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Synthetic Studies Towards the Total Synthesis of the Neocarzinostatin Chromophore

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Statement

I hereby declare that this thesis has not been submitted, either in the same or different form, to this or any other University for a degree.

Signature:

Olivier Thominet.

June 2007

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Abstract

The chromoprotein Neocarzinostatin (NCS) was the first isolated member of the so-called 'enediyne' class of antibiotics and was found to exhibit broad-spectrum antitumor activity. NCS was isolated in 1965 from the bacterium *Streptomyces carzinostaticus* and is made up of a 1:1 non-covalent complex of an extraordinarily reactive nine-membered ring epoxydiyne chromophore (NCS-C) tightly bound to a protein known as apo-NCS. The antitumor activity arises solely from the chromophore which acts as a DNA-cleaving agent initiated by radical hydrogen abstraction of a deoxyribose residue. The apoprotein protects, carries and delivers the chromophore offering potential as a novel, more selective drug delivery system.

Our general strategy towards NCS-C involves the Michael addition of an epoxydiyne to a cyclopentenone followed by cyclisation *via* an aldol reaction. The enantioselective synthesis of the cyclopentenone fragment had already been synthesised within the group *via* enzyme-mediated kinetic resolution. The aim of this project is to report our current efforts to establish a general method for the synthesis of epoxydiynes in order to apply our own Michael/aldol sequence. Different routes to these epoxydiynes have been developed using a Sharpless asymmetric epoxidation. However, these have proven to be extremely difficult due to the formation of unstable intermediates which could not be processed to fully elaborated epoxydiynes. After considerable investigation, a concise and convergent approach to epoxydiynes was finally achieved on a multi-gram scale. This involves a diastereoselective addition of an allenyl zinc bromide to propargylic ketones/aldehydes followed by epoxide formation. This new protocol enables us to synthesise fully functionalised and stereochemically pure epoxydiynes including *C*-8 provides a very simple synthetic route to other functionalised epoxydiynes. Owing to the flexibility of our new method, epoxydiynes with different protecting groups can now be readily prepared enabling us to screen them in new Michael addition reaction studies.

Contents

Abbreviations

A:	deoxyadenosine
Ac:	acetate
Acac:	acetylacetonate
C:	carbon atom
Cat:	catalytic
CDI:	carbonyldiimidazole
CDR:	complementarity determining regions
Co_2CO_6:	dicobalthexacarbonyl
Co_2CO_8:	dicobaltoctacarbonyl
CSA:	10-camphorsulfonic acid
Cys:	cysteine
Da:	dalton
DABCO:	1,4-diazabicyclo[2.2.2]octane
Dba:	dibenzylideneacetone
DBU:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC:	1,3-dicyclohexylcarbodiimide
DCE:	dichloroethane
DCM:	dichloromethane
DDQ:	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEI:	diethylisopropyl
DET:	diethyl tartrate
$(DHQD)_2PYR$:	1,4-bis(9-*O*-dihydroquinidine)-diphenylpyrimidine
DIBAL:	diisobutylaluminium hydride
DIPEA:	*N,N*-diisopropylethylamine
DMAP:	dimethylaminopyridine
DMF:	*N,N*-dimethylformamide
DMP:	Dess-Martin periodinane
DMSO:	dimethylsulfoxide
DNA:	deoxyribonucleic acid
E:	Entgegen
EDC:	1-ethyl-3-[3-dimethylaminopropyl]carbodiimide

Et:	ethyl
Gly:	glycine
H:	hydrogen atom
HMDS:	hexamethyldisilazide
HRMS:	high resolution mass spectroscopy
*i*Pr:	*iso*-propyl
IR:	infra-red
K_d:	dissociation constant
LDA:	lithium diisopropylamine
LHMDS:	lithium hexamethyldisilazide
*m*CPBA:	*meta*-chloroperoxybenzoic acid
Me:	methyl
mM:	millimolar
MOM:	methoxymethyl
MPM:	4-methoxybenzyl
Ms:	methanesulfonyl
NBS:	*N*-bromosuccinimide
NCS:	Neocarzinostatin
NCS-C:	Neocarzinostatin chromophore
NIS:	*N*-iodosuccinimide
nM:	nanomolar
NMR:	nuclear magnetic resonance
nOe:	nuclear Overhauser effect
O_2:	dioxygen
PDC:	pyridinium dichromate
$Pd(Ph_3)_4$:	tetrakis(triphenyl)phosphine palladium(0)
Ph:	phenyl
Ph_3:	triphenyl
Phe:	phenylalanine
Piv:	pivaloyl
ppm:	parts per millions
pro-*S*:	pro-sinister
py:	pyridine
rt:	room temperature

SAE:	Sharpless asymmetric epoxidation
Ser:	serine
SMANCS:	poly(styrene-co-maleic acid/anhydride) Neocarzinostatin
T:	deoxythymidine
TBAF:	tetrabutylammonium fluoride
TBHP:	*tert*-butylhydroperoxide
TBDPS:	*tert*-butyldiphenylsilyl
TBS:	*tert*-butyldimethylsilyl
TDS:	thexyldimethylsilyl
TES:	triethylsilyl
TFA:	trifluoroacetic acid
THF:	tetrahydrofuran
TLC:	thin layer chromatography
TMS:	trimethylsilyl
TMSA:	trimethylsilylacetylene
Tf:	trifluoromethanesulfonyl
p-TsOH:	*para*-toluenesulfonic acid
μM:	micromolar
UV:	ultra-violet
Z:	Zusammen

1 INTRODUCTION

1.1 Introduction

The chromoprotein Neocarzinostatin[1] (NCS or holo-NCS) is the first representative of a chemical class of antibiotics with broad-spectrum antitumour activity. NCS was found to have anti-proliferative properties against solid-tumor cell lines. NCS is made up of a 1:1 non-covalent complex of an extraordinary reactive nine-membered ring epoxydiyne chromophore (NCS-C) tightly bound to a protein known as apo-NCS (Figure **1**).

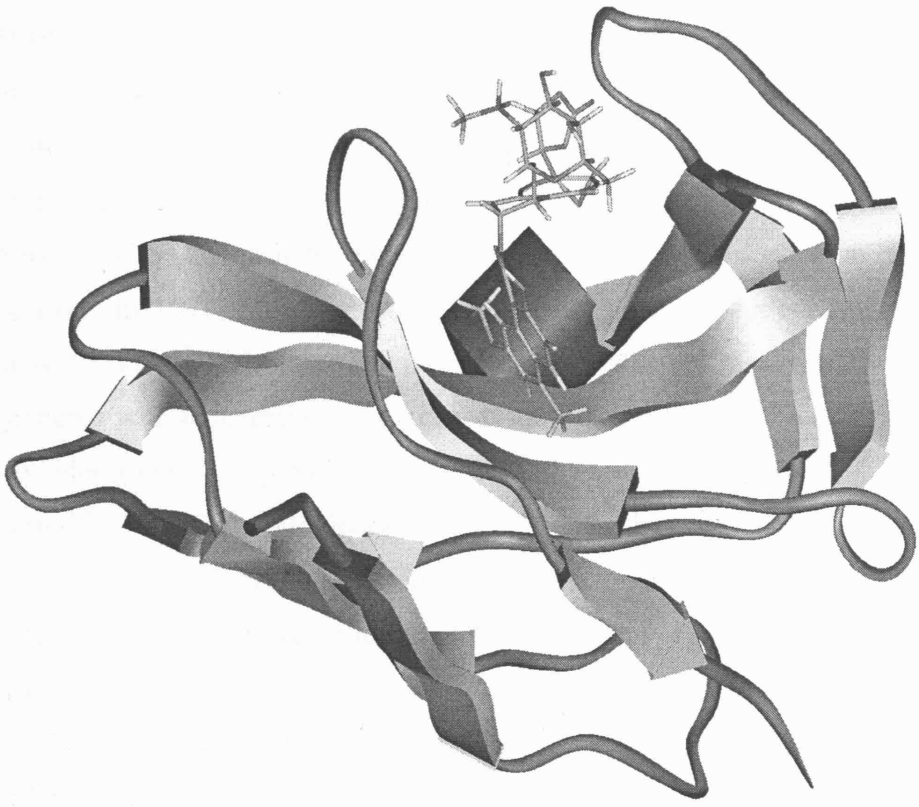


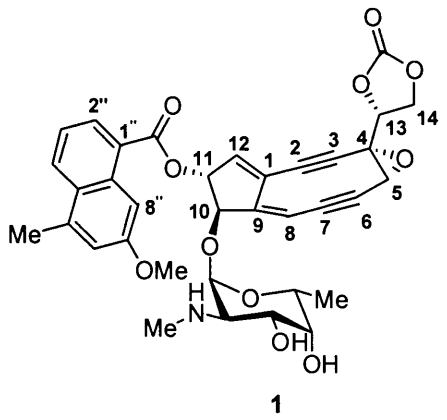
Figure 1. NCS (or holo-NCS): NCS-C + apo-NCS.

The antitumour activity arises from the chromophore that acts as DNA-cleaving agent following activation by a thiol. The apoprotein protects, carries and delivers the chromophore to DNA.

1.2 History of NCS

In 1956, Ishida's laboratory were focused on screening antitumour agents from *Streptomyces* culture broths. During this time Carzinostatin was discovered by Shoji from Streptomyces E-743, a soil bacteria harvested in Sendai, Japan and was found to possess curative effects on mice bearing tumours as well as an antibiotic activity against *Lutea sarcina*.[2] Shoji clearly established that carzinostatin consists of two components A and B. The antitumour activity was only efficient if both A and B were administered. B (probably a chromophore) is highly labile but its stability is recovered in the presence of A (probably an apoprotein). Carzinostatin was technically difficult to analyse and only few biological studies were carried out.[2] It is structurally different from NCS-C.

In 1964, Ishida *et al.* discovered NCS, a proteinaceous substance, from a culture filtrate of *Streptomyces carzinostaticus* Var. F-41, a mutant of the strain E-743 using *Sarcina lutea* as bio-assay.[3] Neocarzinostatin was originally found to have an anti-proliferative effect against Ascitic leukaemia and Sarcoma 180 in mice with an impressive therapeutic index.[3] In 1966, the protein (apo-NCS) was isolated from lyophilised NCS and Ishida already suspected the presence of a non-peptidic component.[4] In 1972, Maeda *et al.* published the primary sequence of the protein[5] which was revised[6] and then confirmed later by NMR.[7] NCS was used clinically to treat patients with leukaemia, gastric cancer and pancreatic cancer in 1977.[8] NCS was initially identified as a protein and it was not until 1979 that NCS-C was finally discovered.[9] In 1980, Goldberg *et al.* found that NCS-C undergoes rapid decomposition at high pH and upon incubation with thiols.[10] In 1985, Edo *et al.* finally disclosed the relative structure of NCS-C.[11] In 1987, Myers proposed a mode of activation of NCS-C through chemical modification using a thiol adduct of the chromophore[12] and determined the assignment of its absolute configuration in 1988 as that of **1** (Figure **2**).[13]



1

Figure 2. Structure of NCS-C.

In 1993, Teplyalov *et al.* and Myers *et al.* crystallised respectively apo-NCS[14] and holo-NCS.[15] In 1994, Myers *et al.* observed a cumulene intermediate at low temperature by NMR spectroscopy and established a mode of activation of NCS-C at the molecular level.[16] The same year, a polymer cojugated version of NCS SMANCS/lipodiol was approved by the ministry of health and welfare in Japan.[1] Myers achieved the first total synthesis of the NCS-C in 1998,[17] followed by Hirama in 2006.[18]

1.3 Role of the NCS-C moieties

In the absence of its binding protein, NCS-C is highly sensitive to light,[19] heat,[20] elevated pH,[21] nucleophiles,[12] and readily cycloaromatises to generate a diradical species.[16] Structurally, NCS-C consists of subunits which play key biological roles (Figure **3**):

a) The naphthoate is responsible for much of the strength of the binding of the chromophore with the protein and it also acts as a DNA intercalating agent.[22]

b) The sugar residue, N-methyl-fucosamine, plays an anchor-like role by forming electrostatic interactions with the negatively charged DNA phosphodiester bridge in the major groove hence, positioning the epoxydiyne core in the DNA minor groove.[22] Myers *et al.* suggested that it also plays a key role in the activation of the chromophore by acting as an internal base in the thiol-activation pathway.[23,24] The sugar residue of the NCS-thioglycolate adduct adopts a chair conformation with the amine functinality oriented above *C*12 approximating the Van der Waals diameter of

a sulfur atom.[15] Lastly, the carbohydrate provides a stabilising effect on the chromophore core protecting *C*12 from thiol attack in solution.[23]

c) The highly reactive epoxybicyclo[7,3,0]dodecadiyne is responsible of the cytotoxic activity following nucleophilic activation. A subsequent Bergman-type rearrangement[25] produces diradical species which abstracts a hydrogen atom from DNA resulting in single and double-stranded breaks.[22, 26, 27]

d) The cyclic carbonate takes part in the passage of the NCS-C through cellular and nuclear membrane.[28]

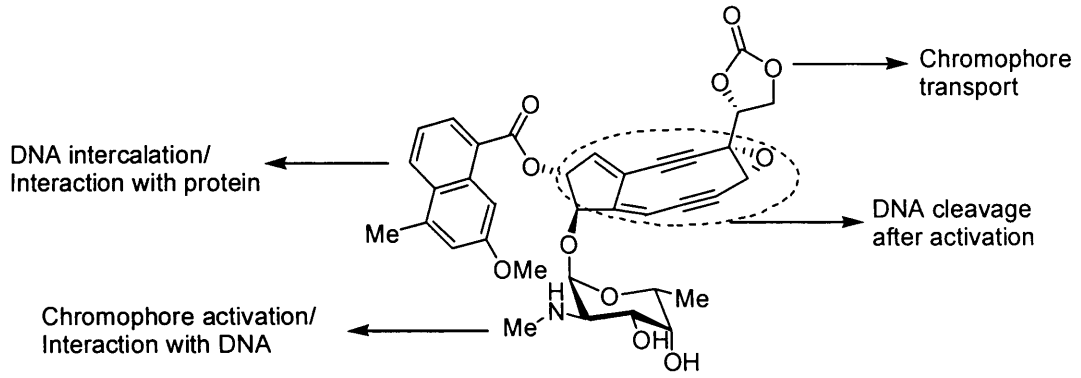


Figure 3. Biological role of the NCS-C.

1.4 Mode of activation

NCS-C exists in a pro-drug state and requires activation *via* nucleophilic addition to exert its cytotoxicity. Myers *et al.* established the precise mechanism for NCS-C activation at the molecular level (Figure **4**). The activation cascade is triggered by a Michael-like addition of a thiol to the naphthoate at *C*12 in a *trans* manner.[29] This leads to epoxide ring opening and the formation of a highly reactive cumulene intermediate **2** which undergoes a radical Myers-Saito cycloaromatisation to form the biradical **3**. **3** cleaves DNA in a single and double stranded manner by radical hydrogen abstraction on the deoxyribose residue leading to the formation of **4** and DNA fragments.

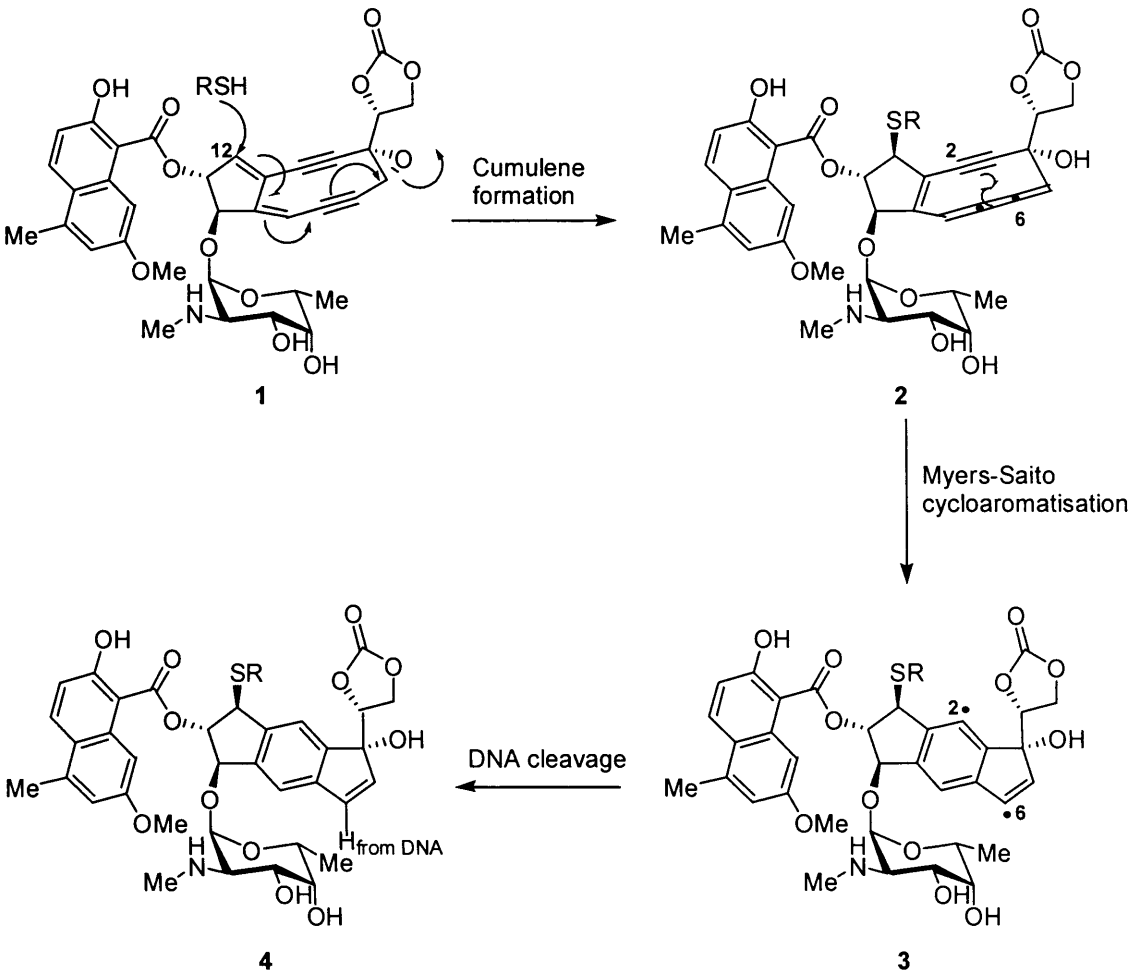


Figure 4. Thiol-dependant mechanism of activation.

Goldberg et al. alternatively proposed a base-catalysed thiol independent mechanism (Figure **5**).[30] The activation begins by intramolecular Michael addition at *C*12 from the enolate at *C*1" of the naphthoate leading to the spirolactone cumulene **5**. Myers-Saito cycloaromatisation then leads to the spirolactone (σ,σ)-1,4-diradical **6**. The radical at *C*2 is then quenched by *C*8" to give the spirolactone (σ,π)-1,4-diradical **7** which abstracts hydrogen atom from particular DNA segments forming bulges to afford **8**.

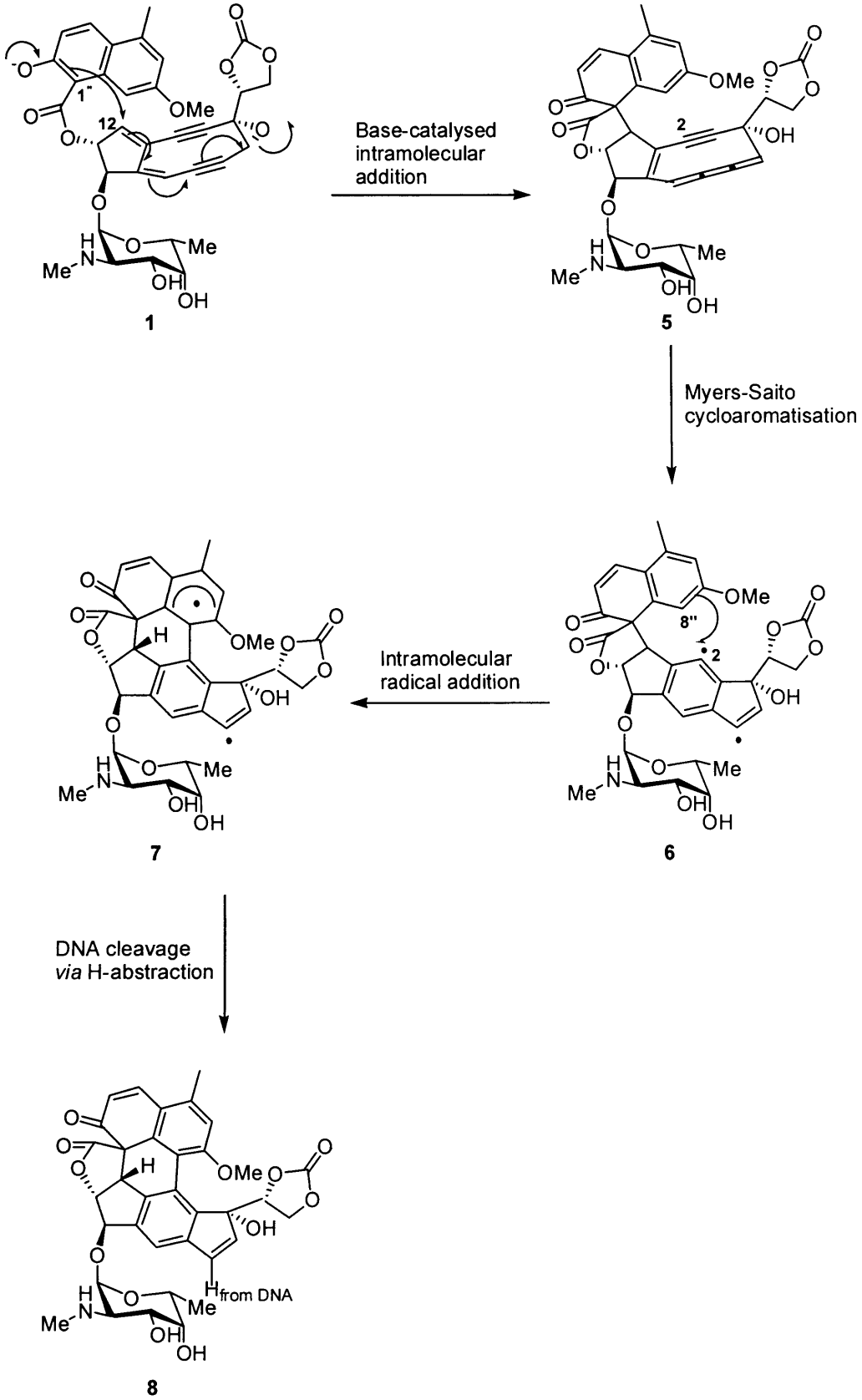


Figure 5. Base-catalysed thiol independant mechanism of activation.

