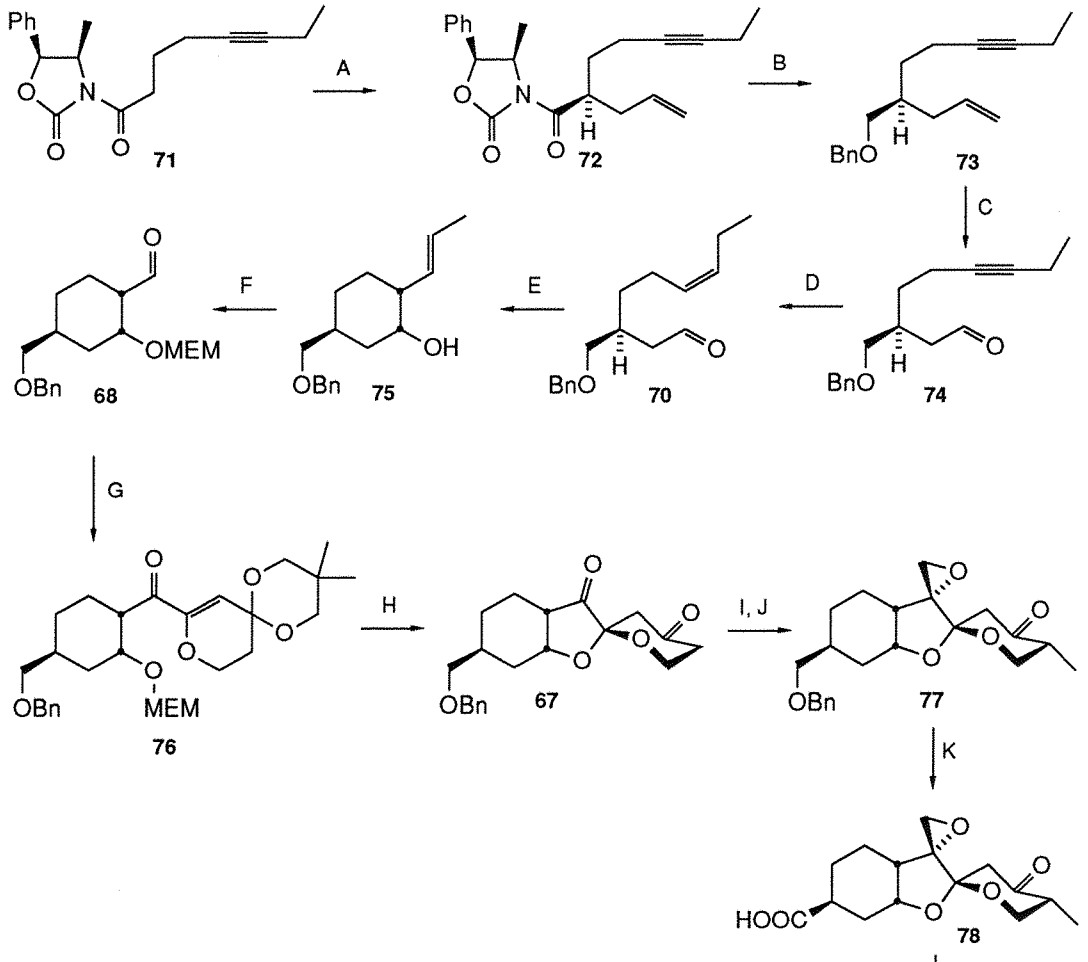
aldol adduct **62b** was converted in 70-80% yield to a mixture of the acetals **65a** and **65b** in the ratio 2.7:1. Both **65a** and **65b** underwent reductive cleavage of the isoazoline ring followed by acid-catalysed cyclisation to afford the spiroacetal **66** (separable 18:1 mixture of diastereoisomers at the anomeric centre) which is akin to an intermediate in the Williams and Sit synthesis (*vide supra*).

II.5 *The Smith Strategy*

The four syntheses discussed so far were convergent in that they depended on the linkage of a homochiral A-ring cyclohexane unit with a C-ring carbon fragment incorporating the correct methyl-bearing stereogenic centre at C-11. By using a convergent approach, these syntheses deftly avoided the problem of fixing the relative stereochemistry between the A-ring and C-11. Smith and Fukui[23] have accomplished a linear synthesis of (+)-phyllanthocin which is remarkable for its simplicity. Their strategy, outlined in Scheme 14, shows that six stereogenic centres were created by diastereoselective reactions starting with the simple aldehyde **70** as the sole stereocontrol element. A further novelty in their synthesis was the use of metallated dihydropyran **69** to introduce the C-ring intact.



SCHEME 14



SCHEME 15 Experimental conditions and yields

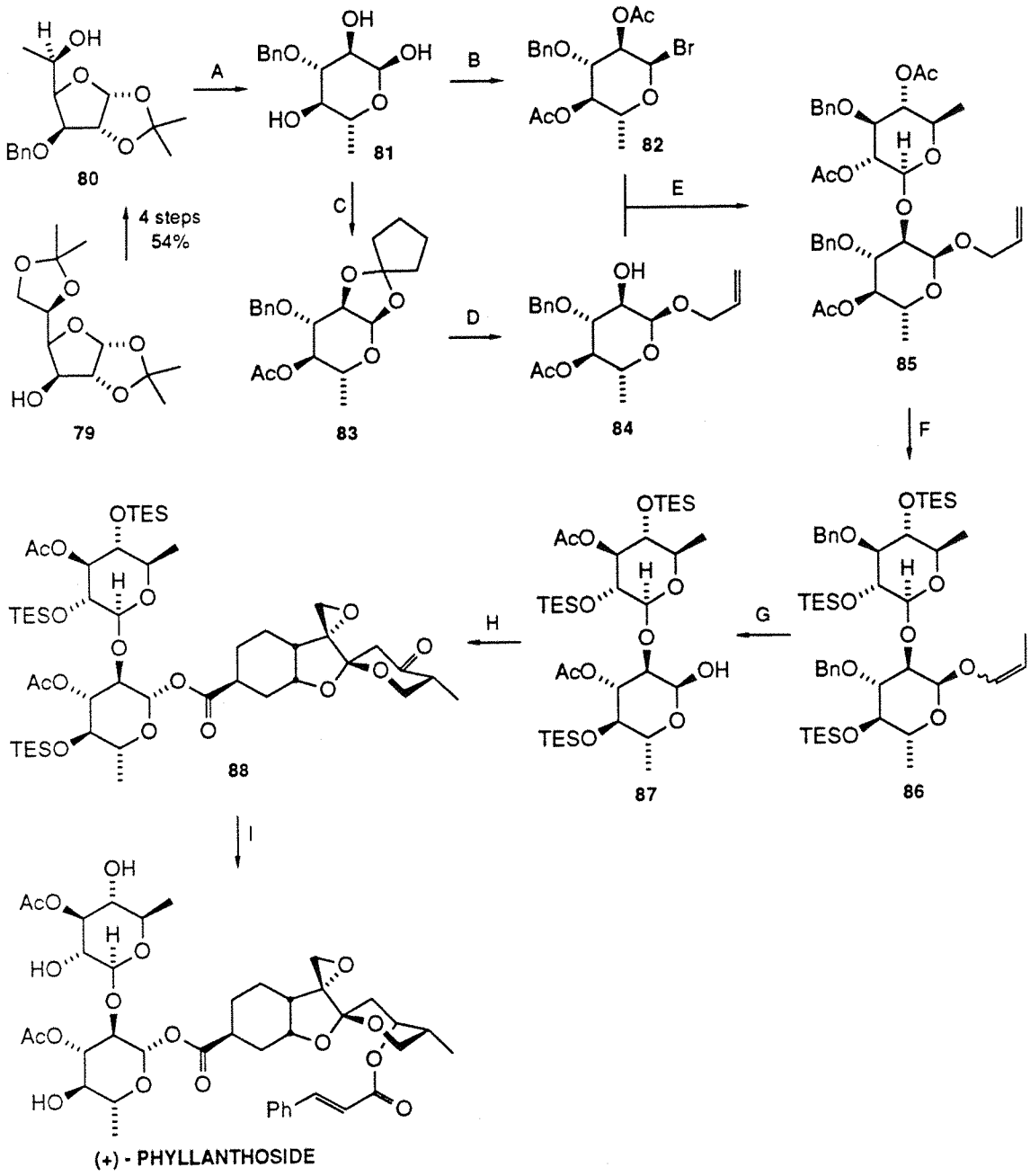
A (i) $(Me_3Si)_2NLi$, THF; (ii) Allyl bromide (98%)
B (i) $LiAlH_4$, THF; (ii) Bn-Br, KH
C O_3, DCM (62%, 3 steps)
D Lindlar cat, H_2 (98%)
E Me_2AlCl, DCM (83%)
F (i) MEM-Cl; (ii) O_3 (75%)
G (i) Lithiated dihydropyran **68**, (ii) H_3O+; (iii) Swern oxidation (79%)
H (i) $ZnBr_2$,; (ii) CSA (71%)
I Dimethylsulphoxonium methylide (79%)
J (i) LDA, Me_3SiCl; (ii) $BnNMe_3F$, MeI ; (iii) DBU, THF (71%)
K (i) H_2, Pd/C; (ii) RuO_2, $NaIO_4$ (76%)
L (i) CH_2N_2; (ii) $NaBH_4$; (iii) Cinnamoyl chloride (66%)

The crucial stereogenic centre at C-3 in the aldehyde **70** was introduced (Scheme 15) by an asymmetric alkylation of the oxazolidinone **71**. The alkylation was efficient (92%) and diastereoselective (96:4). The product **72** was converted in four simple steps (61% overall) to the aldehyde **70**. The A-ring and the two stereogenic centres at C-5 and C6 were created simultaneously (84% yield) by a Lewis acid-catalysed intramolecular ene reaction (step E, Scheme 15). Ozonolysis then provided the aldehyde **68** which had previously been prepared by Williams and Sit albeit with a different protecting group (see Scheme 7).

The C-ring was introduced by nucleophilic addition of the metallated dihydropyran **69** to the aldehyde **68** followed by oxidation. After removal of the MEM protecting group of the enedione **76** with zinc chloride, spirocyclisation took place on treatment with camphorsulphonic acid to give the spiroacetal **67** ((71%) along with 2% of the C-8 isomer[24].

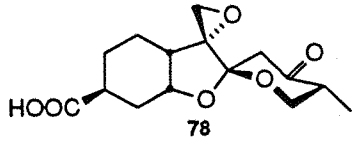
Three stereochemically demanding operations remained to complete the synthesis: methylenation[25] at C-7, α-alkylation at C-11, and reduction of the ketone at C-10. Of these, the first and third goals were precedented in the previous syntheses and worked well. However, regioselective alkylation α to the ketone proved problematic owing to selective alkylation of **67** at C-9 using the standard kinetic alkylation methods. However, the problem was circumvented[26] by regioselective conversion of **67** to the C-10/C-11 enol silane followed by alkylation with a large excess of methyl iodide in the presence of benzyltrimethylammonium fluoride. As expected, alkylation took place predominantly from the axial face of the ring to afford the methyl group in the axial position but the stereochemistry was easily corrected by equilibration to the more thermodynamically favourable equatorial isomer by treatment with DBU. The alkylation product **77** converged with the synthesis of McGuirk and Collum (*vide supra*) whose established methodology served to complete the synthesis.

Smith and Rivero[27] have accomplished the only synthesis of the glycoside (+)-phyllanthocin (**1**) reported to date (Scheme 16). Both monosaccharide units **82** and **84** of the disaccharide phyllanthose were ultimately prepared from 1,2:5,6-di-isopropylidene glucofuranose **79** which was first converted to the 6-deoxyfuranose **80** in 4 steps using known methodology. β-Glycosidation using a modified Koenigs-Knorr[28, 29]



SCHEME 16 Experimental conditions and yields

A 2N H_2SO_4, THF (1:1) (94%)
B (i) Ac_2O, DMAP, pyr (85%); (ii) HBr, HOAc (85%)
C (i) 1,1-dimethoxycyclopentane (68%), (ii)Ac_2O, DMAP (100%)
D allyl alcohol, CSA (96%); separate anomers (1:1)
E $Hg(CN)_2$, PhH-$MeNO_2$ (1:1) (68%)
F (i) Pd/C (76%); (ii) K_2CO_3, MeOH; (iii) TESCl (85% 2 steps)
G (i) O_3 (90%); (ii) Pd/C, H_2; (iii) Ac_2O, 4-pyrollidinopyridine; (iv) NEt_3, MeOH (67% 3 steps)
H acid **78**, i-PrOOC-N=N-COO-i-Pr, Ph_3P (55%) 2:1 mixture of anomers
I (i) $NaBH_4$, MeOH (85%); (ii) cinnamoyl chloride, 4-pyrollidinopyridine (91%); (iii) aq HOAc (100%)



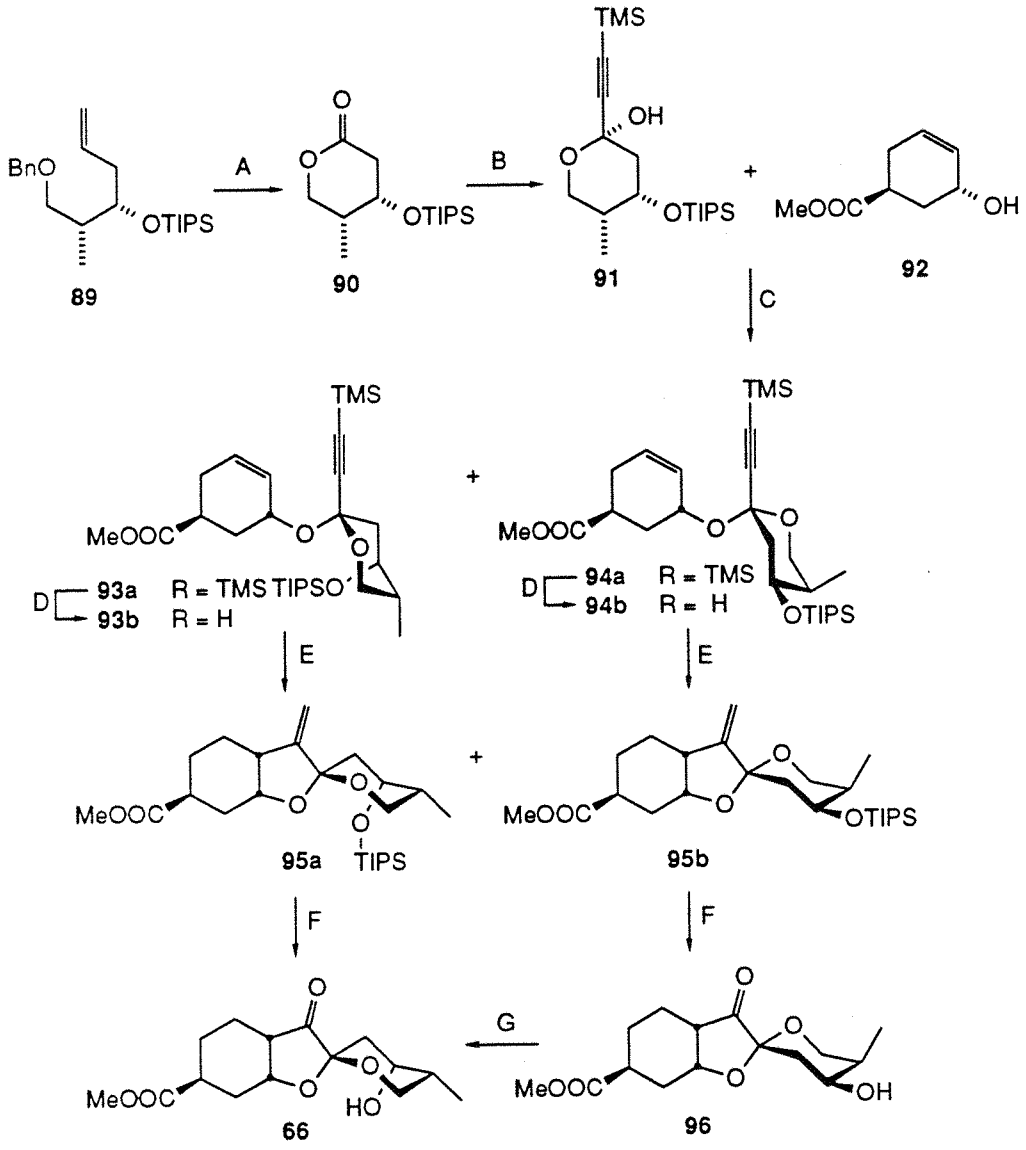
78

procedure gave the phyllanthose derivative **85** which was subsequently transformed to the lactol **87**. Unfortunately, the stereochemistry at the lactol centre which had been carefully preserved throughout the synthesis was scrambled during the mild conditions required to free the lactol **87** from its formate ester precursor and a 2:1 mixture of anomers resulted with the desired α-anomer predominating. A Mitsunobu reaction[30] between the mixture **87** and the acid **78** (Scheme 15) gave the acylglycosides (α:β =1:2, 55% yield) with clean inversion of sereochemistry. The desired β-glycoside **88**, the main product of the reaction, was separated by HPLC and converted to (+)-phyllanthoside in three further steps.

II.6 *The Trost Strategy*

Trost and co-workers[31] have used the synthesis of (+)-phyllanthocin as a vehicle for demonstrating the use of Pd(II)-catalysed cycloisomerisation of enynes[32] in the synthesis of tetrahydrofuran rings[33]. Thus the strategy adopted by Trost involved the synthesis of the acetals **93** and **94** (Scheme 17) which incorporated rings A and C; the B-ring tetrahydrofuran was then introduced using Pd-catalysed cycloisomerisation chemistry. The reaction of hemiacetal **91** with the secondary alcohol **92** was problematic owing to the acid sensitivity of the propargylic alcohol. However, the desired consensation was eventually achieved using K 10 montmorillonite clay and powdered 5A molecular sieves at 30°C in benzene. Under these conditions, the desired acetals **93a** and **94a** were obtained in 74% yield and these could be chromatographically separated after desilylation of the acetylene.

The individual isomers **93b** and **94b** were cycloisomerised using $(dba)_3Pd_2$ (2.5 mol %), N,N'-bis(benzylidene)ethylenediamine (BBEDA)(6 mol %), 1.5 equivalents of acetic acid, and 10 equivalents of polymethylhydrosiloxane (PMHS) which served as a reducing agent. In both cases the reductive cyclisation under the acidic conditions resulted in formation of a mixture of the desired methylene tetrahydrofuran derivatives **95a** and **95b** . After ozonolysis of the methylene group, the mixture of was equilibrated in the presence of zinc chloride to give the desired spiroacetal **66** as the main product along with minor amounts of its diastereoisomer **96**. Spiroacetal **66** was then transformed to (+)-phyllanthocin along lines well-established by previous workers



SCHEME 17 Experimental conditions and yields

A (i) $NaIO_4$, $KMnO_4$, *t*-BuOH, RT, pH 7; (ii) H_2, 10% Pd/C, EtOH; (iii) ppts, 5A mol sieves, PhH (74%)
B TMS-CC-Li, THF, -78°C (98%)
C PhH, K 10 montmorillonite clay, 5A mol sieves, RT
D K_2CO_3, CH_3OH, 0°C
E Polymethylhydrosiloxane, ([dba] $_2Pd_2CHCl_3$), N,N'-dibenzylidenethylenediamine, HOAc, RT
F O_3, CH_3OH, DCM, -78°C
G $ZnBr_2$, DCM, -78°C

(Williams, Martin, and co-workers).

II.7. *Conclusion.*

The six published total syntheses of (+)-phyllanthocin have largely depended upon adaptations of well-known reactions to achieve the final goal. Comparatively little new or seldom used chemistry has evolved. There are three noteworthy exceptions. Burke's hydroformylation chemistry represented a rare attempt to exploit a reaction which is well-known in the bulk chemical industry to the problem of ring appendage construction. Smith's clever elaboration of six stereogenic centres from a single simple homochiral fragment deserves special mention as does his use of a metallated dihydropyran as an acyl anion equivalent. It is unfortunate that the ample precedent for this procedure went unacknowledged[34]. Finally Trost's Pd-catalysed reductive cycloisomerisation chemistry represented a new development with considerable potential for the synthesis of other oxacyclic natural products.

In the next chapter, some preliminary experiments aimed at exploring the use of cationic moybdenum complexes to the synthesis of tetrahydrobenzofuran precursors to the A and B rings of phyllanthocin will be presented.

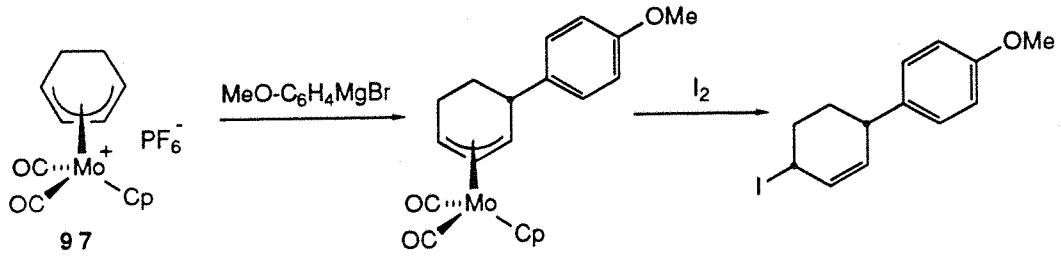
CHAPTER 2
RESULTS AND DISCUSSION.

III. *INTRODUCTION*

In Chapter 1 of this thesis we described various approaches to the synthesis of the potential antineoplastic agent phyllanthocin which have appeared over the last decade. In this chapter we describe progress towards an alternative synthesis of phyllanthocin in which an early key step involves a chain appendage strategy based on the alkylation and cyclofunctionalisation of cationic molybdenum complexes[34]. We will describe in turn a) the preparation and literature precedent for the alkylation of η^4-cyclohexadiene-$Mo(CO)_2Cp$ complexes; b) the application of such reactions to potential phyllanthocin intermediates; and c) some preliminary experiments directed toward the elaboration of the spiroacetal ring system of phyllanthocin.

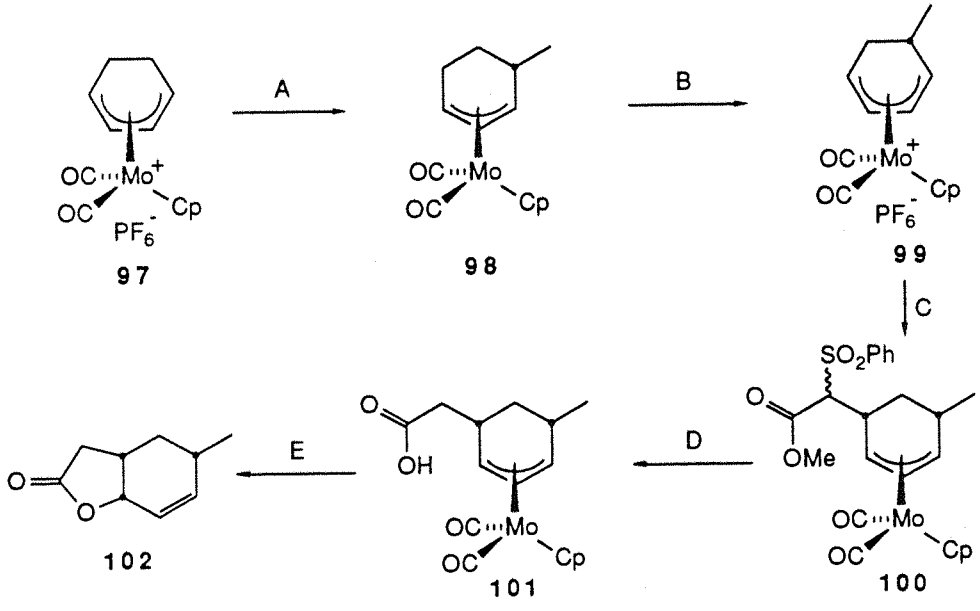
III.1. THE PREPARATION AND USE OF η^4-CYCLOHEXADIENE-$Mo(CO)_2Cp$ COMPLEXES IN RING APPENDAGE REACTIONS.

The appendage of a carbon chain onto a ring is a fundamental operation in organic synthesis. Classical methods[35] involving the alkylation of enolates or carbanions by cycloalkyl electrophiles is complicated by problems of elimination as a major competing reaction and the general lack of opportunity for stereocontrol. In 1976 Faller and Rosan[36] reported a new method for the appendage of chains onto cyclohexyl rings which circumvents some of these problems and provides new protocols for the creation of C-C bonds at 'unactivated'



centres. Their method involves the alkylation of η^4-cyclohexadiene-Mo(CO)$_2$Cp complexes (e.g. **97**) with a variety of nucleophiles followed by decomplexation of the metal as illustrated in Scheme 18.

More recently Pearson and co-workers[37] have reported transformations which greatly extend the scope and synthetic utility of cationic diene complexes of Mo (and Fe) as illustrated in Scheme 19 for the synthesis of **102** - an intermediate in a projected synthesis of the antibiotics magnamycin B and tylosin. Several aspects of these transformations are worthy of comment:



SCHEME 19 Experimental conditions and yields

A MeMgBr, ether (61%)
B Ph_3CPF_6 (86%)
C NaCH(SO_2Ph)COOMe, THF, 0°C (70-90%)
D (i) Na(Hg); (ii) KOH, aq MeOH; (iii) HCl (74%)
E I_2 (3 eq), MeCN (5%)

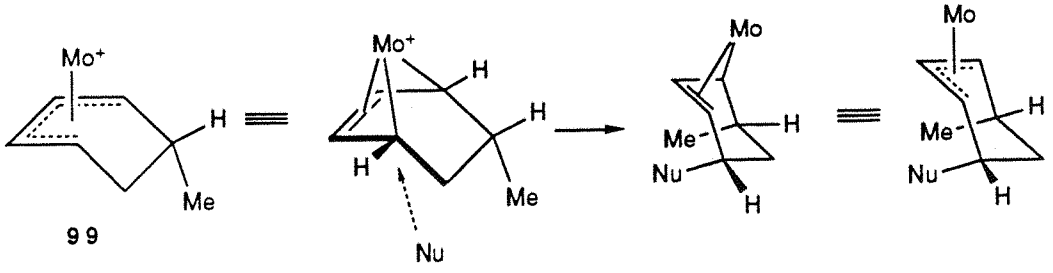
1) Addition of the nucleophile to the 18-electron η^4-cyclohexadiene-Mo(CO)$_2$Cp complexes **97** and **99** occurs stereospecifically *trans* to the metal (steps A and C).

2) Both hard nucleophiles (e. g. Grignard reagents) and soft nucleophiles (e.g., stabilised enolates) react with the cationic complexes.

3) Hydride abstraction (step B) from the η^3-allyl complex **98** is regiospecific (loss of hydride *trans* to the metal).

4) The η^3-allyl complexes **98, 100,** and **101** are sufficiently stable to survive several transformations including base hydrolysis and dissolving metal reduction (step D).

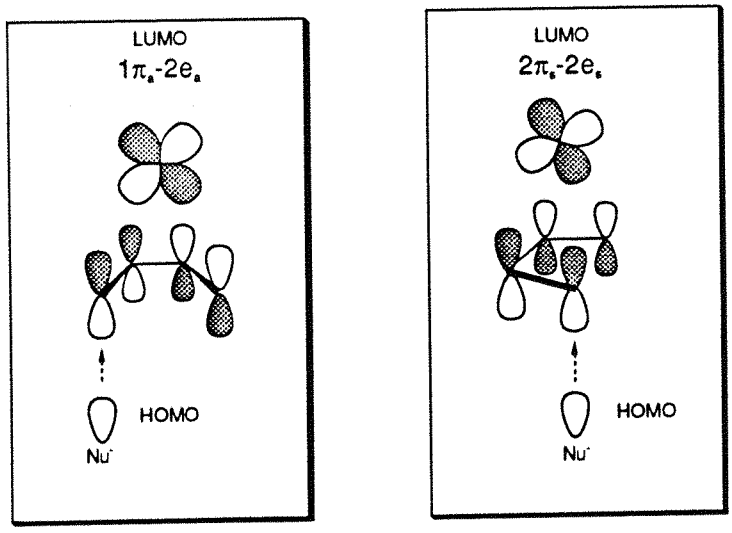
5) The η^3-allyl-$Mo(CO)_2Cp$ complex **101** with a pendant nucleophilic group undergoes demetallation and cyclofunctionalisation on treatment with an excess of iodine (step E).



SCHEME 20

An extremely significant feature of the sequence outlined in Scheme 19 was the high level of stereocontrol resulting from *trans* attack by the nucleophiles on the carbon-metal bond of the cationic complex. This is effectively an S_N2 displacement with *pseudo*-inversion at the reaction centre as depicted in Scheme 20. Pearson[38, 39] has provided a frontier molecular orbital analysis of the observed stereochemistry which involves interaction of the HOMO of

Fig. 1.

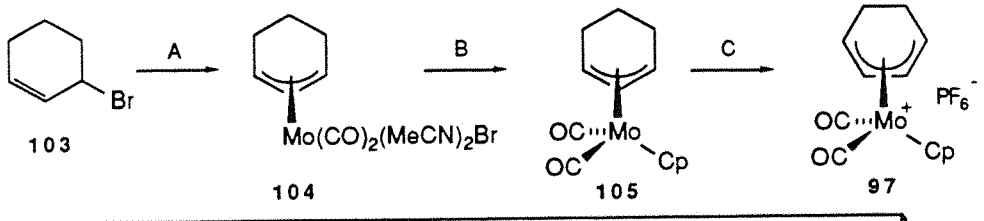


the nucleophile with either one of two potential LUMOs ($1\pi_a$-$2e_a$ or $2\pi_s$-$2e_s$) of the metal complex (*Fig* 1). This frontier molecular analysis reinforces the analogy with the classical S_N2 displacement and suggests that the stereochemistry is dictated by stereoelectronic effects rather than simple steric constraints.

III.2. SYNTHESIS OF TETRAHYDROBENZOFURANS *VIA* ALKYLATION-CYCLOFUNCTIONALISATION OF η^4-CYCLOHEXADIENE-$Mo(CO)_2Cp$ COMPLEXES.

In section I we described some of the synthetically useful properties of η^4-complexes. In this section we will describe the preparation of the parent η^4-cyclohexadiene-$Mo(CO)_2Cp$ complex **97** and its use in the synthesis of a tetrahydrobenzofuran which was a projected intermediate in the synthesis of phyllanthocin (*vide infra*). Included in the discussion will be a proposed mechanism for the iodine-induced decomplexation-cyclofunctionalisation of η^3-allyl complexes.

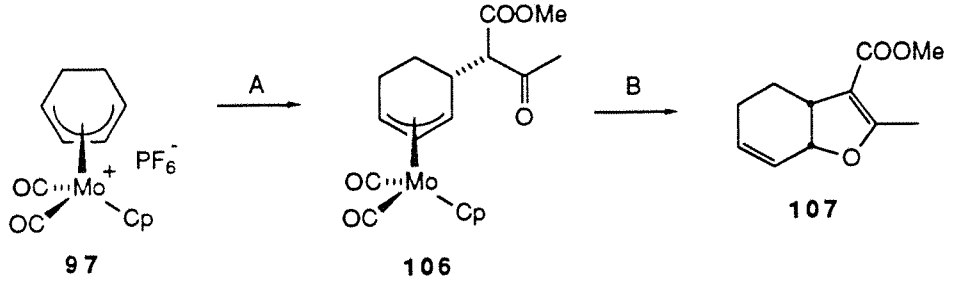
One of the appealing features of η^4-cyclohexadiene-$Mo(CO)_2Cp$ complexes is the comparative ease of their preparation and their stability. The parent η^4-cyclohexadiene-$Mo(CO)_2Cp$ complex **97** was prepared in three steps by the method of Faller[34] as shown in Scheme



SCHEME 21 Experimental conditions and yields
(i) $Mo(CO)_6$, acetonitrile, reflux, 5 h; (ii) bromocyclohexene, 0°C (61%)
THF, lithium cyclopentadienide, 2 h, RT (91%)
(i) Ph_3CPF_6, DCM, 0°C, 1 h; (ii) Et_2O (58%)

21 The sequence began with the reaction of comparatively cheap $Mo(CO)_6$ with excess acetonitrile under reflux which results in the formation of $Mo(CO)_4(NC\text{-}Me)_2$ with loss of two molecules of carbon monoxide. Commercial bromocyclohexene **103** was then added to the

refluxing solution and the reaction mixture immediately cooled to 0°C to give the air-sensitive yellow crystalline η^3-allyl complex **104** (61%) which was sufficiently stable to be handled in air for brief periods but which was best used in the next step without further manipulation. The replacement of the carbon monoxide ligands by the more nucleofugal acetonitrile ligands are obviated in the next step which involves reaction of complex **104** with cyclopentadienyl-lithium in THF. The resultant η^3-allyl complex **105** was obtained as an air-stable yellow crystalline solid in 91% yield after column chromatography. The final step in the sequence required hydride abstraction which was accomplished in dichloromethane at 0°C using triphenylcarbenium hexafluorophospate. On addition of ether, the desired η^4-cyclohexadiene-$Mo(CO)_2Cp$ complex **97** was isolated as an air-sensitive pale green hexafluorophosphate salt which could be stored for months at -4°C under Argon. By this route the parent complex **97** could be routinely prepared in 15 g quantities.