1.5 DNA cleavage mechanism

The proposed DNA cleavage mechanisms[22,26,31] have been supported with evidence from electrophoretic analysis of the DNA fragments generated. It has been demonstrated that at least 80% of the DNA cleavage leads to the 5'-aldehyde of the A and T residues selectively. The cleavage is initiated by radical pro-*S* *H*-abstraction from *C*5' of the deoxyribose residue **9**. The resulting radical **10** is then trapped at *C*5' by O_2 coming from the major groove in *anti* fashion. The resulting peroxyradical **11** undergoes a thiol reduction *via* **12** that leads to strand cleavage and the formation of the 5' aldehyde-ended fragment **13** (Figure **6**).

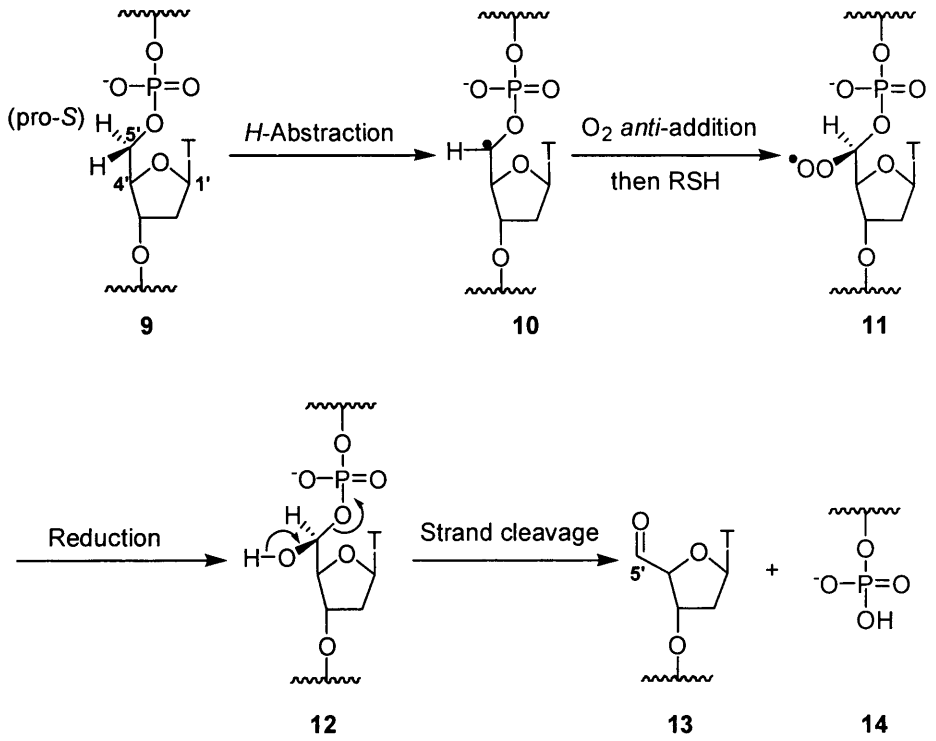


Figure 6. DNA cleavage mechanism.

Less than 20% of the strand breaks result from pathways initiated by hydrogen atom abstraction from C4' and C1'.

1.6 holo-NCS

holo-NCS is made up of a 1:1 complex of a highly reactive chromophore, NCS-C, tightly bound to a protein known as apo-NCS (Kd = 0.1nM).[32] Myers *et al.* have reported the crystal structure of holo-NCS in 1993.[15] The 2 π faces of the nine membered ring are sandwiched between Phe78 on one side and Phe52 and the Cys 37-Cys47 disulfide bond on the other. The epoxide faces down into the hydrophobic binding pocket preventing access from the solvent and subsequent ring opening. The aminosugar moiety is protonated and stacks against the Phe78 with partial contact with the solvent. The naphthoate lies in the bottom of the cleft and is involved with hydrogen-bonding interactions, for example the carbonyl group with the hydroxyl side chain of Ser98, and the methoxy group with the NH of Gly35. holo-NCS represents a particular protein/ligand interaction in that the carrier protein controls the release of its chromophore. In the crystal structure, only the orientation of Phe78 side chain shows a significant difference between holo- and apo-NCS structures. Furthermore, mutation studies using recombinant apo-NCS mutated on the Phe 78 exhibit an increase in the release rate of the chromophore.[33] This suggests that the releasing mechanism potentially involves the side chain of Phe 78. It is not clear whether holo-NCS enters the cell and delivers the chromophore to DNA or whether it releases the chromophore at the cell surface. *In vitro* inhibition experiments using agarose covalently immobilised NCS against leukemic human cell have shown that the released chromophore can enter the cell and reach the nucleus.[34] Alternatively, fluorescent holo-NCS can be detected in the cytoplasm as well as the nucleus of human cells.[35] Further fluorescence studies have shown that holo-NCS is readily taken up by *Saccharomyces cerevisiae* and triggers the overexpression of DNA-repairing genes.[36]

1.7 SMANCS

The potent cytotoxicity of NCS surpasses that of the widely used antitumour agents 5-fluorouracil, adriamycin and *cis*-platinium at their minimum effective concentrations.[37] NCS can inhibit tumour cell growth at the nM range, whereas many

of the low-molecular weight do so at the μM or mM range. However, the major limitations to the clinical use of NCS is its high toxicity towards healthy organs and its very short *in vivo* half life ($t_{1/2}$~1.9 min) in mice which require controlled infusion to increase plasma concentration and less systemic toxicity. These limitations were partially solved by the use of SMANCS, a polymer conjugated version of NCS. This is prepared by cross-linking the apo-NCS with two chains of poly(styrene-co-maleic acid/anhydride) (SMA) *via* its residues alanine 1 and lysine 20 (Figure **6**). The polymer conjugation does not alter the biological activity of NCS.

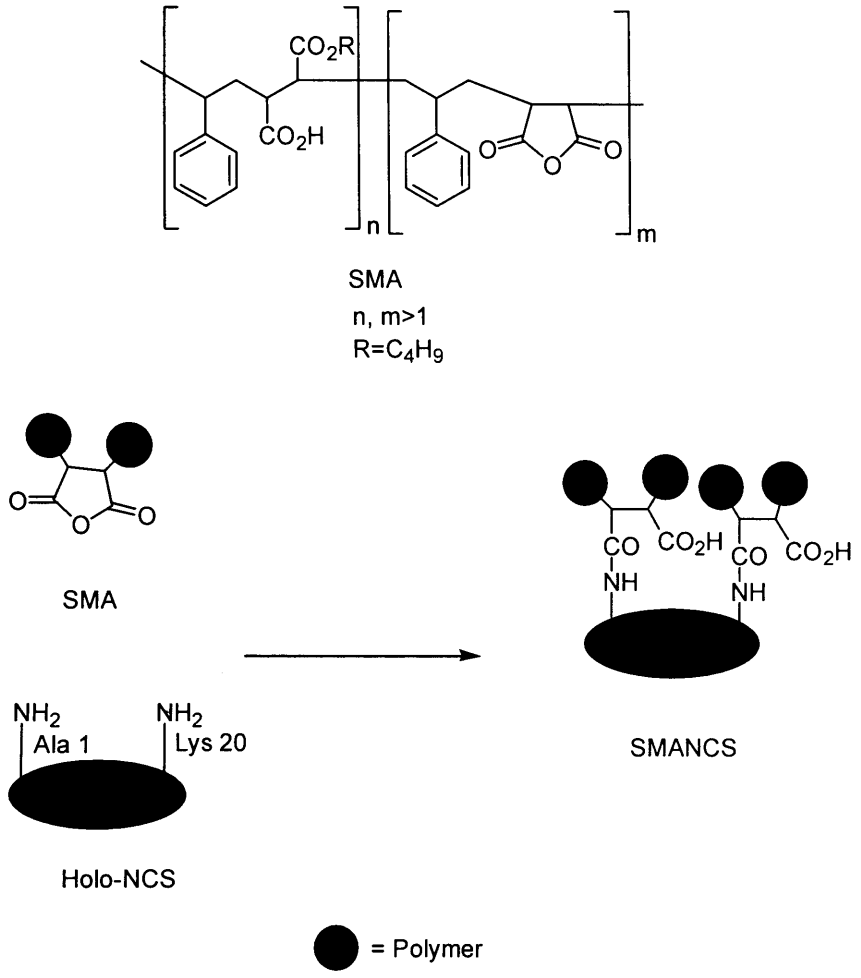


Figure 7. Chemistry of SMANCS.

SMANCS exhibits an *in vivo* half-life 10 times longer than that of NCS and reduces its immunogenicity. It preferentially targets solid tumour *via* a mechanism known as Enhancement Permeability and Retention (EPR). Hypervasculature surrounding the solid tumour increases the permeability towards SMANCS and limits its clearance *via*

the lymphatics. These major differences between the healthy tissue and tumour tissue contribute to the selective accumulation of SMANCS in tumours and hence, its increased efficacy over NCS alone. The clinical use of SMANCS has been approved by the Ministry of Health and Welfare in Japan in 1994 for treatment of liver, bladder, lungs, kidneys and brain cancer. Some recent applications of SMANCS have been reported.[37,38] In the case of hepatoma, arterial administration of SMANCS through catheter decreased tumour size in 90% of patients. A patient receiving such treatment might expect to have a 90% chance of survival after treatment for at least 5 years for a controlled hepatoma.

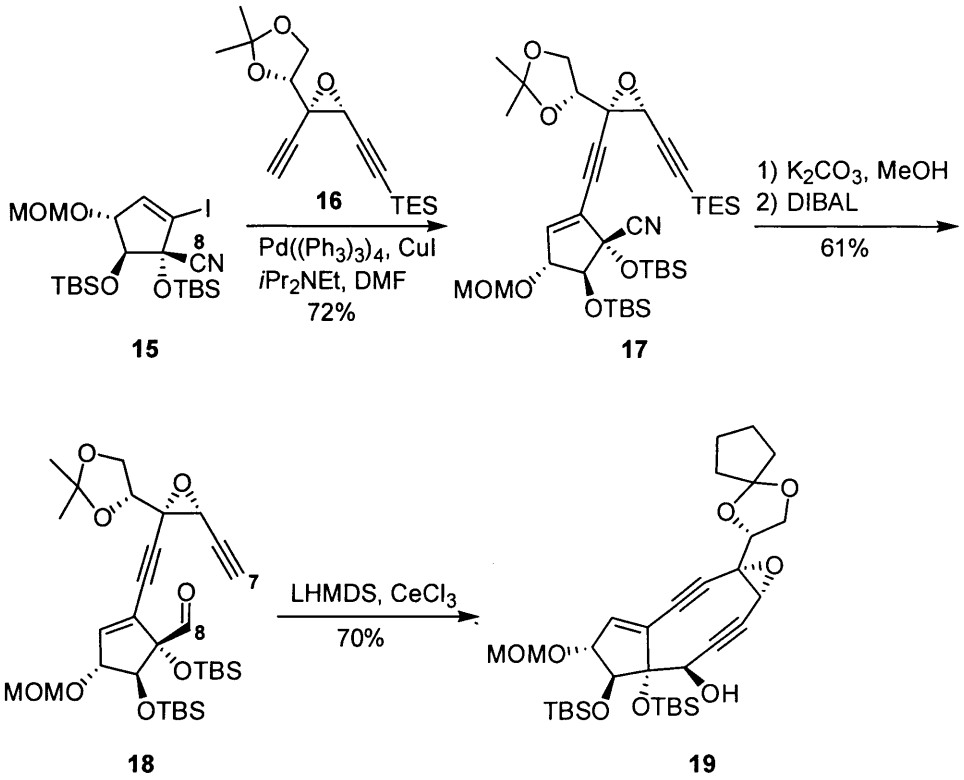
1.8 apo-NCS

apo-NCS (11,000 Da) consists of 113 amino-acid residues with two disulfide bridges between Cys37-Cys47 and Cys72-Cys87. The three dimensional structure was determined by NMR[39,40] and X-ray crystallography.[14] The largest domain consists of a seven-stranded antiparallel β sandwich formed by an external three-strand and an internal four-strand β-sheet. The smaller domain is composed of two-stranded β-ribbons perpendicular to each other. The internal β-sheet, the smaller domain and the helix loop between Asp48 and Phe52 define a deep hydrophobic U-cleft in which the chromophore is encapsulated. apo-NCS displays the same overall fold as immunoglobulin. apo-NCS protects, transports and delivers directly or indirectly the chromophore to its target, the DNA. The protein represents therefore a potential in generating a new drug delivery system as well as in targeting tumours more selectively. The NCS-C binding pocket was found to bind ethidium bromide,[41] the antitumour agent daunomycin[40] and naphthoate analogues of NCS-C.[42] Caddick *et al.* have used the natural naphthoate to anchor nitrogen mustards of therapeutic interest in the binding cleft with promising results.[43] They also discovered flavones as efficient apo-NCS binders in the μM range.[44] This opens up possibility of transporting covalently bound flavone-chemotherapeutic constructs using apo-NCS and allowing their controlled release. Minard *et al.* have extended the binding properties of apo-NCS *via* directed evolution on residues located in the binding cleft.[45] The resulting apo-NCS mutant was found to bind testosterone and streptavidin bound testosterone at the μM and nM range respectively. They also attempted to find new recognition

capabilities by exchanging the immunoglobulin CDR-like loop by the CDR3 loop of the camel antilysozyme immunoglobulin.[46] The newly engineered apo-NCS was able to bind lysozyme. These interesting results suggest that engineered apo-NCS is potentially able to transport various chemotherapeutics and also to target selectively proteins present at the surface of tumour cells.

1.9 Studies towards the synthesis of the NCS-C core structure

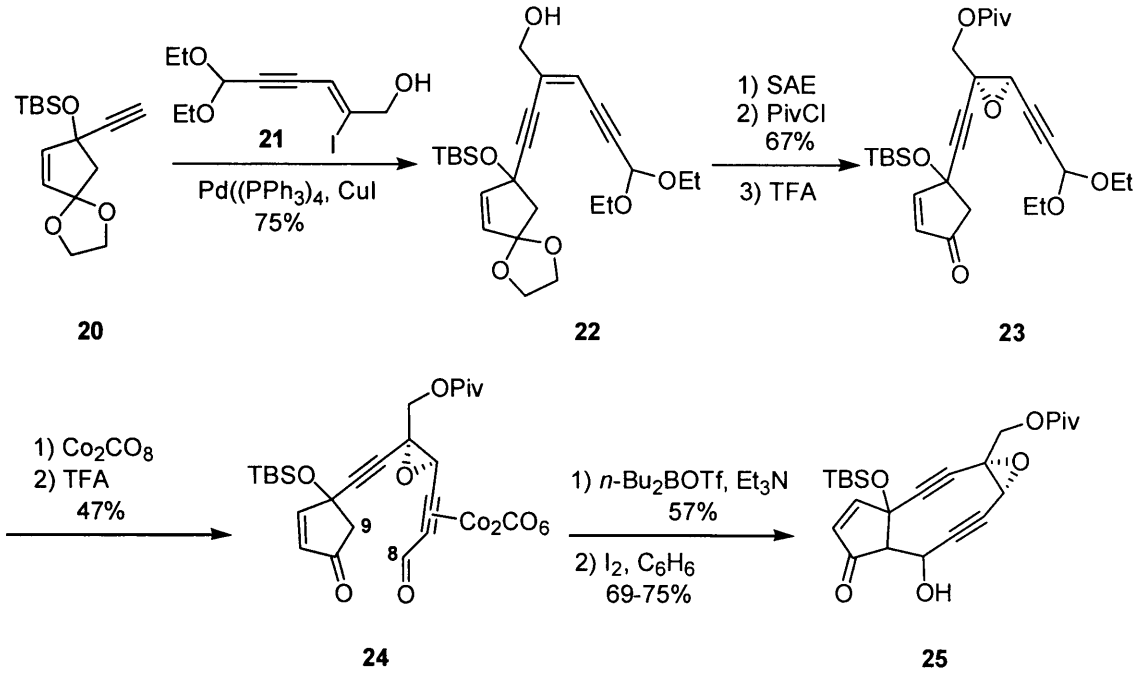
Hirama *et al.* have reported the synthesis of a NCS-C-related analogue.[47] using a highly functionalised iodo-cyclopentenone **15** including *C*8 and the epoxydiyne **16**. Sonogashira coupling leads to **17** and then desilylation and DIBAL reduction afforded the aldehyde **18** which undergoes LHMDS/$CeCl_3$ promoted ring closure at *C*7-*C*8 to give the NCS-C core **19** (Scheme **1**).



Scheme 1. Synthesis of the NCS core structure *via* 1,2-addition.

In 1991, Magnus *et al.* pioneered a successful strategy for the construction of a related-NCS core structure adopting a boron/cobalt-mediated aldol reaction in which

the epoxide at *C*4-*C*5 is surprisingly left untouched (Scheme **2**).[48] The synthesis begins with a coupling of iodo-alkene **21** and the cyclopentenone derivative **20** under Sonogashira conditions to give **22**. Epoxidation of **22** using Sharpless asymmetric epoxidation followed by alcohol protection lead to the epoxydiyne derivative **23**. Complexation of the less hindered *C*6-*C*7 alkyne bond with Co_2CO_8 followed by hydrolysis of the activated diethyl acetal affords **24**. Subsequent cobalt-mediated aldol reaction at *C*8-*C*9 under Lewis acid conditions followed by oxidative decomplexation lead to the NCS core analogue **25**.

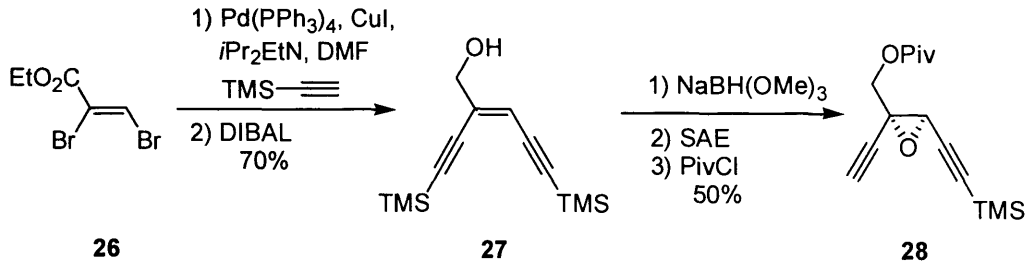


Scheme 2. Synthesis of the NCS-C core *via* cobalt-mediated aldolisation.