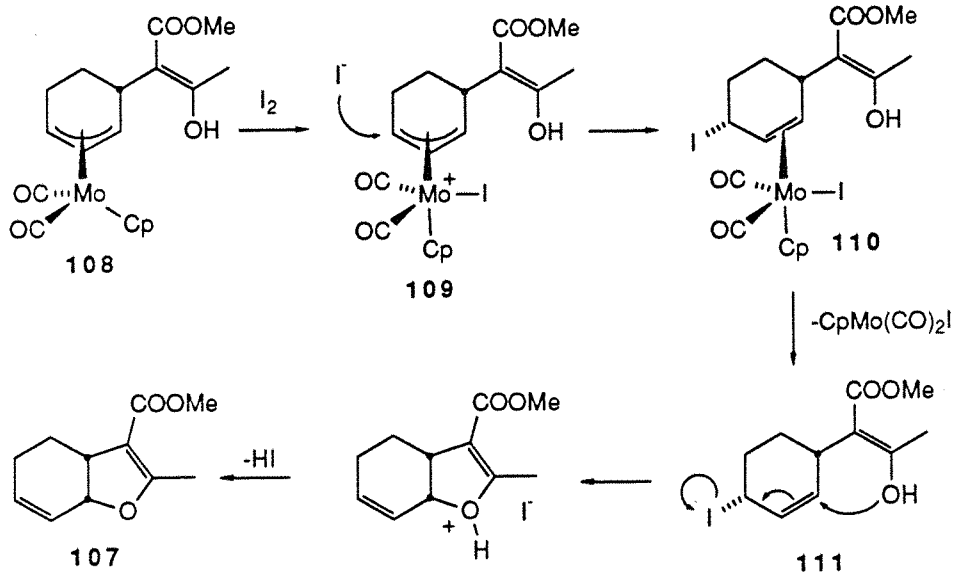


SCHEME 22 Experimental conditions and yields
A NaCH(COOMe)COMe, THF, RT
B I_2 (3 equiv), MeCN (58% overall)

Our next goal was to evaluate the η^4-cyclohexadiene-$Mo(CO)_2Cp$ complex **97** as a precursor to tetrahydrobenzofurans which play a key strategic role in our projected synthesis of phyllanthocin. Our evaluation began with the synthesis of the tetrahydrobenzofuran **107** which was accomplished as shown in Scheme 22. The critical alkylation reaction took place on addition of the complex **97** to a solution of the sodium enolate of acetoacetic ester in THF at room temperature. On aqueous workup the yellow η^3-allyl complex **106** was obtained which was sufficiently stable to be purified by column chromatography. On

treatment of complex **106** with three equivalents of iodine in acetonitrile, the desired decomplexation-cyclofunctionalisation reaction took place to give the desired tetrahydrobenzofuran **107** in 58% yield after column chromatography.

SCHEME 23

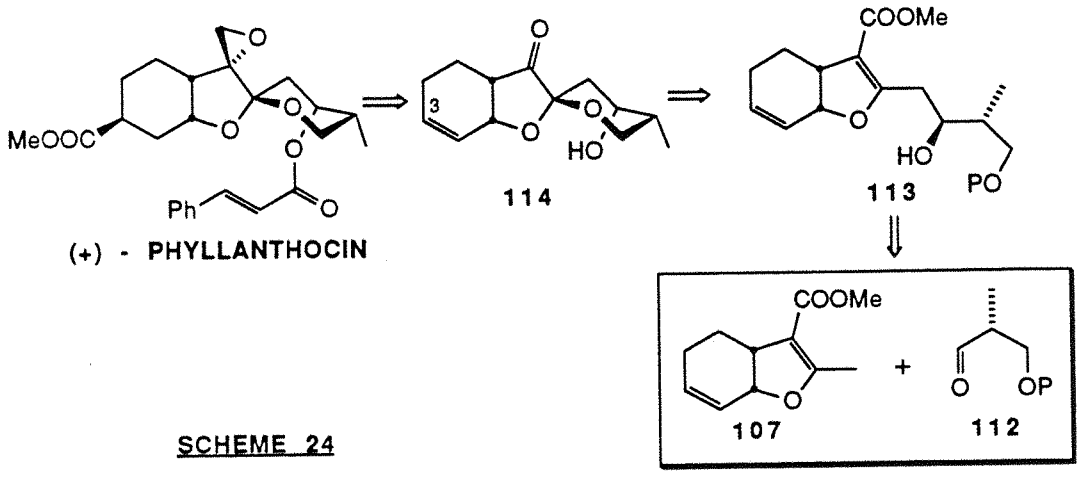


Pearson[37,38,39] has suggested a mechanism for the iodine-induced decomplexation-cyclofunctionalisation (Scheme 23). The proposed sequence involves nucleophilic attack on the iodine by the Mo in complex **108** followed by nucleophilic attack by iodide ion on the resultant cationic iodomolybdenum complex **109** to give η^2-complex **110**. Decomplexation of **110** by some unknown mechanism then accounts for the formation of allylic iodide **111** which can then suffer intramolecular S_N2' displacement by the enolate oxygen to give the final product **107**.

III.3. ATTEMPTED ELABORATION OF TETRAHYDROBENZO-FURAN (107) TO THE PHYLLANTHOCIN SKELETON.

The tetrahydrobenzofuran **107** incorporates rings A and B of

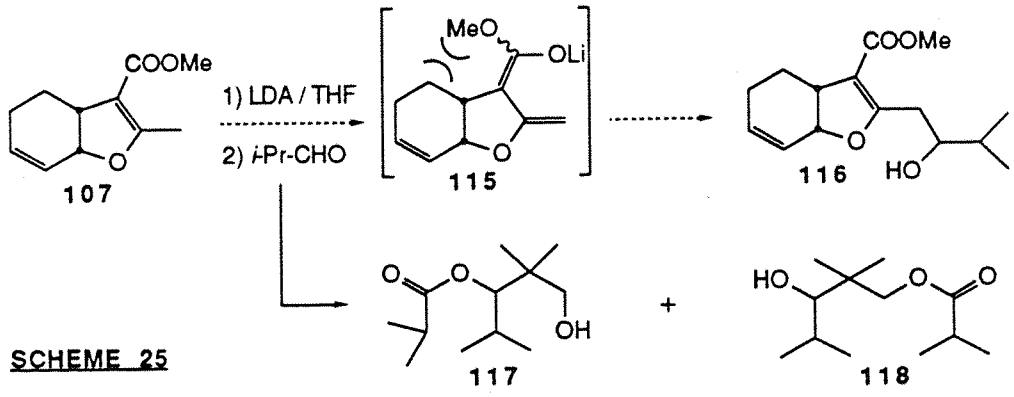
phyllanthocin. Since the B-ring contains an alkene which is both an enol ether and an α,β-unsaturated ester (making C-9 electrophilic on



SCHEME 24

two counts), it seemed to us that the C-ring spiroacetal ensemble could be fashioned from the tetrahydrobenzofuran **107** using simple enolate chemistry. To that end we examined the strategy outlined in Scheme 24. Thus, γ-alkylation of **107** with the aldehyde **112** followed by heterocyclisation of the adduct **113** should provide the 1,6-dioxaspiro [4,5]decane ring system in **114**. Completion of the synthesis would then involve appendage of a carbomethoxy unit onto C-3 (perhaps by a hydroformylation process) and construction of the oxiran ring.

The critical step in the strategy outlined in Scheme 24 is the vinylogous aldol-type reaction between the enolate derived from **107** and the aldehyde **112** which was first examined in a simpler model system Scheme 25. Treatment of **107** with lithium di-isopropylamide in THF at low temperature followed by addition of isobutyraldehyde failed to give any of the desired adduct[40, 42] **116**. The only products from the reaction were recovered **107** and products which appeared to be derived from the self-condensation of the aldehyde with further complications arising from Cannizzaro reactions. The Infrared and ^{1}H NMR spectra (270 MHz) of two of the components **117** and **118** isolated from the reaction suggested the presence of ester and hydroxyl functionality appended to a carbon skeleton derived from three isobutyraldehyde units. These results suggested that the enolate **115** from **107** was not



SCHEME 25

formed or the adduct **116** underwent easy retroaldolisation. Attempts to generate the enolate **115** (in the presence and absence of HMPA) followed by quenching with D_2O[41] demonstrated that the problem was at the stage of enolate formation since the starting material recovered was devoid of deuterium. It is not immediately obvious why enolate formation should have been inhibited but one possibility is the introduction of a severe non-bonded steric interaction between one of the oxygen atoms of the enolate and the proximate carbon of ring-A in **115**.

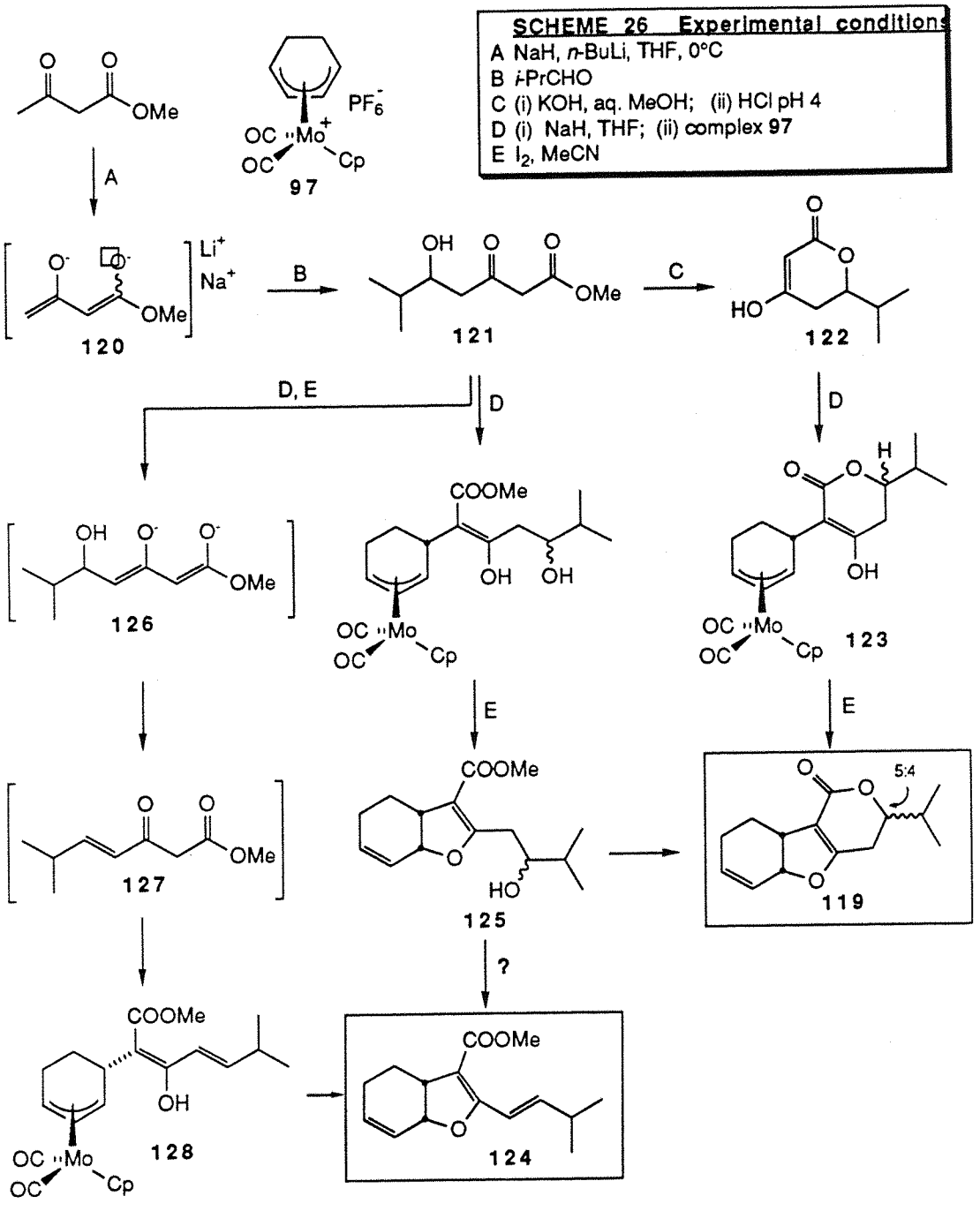
Our failure to accomplish the aldol reaction in Scheme 25 prompted a revision of our plan which incidentally led to a strategic improvement. The revised strategy is illustrated by the synthesis of the model **119** (Scheme 26) which is simply the lactone analogue of the aldol adduct **116**. In this revised strategy the requisite aldol reaction is accomplished before alkylation of the cationic η^4-cyclohexadiene-Mo $(CO)_2Cp$ complex **97**. Thus the dienolate **120** of methyl acetoacetate reacted with isobutyraldehyde to give adduct **121** which afforded the β-ketolactone **122** after base hydrolysis of the ester followed by acid-catalysed lactonisation. According to spectrocopic analysis, the lactone **122** existed almost exclusively in the enolic form. The sodium enolate of β-ketolactone **122** was then treated with the cationic molybdenum complex **97** to give the η^3-allyl complex **123** which, without further purification, was treated with iodine as described previously to yield the desired tricyclic tetrahydrobenzofuran **119** (68%) as an inseparable mixture of diastereoisomers (5:4 by ^1H NMR analysis).

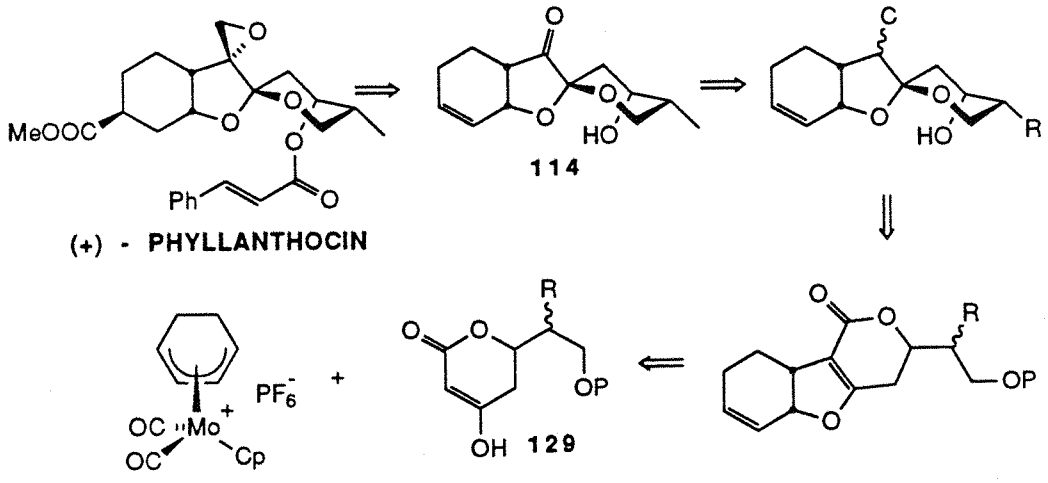
Before proceeding we wish to describe the results of the reaction of

the cationic molybdenum complex **97** with the γ-hydroxy-β-ketoester **121**, which was an intermediate in the synthesis of the β-ketolactone **122**. In this case two annulated products were obtained which were easily separated by column chromatography. The lactone **119** previously observed was formed in 30% yield and the dehydration product **124** was isolated in 28% yield. The formation of the two annulation products can be explained as shown in Scheme 26. Alkylation of the γ-hydroxy-β-ketoester **121** in the usual way followed by cyclofunctionalisation accounts for the formation of the tetrahydropyranone **125** which can then lactonise to give **119**. A more complex mechanism must be invoked for the formation of **124**. We suggest as one possibility a competing β-elimination reaction of the γ-hydroxy-β-ketoester **121** during the alkylation of the Mo complex which generates the α,β-unsaturated ketone **127**. Alkylation followed by cyclofunctionalisation then generates then generates the tetrahydrobenzofuran **124**. Alternatively, elimination of water from the tetrahydrobenzofuran **125** could account for the formation of the observed by-product. Interestingly, the lactone **119** formed by this route was largely one diastereoisomer (of unknown configuration) whereas **119** formed by alkylation-cyclofunctionalisation of β-ketolactone **122** was isolated as a 5:4 mixture of diastereoisomers.

III.4. SYNTHESIS OF THE PHYLLANTHOCIN SKELETON *VIA* ALKYLATION OF A CATIONIC η^4-CYCLOHEXADIENE-Mo(CO)$_2$Cp COMPLEX WITH A β-KETOLACTONE.

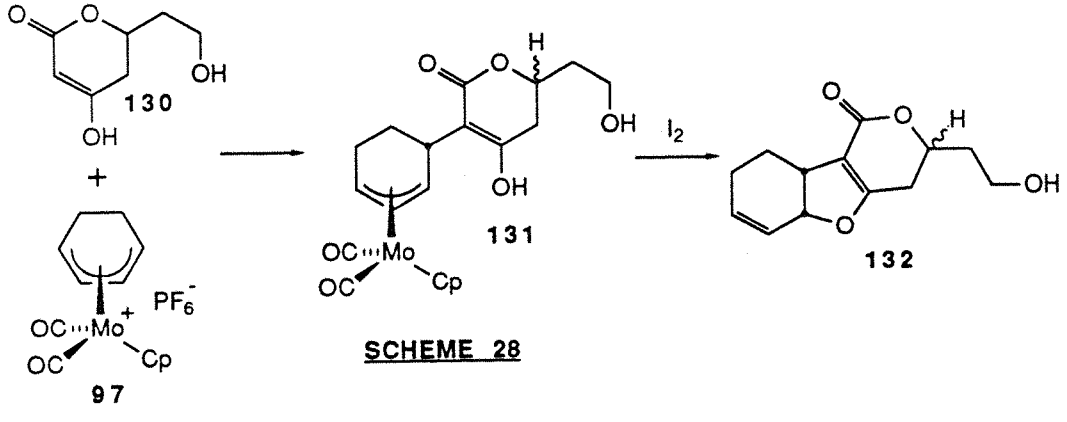
In section IV we showed that an enolate of a substituted β-ketolactone could be used in an alkylation-cyclofunctionalistion sequence to generate a tricyclic tetrahydrobenzofuran. These results suggested that a suitable modification could lead to a synthesis of the entire phyllanthocin skeleton minus the carbomethoxy group at C-3. The new strategy, outlined in Scheme 27, required the synthesis of a β-ketolactone of general structure **129** having an O-functionalised two-carbon side chain. Ultimate success required that the oxygen atom bear a protecting group which would survive the alkylation-cyclofunctionalisation sequence intact but undergo selective


SCHEME 26 Experimental conditions
A NaH, n-BuLi, THF, 0°C
B i-PrCHO
C (i) KOH, aq. MeOH; (ii) HCl pH 4
D (i) NaH, THF; (ii) complex 97
E I2, MeCN
97
120
121
122
123
125
126
127
128
119
124
5:4
?



SCHEME 27

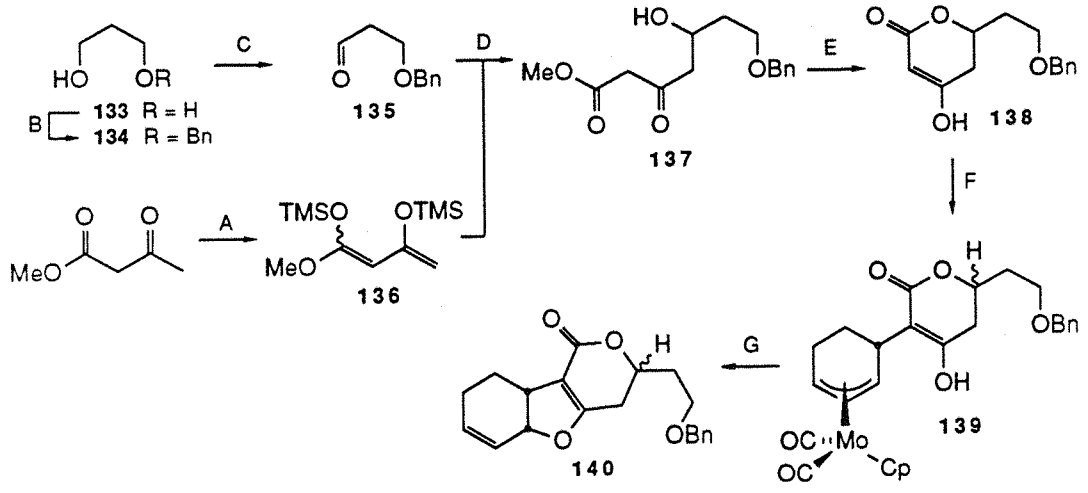
deprotection prior to spiroacetalisation. The requirement of a suitable protecting group was demonstrated by reacting lactone **130** possessing a primary hydroxyl group with the η^4-organomolybdenum complex **97**, to afford a very poor yield of the tricyclic tetrahydrobenzofuran **132** (5%, Scheme 28). Circumstantial evidence suggests that the absence of a protecting group on the hydroxyl had no deleterious effect on the alkylation step but rather problems arose at the stage of oxidative cyclofunctionalisation of **131** induced by iodine. Unfortunately, attempts to use other oxidising agents such as Ag(I) or KCN failed as did attempted decomplexation with ultraviolet light[43].



SCHEME 28

Our failure with the unprotected hydroxyl group in β-ketolactone **130** outlined above prompted an investigation with the O-benzyl protected β-ketolactone **138** which was prepared as summarised in

Scheme 29. The 'traditional' base-catalysed aldol reaction, which was adequate for the synthesis of β-ketolactone **122**, could not be used in the case **138** because of competing β-elimination of benzyl alcohol from aldehyde intermediate **135**. Consequently, a Mukaiyama directed aldol reaction[44] was used employing aldehyde **135** and the *bis*-silyl ether **136** which was a precedented partner in Lewis acid-catalysed directed aldol chemistry[45].

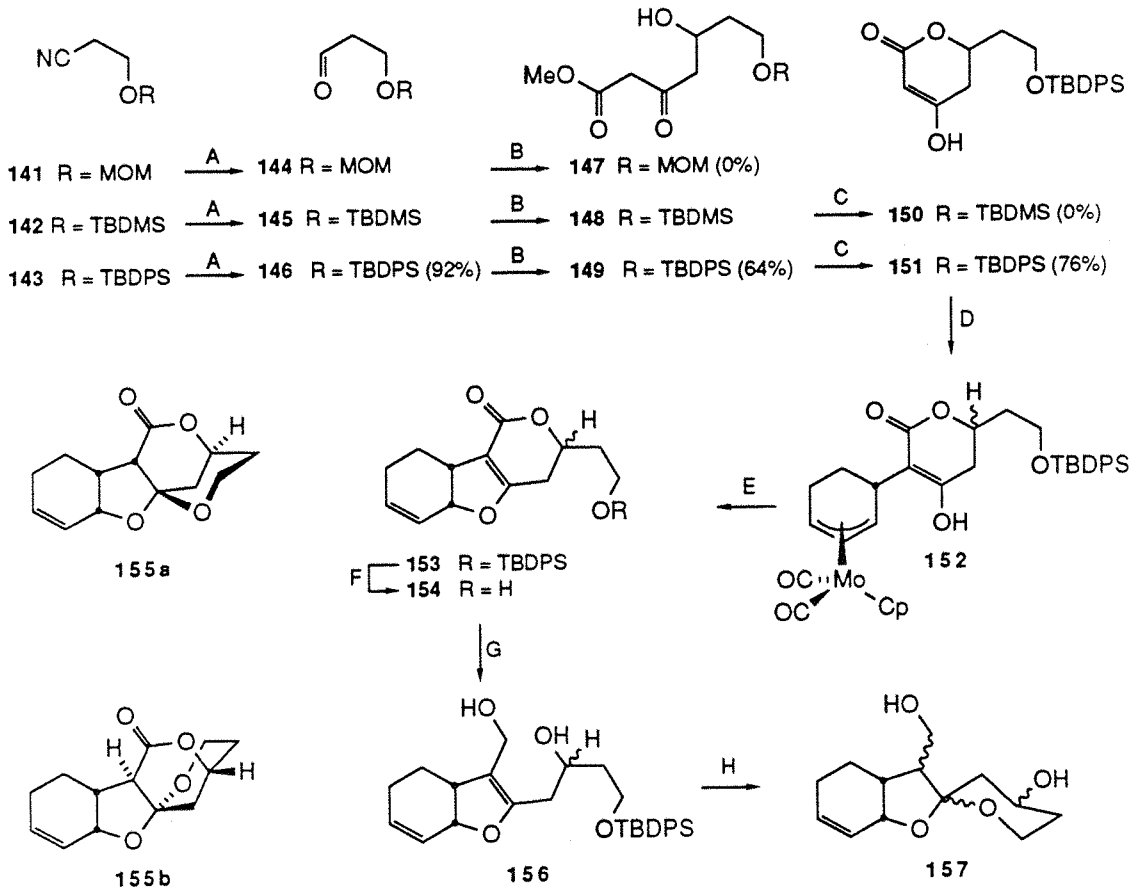


SCHEME 29 Experimental conditions and yields

A (i) TMSCl, NEt_3, $ZnCl_2$; (ii)LDA, TMSCl
B BnBr, NaH, THF (57%)
C Swern oxidation (93%)
D (i) add 1 equiv $TiCl_4$ to aldehyde **135** in DCM, -80°C; (ii) add *bis*-silyl ether **136**, -80°C, 3 h (68%)
E (i) KOH, aq. MeOH; (ii) acidify with HCl to pH 4 (75%)
F (i) NaH, THF, RT, 15 min; (ii) add complex **97**, RT, 30 min
G I_2, MeCN, RT, 30 min (63% overall from **138**)

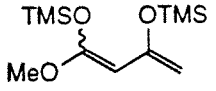
The preparation of **136** from methyl acetoacetate according to literature procedures* required two steps. First, a mono-silyl ether intermediate which was then treated with lithium di-isopropylamide, followed by trichlorosilane to afford *bis*-silyl ether **136**. The synthesis of the *bis*-silyl ether proved problematic due to its susceptibility to oxidation and hydrolysis but these practical problems were overcome by conducting all experiments under argon under scrupulously anhydrous conditions.

The reaction of the aldehyde **135** with the *bis*-silyl ether **136** (Scheme 29) in the presence of $TiCl_4$ gave the desired aldol product in 68% yield. Hydrolysis of ester **137** using lithium hydroxide in methanol and water



SCHEME 30 Experimental conditions and yields.

A DIBAL-H, THF, -50°C, NH_4Cl, citric acid
B *bis*-silyl ether **136**, Lewis acid, THF
C LiOH, MeOH, H_2O, RT
D (i) NaH, THF, RT, 30 min; (ii) Mo-complex **97**, RT, 1 h
E I_2 (3eq), CH_3CN, RT, 0.5 h (58%, 3 steps)
F TBAF, THF
G Red-Al, Ether, -60°C, 10% sodium sulphate, $MgSO_4$ (74%)
H HF (40%), MeCN, RT, 6 h 80-85% (mixture)



136

followed by acidification afforded the β-ketolactone **138** in 75% yield. The advantages of the protected side chain were underlined in the alkylation-cyclofunctionalisation reaction sequence which now afforded the tetrahydrobenzofuran **140** in 63% overall yield.

For the purposes of the synthesis at hand, the benzyl protecting group had one serious disadvantage in that it could not be removed selectively by catalytic hydrogenation or dissolving metal reduction without competing reaction with the alkene or ester functions in the adduct **140**. Therefore, it was necessary to examine alternative protecting groups whose removal would not be problematic. Candidates examined included methoxymethyl (MOM), *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl and the substrates were prepared as summarised in Scheme 30.

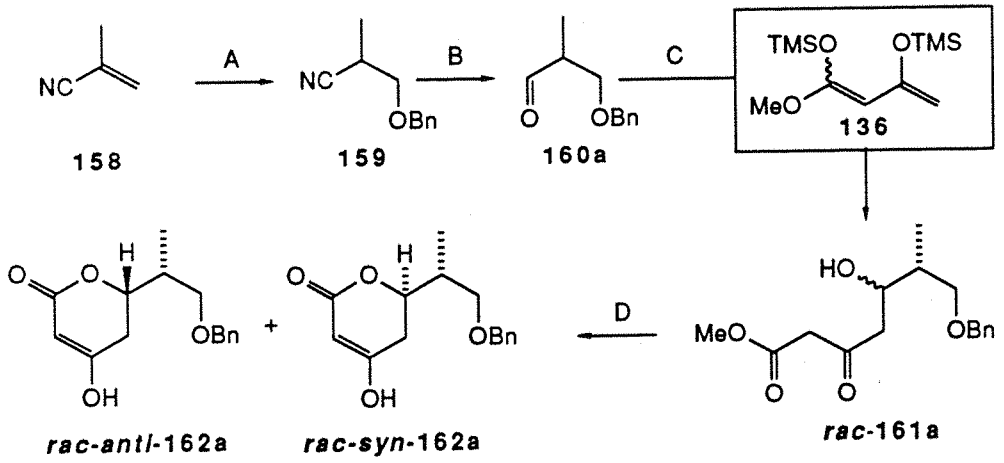
The MOM protecting group proved to be a poor choice because it was unstable under the conditions required to effect the Mukaiyama directed aldol condensation between aldehyde **144** and the *bis*-silyl ether **136** (Scheme 28). The *t*-butyldimethylsilyl group survived the Lewis acidic conditions used in the directed aldol reaction but was subsequently lost under the acidic conditions required to close the lactone ring in **148**. Fortunately, the *t*-butyldiphenylsilyl protecting group was sufficiently stable to withstand all the reaction conditions used in Scheme 29 allowing, thereby, the preparation of β-ketolactone **151** in 37% overall yield from β-hydroxypropionitrile and the conversion of **151** to the tetrahydrobenzofuran **153** in 48% overall yield.

With adequate supplies of the tetrahydrobenzofuran **153** in hand, we next turned to a study of the spirocyclisation reaction (Scheme 30). Thus, treatment of **153** with tetra-*n*-butylammonium fluoride or HF released the hydroxyl group in virtually quantitative yield but the resultant alcohol **154** was stable under these conditions and further reaction to give the desired spiroacetal(s) **155 a,b** did not take place. Attempts to induce the cyclisation by treatment of **154** with *p*-toluenesulphonic acid or BF_3 gave recovered starting material. Molecular models indicated that **155 a,b** was not particularly strained; therefore, its failure to form the spiroacetal ring suggests that the desired conjugate addition, if it took place at all, was reversible with the

starting material **154** being favoured at equilibrium.

The desired spiroacetalisation reaction was eventually achieved by simply reducing the ester function in **153** to give the diols **156** which, without further purification, were treated with HF. Under these conditions the protecting group was removed and spiroacetalisation took place to give **157** (*ca.* 20% yield) as a single component by thin layer chromatogrtaphic analysis. However, ^{1}H and ^{13}C NMR indicated a mixture of diastereoisomers and the presence of the spiroacetal could only be surmised by the presence of the characteristic signal for the spiroacetal carbon at δ 104 in the ^{13}C NMR spectrum. No further concrete spectroscopic details are available at the present time to allow more conclusve assignment of the structure of **157** and, in any event, the complexity of the mixture did not warrant a detailed study. Nevertheless, we were sufficiently encouraged by these results to proceed with the synthesis of more complex systems directed toward phyllanthocin as descibed below.