1.10 Myers' total synthesis of the NCS-C

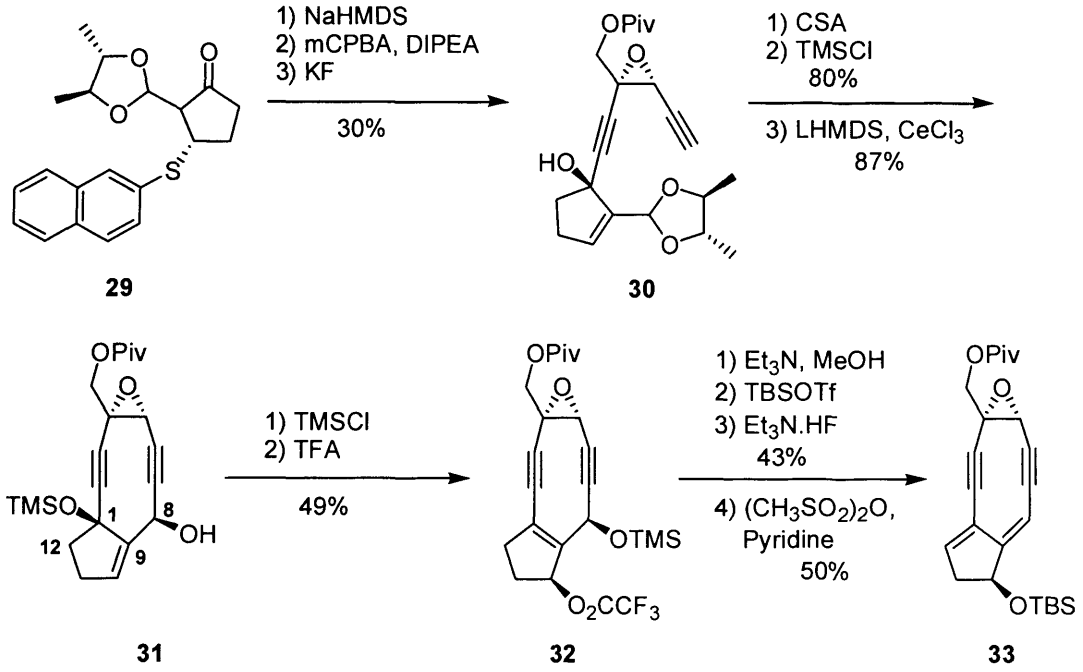
1.10.1 NCS-C model studies

Myers *et al.* have reported an enantioselective synthesis of the epoxydiyne core of the NCS-C.[49] Their synthesis requires the preparation of the unsymmetrical epoxydiyne fragment **28** *via* a double palladium cross-coupling from ethyl-2,3-dibromopropenoate **26**,[50] followed by a selective desilylation of **27**, a SAE and alcohol protection (Scheme **3**).



Scheme 3. Synthesis of an epoxydiyne.

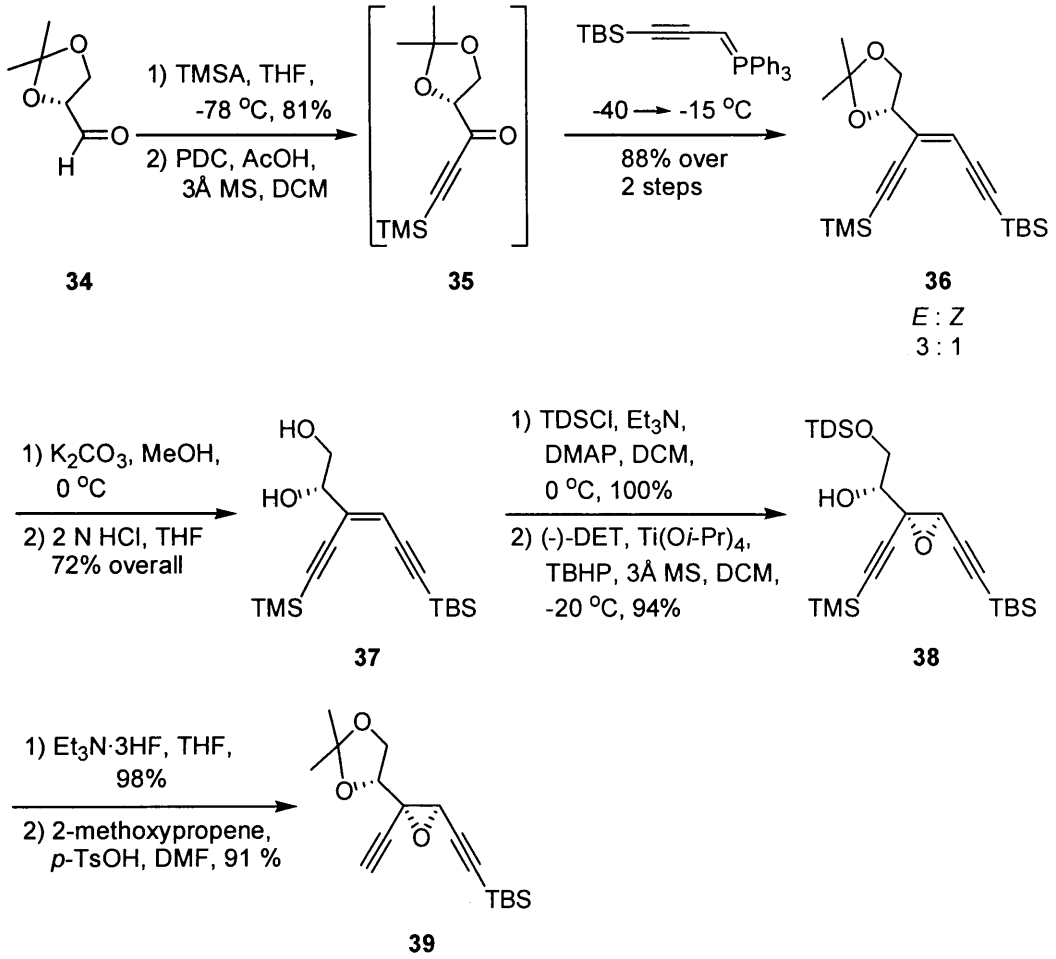
Addition of the fragment **28** to the cyclopentanone **29** followed by sulfoxide formation/elimination and desilylation lead to **30**. This is followed by acetal hydrolysis, silylation of the tertiary hydroxyl group and LHMDS/$CeCl_3$ mediated ring closure to give the NCS-C core intermediate **31**. The olefin formation at *C*1-*C*12 and *C*8-*C*9 are achieved from **31** *via* acid-catalysed allylic transposition. Accordingly, silylation and treatment with TFA afford **32** which undergoes trifluoroacetate hydrolysis and protective group adjustment followed by a methanesulfonic acid anhydride/pyridine-mediated alcohol elimination at *C*8 to give **33** (Scheme **4**).[24]



Scheme 4. Synthesis of the NCS core *via* 1,2-addition followed by allylic transposition.

1.10.2 Total synthesis

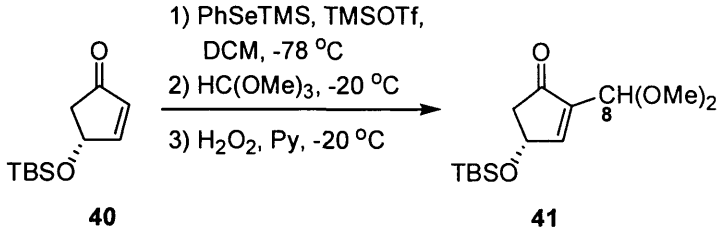
Myers *et al.* have also reported the first complete total synthesis of the NCS-C.[17, 51] Their strategy involves the convergent assembly of four components: a naphthoate, an epoxydiyne, a cyclopentenone and a carbohydrate. The epoxydiyne **39** was prepared in 9 steps from D-glyceraldehyde **34**. The route includes a diastereoselective Wittig olefination (**35**→(*E*)-**36**), protective group manipulations (**36**→**37**), a primary alcohol silylation followed by Sharpless asymmetric epoxidation (**37**→**38**) and a selective silyl cleavage/diol protection affording **39** (Scheme **5**).[51]



Scheme 5. Synthesis of a key epoxydiyne.

The cyclopentenone (+)-**41** was prepared in a one-pot procedure from the well known prostaglandin intermediate (+)-**40**[52] *via* a carefully optimised application of the method of Noyori *et al.*[53] In order to include *C*8 onto **40**, trimethylsilylphenyl

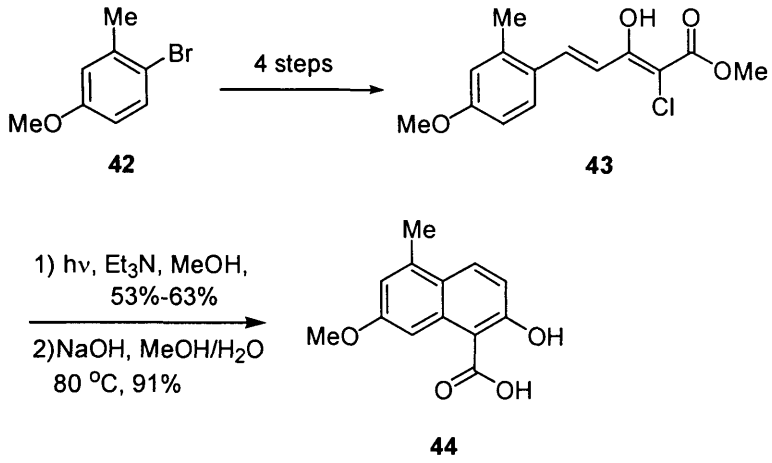
selenide, trimethyl orthoformate and hydrogen peroxide/pyridine were sequentially added affording **41** in good yield (Scheme **6**).



40 **41**

Scheme 6. Synthesis of a cyclopentenone including *C*8.

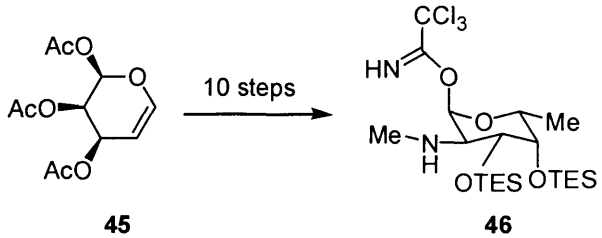
The naphthoate **44** was prepared from 4-bromo-3-methylanisole **42** in six steps in ~ 40% overall yield.[54] The synthesis features the photocyclisation of **43** followed by a saponofication to give **44**. (Scheme **7**).



42 **43** **44**

Scheme 7. Synthesis of the naphthoate *via* photocyclisation.

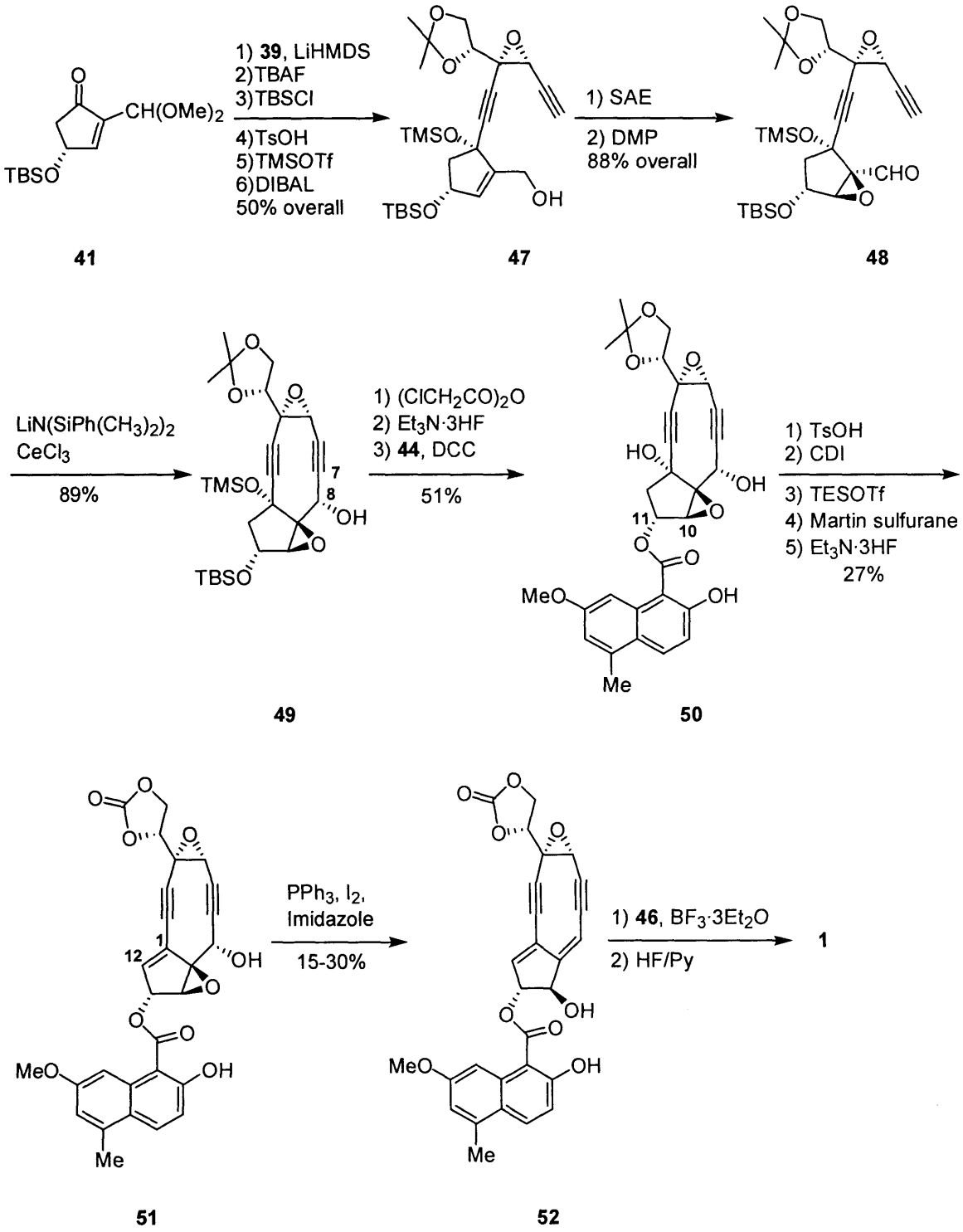
The N-methylamino sugar donor **46**[17] was synthesised in a 10 steps sequence from trio-O-acetyl–D-galactal **45** (Scheme **8**). The sugar was activated as a Schmidt trichloroacetimidate for its high reactivity and its α-selectivity.[55]



45 **46**

Scheme 8. Activation of the sugar residue *via* Schmidt trichloroacetimidate.

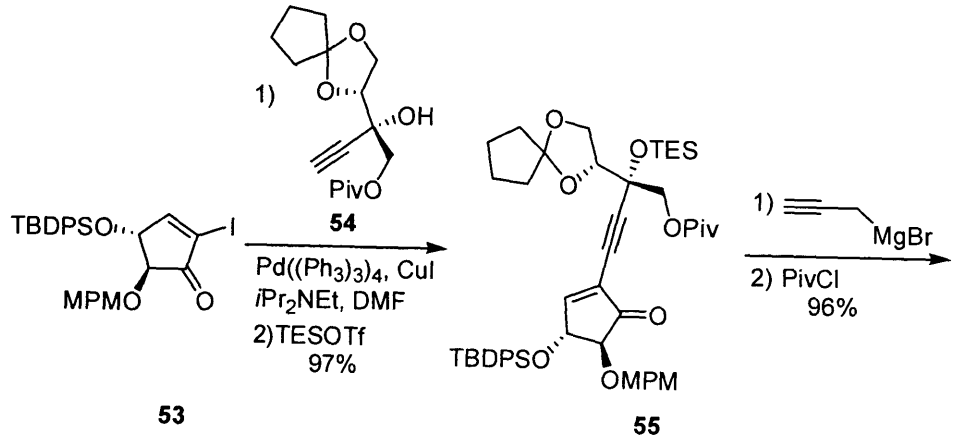
The fragments were then combined towards the synthesis of the NCS-C (Scheme **9**). However problems occurred when trying to induce the allylic alcohol transposition[24] and this strategy was abandoned. 1,2-addition of the epoxydiyne **39** to the cyclopentenone derivative **41** and further transformations led to the adduct **47**. Subsequent asymmetric epoxidation and alcohol oxidation give **48** with the introduction of the stereocenter at *C*10-OH, the site of the impending glycosylation. Cerium-mediated ring closure to form the *C*7-*C*8 bond led to the NCS core analogue **49**. Following protective group manipulations, the naphthoate group at *C*11-OH is installed *via* DCC-mediated esterification to afford **50**. Carbonate incorporation after diol deprotection followed by selective silylation, *C*12-*C*1 olefin formation using the Martin sulfurane dehydrating agent[56] and subsequent desilylation lead to **51**. Epoxide ring opening and concomitant dehydration under PPh_3/I_2 conditions affords the NCS-C aglycon **52** in 15-30% yield.[51] Lastly, the sugar residue is coupled at *C*10-OH *via* Schmidt glycosylation to provide exclusively the required α-anomer intermediate which is fully deprotected in one step to give NCS-C.



Scheme 9. Total Synthesis of the NCS-C.

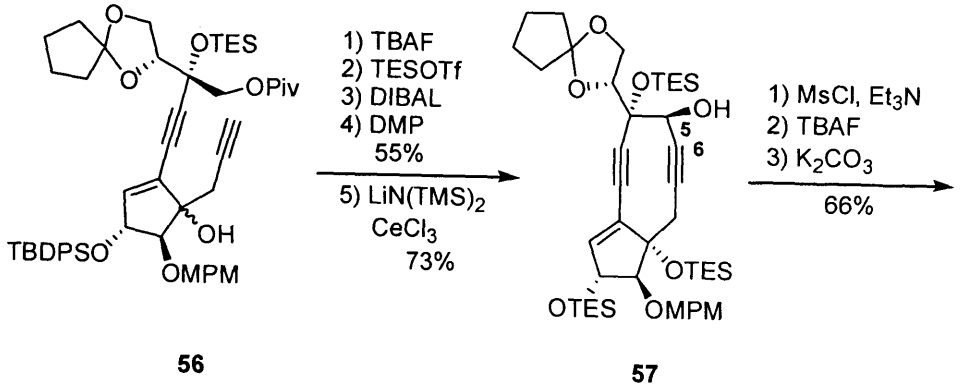
1.11 Hirama's formal total synthesis of the NCS-C

Hirama *et al.* have recently reported the synthesis of the NCS aglycon in 2006.[18] Their strategy relies on an acetylide/aldehyde ring closure at *C*5-*C*6 leading to the core structure of NCS-C (Scheme **10**). Key steps in the synthesis involves 1) A Sonogashira coupling between a functionalised iodo-cyclopentenone **53** and the acetylenic precursor **54**[57] followed by tertiary alcohol protection to afford **55**; 2) The addition of propargylmagnesium bromide to **55** affording **56** as a separable diastereoisomeric mixture in a 1.2:1 ratio respectively; 3) Protective group manipulations, reduction/oxidation sequence and a diastereoselective LHMDS/$CeCl_3$ mediated ring closure to give **58** with the required *trans* geometry at *C*4-*C*5; 4) Introduction of the α-epoxide *via* mesylation/desilylation and base mediated ring closure (**58**→**59**). Lastly, naphthoate[58] and carbonate installation (**59**→**60**), protective group manipulations (**60**→**61**), *C*8-*C*9 olefin formation using Martin sulfurane dehydrating reagent[56] from **61** and controlled desilylation lead to the NCS-C aglycon **52**.



53

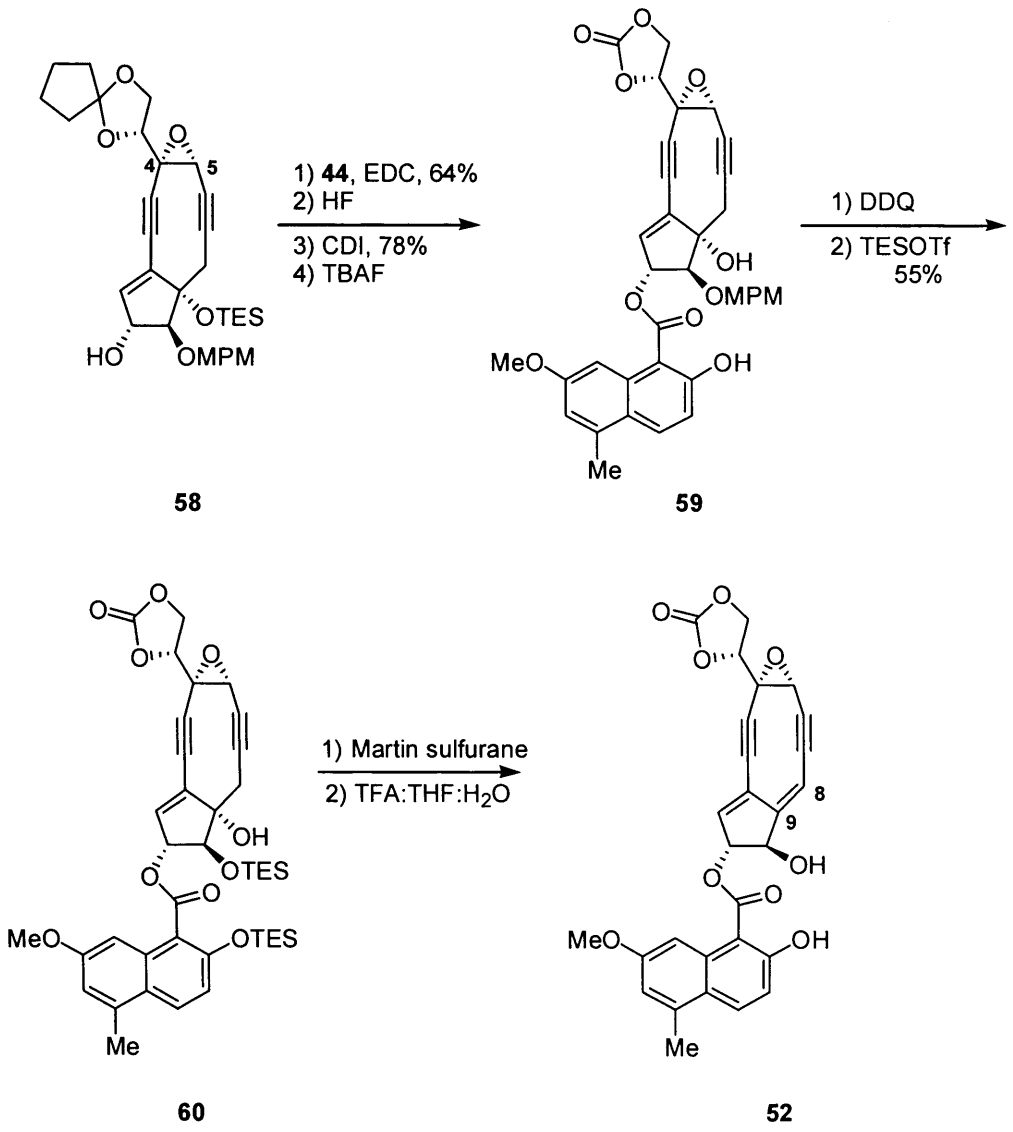
55



56

1.2 : 1

57

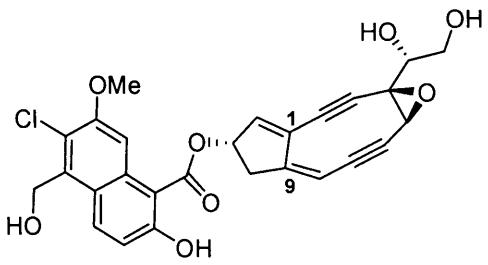


Scheme 10. Total synthesis of the NCS-C.

The first total synthesis of N1999-A2, a structurally related NCS-C natural product, was also accomplished earlier *via* the same strategy.[57]

1.12 Total synthesis of the N1999-A2

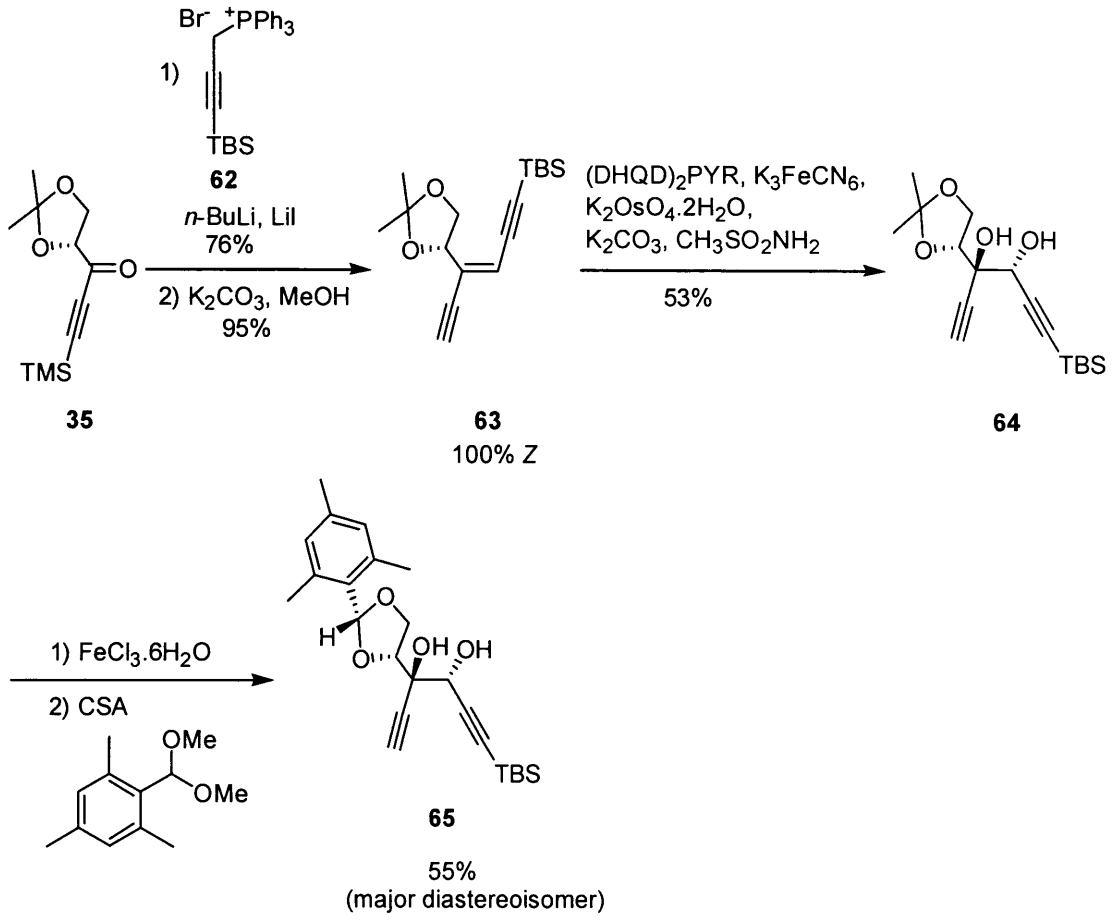
N1999-A2 is a NCS-related nine-membered ring epoxydiyne which exhibits antitumour activity in human cancers (Figure **7**).[60] It lacks an amino-sugar residue and was isolated without a carrier protein.[61] Its absolute stereochemistry elucidation and the first total synthesis was achieved by Hirama *et al.*[57] In 2006, Myers *et al.* have reported the second total synthesis of **61**.[62] Their strategy highlights a transannular cyclisation at *C*1-*C*9 to generate the bicyclo-epoxydiyne core. This strategy was also devised for Myers' first total synthesis of the Kedarcidin chromophore.[63] As for Hirama's total synthesis of NCS-C,[18] the epoxide is introduced after the core generation.



61

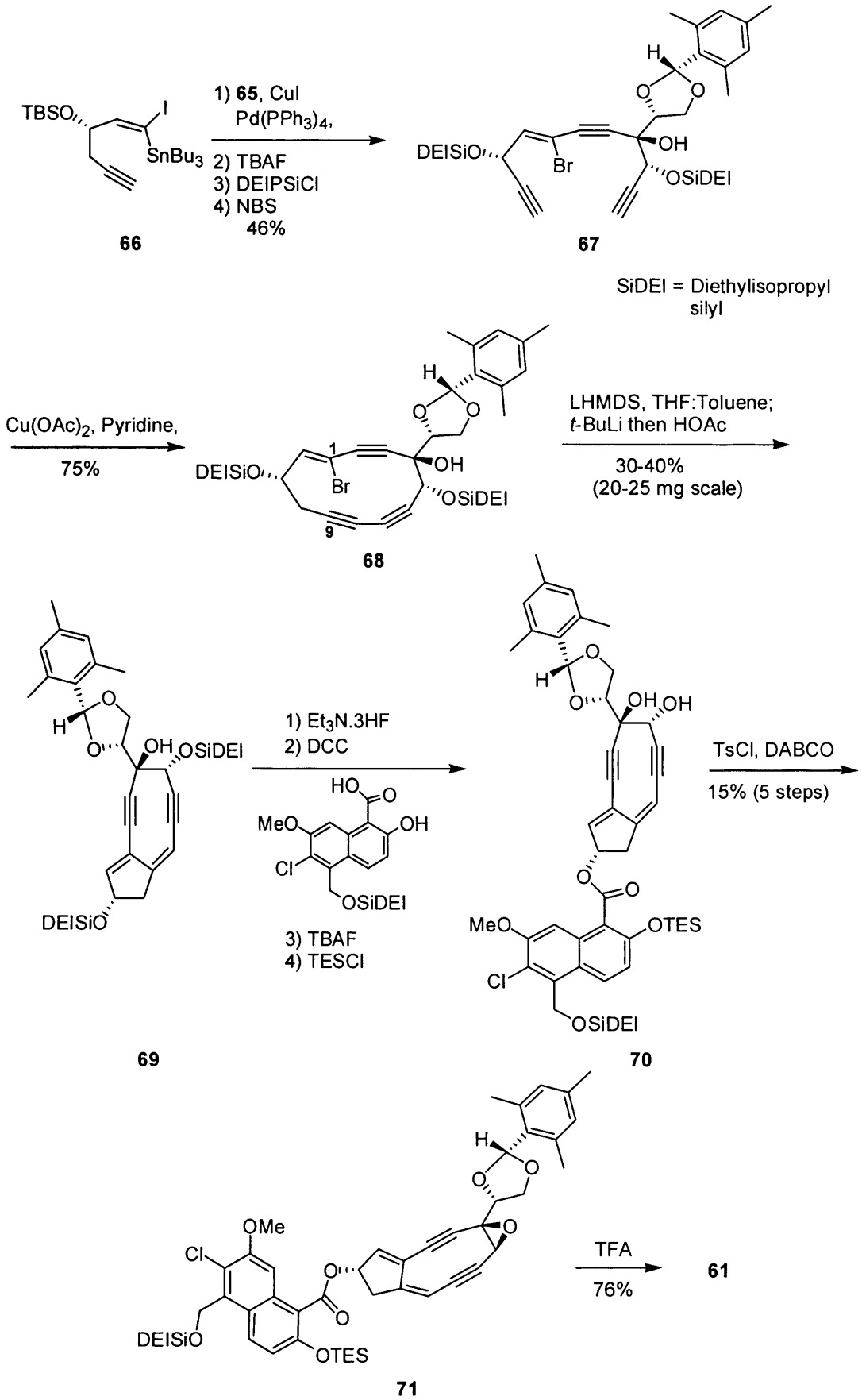
Figure 7. Structure of N19999-A2.

The synthesis of the key starting 1,5-hexadiyne-3,4-diol derivative **65** is described below (Scheme **11**). *Z*-Selective Wittig reaction from the propargylic ketone **35** and the phosphonium salt **62** followed by selective desilylation give the enediyne **63**. Sharpless asymmetric dihydroxylation (SAD)[64,65] from **63** leads to diol **64**. Protecting group manipulations afford the diastereoisomer **65** in 55% yield.



Scheme 11. Synthesis of 1,5-hexadiyne-3,4-diol *via* SAD.

The total synthesis of N19999-A2 then starts with a Sonogashira coupling between **65** and the iodo-vinyl stannane **66** followed by further transformations to give **67** (Scheme **12**). **67** is then subjected to copper-mediated intramolecular oxidative acetylene coupling affording the substrate **68** for the transannular cyclisation. Treatment of **68** under basic conditions and on 20-25 mg scale affords **69** in moderate yields. Larger scale reactions were less efficient. Selective allylic alcohol deprotection from **69**, naphthoate installation *via* DCC-coupling and protecting group adjustments lead to **70**. Epoxide installation from the *trans*-diol function of **70** affords **71** which was subjected to protecting groups cleavage to give **61**.



Scheme 12. Total synthesis of N1999-A2 *via* transannular cyclisation.

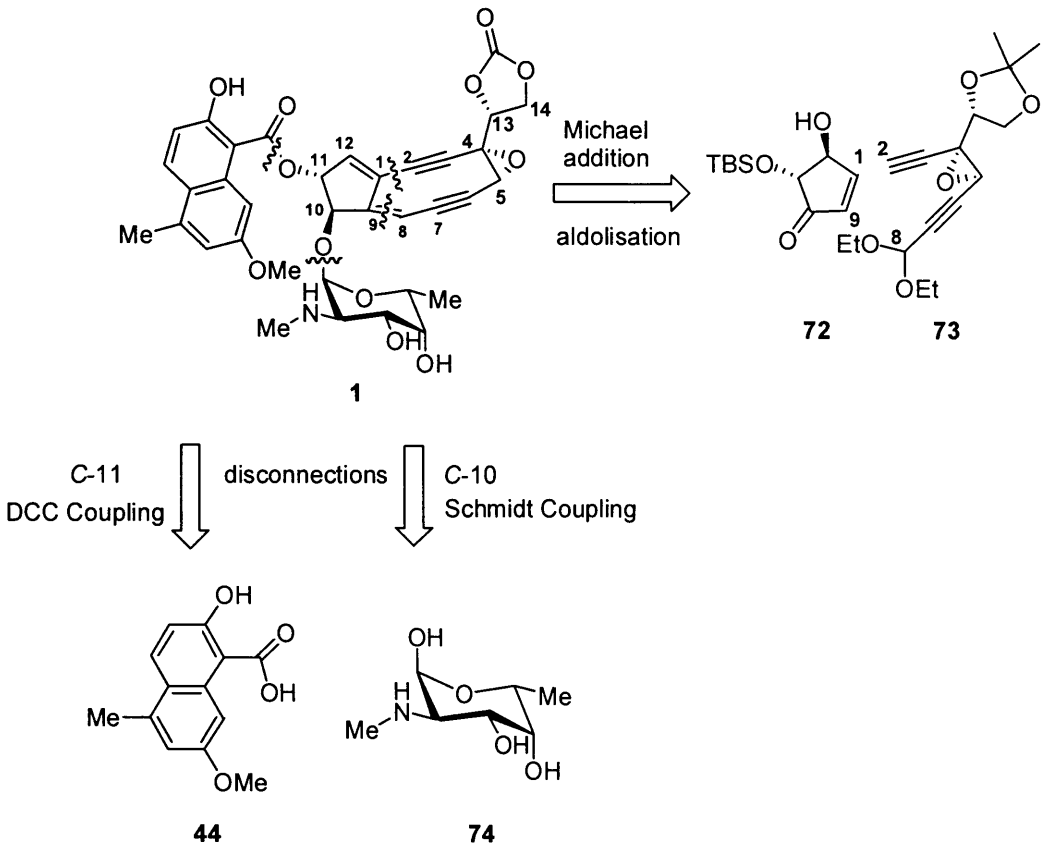
1.13 Conclusions

The epoxydiyne chromoproteins have been the subject of intense investigations from synthetic, biological and medicinal chemists. Due to their unusual structure and their unstability, they represent a real synthetic challenge. The total synthesis of the NCS-C and N1999-A2 has led to the development of original and highly specific methodologies. The different syntheses reported led to a few milligrams of the natural product being obtained. Owing to the scarcity of *Streptomyces carzinostaticus* in the environment, an improved total synthesis of NCS-C would be very valuable. This requires the development of an original, efficient and concise strategy in order to obtain the natural product on a multi-gram scale and to enable structure/function studies. This would represent a better alternative to fermentation sources.

2 RESULTS AND DISCUSSION

2.1 Retrosynthetic analysis

Our convergent strategy for the synthesis of NCS-C (Scheme **13**) involves a key Michael addition of the functionalised cyclopentenone **72** with the epoxydiyne **73** to form the *C*1-*C*2 bond. Conjugate addition of an alkynyl group to a cyclic α,β-enone has only been achieved in a few cases with organozinc[66], organoaluminium[67] and rarely with organo-copper reagents[68]. The conjugate addition of **72** to the epoxydiyne **73** will therefore represent a real synthetic challenge. This should be followed by cyclisation *via* a cobalt-mediated aldol reaction to form the *C*8-*C*9 bond and the bicyclic core.[48] It was already known that under acidic conditions cobalt-complexed acetylenic aldehydes ionise to a stabilised propargyl cation susceptible to nucleophilic attack.[69] Furthermore, the complexation of Co_2CO_6 introduces a C-C≡C bond angle distortion from 180° to 145°. These two factors should release the bicyclic epoxydiyne core strain and ease the cyclisation, the distortion making the propargyl cation at *C*8 closer to the nucleophilic site at *C*9. Finally, the cobalt-capped intermediates should be protected from decomposition for the next steps of the synthesis. This strategy requires a regioselective coordination of Co_2CO_8 to the alkyne *C*6≡*C*7.



Scheme 13. Retrosynthetic analysis.

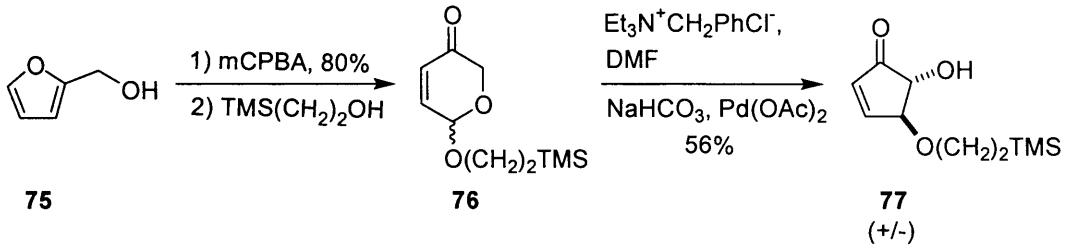
The naphthoate **44** should be installed at *C*11-OH *via* DCC-mediated esterification.[51] The synthesis of the naphthoate has been reported five times in the literature[54, 59, 70] and successfully coupled with various cyclopentenoid species.

Diastereoselective reduction of the carbonyl group at *C*10 would lead to the hydroxyl group necessary for the installation of the amino-sugar **74**. The synthesis of **74** has been already reported in the literature and condensed by means of a Schmidt coupling to the NCS-C aglycon.[17] Dehydration at *C*8-OH and *C*12-OH should afford the cobalt-protected NCS-C. It is then envisaged that removal of the dicobalt hexacarbonyl group by mild oxidation in the presence of the apo-NCS will prevent the reactive natural product from decomposition *via* cycloaromatisation and give NCS.

2.2 A-ring synthesis

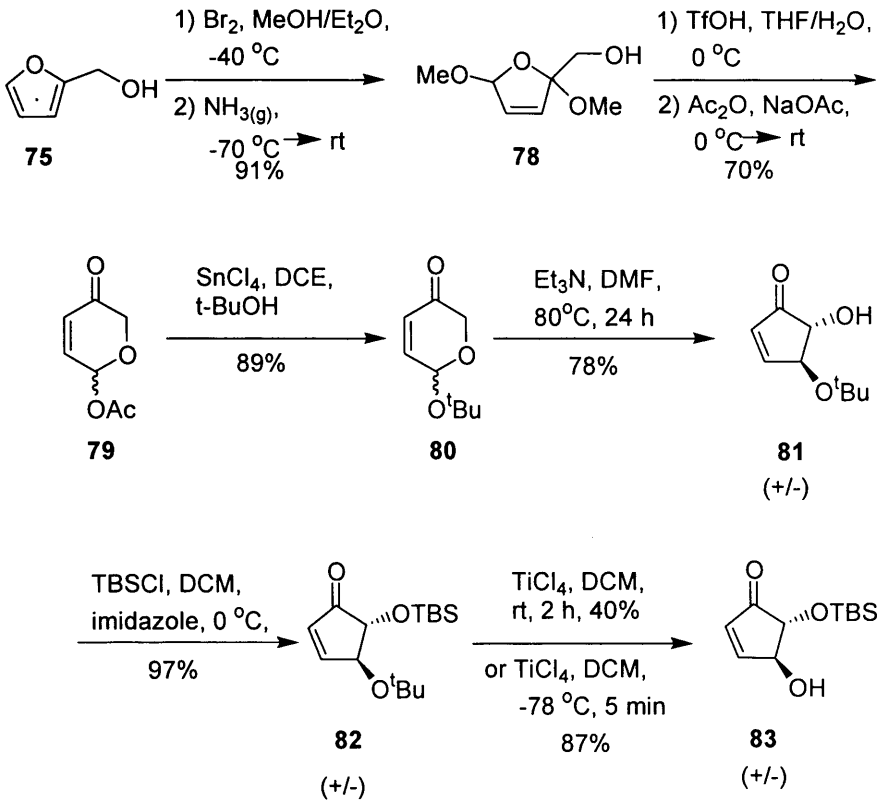
Building on work carried out by Hoffmann *et al.*,[71] a practical approach has been developed within the Caddick group for the preparation of a highly functionalised cyclopentenone. Hoffmann *et al.* had synthesised the cyclopentenone **77** *via* oxidative

rearrangement of furfuryl alcohol **75** followed by protection and palladium/base-mediated ring contraction of **76** (Scheme **14**).



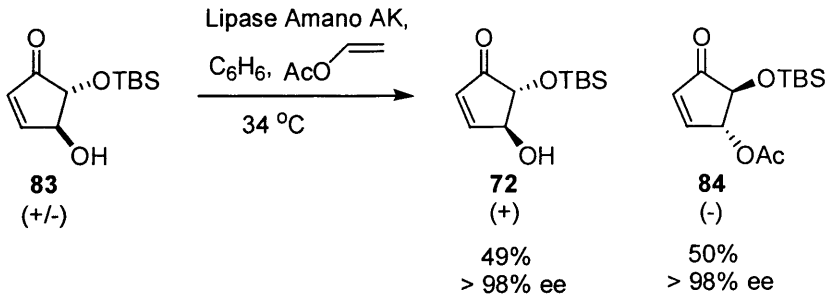
Scheme 14. Hoffmann's synthesis of cyclopentenone.

To be suitable and practical on a large scale, the procedure was greatly optimised within the Caddick group.[72] We started our studies towards the total synthesis of the NCS-C by carrying out a large scale preparation of the cyclopentenone **82** following the procedure developed in the group with some modifications. Furfuryl alcohol **75** was treated with methanolic bromine which, following quenching with gaseous ammonia, gave rise to the dihydrofuran species **78**. We found that it was important to maintain the saturation of the solution with gaseous ammonia for 2 h to obtain **78** in high yield. Acid-catalysed ring expansion followed by acetylation gave the acetoxy-pyranone **79**. This could be transformed to *tert*-butyl ether pyranone **80** by substitution of the acetate group under acidic conditions. Finally base-mediated ring contraction (**81**) and TBS-protection led to the functionalised cyclopentenone **82** as a racemic mixture. The *tert*-butyl ether removal under Lewis acidic conditions using the original procedure led to the cylopentenone **83** in only 40% with notable decomposition of the starting material **82**. We then decided to carry out the transformation at low temperature controlling the reaction time. The *tert*-butyl ether was found to be easily removed at -78 °C in 5 min in an improved yield (Scheme **15**).