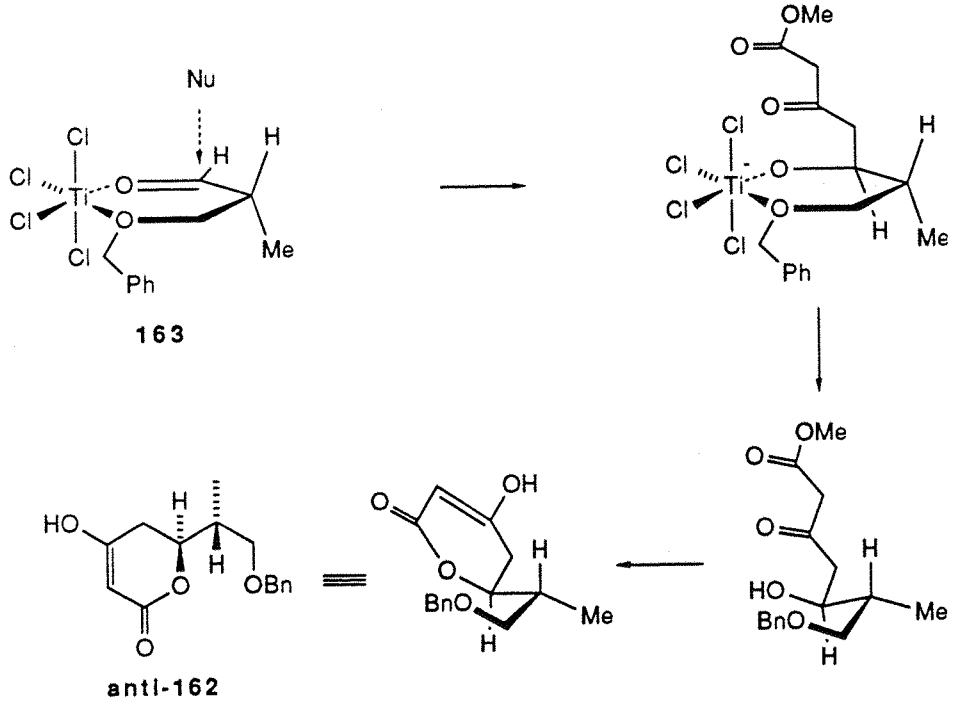
In order to achieve maximum convergence in our synthesis of phyllanthocin, we require the homochiral lactone *ent-anti*-**162** as the substrate for the alkylation-cyclofunctionalisation sequence. Therefore, we began by investigating the problem of controlling the relative stereochemistry between the two stereogenic centres in *ent-anti*-**162**



SCHEME 31 Experimental conditions and yields

A $PhCH_2OH$, NaH, THF 69%
B DIBAL-H, DCM 71%
C add $TiCl_4$ followed by *bis*-silyl ether **136**
D (i) LiOH or KOH, aq. MeOH; (ii) HCl to pH 4

using, in the first instance, racemic compounds. Thus, benzyl-protected lactone was prepared from methacrylonitrile **158** as shown in Scheme 31. The addition of benzyl alcohol to **158** in the presence of sodium hydride[46] gave adduct **159** in 69% yield. The nitrile was then reduced to the aldehyde **160** in one step using DIBAL-H[47] in good yield. Treatment of a mixture of aldehyde **160** and silyl ether **136** with one equivalent of $TiCl_4$ gave the aldol product *rac*-**161** in a 57% yield which, after hydrolysis and acid-catalysed lactonisation, afforded the separable mixture of diastereomeric β-ketolactones *rac-anti*-**162** and *rac-syn*-**162** (*anti:syn* = 1:2, *vide infra*) in 96% yield (55% overall). However, by simply inverting[48] the order of adding the reagents, i.e., by adding the Lewis acid to the aldehyde prior to the addition of the *bis*-silyl ether, the diastereoselectivity of the reaction was reversed. Under these conditions, the desired *anti*-isomer *rac-anti*-**162** was favoured (*anti:syn* = 3.3:1).

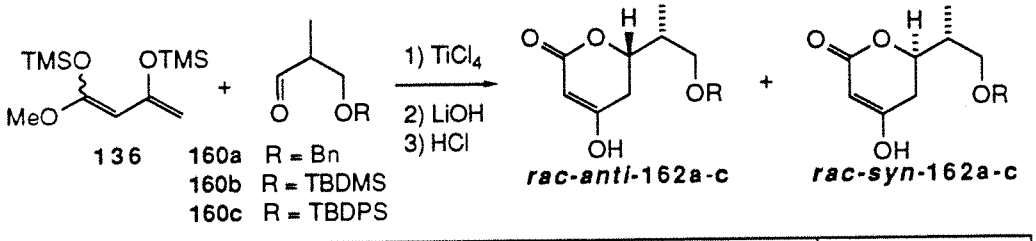


Spectroscopic evidence alone was insufficient to allow a conclusive assignment of the stereochemistry of the two diastereoisoers. Consequently, our tentative assignment of *anti*-stereochemistry for the

major diastereoisomer in the 'inverse addition' experiment was based on the assumption that the directed aldol reaction took place according to the chelation-controlled model of Cram[49, 20, 8] thereby favouring addition of the nucleophile from the less hindered face (opposite the methyl group) of structure **163** (Scheme 32).

In order to assess the influence of the hydroxyl protecting group on the chelation-controlled addition, aldehydes **160 a-c** (Table 1) were converted to the diastereoisomeric β-ketolactones according to the procedure shown in Scheme 31. For reference, the addition of the sodium, lithium dienolate of acetacetic ester to aldehyde **160c** was also examined. As can be seen from the results summarised in Table 1, the nature of the protecting group in the aldehyde had only a minor effect on the diastereoselectivity and yield of the reaction.

TABLE 1 **The effect of reaction conditions on the stereochemistry of the directed aldol reaction used to prepare β-ketolactones *rac-anti*-162a-c and *rac-syn*-162a-c**

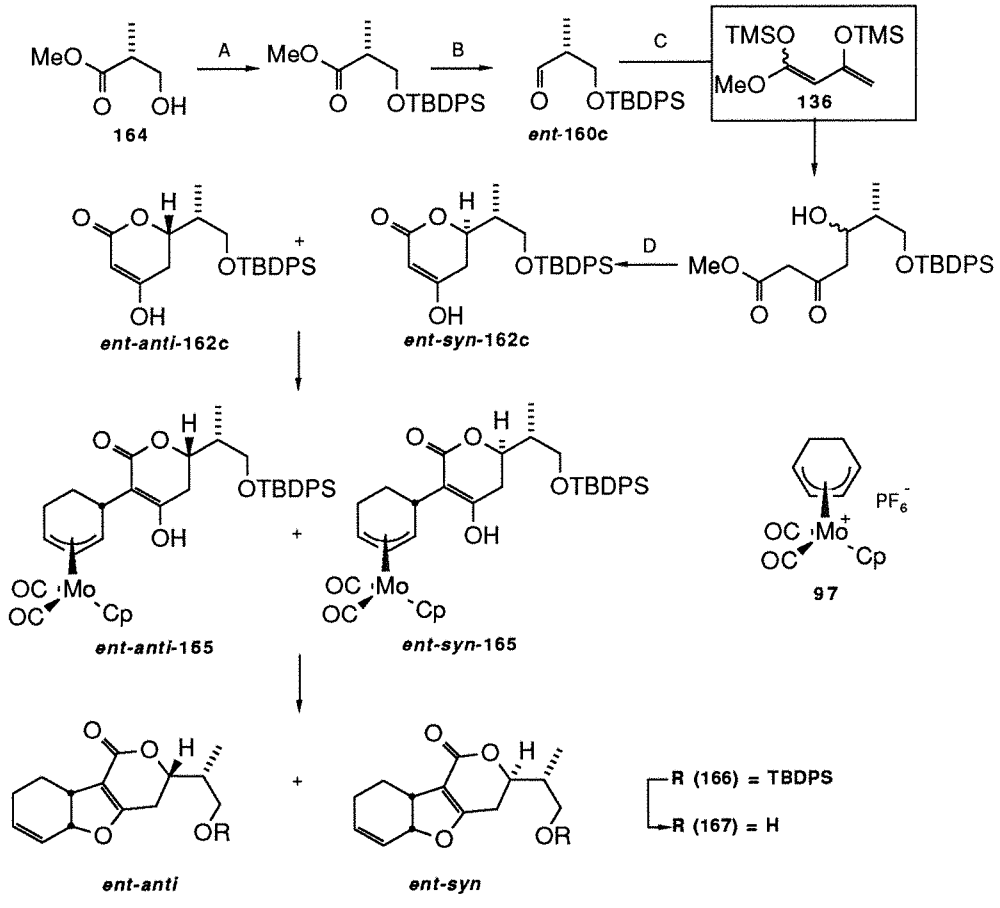


136 160a R = Bn
160b R = TBDMS
160c R = TBDPS

Protecting Group (R)	Reaction Conditions	Yield *anti* + *syn*	Ratio *anti:syn*
(a) $PhCH_2$	B	55%	1:2
(a) $PhCH_2$	C	64%	3.3:1
(b) TBDMS	A	36%	1.2:1
(b) TBDMS	B	37%	1:3.5
(c) TBDPS	C	50%	3.5:1

A. Aldehyde added to the solution of the Na, Li dienolate of methyl acetoacetate inTHF
B. $TiCl_4$ was added to the mixture of aldehyde **160a-c** and *bis*-silyl ether **136** in DCM at -90°C
C. First $TiCl_4$ was added to the aldehyde **160a-c** at -80°C in DCM; then add *bis*-silyl ether **136**

The studies described above showed that diastereocontrolled formation of the β-ketolactone *anti*-**162c** required for the synthesis of phyllanthocin was feasible and reasonably efficient. However, these studies were only concerned with *diastereocontrol* and the issue of absolute stereochemistry had not been addressed. To complete our account, we now describe the synthesis of the requisite homochiral β-ketolactone *ent-anti*-**162c** and its alkylation-cyclofunctionalisation



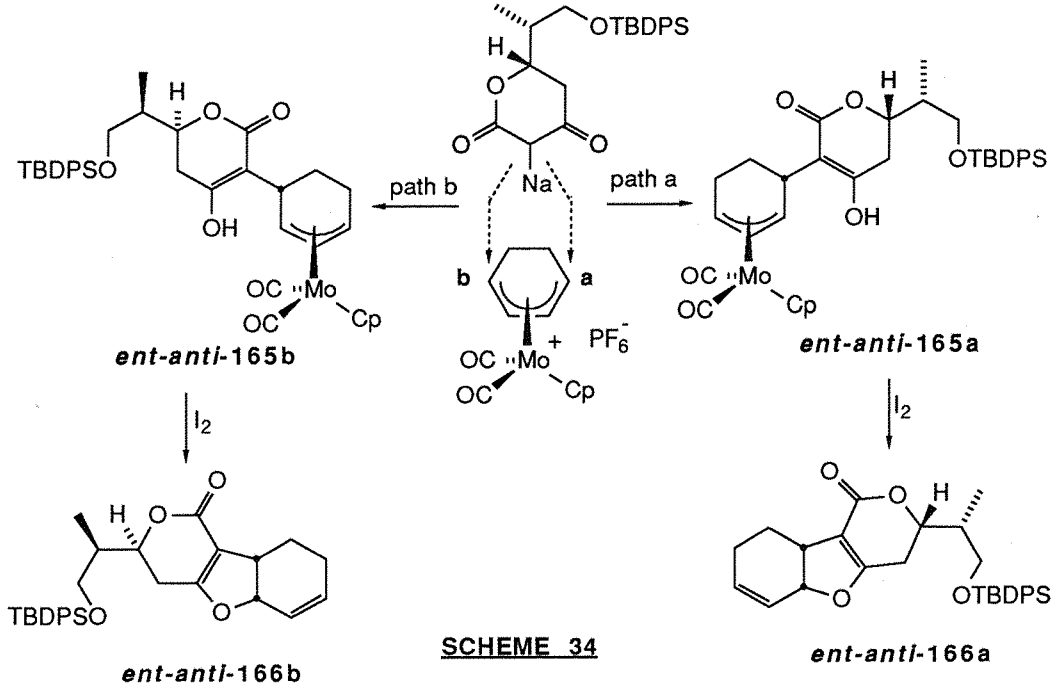
Scheme 33 Experimental conditions and yields

A TBDPS-Cl, DMF, imidazole, DMAP [98%]
B DIBAL-H, DCM, NH_4Cl, citric acid [95%]
C (i)$TiCl_4$, DCM, -80°C, 15 min; (ii) add *bis*-silyl ether **136** [67%]
D (i) LiOH, aq MeOH,1 h; (ii) HCl, pH = 3 [79%]
E (i) NaH, THF; (ii)complex **97** [*ca.* 100%]
F I_2, MeCN [55%]

chemistry.

The homochiral aldehyde *ent-anti*-**162c** was prepared in two steps from the commercial (R)-(-)-methyl 3-hydroxypropionate **164** as outlined in Scheme 33. Mukaiyama[44] directed aldol condensation of *ent*-**160c** with the *bis*-silyl ether **136** provided a mixture of adducts which were transformed to the β-ketolactones *ent-anti*-**162c** and *ent-syn*-**162c** with the desired *ent-anti*-**162c** being the major product (*anti:syn* = *ca.* 3.5:1) as described previously. Unfortunately, the diastereoisomers could not be separated at this stage by column chromatography and the mixture had to carried through the next step.

Alkylation of the η^4-molybdenum complex **97** with the mixture of sodium enolates derived from the β-ketolactones *ent-anti*-**162c** and *ent-syn*-**162c** (3.5:1) followed by cyclofunctionalisation gave an inseparable mixture of two tetrahydrobenzofurans *ent-anti*-**166** and *ent-syn*-**166.** Analysis of the mixture by ^{1}H NMR (270 MHz) and ^{13}C NMR revealed a mixture of two diastereoisomers in the ratio 3.5:1 but it was not possible to ascertain which structure corresponded to the major product within the time constraints. Nevertheless, the fact that the diastereomeric ratio of alkylation products corresponded exactly



SCHEME 34

with the diastereomeric ratio of starting β-ketolactones would suggest that the alkylation reaction had proceeded with a remarkable degree of stereocontrol which is not easy to account for.

The stereochemical course of the alkylation is summarised in Scheme 34. Alkylation of the symmetrical complex **97** can take place at position a or position b with attack occurring *trans* to the metal as previously discussed (*vide supra*). Two diastereomeric adducts *ent-anti*-**165a** and *ent-anti*-**165b** can be formed which, upon cyclofunctionalisation, give rise to the tetrahydrobenzofurans *ent-anti*-**166a** or *ent-anti*-**166b**. Diastereoisomer *ent-anti*-**166a** corresonds to the stereochemistry of phyllanthocin. Unfortunately molecular models provided no convincing guide for the stereochemical course of the reaction or any insight into possible causes for selectivity. Whether *ent-anti*-**166a** is the major product or not will require further experiments which are currently underway.

III.5. CONCLUSIONS AND FUTURE WORK

We have attained three of our goals *en route* to phyllanthocin. First, we have shown that homochiral β-ketolactones can be prepared with modest diastereocontrol using a chelation-controlled Mukaiyama directed aldol reaction. Secondly, the alkylation of the parent η^4-cyclohexadiene-$Mo(CO)_2Cp$ complex is efficient and subsequent cyclofunctionalistion permits the synthesis of terahydrobenzofurans with excellent stereocontrol. Finally, preliminary evidence suggests that the tetrahydrobenzofurans can be transformed to spiroacetals related to phyllanthocin. The principal detraction to our work thus far is the uncertainty with regard to stereochemistry in the formation of the tetrahydrobenzofurans and the spirocyclisation. However, these are problems which should be solved in the near future.

CHAPTER 3

IV.1. *GENERAL INTRODUCTION FOR EXPERIMENTAL.*

Where appropriate, solvents and reagents were dried according to the following procedures: THF was distilled from sodium wire and benzophenone; DCM was distilled from P_2O_5; acetonitrile, DMF, and DMSO were distilled from CaH_2; diethyl ether and benzene were stored over sodium wire.

Thin layer chromatography was carried out using Alugram Sil G/UV 254 (0.25 mm thickness) mounted on aluminium. Quantitative chromatographic separation was performed by either of two methods: (i) flash chromatography on Sorbsil C60, 40-60 mesh flash silica or (ii) column chromatography (atmospheric pressure) on grade 1 basic alumina (Fluka type 5016) deactivated to grade 3 by addition of distilled water (6% by weight) for acid-sensitive compounds. Column dimensions are given in cm (length x diameter) and eluents are specified in parenthesis.

All extracts were dried over $MgSO_4$ unless otherwise specified and solvents were evaporated at water pump vacuum using a rotary evaporator.