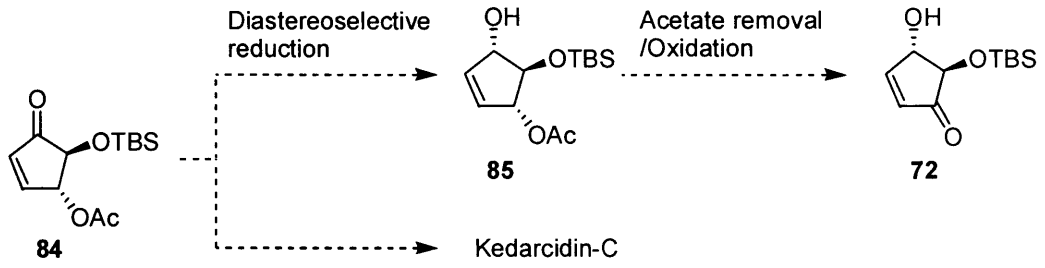
Scheme 15. Synthesis of the functionalised cyclopentenone *via* base-mediated ring contraction.

To carry out the total synthesis of the NCS-C, the cyclopentenone was required to be enantiomerically pure. Inspired by Hirama *et al.*,[47,73] Etheridge within the Caddick group investigated an asymmetric desymmetrisation of the dihydroxylated cyclopentenone **83**.[74] The reaction involves a lipase-mediated kinetic resolution in which the lipase Amano AK performs a selective acylation of **83** leaving the required cyclopentenone enantiomer **72** untouched. We carried this out on a large scale, in excellent yield and high enantioselectivity.



Scheme 16. Lipase-mediated kinetic resolution.

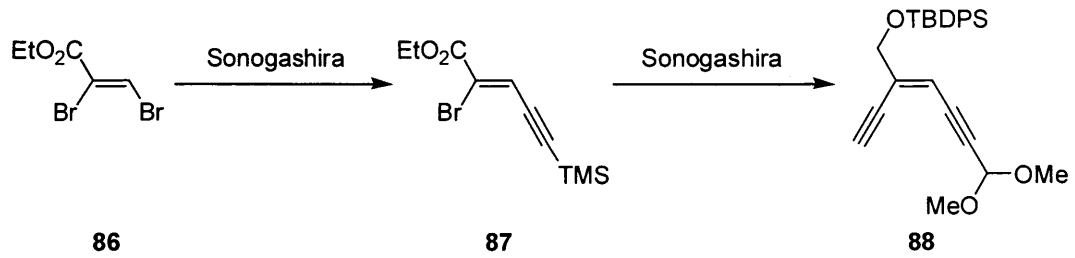
Interestingly, **84** could be recycled in a reduction/oxidation sequence *via* protecting group manipulation to give back the cyclopentenone **72** or alternatively **84** can be used as a synthon towards the total synthesis of the Kedarcidin chromophore (Scheme **17**).



Scheme 17. Recycling of the undesired cyclopentenone.

2.3 Model study

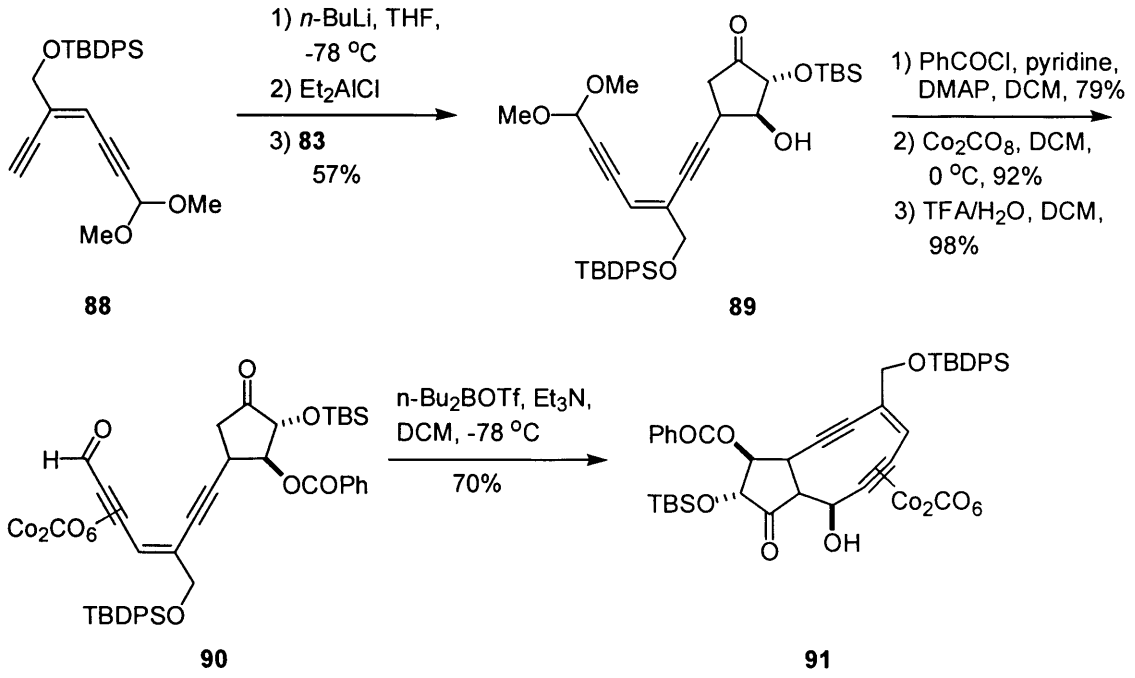
In order to investigate our own Michael addition/intramolecular aldol sequence, the enediyne model **88** has been synthesised efficiently within the group and on a large-scale.[75] Inspired by Myers *et al.*,[50] the enediyne **88** was readily prepared using palladium cross-coupling methodology to incorporate the acetylenic moieties (Scheme **18**).



Scheme 18. Synthesis of an enediyne *via* Sonogashira coupling.[75]

The conjugate addition/intramolecular aldol sequence was first investigated by Delisser.[75] The intermediate **89** has been synthesised *via* diastereoselective aluminium-mediated Michael addition of the enediyne **88** on the cyclopentenone **83** taking advantage of the free alcohol to guide the addition by aluminium chelation.[67c] Protection of the alcohol, regioselective alkyne cobalt-complexation, followed by

acetal cleavage led to the aldol precursor **90**. Boron/cobalt-mediated aldolisation[48] gave rise to **91** in good yield (Scheme **19**).



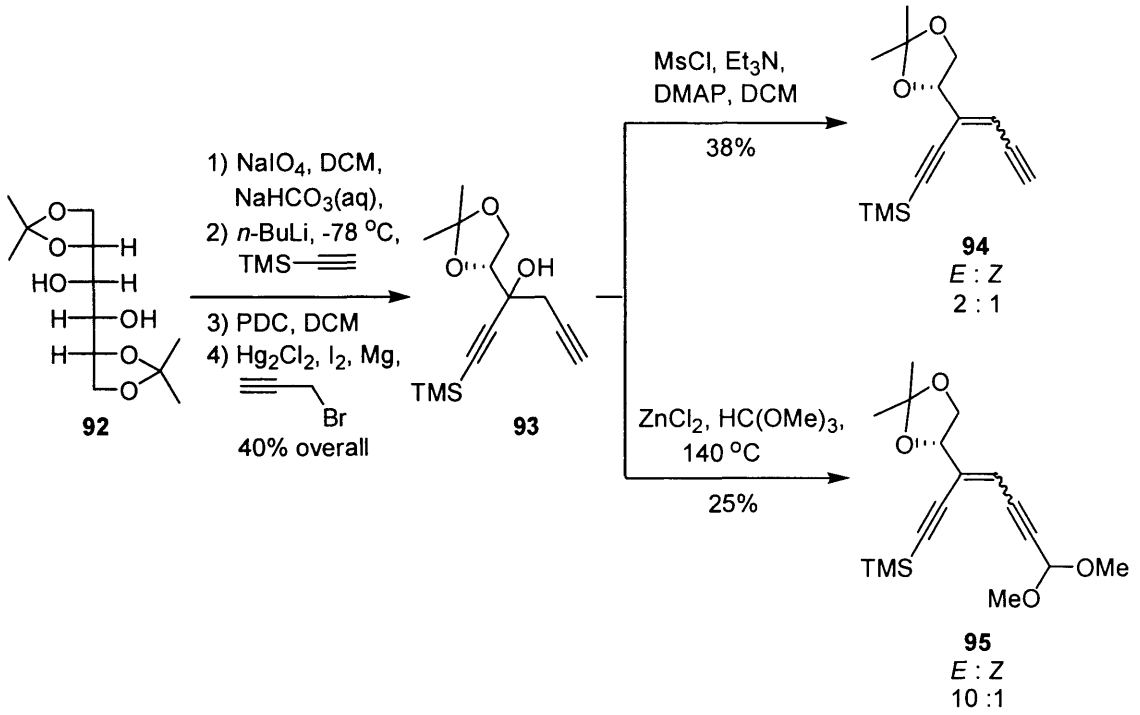
Scheme 19. Conjugate addition/intramolecular aldol strategy.

With this model study proving the viability of the Michae/aldol sequence, efforts in our laboratory have been directed to the key epoxydiyne synthesis to which this sequence will be applied towards the NCS-C.

2.4 Previous work towards the synthesis of enediynes within the Caddick group

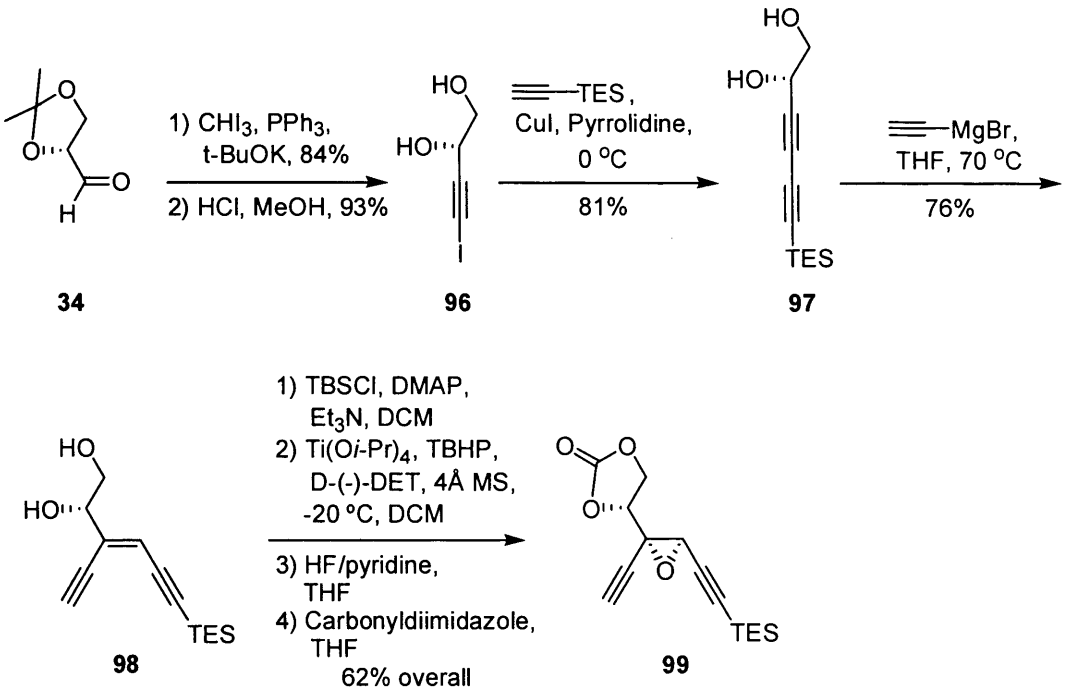
Preliminary work focused on the synthesis of enediynes with the correct stereochemistry for the introduction of the epoxide ring using a Sharpless asymmetric epoxidation.[76,77] A route developed within the Caddick group involved a dehydration strategy leading to enediyne **94**. Alcohol **93** was prepared by oxidative cleavage of the D-mannitol derivative **92**, addition of (trimethylsilyl)acetylene to the resulting aldehyde, oxidation with PDC and finally nucleophilic addition of propargyl Grignard.[78] Dehydration of **93** via base-mediated elimination of the mesylate led to

the enediyne **94** in 38% yield with a *E*:*Z* ratio of 2:1.[79] Alternatively, dehydration of **93** and concomitant introduction of the acetal functionality *via* a zinc-mediated acetalisation at high temperature led to the separable enediynes **95**, in poor yield but with good diastereoselectivity (*E*:*Z* / 10:1) (Scheme **20**).[79]



Scheme 20. Enediyne synthesis *via* dehydration.

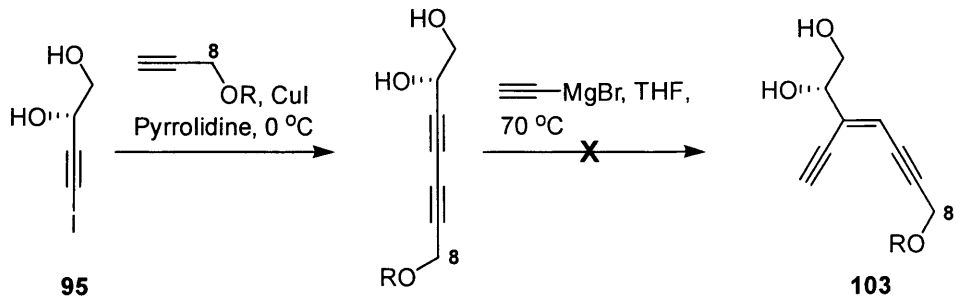
Hirama *et al.* have published a new and concise route to epoxydiynes (Scheme **21**).[80] The synthesis involves a magnesium-mediated carbometalation pioneered by Fallis,[81] to give a key *E*-enediyne. The intermediate diynediol **96** was prepared from the D-glyceraldehyde acetonide **34**. Treatment of **34** with triphenylphosphine, potassium *tert*-butoxide and iodoform followed by acetonide deprotection led to the iodo-alkyne **96**. Copper-mediated coupling of **96** with (triethysilyl)acetylene gave rise to the diynediol **97**. Carbometalation with ethynyl Grignard in THF afforded the key *E*-enediyne **98** exclusively in a good yield. Selective TBS-protection of the primary alcohol, followed by Sharpless epoxidation and protecting group adjustments led to the epoxydiyne **99**.



34 **96** **97** **98** **99**

Scheme 21. Hirama's epoxydiyne synthesis *via* carbometalation.

This approach towards the synthesis of our key epoxydiyne was attempted within the group preparing substrates including *C*8 as discussed earlier.[82] Copper-mediated coupling of the iodo-alkyne **95** was achieved using protected propargyl alcohols affording **100**, **101**, **102** in yields ranging from 25% to 78%. Unfortunately, the magnesium-mediated metalation on these substrates failed to give the corresponding *E*-enediyne **103** and only starting material was recovered (Scheme **22**).

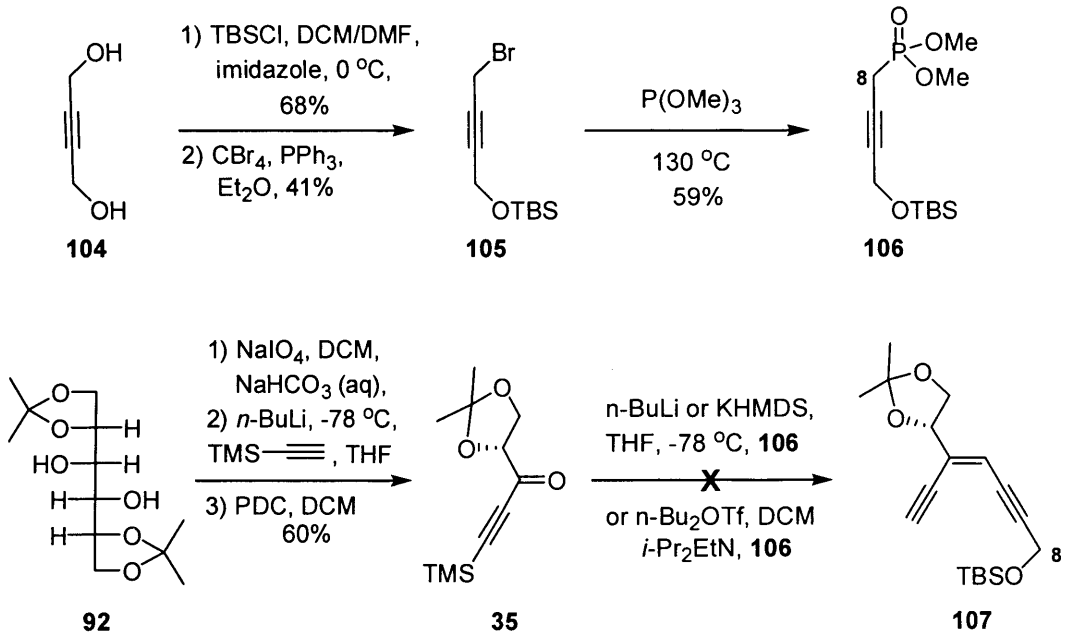


95 **103**

100 R = TBS 78%
101 R = TBDPS 54%
102 R = Bn 25%

Scheme 22. Attempted enediyne synthesis *via* carbometalation strategy.

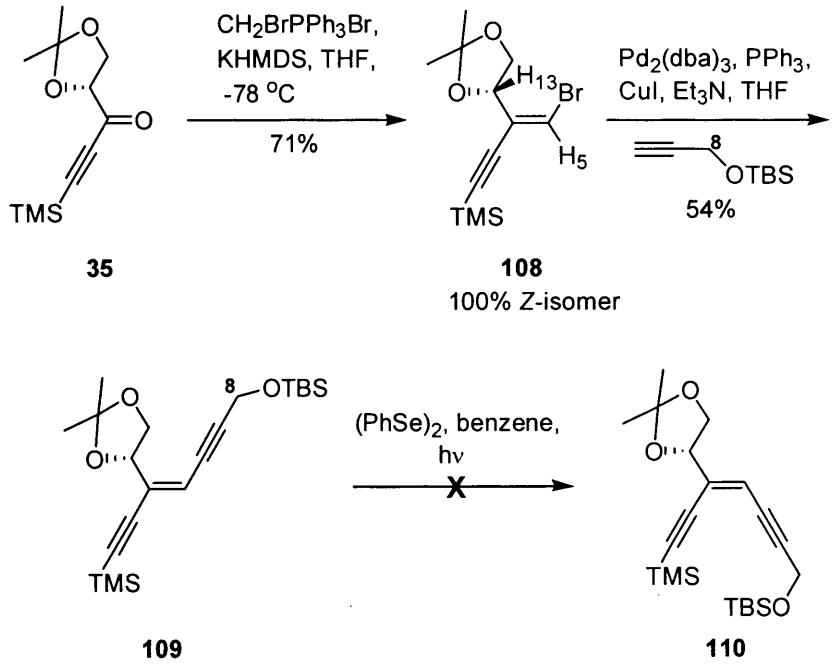
Other olefination strategies were investigated in the Caddick group. Building from Myers' methodology to epoxydiynes[51] (Scheme **5**, above), Etheridge examined a fairly conventional potential strategy involving a Horner-Wadsworth-Emmons (HWE) reaction (Scheme **23**).[82] The first approach aimed at synthesising the required *E*-enediyne using a phosphorus reagent incorporating *C*8. The phosphonate ester reagent **106** was synthesised from but-2-yn-1,4-diol. Monosilylation followed by bromination led to **105** which was subjected to the Arbuzov conditions to give the phosphonate ester **106** in 59% yield. The propargylketone **35** was made from the D-mannitol derivative **92** *via* oxidative cleavage, trimethylsilylacetylene addition and oxidation with PDC. **35** were then subjected to **106** under HWE conditions. However, all attempts to isolate the intermediate **107** resulted in decomposition of the starting material. These results were attributed to the instability of the phosphonate perhaps *via* cumulene formation.



Scheme 23. Attempted enediyne synthesis *via* Horner-Wadsworth-Emmons methodology.

A second olefination approach was examined within the group[82] and involved a reaction of the propargyl ketone **35** with the commercially available bromomethyltriphenylphosphonium salt. This reaction proceeded in good yield but unfortunately gave exclusively the *Z*-vinyl bromide **108** (Scheme **24**). The stereochemistry was confirmed by nOe studies in which no enhancement between *H*5

and *H*13 were observed. Despite this we decided to examine a possible isomerisation strategy and hence installed the second acetylenic moiety including *C*8 *via* a Sonogashira coupling which led to the isolation of the *Z*-enediyne **109** in 54% yield. This methodology provides an expeditious access to *Z*-enediynes including *C*8 but failed to give the desired *E*-enediyne. Photochemical isomerisation of **109** was then attempted under the conditions reported by Trost *et al.*[83] Unfortunately, no isomerisation to generate **110** was observed and the starting material was recovered in good yield.



Scheme 24. Attempted enediyne synthesis *via* Wittig/Sonogashira approach.

In summary, previous work in the Caddick group has resulted in an asymmetric synthesis of the cyclopentenone, which I have optimised for scale up, and the Michael addition/intramolecular aldol sequence has been evaluated successfully on an enediyne model. However, the synthesis of the required epoxydiyne is yet to be realised and represents therefore a significant synthetic challenge towards the total synthesis of the NCS-C.