IV.2. *INSTRUMENTATION*

Infrared spectra, recorded on a Perkin-Elmer FT-IR spectrophotometer, were calibrated with a polystyrene film. Absorptions are referred to as strong (s), medium (m), broad (br), weak (w), or shoulder (sh).

Proton NMR spectra were recorded at 60 MHz on a Perkin-Elmer R24B continuous wave spectrometer using TMS as an external standard; at 90 MHz on a Jeol FX90Q FT NMR spectrometer, at 270 MHz on a Jeol GX 270 FT NMR spectrometer; and at 360 MHz on a Bruker AM 360 FT NMR spectrometer. Samples were dissolved in deuterochloroform unless otherwise stated. Peak positions are quoted against the δ-scale relative to an internal standard [chloroform = δ 7.27] using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (J) are given in Hertz.

Carbon-13 NMR spectra were recorded at 67.5 MHz on the Jeol GX270 machine, and at 90.6 MHz on the Bruker AM 360. Peak positions are quoted against the δ-scale relative to an internal standard [chloroform = δ 77.15]. The multiplicities of the carbon-13 signals were elucidated using the Distortionless Enhancement by Phase Transfer (DEPT) spectral editing technique with second pulse at 90° and 135°. C-H coupling is defined as s = singlet (due to quarternary carbon), d = doublet (methine), t = triplet (methylene), and q = quartet (methyl).

Where a mixture of diastereoisomers was observed the relavent data has been described as being due to either the major or minor isomer and the spectral data for the specified atom is enclosed in brackets { }. In such cases the integration refers to the sum of the two signals.

Mass spectral data was obtained on Kratos MS30 or VG 70-250 GC/MS spectrometers.

IV.3. *STRUCTURE CONFIRMATION AND ANALYTICAL PROCEDURES*

The structures of a number of compounds prepared during the studies described in this thesis were confirmed by comparision with well documented published data, or by comparision with samples prepared by established methods. Where applicable the relavent references are provided. The isomeric distribution of products was assessed either by gas chromatography or high field NMR. The latter was useful only where signals due to different isomers were clearly separated.

IV.4. *EXPERIMENTAL PROCEDURES*

6-Isopropyl-4-oxo-tetrahydropyran-2-one (122):- To a solution of KOH (28 mg, 0.5 mmol) and water (0.33 ml) in methanol (2.5 ml) the aldol product **121** (*Prepared using isobutyraldehyde and dianion of methyl acetoacetate in THF, at 0*℃) was added and the mixture stirred at RT for 30 min. The mixture was then acidified by dropwise addition of 2M HCl until the pH was approximately 4 and then poured into water and the product extracted into DCM (10 ml x 3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the β-ketolactone **122** as a colourless oil (97%, 75.6 mg, 0.48 mmol): IR (film) 3100br, 2960s, 1770s, 1740s, 1670s, 1620s, 1280 cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 4.41 (1H, ddd, J = 12, 6, 3Hz), 3.58 (1H, d, J = 19Hz), 3.40 (1H, d, J = 19Hz), 2.67 (1H, dd, J = 18, 3Hz), 2.48 (1H, dd, J = 18, 12Hz), 2.01 (1H, m, J = 7, 6Hz), 1.06 (3H, d, J = 7Hz), 1.03 (3H, d, J = 7Hz); ^{13}C NMR (67.5 MHz; $CDCl_3$) 200.7(s), 167.7(s), 80.2(d), 47.1(t), 40.9(t), 32.0(t), 17.8(q), 17.6(q).

η^4-Cyclohexadiene-Mo(CO)$_2$Cp hexafluorophosphate (97):- The complex, prepared according to the procedure of Faller[36], gave spectral data identical to those detailed in the literature. ^1H NMR (270 MHz; $CDCl_3$) 6.07 (2H, m), 5.98 (3H, s), 5.23 (2H, m), 2.48 (1H, s), 2.44 (1H, s), 2.13 (4H, m); ^1H NMR (270 MHz; $CDCl_3$) 206.47 (s), 95.17 (d), 88.03 (d), 84.07 (d), 30.72 (d), 30.43 (t), 30.15 (t), 29.57 (t), 29.28 (d), 29.01 (d), 24.62 (d), -11.25 (d)

Reaction of β-ketolactone 122 with η^4-cyclohexadiene-Mo(CO)$_2$Cp hexafluorophosphate (97):- To a suspension of NaH (12 mg, 0.26 mmol) in THF (1 ml) at RT, a solution of the lactone **122** (46 mg, 0.29 mmol) in THF (3 ml) was added dropwise and the mixture stirred for 1 h. The complex **97** was added in one portion and the mixture stirred at RT for a further 30 min, whereupon it was poured into water and extracted with ether (20 ml x 3). After being dried over $MgSO_4$ and concentrated *in vacuo*, a green oil (0.124 g) was obtained which was dissolved in acetonitrile (10 ml) and iodine (0.167g, 0.725 mmol) added. The mixture was then stirred at RT for 30 min, poured into water and extracted with ether (15 ml x 4). The combined extracts were washed with sodium thiosulphate and brine and then dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil (65 mg) which was further purified by flash chromatography (silica gel, 3 x 3 cm, petrol : ether = 5 : 1 -> 3 : 1) to give the tricyclic tetrahydrobenzofuran **119** (36 mg, 52% yield from lactone) as a colourless oil. Although TLC showed one spot (petrol : ether = 1 : 1), high field NMR showed a mixture of two

diastereoisomers in a ratio of 5:4: IR (film) 3040m, 2980s, 1720s, 1660s, 1400m cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 6.28-6.18 (1H, m), 5.98-5.86 (1H, m), {5.06 (m, major isomer) and 4.96 (m, minor isomer), 1H}, {3.27 (ddt, J = 9, 5, 2Hz; major isomer) and 3.20-3.06 (m, minor isomer) 1H}, {2.485 (ddd, J = 17, 12.5, 1.25Hz; minor isomer) and 2.48 (dd, J = 17, 12.5Hz), 1H}, {2.345 (dd, J = 17, 4.5Hz; minor isomer) and 2.34 (dd, J = 17, 4.5Hz; major isomer), 1H}, 2.25-1.8 (4H, m), {1.5 (dddd, J = 14, 8, 8, 4Hz; major isomer) and 1.32 (m, minor isomer), 1H}, {1.036 (d, J = 7Hz; major isomer) and 1.034 (d, J = 7Hz; minor isomer), 3H}, 0.997 (3H, d, J = 7Hz); ^{13}C NMR (67.5 MHz; $CDCl_3$) major isomer 172.4(s), 165.9(s), 135.4(d), 123.3(d), 106.2(s), 82.3(d), 82.5(d), 37.3(d), 32.1(d), 26.4(t), 24.7(t), 22.5(t), 18.0(q);.minor isomer 172.0(s), 165.8(s), 135.7(d), 122.7(d), 106.4(s), 81.8(d), 81.6(d), 38.1(d), 32.2(d), 26.3(t), 24.3(t), 22.9(t), 18.2(q),

3-Benzyloxypropan-1-ol (134):- NaH (4.74 g, 197.36 mmol) was stirred in dry THF (100 ml) under a nitrogen atmosphere. A solution of propan-1,3-diol (15 g, 197.36 mmol) was added dropwise at RT and allowed to stir for 2 h. The reaction was cooled to 0°C, whereupon benzyl bromide (11.5 g, 65.78 mmol) was added dropwise and the mixture stirred for 14 h. The reaction mixture was poured into 0.5M HCl (50 ml) and extracted with DCM (3 x 25 ml). The combined extracts were washed with $NaHCO_3$ and NaCl, and dried over $MgSO_4$. The crude product obtained on evaporation of the extracts was purified by flash chromatography (silica gel, 5 x 15 cm, petroleum ether : diethyl ether 1:2 -> 3:1) to afford the title compound as a colourless oil (15.75 g, 103.6 mmol, 51%) having spectroscopic properties comparable with those reported in the literature [50] ^1H NMR (270 MHz; $CDCl_3$) 7.25 (5H, m), 4.42 (2H, s), 3.72 (2H, s), 3.56 (2H, t, J = 7Hz), 2.7 (1H, br), 1.8 (2H, dd, J = 6.5, 8 Hz); ^{13}C NMR (67.5 MHz; $CDCl_3$) 138.16 (d), 128.5 (d), 128.49 (s), 127.75 (d), 73.27 (t), 69.1 (t), 32.2 (t)

3-Benzyloxypropanal (135):-Oxalyl chloride (3.19 g, 25.2 mmol) was added to DCM (28 ml) under nitrogen and stirred while the temperature was lowered to -80°C. A solution of DMSO (4.32 g, 55.3 mmol) was added dropwise, resulting in a large exotherm and vigorous evolution of CO and CO_2. After 10 min. stirring, a solution of protected alcohol **134** (4.85 g, 23.06 mmol) was added dropwise. After 25 min N-methylmorpholine (11.66 g, 115.3 mmol) was added and the reaction warmed to -10°C over a period of 3 h. The resulting white suspension was poured into water (50 ml), and the organic material extracted into DCM (3 x25 ml). The extracts were dried over $MgSO_4$ concentrated *in vacuo* and the crude product purified by flash chromatography (silica gel, 5 x 20 cm, petroleum ether : diethyl ether 15:1->1:1) to give the sensitive title compound **135**

(2.61g, 13.4 mmol, 93%) as a colourless oil which was used immediately in the next step.

The following alternative preparation using pyridinium chlorochromate (PCC) gave lower yields. PCC (6.86 g, 31.8 mmol) and crushed 4A molecular sieves (6.86 g) were stirred under nitrogen at RT in DCM. The protected alcohol **134** (1.76 g, 10.6 mmol) was added dropwise to the orange solution and the mixture stirred for 8 h. The mixture was decanted from a black precipitate, the precipitate was washed with diethyl ether (3 x 10 ml) and the combined extracts concentrated *in vacuo* to give a yellow oil which was purified by flash chromatography (silica gel, 5 x 10 cm, petroleum ether : diethyl ether 10:1 -> 3:1). The title compound **135** (795 mg, 5.3 mmol, 75%), obtained as a colourless oil, gave IR and NMR spectra consistent with the data published in the literature[50]. ^{1}H NMR (270 MHz; $CDCl_3$) 9.72 (1H, t, J = 8Hz), 7.36 (5H, m), 5.2 (2H, s), 4.46 (2H, d, J = 4Hz), 3.67 (2H, t, J = 4Hz), 2.26 (2H, ddd, J = 7 , 4.5, 4.5 Hz) ; ^{13}C NMR. (67.5 MHz; CDCl3) 201.31 (d), 137.9 (s), 128.5 (d), 128.47 (d), 73.3 (t), 61.9 (t), 43.94 (t)

Methyl 7-benzyloxy-5-hydroxy-3-oxo-heptanoate (137):- To a suspension of NaH (0.928 g, 38.7 mmol) in THF (60ml) at -10°C, was added methyl acetoacetate (4.5 g, 38.7 mmol) dropwise over a 10 min period. The mixture was stirred at 0°C for a further 15 min whereupon a solution of n-BuLi (12.5 ml, 1.6M) was added dropwise over a 5 min period to give a dark red solution of the dianion. After stirring for 15-20 min, aldehyde **135** (16.3 g, 38.7 mmol) was added dropwise over a 20 min period and the mixture stirred for a further hour. The reaction mixture was concentrated *in vacuo*, washed with water (25 ml), extracted with diethyl ether (3 x 25 ml), and dried over $MgSO_4$ The residue obtained on concentration *in vacuo* was purified by flash chromatography {silica gel, 5 x 10 cm, petroleum ether:diethyl ether 5:1 -> 3:1, ether} to give the title compound **137** (67%, 7.26 g, 25.9 mmol) as a colourless oil: IR (film); 3520br, 2960s, 1750s, 1720s, 1660m, 1640m cm^{-1}; ^{1}H NMR (270 MHz; $CDCl_3$) 7.4-7.2 (5H, m), 4.52 (2H, s), 4.30 (1H, m), 3.74 (3H, s), 3.73-3.60 (2H, m), 3.50 (2H, s), 3.31 (1H, d, J = 3Hz, OH), 2.74-2.71 (2H, 4 lines of equal intensity), 1.90-1.70 (2H, m); ^{13}C NMR. (67.5 MHz; CDCl3) 202.9(s), 167.6(s), 138.0(s), 128.5(d), 127.8(d), 127.7(d), 73.3(t), 68.0(t), 66.7(q), 52.4(d), 49.9(t), 49.7(t), 36.0(t).

Reaction of aldol product 121 with η^4-cyclohexadiene-Mo(CO)$_2$Cp hexafluorophosphate (97):- To a suspension of NaH (14.4 mg, 0.3 mmol) in THF (1 ml) a solution of the aldol product **121** (92.4 mg, 0.33 mmol) in THF (3.5 ml) was added dropwise at RT and the reaction mixture stirred for 1 h. Then the molybdenum complex **97** (152 mg, 0.33 mmol) was added in one portion and the reaction stirred for 15 min. The

reaction mixture was poured into water, extracted with ether (10 ml x 3) and the combined extracts washed with water (5 ml x 5) and dried over $MgSO_4$. The yellow oil obtained on concentration *in vacuo* (0.175 g) was dissolved in acetonitrile (11 ml) and iodine (0.201 g, 0.79 mmol) added, and the mixture stirred at RT for 30 min after which the reaction mixture was poured into water and extracted with ether (25 ml x 3). The combined extracts were washed with aqueous sodium sulphite followed by brine, dried over $MgSO_4$,and concentrated *in vacuo* to give a yellow oil (85 mg). TLC (petrol : ether = 1 : 1) showed that the product was a mixture of two major components. The mixture was separated by flash chromatography (silica gel, 3 x 9 cm, petrol : ether 10:1 -> 3:1) to afford a less polar product assigned structure **124** (28.3 mg, 0.092 mmol, 28%) and a more polar product which appeared to be a single diastereoisomer of the lactone **119** (30%, 40.8 mg, 0.1 mmol).

Methyl 4-[3-carbomethoxy-4,5,7a,3a-tetrahydrobenzo[b]furan-2-yl]-2-methylbut-3-ene (124):- IR (film) 3040w, 2960s, 1700s, 1650s, 1580s cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 6.89 (1H, dd, J = 16, 1Hz), 6.46 (1H, dd, J = 16, 7Hz), 6.25-6.14 (1H, m), 5.96-6.05 (1H, m), 4.77-4.68 (1H, m), 3.75 (3H, s), 3.05 (ddd, 1H, J = 13, 8, 5Hz), 2.49 (1H, dd, J = 7, 1Hz), 2.22-1.18 (4H, m), 1.07 (3H, d, J = 7Hz), 1.06 (3H, d, J = 7Hz); ^{13}C NMR (67.5 MHz; $CDCl_3$) 166.5(s), 164.2(s), 147.9(d), 134.7(d), 123.5(d), 116.4(d), 77.7(d), 51.0(q), 40.7(d), 31.8(d), 24.9(t), 23.5(t), 22.0(q), 21.9(q).

Tetrahydrobenzofuran 119:- IR (film) 3030m, 1660s, 1640m, 1400s cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 6.30-6.19 (1H, m), 6.00-5.90 (1H, m), 5.02-4.93 (1H, m), 4.20 (1H, ddd, J = 12, 6, 4Hz), 3.21-3.08 (1H, m), 2.49 (1H, ddd, J = 17, 12, 1Hz), 2.35 (1H, ddd, J = 17, 4, 1Hz), 1.04 (3H, d, J = 7Hz), 1.01 (3H, d, J = 7Hz); 13C (67.5 MHz; $CDCl_3$) 172.1(s), 165.8(s), 135.7(d), 122.7(d), 106.5(s), 81.8(d), 81.4(d), 38.1(d), 32.2(d), 26.3(t), 24.3(t), 22.9(t), 18.2(q), 18.0(q).