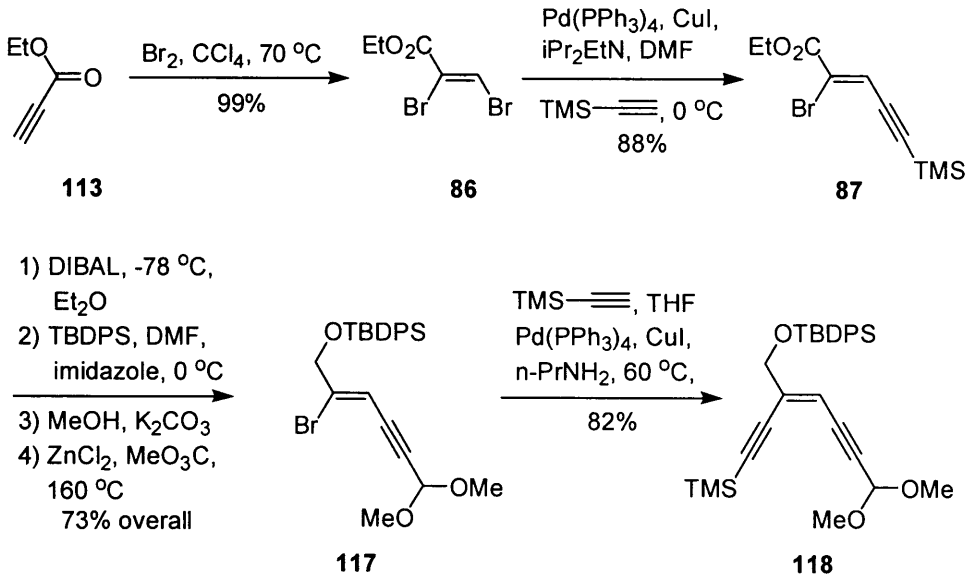
2.5 Synthetic strategies towards epoxydiynes

2.5.1 First strategy: the allylic alcohol elongation approach

In order to carry out our Michael/aldol strategy to the synthesis of NCS-C, we needed to prepare the appropriate epoxydiyne to include *C*8. Our first approach considered the preparation of the epoxydiyne **111** from the enediyne **112** *via* a Sharpless asymetric epoxidation (SAE) then an oxidation-Wittig olefination/Sharpless asymmetric dihydroxylation (SAD)[64] sequence to install the diol at *C*13 and *C*14 (Scheme **25**).

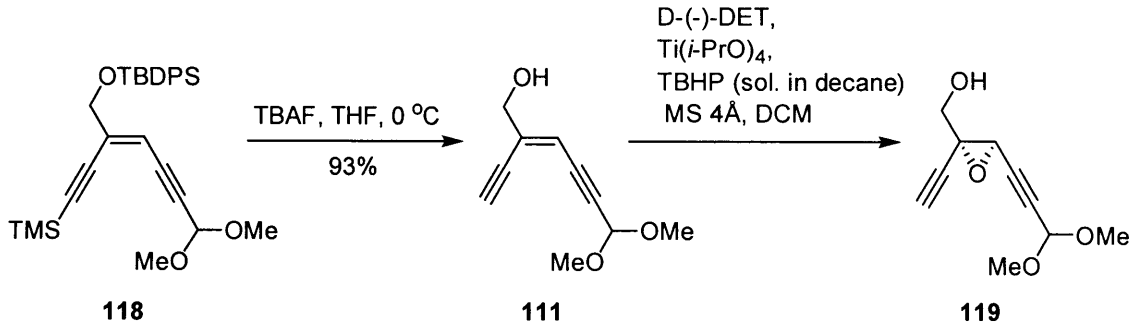
Scheme 25. Retrosynthetic analysis towards epoxydiyne.

118 was prepared using palladium chemistry to install the two acetylenic moieties. Stereospecific addition of bromide to ethylpropiolate **113** gave the *cis*-dibromide **86**[50] which could undergo a regioselective Sonogashira coupling to give **87** in good yield. Ester reduction (**114**), alcohol silylation (**115**), desilylation (**116**) and zinc-mediated acetalisation under Dean-Stark conditions led to the functionalised enyne **117**. The other alkyne was incorporated *via* a Sonogashira coupling to give the enediyne **118** (Scheme **26**).[75,84]



Scheme 26. Enediyne synthesis *via* Sonogashira approach.

The allylic alcohol **111** was prepared in high yield by treating the enediyne **118** with TBAF and then subjected to the SAE (Scheme **27**).



Scheme 27. Sharpless asymmetric epoxidation.

We first applied the standard conditions reported by Sharpless (Table **1**, entry **1**).[76] Unfortunately, no epoxydiyne **119** was isolated under these conditions. We then increased the amount of titanium/tartrate catalyst, but no reaction occurred and notable decomposition of the starting material was seen (Entry **2**). Warming the temperature to -5 °C led to only 10% conversion to the desired epoxydiyne **119** (Entries **3-4**). No reaction occurred using a small amount of catalyst to avoid decomposition of the starting material (Entries **5-7**) and the increase of the

temperature to +4 °C led to decomposition of the starting material (Entry **8**). Finally, varying the amount of TBHP resulted in no change (Entry **9**).

Entry	D-(-)-DET equiv.	Ti(*i*-PrO)$_4$ equiv.	T °C	TBHP 5 equiv.	Results
1	1.1	1.1	-20 °C	5	No reaction, **112** recovered in 62% yield.
2	2	2	-20 °C	5	No reaction, **112** recovered in 25% yield.
3	1.1	1.1	-5 °C	5	10% yield, **112** recovered in 27% yield
4	1.1	1.1	-5 °C	5*	**119** (10% yield), **112** recovered in 30% yield
5	0.2	0.2	-20 °C	5	No reaction, **112** recovered in 85% yield.
6	0.2	0.2	-5 °C	5	No reaction, **112** recovered in 75% yield
7	0.2	0.2	+4 °C	5	No reaction
8	1.1	1.1	+4 °C	5	Decomposition
9	1.1	1.1	-20 °C	10	No reaction, **112** recovered in 58% yield

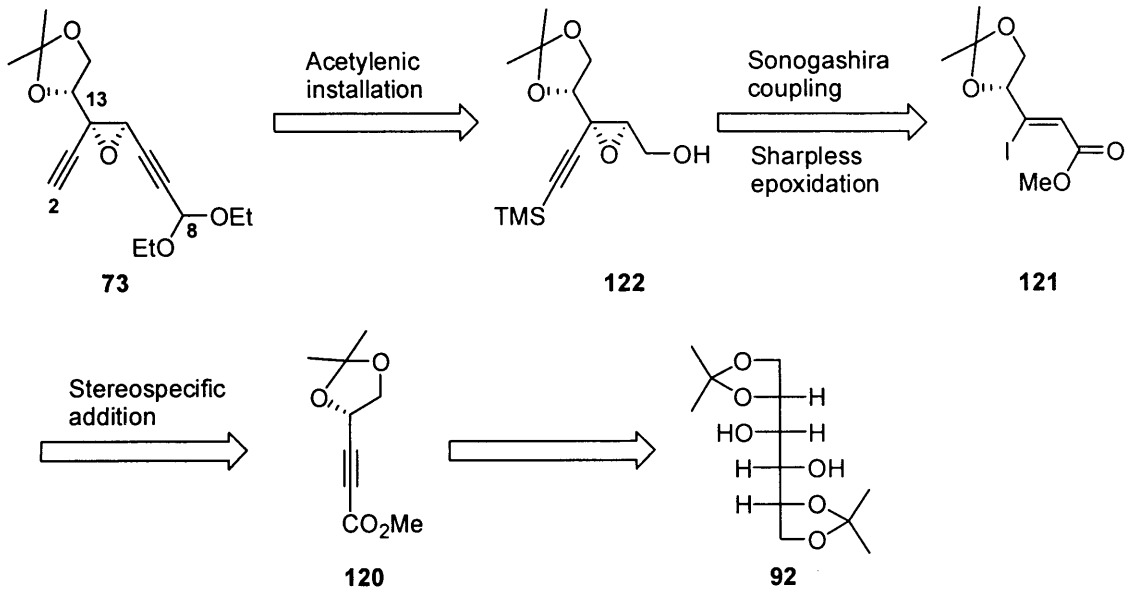
*: TBHP prepared in a DCM solution (5.2 M)

Table 1. SAE conditions.

The epoxydiyne **119** was formed in poor yield making this route non-viable for future work. Myers *et al.* have achieved the epoxidation on similar enediynes[49,51] and from this, we proposed that the pendant acetal functionality might coordinate the titanium/tartrate catalyst suppressing its catalytic effect and undergoes decomposition. Facing this disappointing result, we sought an alternative route towards the required epoxydiyne.

2.5.2 *Z*-iodo-alkenyloate precursor for SAE and acetylenic-group installation

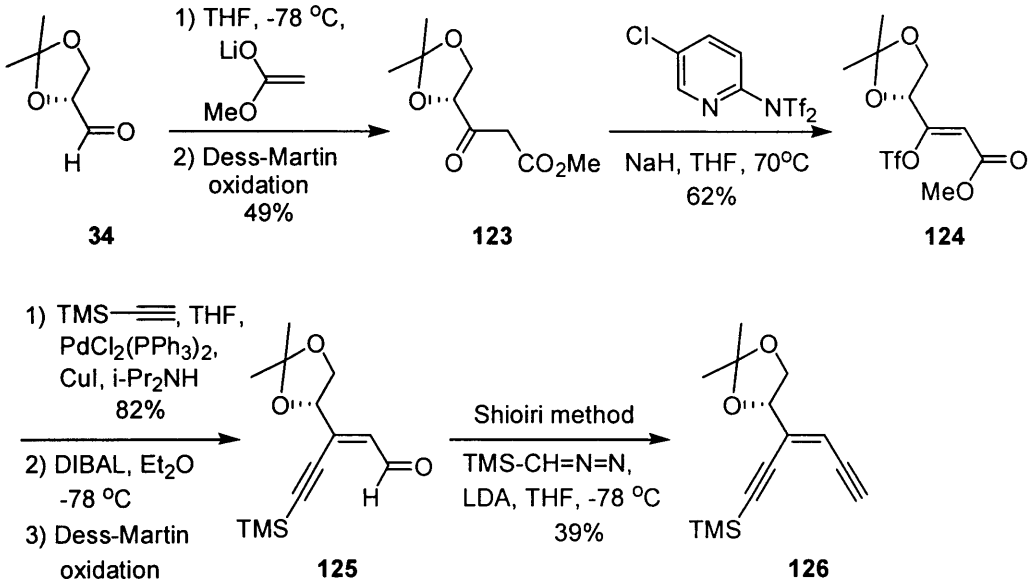
Our second approach towards the key epoxydiyne synthon is based on the elaboration of an iodo-alkenyloate ester intermediate with the required *Z*-stereochemistry set for the Sharpless asymmetric epoxidation (Scheme **28**). **73** should be prepared from the epoxy-alcohol **122** through Corey-Fuchs homologation[85] followed by *C*8-incorporation and TMS-removal at *C*2. **122** would be elaborated from **121** *via* Sonogashira coupling to introduce the TMS-acetylenic unit followed by Sharpless asymmetric epoxidation. **121** should be available from the α,β-acetylenic ester **120** *via* stereoselective acid-catalysed iodide addition; the stereocentre at *C*13 deriving from the chiral pool D-mannitol derivative **92**.



Scheme 28. Retrosynthetic analysis toward our key fragment.

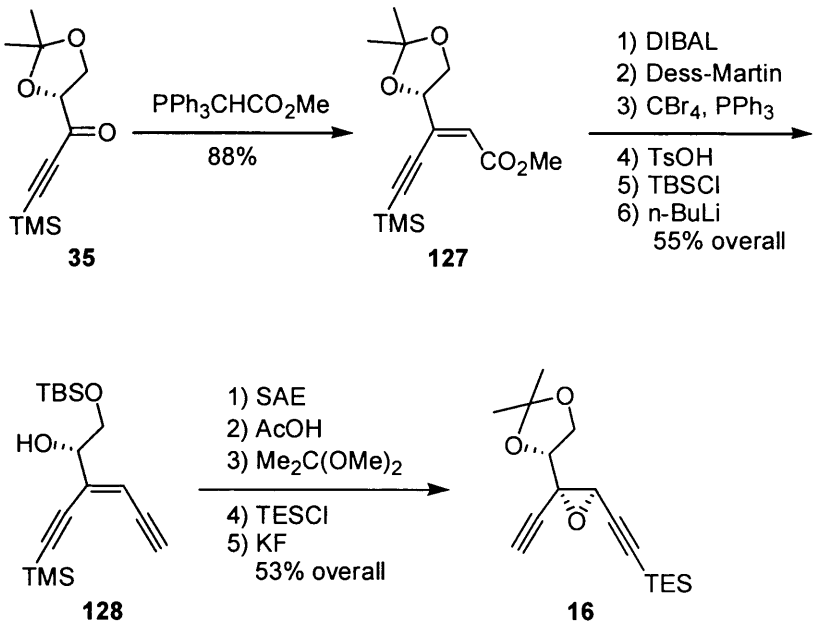
Precedent for this strategy came from the work of Bruckner and Hirama. Bruckner *et al.* have reported a synthesis of the enediyne **126**,[86] related to our key epoxydiyne **73**, from the corresponding *Z*-enol triflate **124** as key intermediate (Scheme **29**). Addition of ethyl lithioacetate to the D-glyceraldehyde **34** and subsequent Dess-Martin oxidation led to the β-oxo ester **123** in 49% overall yield. Treatment of **123** with NaH and the chlorinated Comins reagent led to **124** in 62% yield. The trimethylsilylacetylene could be incorporated on **124** by Cacchi coupling[87] in 82% yield and the aldehyde **125** resulting from a reduction-oxidation manipulation, was

homologated using lithio(trimethylsilyl)diazomethane to give the enediyne **126** in a moderate yield.



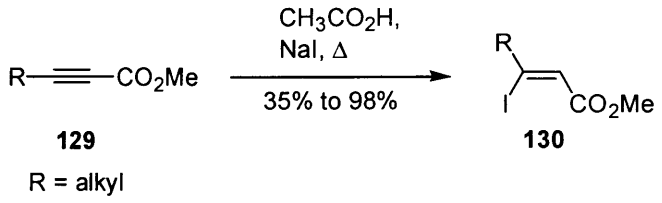
Scheme 29. Bruckner's enediyne synthesis *via* a *Z*-enol triflate intermediate.

Hirama *et al.* have reported the synthesis of the epoxydiyne **16**, a key fragment of the NCS-C.[47] Their strategy involves a Wittig reaction on the propargylic ketone **35** leading to the *E*-alkenyloate intermediate **127** with the correct stereochemistry for the Sharpless epoxidation. A reduction/oxidation sequence gave the aldehyde to which a Corey-Fuchs reaction was carried out to give the intermediate vinyldibromide. Protecting group manipulations, followed by treatment with *n*-BuLi gave the *E*-enediyne **128**. Subsequent SAE followed by protecting group adjustments gave the *trans*-epoxydiyne **16** (Scheme **30**).



Scheme 30. Hirama synthesis of a valuable epoxydiyne *via* SAE/Corey-Fuchs approach.

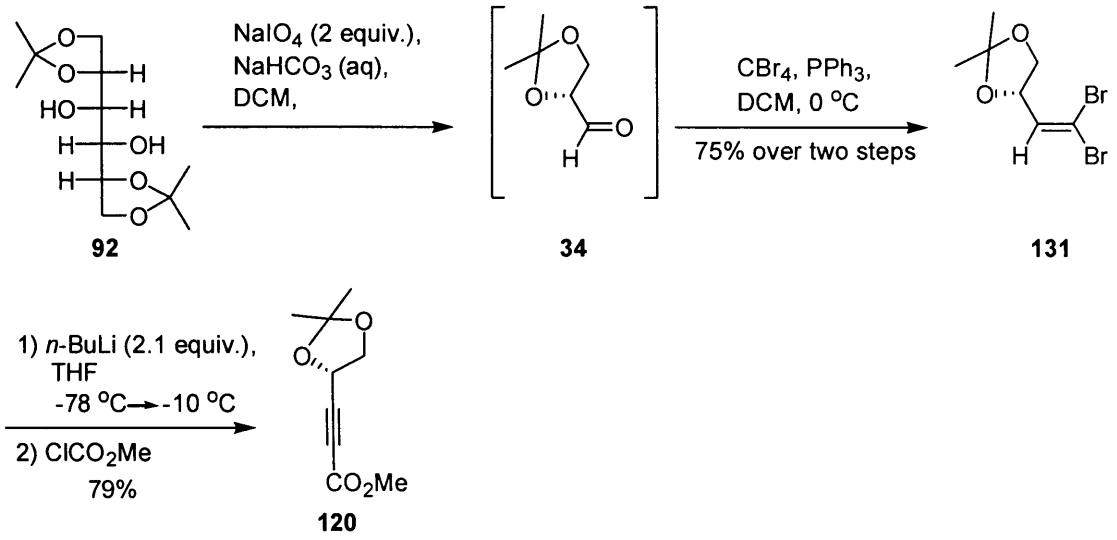
Both reported strategies suggested the feasibility of our approach. Our strategy would shorten the route of Hirama and circumvent the use of the non-commercially available chlorinated Comins' reagent. The major synthetic challenge relies upon the stereospecific synthesis of the acetonide-*Z*-iodo-alkenyloate **120**. Piers *et al.* have reported a facile method to prepare substituted (*Z*)-iodo-alkenyloate **130** by stereoselective addition of iodide on the alkyl α,β-acetylenic ester **129** using sodium iodide and acetic acid at high temperature in yields ranging from 35% to 98% (Scheme **31**).[88]



Scheme 31. *Z*-iodo-alkenyloate ester synthesis *via* stereocontrolled halide addition.

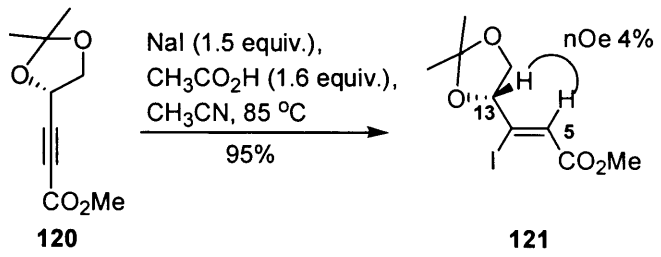
To test the feasibility of this method, we decided to synthesise the appropriate acetylenic ester **132**. This was prepared in a four-step sequence in an overall yield of 60% from the D-mannitol derivative **92**. D-Glyceraldehyde **34** was prepared from oxidative cleavage of **92** with sodium periodate in DCM/$NaHCO_{3(aq)}$ and was

converted to the ester **131** *via* the Corey-Fuchs procedure.[89] Accordingly, the aldehyde **34** was treated with carbon tetrabromide and triphenylphosphine in DCM to afford the 1,1-dibromoalkene **131**. Subsequent treatment of **131** with 2 equiv. of *n*-BuLi in THF at -78 °C followed by quenching with methyl chloroformate led to required ester **120** (Scheme **32**). This sequence could be carried out on a 100 g scale.



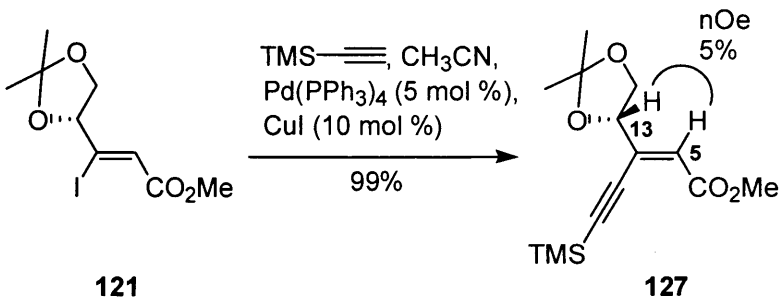
Scheme 32. Synthesis of the acetylenic ester *via* Corey-Fuchs protocol.

Initially, Dr H. Britton also working in this area in the Caddick group, established good conditions for the conversion of **120** to the Z-iodo alkenyloate **121**. Employing 1.5 equiv. of sodium iodide and 1.6 equiv. of acetic acid in acetonitrile at reflux gave the required product **121** in 95% yield revealing the stability of the acetonide group under the reaction conditions (Scheme **33**). We carried out nOe experiments, which caused enhancement between H_5 and H_{13}, demonstrated the stereochemistry of the double bond and that no isomerisation of the double bond occurred under these conditions.



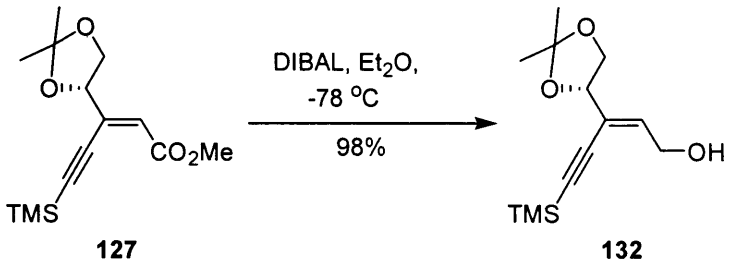
Scheme 33. Z-iodo-alkenyloate ester synthesis *via* stereocontrolled halide additon.