Tetrahydrobenzofuran 119 *via* reaction of β-ketolactone 122 with η^4-cyclohexadiene-$Mo(CO)_2Cp$ hexafluorophosphate (97):- To a stirred suspension of NaH (428 mg, 17.86 mmol) in THF (30 ml) under nitrogen at RT was added β-ketolactone **122** (2.8 g, 14.89 mmol) dropwise. After stirring for 30 min, the molybdenum complex **97** (6.57 g, 14.89 mmol) was added in one portion and the reaction mixture stirred at RT for a further 30 min, whereupon the mixture was poured into water and the product extracted into ether (3 x 25 ml). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil (3.58 g) which was dissolved in acetonitrile (35 ml) under a nitrogen atmosphere at RT and iodine (5.6 g, 22.2 mmol) added. The reaction mixture was stirred for 1 h, poured into water and then extracted with ether (4 x 25 ml). The combined extracts were washed with sodium thiosulphate (4 x 30 ml), brine (30 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow oil (987 mg) which was purified

by flash chromatography (silica gel, 3 x 3 cm, petrol : ether = 5 : 1 -> 3:1) to give the tricyclic tetrahydrobenzofuran **119** (42%, 808 mg, 2.75 mmol) as an inseparable mixture of diastereoisomers. With IR and NMR data identical with the sample prepared previously (*vida supra*).

6-Benzyloxy-4-oxo-tetrahydropyran-2-one (138):- A solution of KOH (504 mg, 10.72 mmol) in methanol (45 ml) and water (6 ml) was added to the aldol product (3.0 g, 10.72 mmol) and the mixture stirred rapidly for 10 min. Lactonisation was effected by acidification of the mixture to pH = 3-4. The mixture was then poured into NaCl and extracted with DCM (4 x 15 ml). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* and the residue purified by flash chromatography (silica gel, 5 x 10 cm, petroleum ether : diethyl ether 1:1 -> ether) to give the title compound **138** (69%, 325 mg, 1 mmol) as a colourless oil: IR (film): 3040.2w, 2858.2m, 1772s, 1740.8s, 1260s, 1103.1s cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) 7.44-7.25 (5H, m), 4.92-4.83 (1H, m), 4.53 (1H, d, J = 12Hz), 4.51 (1H, d, J = 12Hz), 3.78-3.59 (2H, m), 3.54 (1H, d, J = 19Hz), 3.43 (1H, d, J = 19Hz), 2.72 (1H, dd, J = 16.8, 2.7Hz), 2.5 (1H, dd, J = 16.8, 9.3Hz), 2.18-1.95 (2H, m); ^{13}C NMR (90.6 MHz, $CDCl_3$): 200.1(s), 167.3(s), 138.0(s), 128.6(d), 128.0(d), 127.9(d), 73.4(t), 72.8(d), 65.1(t), 47.3(t), 43.6(t), 34.9(t).

η^3-allyl molybdenum complex (139):- To a two-necked 150 ml R/B flask (flame dried, evacuated, and flushed with argon twice) THF (9 ml) was added, followed by oil-free NaH (76.8 mg, 1.6 mmol). The mixture was stirred for 30 min when a solution of lactone **138** (0.4 g,1.6 mmol) was added dropwise and stirred at RT for 15 min. The molybdenum complex **97** (0.713 g, 1.6 mmol) was added in one portion and the mixture stirred for a further 30 min. The reaction mixture was poured into water (15 ml) and extracted with diethyl ether (3 x 10 ml), dried over $MgSO_4$, and concentrated *in vacuo* to give the title compound **139** (62.4%, 0.7 g, 0.8 mmol) as a brown oil which was not purified further owing to chromatographic instability. The crude product gave IR (film): 3040w, 2938.6m, 2878.9m, 1723.1s, 1659.0s, 1414.2s cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.40-7.25 (5H, m), 6.30-6.18 (1H, m), 6.0-5.86 (1H, m), 5.12-5.03 (2H, m), 5.03-4.94 (1H, m), 4.72-4.58 (1H, m), 4.52 (1H, d, J = 12), 4.5 (1H, d, J = 12), 3.86-3.60 (2H, m), 3.35-3.22 (2H, m), 3.22-3.09 (2H, m), 2.61-1.25 (6H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) 172.1(s), 171.8(s), 165.5(s), 165.4(s), 138.1(s), 135.5(d), 135.3(d), 128.4(d), 127.7(d), 123.1(d), 122.5(d), 106.3(s), 106.2(s), 82.2(d), 81.7(d), 74.1(d), 74.0(d), 73.2(t), 65.8(t), 37.9(d), 37.1(d), 35.1(t), 35.0(t), 29.5(t), 24.5(t), 22.1(t), 22.3(t).

Tetrahydrobenzofuran 140:- To a solution of the crude molybdenum complex **139** (0.835 g) in acetonitrile (61 ml) at RT, resublimbed iodine (0.933 g, 3.7 mmol) was added and the mixture stirred for 30 min. The mixture was then poured into water and extracted with Et_2O (3 x 15 ml). The combined extracts were washed with sodium thiosulphate (3 x 20 ml), NaCl (40 ml), dried over $MgSO_4$, and concentrated *in vacuo* to a brown/yellow oil which was purified by flash chromatography (alumina, 6 x 12 cm, petroleum ether : diethyl ether 3 : 1 -> 1 : 1 ether). The title compound **140** (54%, 0.284 g, 0.87 mmol), obtained as a pale yellow oil, gave IR (film): 3040w, 2940m, 2880m, 1720s, 1660s, 1410s cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): 7.40-7.25 (5H, m), 6.30-6.18 (1H, m), 6.00-5.86 (1H, m), {major isomer 5.12-5.03 (m), minor isomer 5.03-4.94 (m), 1H}, 4.72-4.58 (1H, m), 4.52 (1H, d, J = 12Hz), 4.50 (1H, d, J = 12Hz), 3.86-3.60 (2H, m), {major isomer 3.35-3.22 (m), minor isomer 3.22-3.09 (m), 1H}, 2.61-2.39 (2H, AB system with further coupling); 2.26-1.82 (5H, m), 1.58-1.25 (1H, m): ^{13}C NMR (67.5 MHz, $CDCl_3$) 172.1(s), 171.8(s), 165.53(s), 165.46(s), 138.1(s), 135.5(d), 135.3(d), major isomer 128.4(d), 127.7(d), 123.1(d), 122.5(d), 106.3(s), 106.2(s), 82.2(d), 74.1(d), 74.0(d), 73.2(t), 65.8(t), 37.9(d), 37.1(d), 35.11(t), 35.07(t), 29.4(t), 24.5(t), 24.1(t), 22.3(t), minor isomer 126.0(d), 125.8(d), 122.0(d), 121.5(d), 106.8(s), 106.0(s), 80.0(d), 77.5(d), 74.1(d), 73.2(t), 65.8(t), 36.7(d), 37.5(d), 35.11(t), 34.6(t), 29.4(t), 25.4(t), 24.1(t), 22.3(t).

6-Hydroxy-4-oxo-tetrahydropyran-2-one (130):- The title compound was prepared in quantitative yield by catalytic hydrogenolysis of the benzyl-protected lactone **138** over Pd/C in the usual way. Lactone **130** was obtained as a white powder: M.p 72-73°C; IR (film): 3481.2br, 2858.2s, 1732s, 1698.8s, 1481m, 1260s, 1103.1s cm^{-1}; ^1H NMR (270 MHz, CD_3COCD_3) 4.98 (1H, br), 4.28 (1H, ddt, J = 11, 8, 5Hz), 3.81-3.63 (2H, m), 2.54 (1H, dd, J = 18, 12Hz), 2.43 (1H, dd, J = 19, 4Hz), 2.05-1.79 (2H, m); ^{13}C NMR (67.5 MHz, CD_3COCD_3) : 176.2(s), 171.9(s), 91.5(d), 75.2(d), 58.6(t), 28.6(t), 34.2(t).

3-(Methoxymethoxy)propionitrile (141):- To a stirred suspension of NaH (2.4 g, 103.44 mmol) in DMF (100 ml) was added freshly distilled 3-hydroxy-propionitrile (6.2 g, 86.2 mmol) at 0°C, and the reaction mixture stirred for 2 h whereupon MOM-Cl (6.9 g, 86.2 mmol) was added and the reaction mixture allowed to stir for a further 12 h. The mixture was then poured into water (200 ml) and extracted with ether (4 x 50 ml). The combined extracts were washed with small quantities of water to remove the DMF, dried over $MgSO_4$, and concentrated *in vacuo* to afford the title compound **141** (92%, 9.2 g, 79.3 mmol) as a clear oil giving IR and NMR data consistent with those reported in the literature[50].^1H NMR (270 MHz, $CDCl_3$) 4.57 (2H, s), 3.22 (3H, s), 3.47-3.42 (4H, m), 1.75 (2H, dd, J = 7, 9Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) 95.33 (t), 71.59 (t), 64.4 (t),

58.7 (q), 29.8 (t)

3-(Methoxymethoxy)propanal (144):- The nitrile **141** (9.2 g, 79.3 mmol) was reduced to the aldehyde using DIBAL-H (1.5M, 52 ml) as described below for ester **164** (*vide infra*). The title compound (95%, 8.89 g, 75.3 mmol) gave IR and NMR data consistent with those reported in the literature[50].

(E)-1,3-Bis(trimethylsilyoxy)-1-methoxy-buta-1,3-diene (136):- The title compound was prepared according to the procedure of Chan[51] Di-isopropylamine (2.87 g, 28.5 mmol) in THF (20 ml) was stirred under a nitrogen atmosphere, while *n*-BuLi (20 ml, 1.6M) was added dropwise at -78°C. Methyl-3-trimethylsiloxybut-2-enoate (4.4 g, 28.5mmol) was then added dropwise and the mixture stirred for 2 min. The resultant lithium enolate was quenched with TMSCl (4.12 g, 38 mmol) and the cooling bath removed. When ambient temperature was attained, the mixture was concentrated to one third its original volume by rotary evaporation at *ca.* 15 mm Hg. The residue was diluted with dry pentane (25 ml), filtered twice and concentrated *in vacuo* to yield the title compound in essentially quantitative yield. The sensitive crude product was used immediately in the next step without further purification.

Methyl 7-Benzyloxy-5-hydroxy-3-oxo-heptanoate 137 *via* directed aldol reaction:- To a magnetically stirred solution of aldehyde **135** (219 mg, 1.23 mmol) and 1-methoxy-1,3-bis(trimethylsilyoxy)-but-1,3-diene **136** (0.32 g, 1.23 mmol) in DCM (10 mlg^{-1}) at -90°C under nitrogen was added dropwise $TiCl_4$ (0.23 g, 0.14 ml, 1.23 mmol). After 3 h the mixture was poured into $NaHCO_3$ (10 ml) and extracted with DCM (3 x 10 ml). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (0.310 g) which was purified by flash chromatography (silica gel, 3 x 9 cm, petrol : ether = 5 : 1 -> 2 : 1) to give the aldol product **137** (64%, 231 mg, 0.78 mmol) as a mixture of diastereoisomers having IR and NMR spectra identical with a sample prepared previously (*vide supra*).

By a similar procedure, the following compounds were prepared: **methyl 7-(*t*-butyldimethylsilyloxy)-5-hydroxy-3-oxo-heptanoate (148)** (31%) and **methyl 7-(*t*-butyldiphenylsilyloxy)-5-hydroxy-3-oxo-heptanoate (149)** (64%).

3-Benzyloxy-2-methylpropionitrile (159):- To a solution of benzyl alcohol (5.4 g, 50 mmol) in THF (60 ml) under nitrogen was added NaH (15 mg, 0.03 mmol) and the

mixture stirred at RT for 15 min. To the resulting suspension was added dropwise at RT methylacrylonitrile **158** (16.75 g, 0.25 mmol) over a 40 min period and the resultant mixture heated to 60-65°C for 5 h. The mixture was then cooled to 0°C and acidified with 1M H_2SO_4 and diluted with ether. The solution was poured into water and extracted with ether (25 ml x 3). The combined extracts were washed with $NaHCO_3$ (20 ml), brine (20 ml), dried over $MgSO_4$ and concentrated to give a yellow oil. The crude product was distilled (92-96°C, 0.5 mmHg) to give the desired nitrile **159** as a colourless oil (6.08 g, 69%); IR (film) 3040m, 3000m, 2960m, 2880s, 2260s, 1460s, 1120s cm^{-1}; ^1H NMR (270 MHz; $CDCl_3$) 7.42-7.28 (5H, m), 4.60 (2H, s), 3.59 (1H, dd, J = 9, 7Hz), 3.53 (1H, dd, J = 9, 6Hz), 2.89 (1H, ddq, J = 6, 7, 7Hz), 1.35 (3H, d, J = 7Hz); ^{13}C NMR (67.5 MHz; $CDCl_3$) 137.4(s), 128.5(d), 127.9(d), 127.7(d), 121.4(s), 73.3(t), 70.6(t), 26.5(d), 14.7(q).

***rac*-3-Benzyloxy-2-methylpropanal (160a):-** To a solution of the nitrile (2.1 g, 12 mmol) at -50°C in DCM (50 ml) was added a solution of DIBAL-H in hexane (12 ml, 1.5M, 18 mmol) and the reaction stirred for 3 h. It was then allowed to warm to 5°C whereupon NH_4Cl (30 ml) was added slowly and the mixture stirred for 30 min. The reaction was quenched by pouring into citric acid (saturated aqueous solution, 25 ml) and the product extracted into DCM. The extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a clear oil which was purifed by using column chromatography (silica gel, 3.5 x 3 cm, petrol : ether 1:3) to give the title compound **160a** (62%, 1.32 g, 7.44 mmol) as a colourless oil: IR (film); 3040m, 2980s, 2940s, 2860s, 1740s, 1460s, 1100m cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 9.74 (1H, d, J = 2Hz), 7.41-7.26 (5H, m), 4.54 (2H, s), 3.70 (1H, dd, J = 9, 7Hz), 3.66 (1H, dd, J = 9, 5Hz), 2.75-2.61 (1H, m), 1.15 (3H, d, J = 7Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) 203.9(d), 138.0(s), 128.5(d), 127.8(d), 127.7(d), 73.4(t), 70.2(t), 46.9(d), 10.8(q).

***rac*-6-[2-(Benzyloxy)-1-methyl-eth-1-yl]-4-oxo-tetrahydropyran-2-one (162a) (Method A):-** To a solution of aldehyde **160a** (0.231 g, 1.3 mmol) and (E)-1,3-bis(trimethylsilyoxy)-1-methoxybuta-1,3-diene **136** (0.338 g, 1.30 mmol) in DCM (3 ml) at -95°C under nitrogen, was added dropwise $TiCl_4$ (0.26 g, 1.40 mmol) and the mixture stirred for 3 h. The mixture was poured into $NaHCO_3$ (10 ml) and extracted with DCM (3 x 10 ml) The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*, to give a yellow oil (0.426 g). The crude product was purified by flash chromatography (silica gel, 3 x 9 cm, petrol : ether = 2 : 1 ->1 : 1) to give the aldol product **161a** as a colourless oil (57%, 0.217 g, 0.74 mmol).

A solution of the aldol product (0.217 g, 0.74 mmol) was added to a stirring solution of methanol (13 ml), LiOH (32 mg, 0.76 mmol) and water (1.5 ml) at RT and the mixture stirred for 1 h to give a light yellow solution which was acidified to pH = 3-4 affording a near clear solution of the lactone which was poured into water and extracted with DCM (3 x 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (96%, 0.172 g, 0.68 mmol) which was purified by column chromatography (silica gel: petrol : ether 1:2 -> ether). TLC (ether) and high field NMR show the mixture to be a separable mixture of diastereoisomers in a ratio of 1 : 2; IR (mixture) (film): 3040w, 2980m, 2860m, 1770s, 1740s, 1680s, 1630s, 1270s, 910s cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.41-7.26 (5H, m), {major isomer 4.83 (ddd, J = 10, 6, 4Hz), minor isomer 4.76 (ddd, J = 11, 6, 3Hz), 1H)}, {major isomer 4.51 (s), minor isomer 4.50 (s), 2H)}, 3.64-3.56 (4H, m), 2.72-2.47 (2H, m), 2.40-1.98 (1H, m), {major isomer 1.07 (d, J = 7Hz), minor isomer 1.05 (d, J = 7Hz), 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$); major isomer; 200.6(s), 167.6(s), 138.0(s), 128.6(d), 128.0(d), 127.9(d), 75.7(d), 73.5(t), 71.0(t), 47.2(t), 41.5(t), 37.3(d), 11.2(q); minor isomer; 200.5(s), 167.5(s), 138.1(s), 128.6(d), 127.9(d), 127.8(d), 76.5(d), 73.4(t), 70.7(t), 47.2(t), 40.4(t), 37.3(d), 12.4(q); LRMS m/z: 262 (M^+, 2%), 160 (48%), 145 (29%), 107 (19%), 96 (23%), 91 (100%).