Our approach then involves the incorporation of the first acetylenic moiety to the *Z*-iodo-alkenyloate **121** *via* a Sonogashira coupling.[91] Using the conditions reported by Fiandanese *et al.* with structurally similar compounds,[92] (trimethylsilyl)acetylene was coupled to **121** with tetrakis(triphenylphosphine)palladium (0.05 equiv), copper iodide (0.1 equiv.) and triethylamine (3 equiv.) in acetonitrile to give the acetylenic substituted *E*-alkenyloate **127** in 99% yield. The expected configuration of **127** was confirmed by comparison of the NMR reported by both Hirama[47] and Bruckner[86] by nOe experiments showing that no isomerisation of the double bond occurred under the reaction conditions (Scheme **34**).



Scheme 34. Eneyne synthesis *via* Sonogashira coupling.

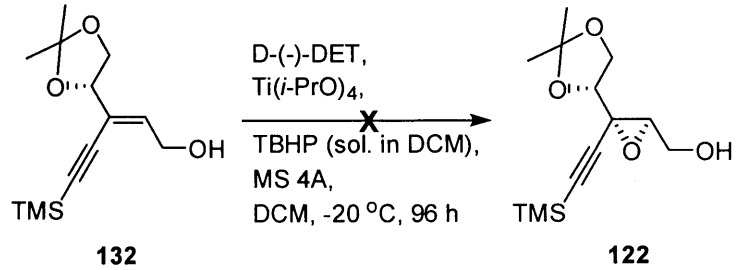
In order to investigate the SAE reaction, the acetylenic *E*-alkenyloate **127** was reduced with DIBAL in ether at low temperature affording the allylic alcohol **132** in high yield (Scheme **35**).



127 **132**

Scheme 35. Ester reduction.

The *E*-allylic alcohol **135** was subjected to SAE. We decided first to use the original conditions reported by Sharpless *et al.* (Scheme **36**).[76] Accordingly, **132** was treated with a stoichiometric amount of chiral titanium IV isopropoxide/D-(-)-diethyltartrate catalyst system, 5 equiv. of *tert*-butyl hydroperoxide (TBHP solution in DCM) and activated powdered molecular sieves in DCM at -20 °C for 96 h. The desired epoxy-alcohol **122** could not be isolated and complex mixtures of unidentified compounds were observed by TLC (Table **2**, entry **1**). Increasing the amount of catalyst led to decomposition (Entry **2**). We then tested using a small amount of catalyst to avoid decomposition, warming the temperature or varying the amount of TBHP, but we were unable to isolate the epoxy-alcohol **122** (Entries **3-6**).



132 **122**

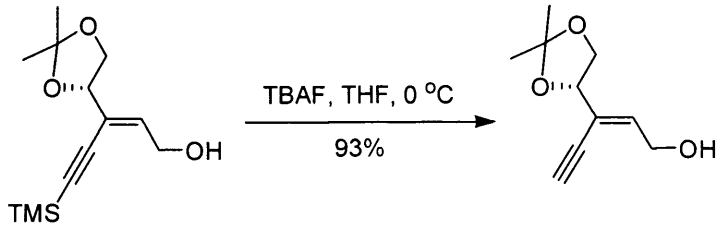
Scheme 36. Sharpless asymmetric epoxidation (SAE).

Entry	D-(-)-DET (equiv.)	Ti(*i*-PrO)$_4$ (equiv.)	TBHP (equiv.)	T °C	Result
1	1.1	1.1	5	-20 °C	No reaction, small amount of unidentified compounds
2	2	2	5	-20 °C	No reaction, significant decomposition (96 h)
3	0.2	0.2	5	-20 °C	No reaction
4	0.2	0.2	5	-5 °C	No reaction
5	0.2	0.2	8	-5 °C	No reaction
6	0.2	0.2	5*	-5 °C	No reaction

*: TBHP in a decane solution (5 M)

Table 2. SAE conditions.

We postulated that the two oxygen atoms of the *C*13/*C*14-diol system might coordinate the catalyst making it inactive or that alternatively there might be a steric clash between the TMS group and the chiral catalyst preventing its efficient complexation to alcohol **132** to guide the oxidation. Finally, we also considered that the alkoxide/catalyst complex may be causing the cleavage of the TMS protecting group to initiate decomposition. In view of these considerations, we hoped that the desilylated allylic alcohol **133** may be a more viable substrate for the SAE. **133** was prepared in one step with TBAF in THF at 0 °C in 93% yield (Scheme **37**).

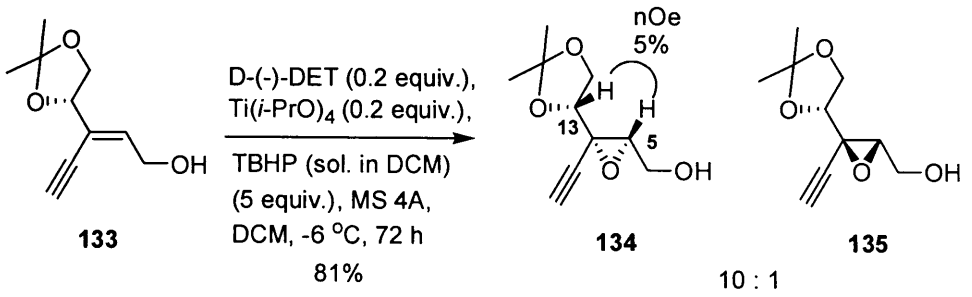


132 **133**

Scheme 37. TMS-deprotection.

The allylic alcohol **133** was subjected to SAE (Scheme **38**). Epoxidation of **133** with the standard Sharpless conditions[76] at -20 °C led to the epoxy-alcohol **134** in 45%

yield (Table **3**, entry **1**). Unidentified by-products were still detected by TLC plate suggesting that the epoxy-alcohol was quite unstable under these conditions likely due to epoxide opening. We then carried out an optimisation study on this reaction. Increasing the amount of catalyst led to a lower yield likely due to decomposition of **134** (Entry **2**). We then chose to decrease the amount of catalyst to avoid decomposition from conditions reported by Sharpless *et al.*[93] and **134** was obtained in a slightly improved yield (Entry **3**). Increasing the amount of TBHP resulted in no change (Entry **4**). Treatment of **133** (0.2 M) with 0.2 equiv. of the titanium-tartrate catalyst and TBHP (in a DCM solution) at -6 °C gave the epoxy-alcohols **134** and **135** in 71% yield in a 10:1 ratio respectively (Entry **5**). Warming the temperature led to a better yield but to an increase in **135**. However, the diastereoisomeric purity was still greatly in favour of **134**. At -20 °C, the diastereoisomer **135** was present in insignificant quantity (Entry **3**). We decided then to increase the concentration of substrate to 0.5 M to speed up the reaction and we found the conditions for an efficient conversion to **134** in 72h (Entry **6**). The type of TBHP used is also very important for the reaction to succeed. Under the same conditions with a commercially available solution of TBHP in decane, the reaction proceeded in low yield (Entry **7**). The reduced amount of catalyst used has greatly simplified the isolation procedures and solved the problem of decomposition. nOe experiments confirmed the *trans* stereochemistry of **134** with enhancement between H_5 and H_{13} confirming that no isomerisation of the double bond occurred. We assumed that the oxygen atom of the epoxide possessed the same stereochemistry as that of the NCS-C from the reliable Sharpless rules.[77]



Scheme 38. Sharpless asymmetric epoxidation.

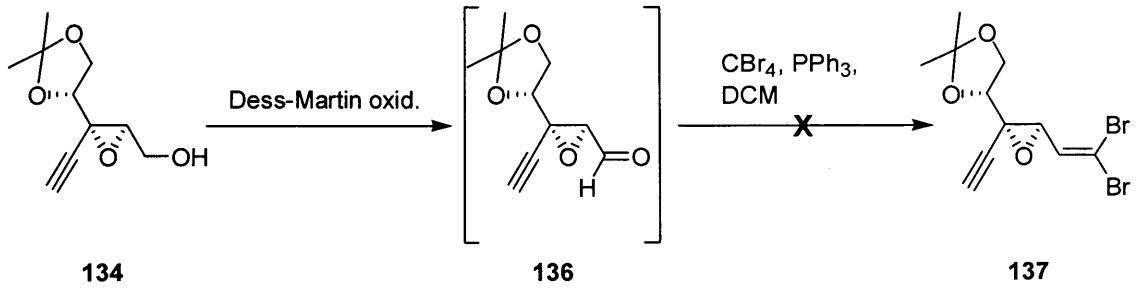
Entry	D-(-)-DET (equiv.)	Ti(*i*-PrO)$_4$ (equiv.)	TBHP (equiv)	T	Concentration of **133** (mol/L)	Yield
1	1.1	1.1	5	-20 °C	0.2	45% **134**
2	2	2	5	-20 °C	0.2	13% **134**
3	0.2	0.2	5	-20 °C	0.2	58% **134**
4	0.2	0.2	8	-20 °C	0.2	48% **134**
5	0.2	0.2	5	-6 °C	0.2	71% **134** : **135** 10 : 1
6	0.2	0.2	5	-6 °C	0.5	81% **134** : **135** 10 : 1
7	0.2	0.2	5*	-6 °C	0.5	32% **134**

*: TBHP in a decane solution

Table 3. Optimisation of the SAE.

Having established a good procedure to synthesise the epoxy-alcohol **134**, we turned our efforts to the conversion of the alcohol into the second alkyne. Unfortunately, the

fact that the SAE proceeded only with the TMS-removed substrate **133**, meant that the homologation reaction would lead to an unprotected epoxydiyne making the *C*8-incorporation rather delicate. However, we carried on the synthesis to study the feasibility of the homologation (Scheme **39**). Oxidation of **134** with Dess-Martin periodinane[94] led to the desired epoxy-aldehyde **136**. NMR of the crude mixture revealed the presence of the characteristic proton at 9.47 ppm and total disappearance of starting material. **136** appeared to be highly silica-sensitive preventing its purification. We then anticipated that the one carbon homologation to the alkyne should be generated through a Corey-Fuchs protocol *via* the dibromoalkene intermediate. However, all attempts to isolate the dibromo-olefin **137** using conditions originally reported,[85] consistently failed and led to decomposition of the sensitive aldehyde **136** (Table **4**, entry **1**). Lowering the amount of the active reagent of the CBr_4/PPh_3 mixture as well as the temperature gave the same results (Entries **2-4**). As mentioned by McKelvie et al., the CBr_4/PPh_3 mixture would lead to the *in situ* formation of the dibromotriphenylphosphine which was discovered to be a strong electrophile as well as a brominating agent.[95] For instance, the byproduct is known to initiate epoxide-ring opening,[96] silyl ether cleavage[97] and TBHP deprotection.[98] It may therefore represent the source of the degradation of **136**.



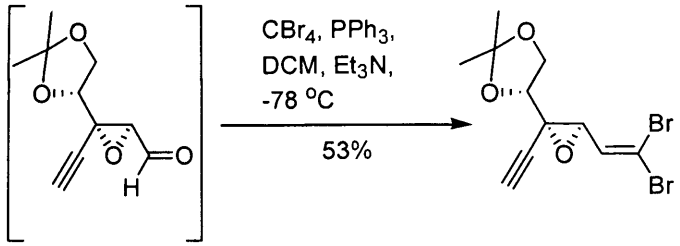
134 **136** **137**

Scheme 39. Attempted homologation *via* Corey-Fuchs approach.

Entry	PPh_3 (equiv.)	CBr_4 (equiv.)	T	Result
1	4	2	0 °C	No reaction/Decomposition of **136**
2	2	2	0 °C	No reaction/Decomposition of **136**
3	4	2	-78 °C	No reaction/Decomposition of **136**
4	2	2	-78 °C	No reaction/Decomposition of **136**

Table 4. Investigations studies towards the dibromoalkene.

A modified procedure of the Corey-Fuchs protocol applied to sensitive aldehydes has been widely reported.[99] This employs Et_3N which likely makes the reaction conditions less vigorous by suppressing the side effects of Br_2PPh_3. We decided to submit **136** to these conditions (Scheme **40**). We found that addition of a preformed solution of the epoxyaldehyde **136** with Et_3N to the CBr_4/PPh_3 mixture at -78 °C led to the expected epoxy-dibromoalkene **137** in moderate yield (Table **5**, entry **1**). **137** was isolated in poorer yield by increasing the temperature (Entry **2**) or the amount of Et_3N (Entry **3**).



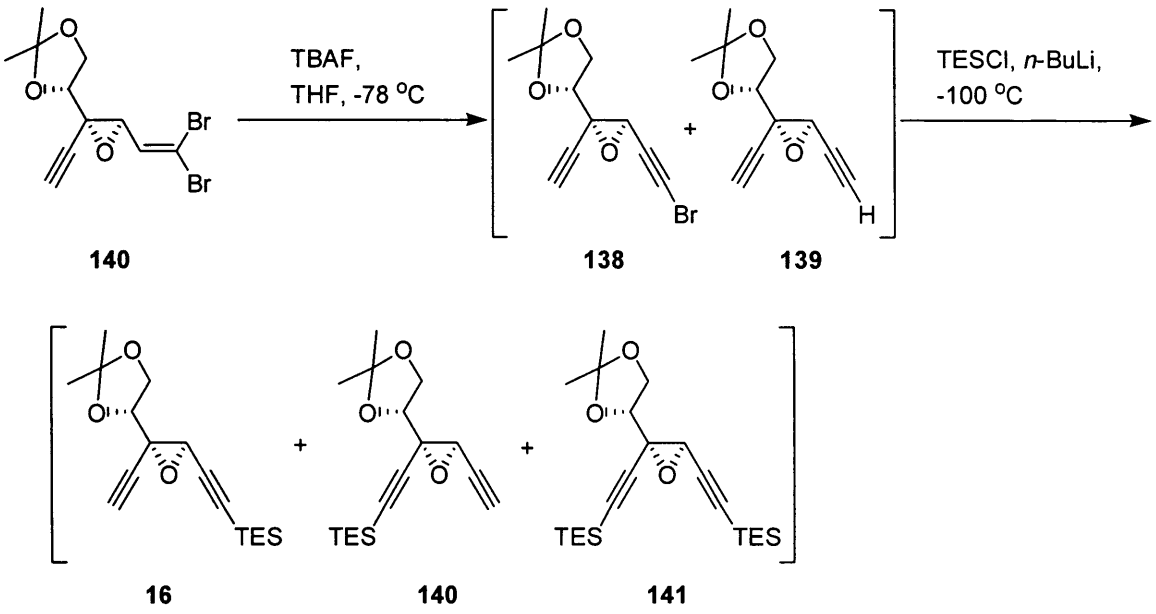
136 **137**

Scheme 40. Homologation of epoxyaldehyde *via* milder Corey-Fuchs conditions.

Entry	PPh_3 (equiv.)	CBr_4 (equiv.)	Et_3N (equiv.)	T	Yield
1	2	2	1.5	-78 °C	53%
2	2	2	1.5	0 °C	15%
3	2	2	6	-78 °C	32%

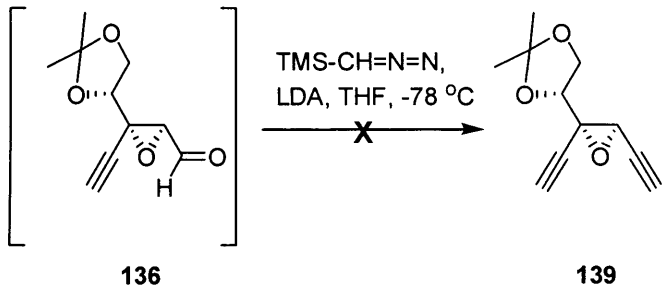
Table 5. Optimisation of Corey-Fuchs procedure.

We then turned our efforts to the conversion of **137** to the epoxydiyne **138** (Scheme **41**). Dibromoalkene intermediates are usually treated with *n*-BuLi at low temperature in THF to give the alkynyl lithium which can be quenched by H_2O or MeOH to give the terminal alkyne. Alternatively, the alkynyl lithium can be trapped by various electrophiles, in this case to incorporate *C*8. The formation of the alkyne from the dibromoalkene **137** turned out to be very difficult. The literature procedure employing *n*-BuLi[85] failed to give the epoxydiyne **138**. We therefore looked for a much milder base to carry out the transformation. Employing NaHMDS,[99c] KHMDS or DBU at low temperature failed to give the bromoalkyne **138** and led to decomposition of the starting material. Finally TBAF proved to be the best reagent for the conversion but still led to a complex mixture, which appeared to include the epoxydiynes **138** and **139**. Despite our best efforts to optimise the reaction, we were unable to isolate **138** and **139** pure and in good yield. Treatment of the crude mixture with 1.0 equiv. of *n*-BuLi followed by trapping with TESCl afforded a complex mixture which was thought to include the monosilylated and disilylated epoxydiynes **16**, **140** and **141** from NMR analysis of the crude mixture.



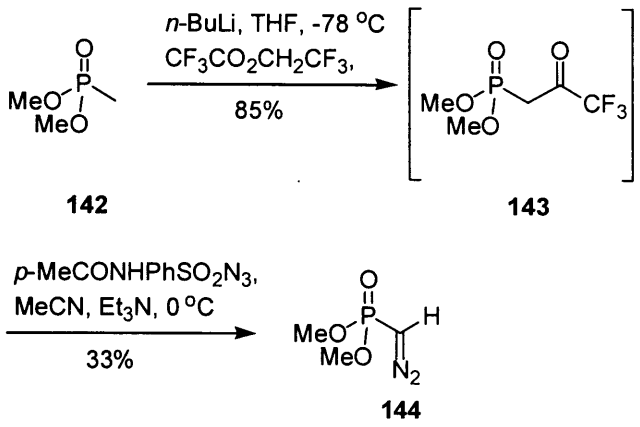
Scheme 41. Preparation of epoxydiynes.

The Shioiri methodology[100] was tested by carrying out the reaction using Bruckner's[86] conditions. We were unable to isolate the epoxydiyne **139** and complex mixture of unknown compounds were obtained instead (Scheme **42**).



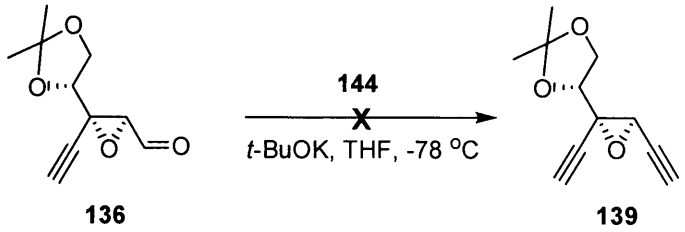
Scheme 42. Attempted epoxydiyne syntheis *via* Shioiri approach.

We also attempted to use other methods to obtain the epoxydiynes. Our first alternative method was to generate the alkyne by employing phosphonate reagents. We prepared the Seyferth-Gilbert reagent,[101] dimethyl diazomethylphosphonate (DAMP), from a recently reported procedure (Scheme **43**).[102] Dimethyl methylphosphonate **145** was trifluoroacetylated to give the intermediate **143**. **143** was then treated with 4-acetamidobenzenesulfonyl azide yielding **144**.



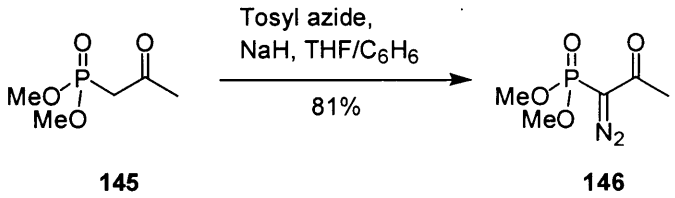
Scheme 43. Synthesis of the Seyferth-Gilbert reagent.

The reaction of the phosphonate **144** with the epoxyaldehyde **136** in the presence of *t*-BuOK failed to give the required epoxydiyne **139** and led to total decomposition of the starting material. We proposed that the anion of the dimethyl diazomethylphosphonate may induce epoxide ring opening.



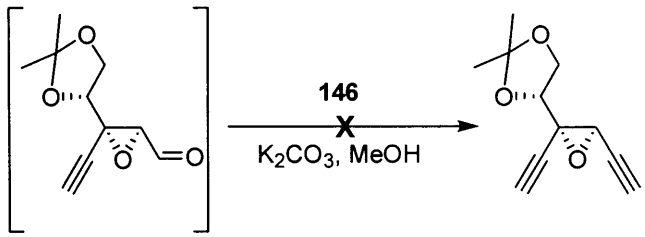
Scheme 44. Attempted epoxydiyne synthesis using Seyferth-Gilbert reagent.

Our next method was to employ dimethyl 1-diazo-2-oxopropylphosphonate, known as Ohira's reagent,[103] in the presence of basic methanol. **146** was obtained in a single step by reacting the commercially available dimethyl-2-oxopropylphosphonate **145** with tosyl azide in good yield (Scheme **45**).



Scheme 45. Synthesis of the Ohira's reagent.