***rac*-6-[2-(Benzyloxy)-1-methyl-eth-1-yl]-4-oxo-tetrahydropyran-2-one (162a) (Method B).-** To a solution of aldehyde **160a** (0.426 g, 2.6 mmol) in DCM (2.2 ml), at -80°C, was added dropwise a solution of $TiCl_4$ (0.988 g, 5.2 mmol) in DCM (8 ml) and the dark solution stirred at -80°C for 15 min. Then a solution of (E)-1,3-bis(trimethylsilyoxy)-1-methoxybuta-1,3-diene **136** (0.806 g, 3.10 mmol) in DCM (1 ml) was added dropwise and the reaction stirred for 3 h. The mixture was poured into $NaHCO_3$ (15 ml) and extracted with DCM (3 x 10 ml) The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil (0.80 g). The crude product was purified by flash chromatography (silica gel, 3.5 x 12 cm, petrol : ether = 2 : 1 ->1 : 1) to give the aldol product as a yellow oil (68%, 0.517 g, 1.76 mmol).

A solution of the aldol product (0.488 g, 1.66 mmol) was added to a stirring solution of methanol (31 ml), LiOH (77 mg, 1.83 mmol) and water (3.6 ml) at RT and stirred for 1 h to give a light yellow solution which was acidified to pH = 3-4 affording a near clear solution of the lactone which was poured into water and extracted with DCM (3 x 30ml). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow oil (0.409 g, 1.56 mmol 94%) which was purified by column chromatography (silica gel, petrol : ether 1:2 -> ether); TLC (ether) and high field

NMR show the mixture to be a mixture of diastereoisomers in a ratio of 3.3 : 1.

***rac*-6-[2-(*t*-Butyldimethylsilyloxy)-1-methyl-eth-1-yl]-4-oxo-tetrahydropyran-2-one (162b):-** The aldehyde **160b** (0.40 g, 1.4 mmol) and (E)-1,3-bis(trimethylsilyoxy)-1-methoxybuta-1,3-diene **136** (0.36 g, 1.40 mmol) were treated with $TiCl_4$ (0.26g, 1.40 mmol) as described above for **162a**. The resultant aldol adduct (18%, 85 mg, 0.25mmol) was then treated with LiOH and acidified to afford the title compound **162b** (96%, 68 mg, 0.24 mmol) as a separable mixture of diastereoisomers: IR (film): 2940s, 1770s, 1740s, 1660s, 1620s cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) {4.81 (ddd, J = 9.2, 5.2, 4Hz) and 4.73 (ddd, J = 12, 7, 4Hz), 1H}, 3.82-3.38 (3H, m), {2.735 (d, J = 18Hz) and 2.722 (d, J = 18Hz) 1H}, {2.575 (d, J = 18Hz) and 2.525 (d, J = 18Hz) 1H}, 2.2-1.8 (1H, m), {1.03 (d, J = 7Hz) and 0.995 (d, J = 7Hz) 3Hz}, 0.89 (9H, s), 0.06 (6H, s).^{13}C NMR (67.5 MHz, $CDCl_3$) [200.8(s), 200.6(s)], [167.6(s), 167.5(s)], [76.6(d), 75.6(d)], [63.9(t), 63.7(t)], [47.3(t), 47.2(t)], [41.7(t), 40.7(t)], [39.4(d), 39.2(t)], 26.0(s), 18.4(s), [12.1(q), 11.0(q)], [-5.3(q), -5.3(q)].

3-(*t*-Butyldiphenylsilyloxy)-propionitrile (143):- To a stirred solution of imidazole (4.7 g, 70.4 mmol), DMAP (25 mg), and 3-hydroxypropionitrile (1 g, 15.69 mmol) in DCM (10 ml) was added at 0°C TBDPS-Cl (4.2 g, 15.6 mmol). The reaction mixture was stirred at RT for 1.5 h after which it was poured into water and extracted with DCM (3 x 25ml), dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **143** (4.5 g, 15.4 mmol, 98%) as a clear oil: IR (film): 2931s, 1960w, 1890w, 1824w, 1472m, 1428m, 112s, 702s; ^1H NMR (270 MHz, $CDCl_3$) 7.82-7.75 (4H,m), 7.48-7.28 (6H, m), 3.83 (2H, t, J = 6.1Hz), 2.55 (2H, t, J = 6.1Hz), 1.11 and 0.99 (9H, 2 x s); ^{13}C NMR (65.7 MHz, $CDCl_3$) 135.7(d), 135.0(d),132.8(s), 130.2(s), 129.7(d), 128.0(d), 127.8(d), 118.1(s), 59.2(t), 26.8(q), 26.7(q), 21.6(t), 19.3(s).

3-(*t*-Butyldiphenylsilyloxy)-propanal (146):- To a solution of the nitrile (4.73 g, 15.31 mmol) at -50°C in DCM (50 ml) was added a solution of DIBAL-H (1.5M, 15.3 ml, 22.9 mmol) slowly and the reaction stirred for 3 h and allowed to warm to 5°C when NH_4Cl (10 ml) was added slowly and the mixture stirred for 30 mins. The reaction was quenched by pouring the mixture into citric acid (saturated aqueous solution, 30 ml) and the product extracted into DCM (3 x 25 ml). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*to give a clear oil which was filtered through a plug of silica gel to give the title aldehyde **146** (96%, 4.35 g, 14.7 mmol) as a colourless oil: IR (film) 2938s, 2872s, 1960w, 1890w, 1825w, 1737s, 1429m, 1431s, 1110s, 704s; ^1H NMR

(270 MHz, $CDCl_3$) 9.8 (1H, t, J = 2Hz), 7.85-7.78 (4H, m), 7.49-7.3 (6H, m), 4.06 (2H, ddd, J = 5.9, 5.9, 2), 2.64 (1H, dddd, J = 5.9, 5.9, 2, 1Hz), 1.1 and 1.08 (9H, 2 x s); ^{13}C NMR (65.7 MHz, $CDCl_3$) 202.1(s), [135.8(d) and 135.6(d)], [134.9(d) and 134.06(d)], 133.3(s), [129.9(d) and 129.7(d)], [127.89(d) and 127.83(d)], 58.3(t), 46.6(t), [26.8(d) and 26.6(d)], [19.2(s) and 19.1(s)].

6-[2-(*t*-Butyldiphenylsilyloxy)-eth-1-yl]-4-oxo-tetrahydro-2-pyranone (151):- To a stirred solution of NaH (60% in oil, 538 mg, 20.54 mmol) in dry THF (15 ml) at -5°C, was added dropwise a solution of methylacetoacetate (2.38 g, 20.54 mmol) in THF at a rate sufficient to maintain the temperature below 0°C. After 10 min, *n*-BuLi (1.6M, 12.83 ml) was added dropwise and the mixture allowed to stir for a further 10 min. A dark red solution of the dianion was observed which was subsequently quenched with a solution of the aldehyde **146** (6.41 g, 20.54 mmol) at 0°C. After 10 min, the reaction was poured into water (50 ml) and extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (silica gel, petrol : ether 4:1 -> ether) to give methyl 7-(*t*-butyldiphenylsilyloxy)-5-hydroxy-3-oxo-heptanoate **149** (68%, 13.9 mmol, 4.6 g) as a colourless oil, which was used immediately in the next step.

To a stirred solution of methanol (30 ml), LiOH (114 mg, 6.02 mmol) and water (4 ml) at RT was added a solution of the aldol product **149** (10 g, 6.02 mmol) and the mixture stirred for 1 h to give a light yellow solution which was acidified to pH = 3-4 affording a clear solution of the lactone which was poured into water and extracted with DCM (3 x 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* and the residue purified by using column chromatography (silica gel, petrol : ether 1:2 -> ether) to give the title compound **151** (83%, 11.5 mmol, 3.6 g) as a colourless oil: IR (film) 2987br, 1966w, 1894w, 1861w, 1729s, 1673s, 1621s; ^1H (270 MHz, $CDCl_3$); 7.81-7.75 (4H, m), 7.58-7.30 (6H, m), 4.91 (2H, m), 4.0-3.8 (2H, dt, J = 28, 14Hz), 3.4 (2H, d, J = 14Hz), 2.7 (1H, dd, J = 10, 2Hz), 1.3 (3H, s), 1.05 (6H, d, J = 10Hz); ^{13}C (65.7 MHz, $CDCl_3$) 202.2(s), 165.3(s), 138.6(d), 127.8(d), 71.6(t), 59.2(d), 49.8(t), 42.8(t), 38.0(t), 29.1(s), 27.1(t), 19.5(q), 9.4(q), -5.2(t); LRMS m/z 414 (M^+-1, 1%), 370(98), 275(51), 187(25), 35(32).

Spiroacetal 157:- To a solution of the tetrahydrobenzofuran **153** (1 g, 2.049 mmol) in dry ether (25 ml), at -5°C, was added dropwise a solution of Red-Al™ (1.2 ml, 4.19 mmol) and the mixture stirred at 0°C for 2 h. The reaction was quenched with 2M HCl (1 ml), washed with $NaHCO_3$ (5 ml), NaCl (10 ml), and dried over $MgSO_4$.. The combined extracts were concentrated *in vacuo* to afford a yellow foam of the intermediate diol

156 (56%, 420 mg, 1.068 mmol). This was taken up in acetonitrile (5 ml) and aqueous HF (40%, 1.5 ml) was added dropwise. The reaction mixture was stirred for 6 h at RT and finally quenched by the addition of solid sodium bicarbonate. The reaction was filtered and concentrated *in vacuo* to afford the title compound **157** (21%, 102 mg 0.43 mmol) as a mixture of diastereoisomers. IR (film) 3458br, 2895s, 1689m, 1108m. The ^{13}C spectrum was complex as expected for a mixture of up to 8 diastereoisomers. However, the presence of the spiroacetal carbon was deduced from the characteristic acetal signal at δ 104. In addition, the presence of a tetrahydrobenzofuran nucleus was evident from the alkene signal at δ 6.34-6.19 and 5.98, as well as the multiplet at δ 5.15 (=CH-CH-O).

2-R-(-)-Methyl-3-(*t*-butyldiphenylsilyloxy)-propanal (160c):- The known[52] ester 2-R-(-)-methyl-3-t-butyldiphenylsilyloxy-propanoate (14.8 g, 41.5 mmol) was stirred in DCM (150 ml) at -80°C with DIBAL-H (1.5M, 28 ml) being added slowly to keep the temperature below -70°C. The reaction mixture was stirred for 2 h and quenched at 0°C with NH_4Cl (25 ml). The reaction mixture was then poured into citric acid (saturated aqueous solution, 150 ml) and extracted with DCM (3 x 25 ml). The extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound **160c** (95%, 13.5 g, 39.4 mmol) as a colourless oil having IR and NMR data consistent with those reported in the literature[45, 52]. ^1H NMR (270 MHz, $CDCl_3$) 9.8 (1H, s), 7.8 (4H, m), 7.5 (6H, m), 3.97 (2H, dddd), 2.65 (1H, ddq), 1.16 (12H, m); ^{13}C NMR (67.5 MHz, $CDCl_3$) 204.45 (s), 135.79 (d), 135.66 (s), 133.2 (d), 129.92 (d), 129.76 (s), 129.5 (d), 128.3 (t), 127.8 (t), 127.7 (t), 64.17 (d), 27.62 (t), 26.84 (t), 19.32 (t), 10.37 (s)

6-[2-(*t*-Butyldiphenylsilyloxy)-1(R)-methylethyl]-4-oxo-tetrahydro-2-pyranone (162c):- To a solution of aldehyde **160c** (478 mg, 1.40 mmol) and (E)-1,3-bis(trimethylsilyoxy)-1-methoxybuta-1,3-diene **136** (0.36 g, 1.40 mmol) in DCM (3 ml) at -90°C under nitrogen was added dropwise $TiCl_4$ (0.26g, 1.40 mmol) and the mixture stirred for 3 h. The mixture was poured into $NaHCO_3$ (15 ml) and extracted with DCM (3 x 10 ml) The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil (0.462 g) which was purified by flash chromatography (silica gel, 5 x 9 cm, petrol : ether = 4 : 1 -> 1 : 1) to give the desired aldol product (48%, 285 mg, 0.675 mmol) as a colourless oil which was used immediately in the next step.

A solution of the above aldol adduct (285 mg, 0.68 mmol) was added to a stirring solution of methanol (7.5 ml), LiOH (28 mg, 0.68 mmol) and water (1.0 ml) at RT and stirred for 1 h to give a light yellow solution which was acidified to pH = 3-4 affording a near clear solution of the lactone **162c** which was poured into water and

extracted with DCM (3 x 30 ml). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* and the residue purified by column chromatography (silica gel, petrol : ether 1:2 -> ether) to give the title lactone **162c** (79%, 214 mg, 0.53 mmol) as an inseparable mixture of diastereoisomers: IR (mixture) (film) 2989br, 1968w, 1884w, 1868w, 1730s, 1672s, 1622s; ^1H NMR (270 MHz, $CDCl_3$) 7.81-7.75 (4H, m), 7.58-7.30 (6H, m), 4.8 (1H, m), 3.96(1H, ddd, J = 14.8, 10.6, 5.3Hz) 3.84 (1H, ddd, J = 14.8, 7.7, 7.7 Hz), 3.48 and 3. 40 (1 H each, AB system, J = 18.6 Hz), 2.66 (1H, dd, J = 19, 3Hz), 2.45 (1H, dd J = 19, 11.4Hz), 2.35 (1H, m), 1.1 (9H, s), 0.85 (3H, 2 overlapping d, J = 7Hz); LRMS m/z 427 (M^+-1, 1%), 370(89), 275(68), 35(48).

Tetrahydrobenzofuran 167:- To a stirred suspension of NaH (13 mg, 0.53 mmol) in THF (5 ml) under nitrogen at RT was added dropwise β-ketolactone **162c** (214 mg, 0.53 mmol) and the mixture stirred for 30 min. The molybdenum complex **97** (210 mg, 0.53 mmol) was then added in one portion and the reaction mixture stirred at RT for a further 30 min, whereupon the mixture was poured in water and extracted into ether (3 x 15 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford a brown oil (480 mg). This brown oil was stirred in acetonitrile (5 ml) under a nitrogen atmosphere at RT as iodine was added (0.4 g, 1.59 mmol) and the reaction mixture stirred for 1 h. The mixture was poured into water and extracted with ether (4 x 15 ml); the combined extracts were washed with sodium thiosulphate (4 x 10 ml), brine (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford a yellow oil (247 mg) which was further purified by flash chromatography (silica gel, 3 x 3 cm, petrol : ether = 5 : 1 -> 1:2) to give the tricyclic tetrahydrobenzofuran **166** (73%, 190 mg, 0.39 mmol) which was still impure by NMR analysis. It was found that removal of the TBDPS protecting group using TBAF afforded the alcohol **167** which could be freed of non-polar contaminants by column chromatography. The resultant alcohol **167** (inseparable 6:1 mixture of diastereoisomers) gave: IR (film) (mixture): 3040w, 2940m, 2880m, 1720s, 1660s, 1410s cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$): 6.28-6.19 (1H, m), 5.19 (1H, ddd, J = 10.1, 1.6, 1.6Hz), {5.09 (m, minor isomer) and 5.06 (m, major isomer), 1H}, {4.62 (dt, J = 12.7, 4Hz; major isomer) and 4.42 (dt, J = 12.7, 4Hz; minor isomer), 1H}, 3.73 (2H, ddd, J = 13.5, 10.8, 5.4Hz), 3.29 (1H, ddt, J = 10, 5, 2Hz), {2.67 (dt, J = 8.5, 2Hz; major isomer) and 2.57 (dt, J = 8.5, 2Hz; minor isomer), 1H}, {2.45 (dd, J = 9, 2.3Hz; major isomer) and 2.33 (dd, J = 9, 2.3Hz; minor isomer), 1H}, 2.21-1.6 (5H, m), 1.59-1.44 (1H, m), {1.05 (d, J = 6.75Hz; major isomer) and 1.01 (d, J = 6.75Hz; minor isomer), 3H}; ^{13}C NMR (67.5 MHz, $CDCl_3$): 172.7(s), 166.0(s), 135.5(d), 123.2(d), 106.4(s), 82.5(d), 77.43(d), 64.4(t), 39.2(t), 26.9(t), 24.6(t), 22.5(t), 12.9(s), 11.4(d).

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