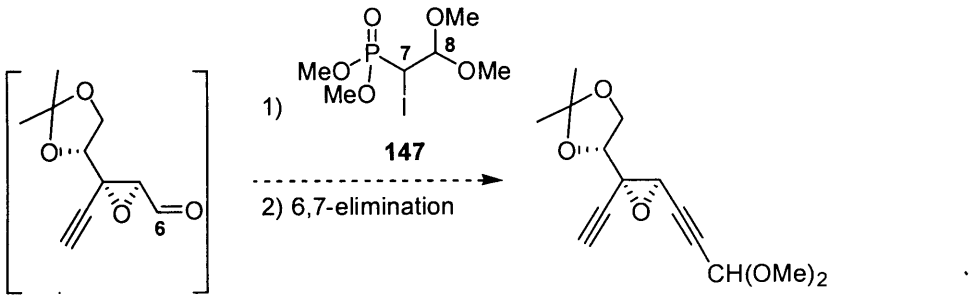
The epoxyaldehyde **136** was then reacted with **146** in potassium carbonate and methanol (Scheme **46**).[104] After stirring for several hours at rt, the epoxydiyne **139** could not be isolated and decomposition of **136** was observed. Carrying out the reaction at low temperature led to the same results. We suspected that methanol could induce epoxide opening. *t*-Butanol was then chosen as solvent to avoid nucleophilic addition but the same result was observed. Phosphonate reagents appeared to behave as strong nucleophiles, leading to the decomposition of the sensitive epoxyaldehyde **136**.



136 **139**

Scheme **46**. Attempted epoxydiyne synthesis using Ohira's reagent.

We also attempted an alternative Horner-Wadsworth-Emmons olefination approach. Our strategy aimed at synthesising the required epoxydiyne **148** from **136** and the α-iodo-phosphonate **147** incorporating *C*8 followed by 1,2-halogeno-elimination (Scheme **47**).

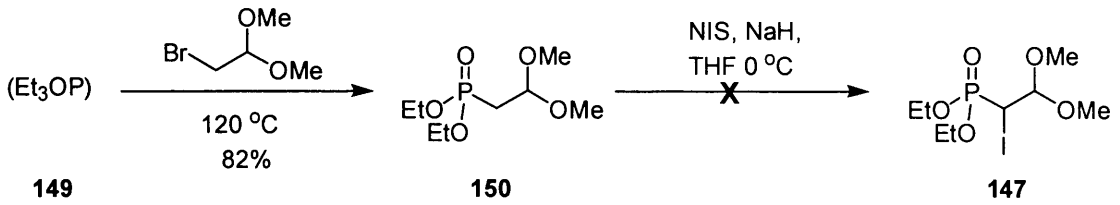


136 **148**

Scheme 47. HWE/elimination strategy.

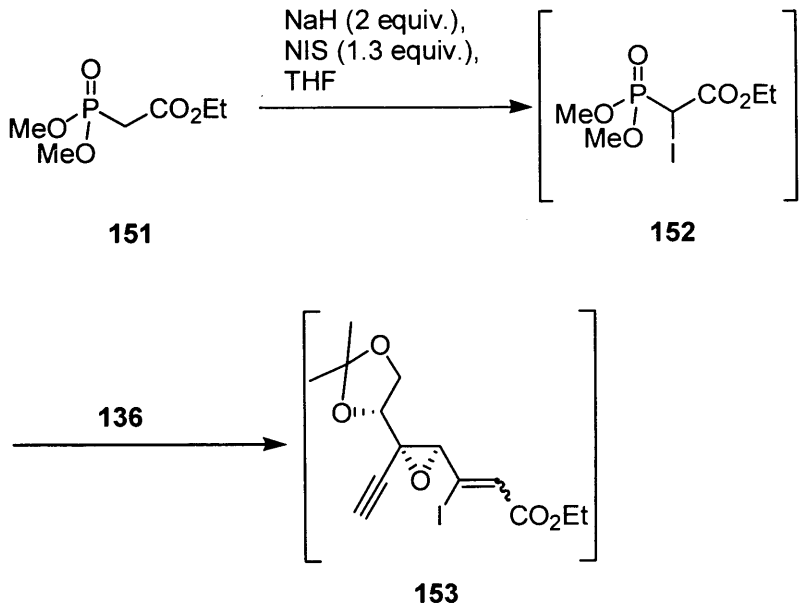
The phosphonate **150** was prepared in good yield using the commercially available 2-bromo-1,1-dimethoxyethane and trimethylphosphite at 120 °C. Unfortunately, α-

iodination of **150** using N-iodosuccinimide and NaH failed to give the required phosphonate **147** (Scheme **48**). This was likely due to β-elimination of methoxide under basic conditions.



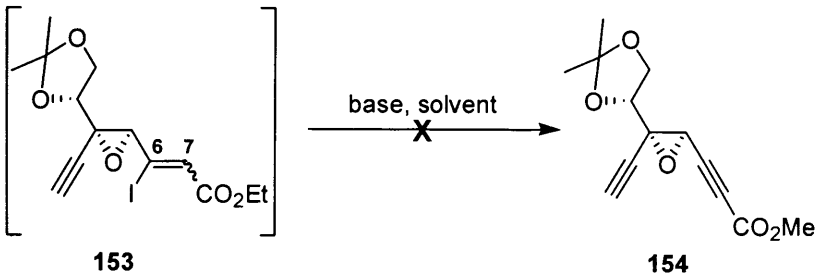
Scheme 48. Attempted phosphonate synthesis.

We decided then to carry out the HWE olefination of **136** by using the known trimethyl α-iodo-phosphonoacetate **152**.[105] **152** was prepared by α-iodination of the commercially available trimethyl phosphonoacetate **151** with NaH and N-iodosuccinimide. It is proposed that olefination of the epoxyaldehyde **136** led to the epoxy-vinyliodide **153** however it was found to be highly silica-sensitive, preventing purification. However NMR of the crude mixture revealed the presence of the characteristic vinylic proton at 6.7 ppm of **153** and total disappearance of starting material (Scheme **49**).



Scheme 49. Attempted vinyl iodide synthesis *via* HWE olefination.

We then concentrated our effort towards the 6,7-elimination of the crude vinyl iodide **153** (Scheme **50**). Attempts to isolate **154** were carried out from conditions reported in the literature[106] and failed to give the epoxydiyne **154**. Varying the solvent and the base led to decomposition of the starting material (Table **6**).



153 **154**

Scheme 50. Attempted epoxydiyne synthesis *via* 6,7-elimination.

entry	solvent	base	Results
1	DME	NaH	Decomposition
2	THF	NaH	Decomposition
3	THF	DBU	Decomposition
4	THF/DMSO	*t*-BuOK	Decomposition
5	THF	TBAF	Decomposition

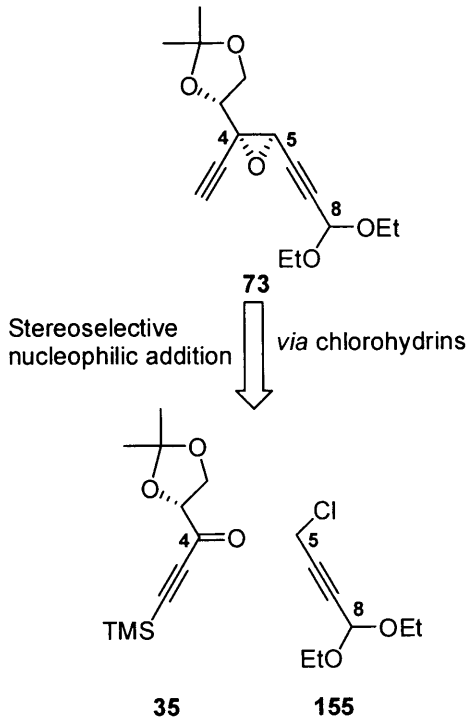
Table 6. Attempted epoxydiyne synthesis *via* 6,7-elimination.

Despite our efforts directed towards the synthesis of epoxydiynes *via* this route, we were unable to obtain the desired products so it was decided to seek an alternative route.

2.5.3 General method to epoxydiynes and a key fragment of the NCS-C

Our initial attempts towards epoxydiynes had unfortunately failed to yield the desired compound. Despite considerable work we had been unable to incorporate the *C*8 carbon on the epoxydiyne fragment essential for our conjugate addition/intramolecular aldol strategy to NCS. We turned then to a potentially more

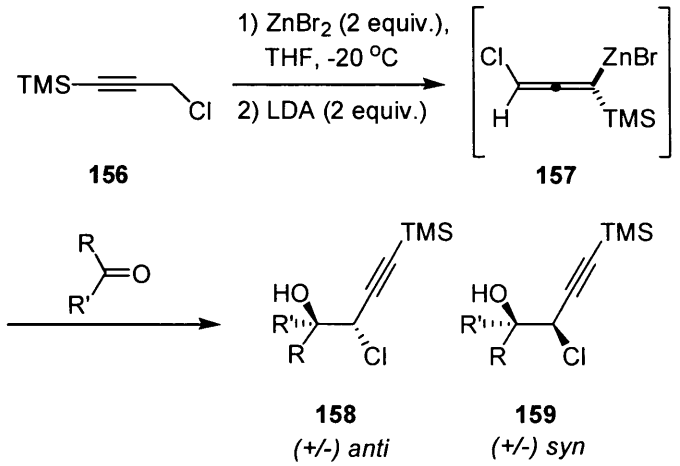
rapid and general alternative to unsymmetrical epoxydiynes.[107] Our convergent strategy towards our key epoxydiyne disconnects at *C*4-*C*5. It involves a Darzens-type condensation[108] of a propargylic halide with the corresponding propargylic ketone (Scheme **51**). This has the potential to deliver a highly practical and convergent methodology to the desired fragment and circumvents a Sharpless asymmetric epoxidation that requires the synthesis of the corresponding enediyne with the correct stereochemistry and protecting group adjustments.



Scheme 51. Retrosynthetic analysis towards the key epoxydiyne using a Darzens-type approach.

In using this approach we face three synthetic challenges, namely the diastereoselectivity of the condensation, the nucleophilicity and the stability of the propargylic halide. Normant *et al.* have recently reported that an allenyl zinc bromide **157**, made from the corresponding propargylic chloride, can be added to various aldehydes and selected ketones to give chlorohydrins which can be readily cyclised to propargylic epoxides in good overall yield.[109] The organo-zinc reagent was chosen because of their good regioselectivity in nucleophilic addition to aldehydes and their improved thermal stability by comparison with other organo-metal counterparts. The allenyl zinc reagent was prepared at low temperature from the starting propargylic chloride **156** using 2 equiv. of zinc bromide followed by dropwise addition of 2 equiv.

of LDA. The reactivity of this new, nucleophilic reagent was tested by Normant *et al.* on a variety of aldehydes and ketones to give the corresponding chlorohydrins in good yields (Scheme **52**).



Scheme 52. Normant's preparation of the allenyl zinc bromide and diastereoselective synthesis of chlorohydrins.[109]

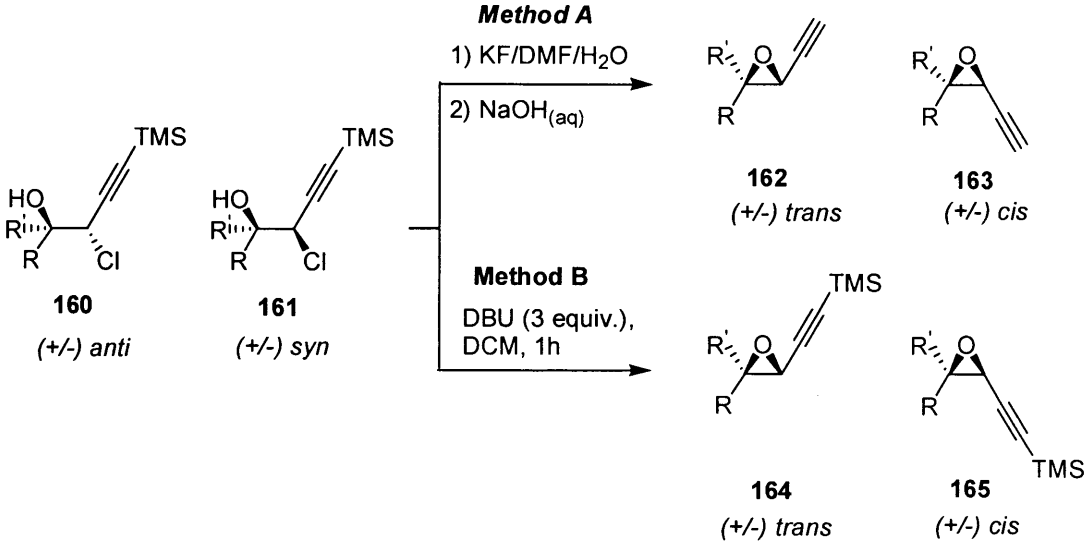
Entry	R	R'	Yield (%)	*anti/syn* ratio
1	*n*-Bu	H	81	85/15
2	*i*-Pr	H	75	95/5
3	*t*-Bu	H	82	98/2
4	CH_3-CH=CH_2	H	82	84/16
5	Ph-CH=CH_2	H	75	80/20
6	CH_2=CH	CH_3	91	50/50
7	Ph	H	85	64/36
8	4-MeO-Ph	H	66	63/37
9	3,4,5-MeO-Ph	H	85	71/29
10	4-NO_2-Ph	H	74	47/53
11	2,4-NO_2-Ph	H	74	35/65

Table 7. Influence of the substituents on the diastereoselectivity of the reaction.[109]

In the case of aliphatic aldehydes, the diastereoselectivity of the condensation is in favour of the *anti*-isomers (*anti/syn*: 85/15 to 98/2) (Table **7**, entries **1-3**).

Furthermore, they found that the bulk of R greatly influences the diastereoisomeric ratio in favour of the *anti*-adducts. Slightly less diastereocontrol is observed in the case of alkenyl-aldehydes (*anti*:*syn* / 84:16 to 80:20) (Entries **4-5**). No diastereocontrol was observed in the case of the ketone used (*anti*:*syn* / 50:50) (Entry **6**). A remarkable drop in diastereoselectivity was observed in the case of the aromatic aldehydes even leading to inversion of stereocontrol when electron-withdrawing substituents such as NO_2 were present on the aromatic ring (*anti*:*syn* / 64:36 to 35:65) (Entries **7-11**).

The corresponding chlorohydrins were converted into propargylic epoxides in 35% to 99% yield. The preparation of desilylated propargylic epoxides **162** and **163** was achieved by protodesilylation with KF in wet DMF followed by ring closure in 10% aqueous NaOH. Alternatively, treatment of the chlorohydrins with DBU leads to TMS-protected propargylic epoxides **164** and **165**. (Scheme **53**).



Scheme 53. Diastereospecific cyclisation of chorohydrins into propargylic epoxides.[109]

Chlorohydrins cyclised in a diastereospecific manner; the diastereoisomeric *anti*/*syn* ratio of chlorohydrins predicting respectively the diastereoisomeric *trans*/*cis* ratio of the resultant epoxides (Table **8**).

Entry	R	R'	Method	Yield (%)	*trans/cis* ratio
2	*i*-Pr	H	A	35	95/5
3	*t*-Bu	H	B	97	98/2
4	CH_3-CH=CH_2	H	B	93	84/16
5	Ph-CH=CH_2	H	A	90	80/20
			B	98	80/20
6	Ph	H	A	95	64/36
			B	99	64/36
7	4-MeO-Ph	H	A	97	63/37
			B	94	63/37
11	-$(CH_2)_5$-		A	74	Not given
			B	96	Not given
12	CH_2=CH	CH_3	B	98	50/50

Table 8. Conversion of chlorohydrins to propargylic epoxides.[109]

To explain the formation of the major (+/-) *anti*-chlorohydrins, the authors invoked a favoured chelate transition state in which the allenyl moiety and the C=O bond are eclipsed and in which the chlorine atom and the substituents R of the carbonyl adopt an *anti* position. The *syn* chlorohydrins come from the disfavoured transition state in which the *R* substituents and the halogen atom are in a *syn* position and thus involve a steric clash (Figure **8**). Subsequent cyclisation of the *anti* and *syn* isomers then led to the *trans* and *cis* epoxydiynes respectively.

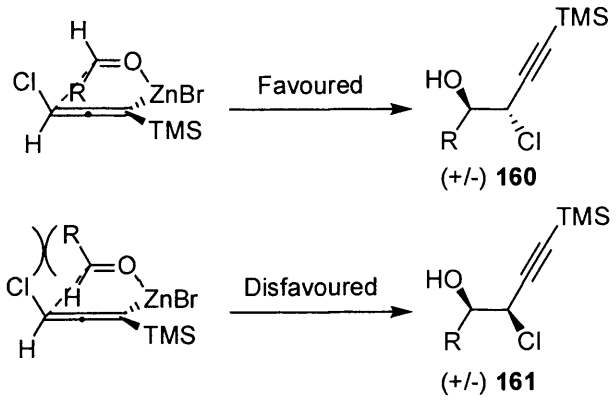
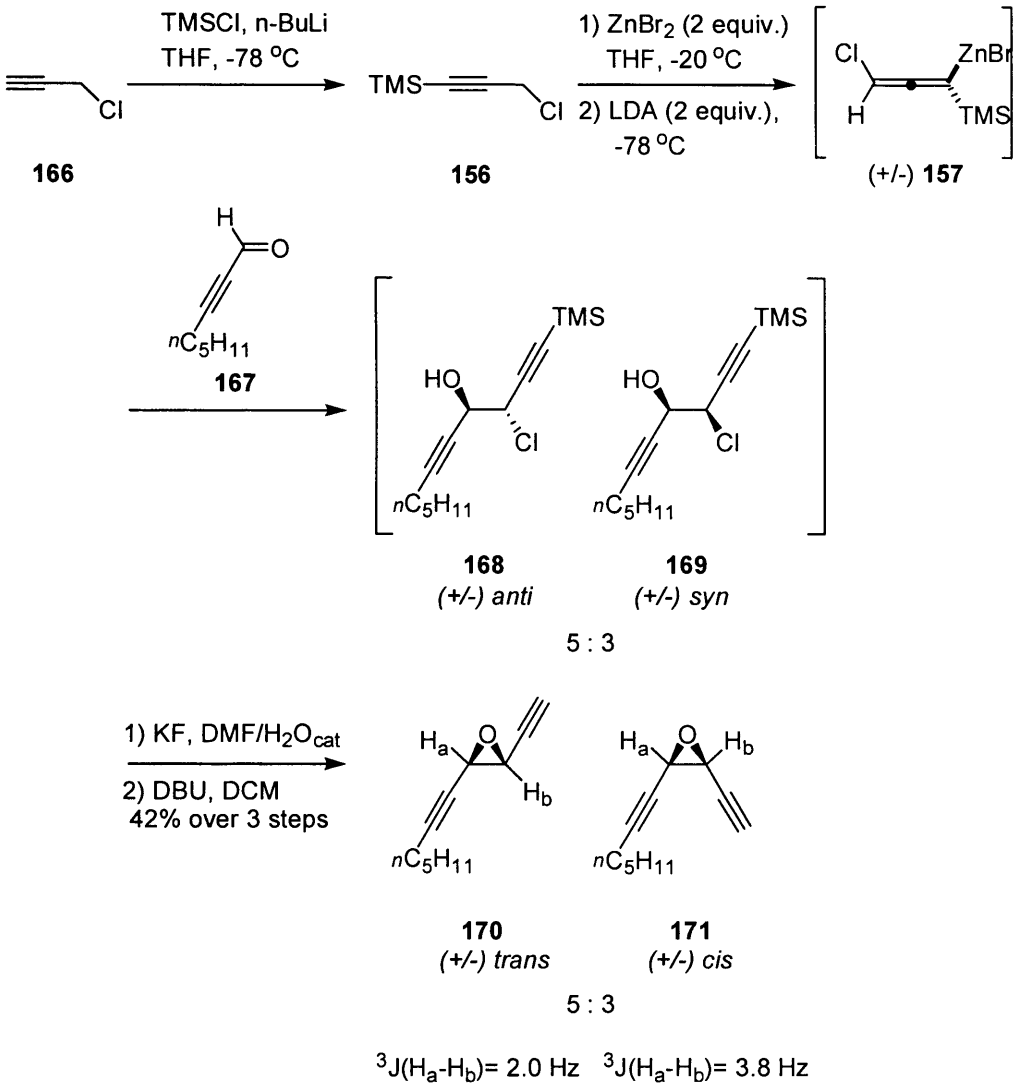


Figure 8. Proposed transition state model to explain the diastereoselectivity.

Inspired by their work, preliminary studies were performed to test the feasibility of this approach toward epoxydiynes and to investigate the stereoselectivity (Scheme **54**). Trimethylsilylation of the commercially available propargyl chloride with *n*-BuLi gave the propargylic chloride **156**. Treatment of **156** with 2 equiv. of zinc bromide followed by dropwise addition of 2 equiv. of LDA at low temperature was assumed to afford the allenyl zinc bromide reagent **157**. Promisingly the addition of 2-octynal to this mixture gave the 2 inseparable chlorohydrin diastereoisomers **168** and **169**. Isolation and purification of the chlorohydrins could not be achieved due to their instability. Immediate desilylation of the crude chlorohydrins using KF in DMF followed by cyclisation with DBU gave rise to the inseparable diastereoisomeric epoxydiynes **170** and **171** in a *cis*:*trans* / 3:5 ratio and in 42 % overall yield. Extensive purification allowed small amounts of each epoxide to be obtained for full characterisation. The *trans* isomer was thus confirmed to be the major product due to its smaller coupling constant.[110] Attempts at cyclisation with potassium carbonate in methanol or H_2O/NaOH failed to give the epoxydiynes and the TMS-deprotected chlorohydrins were obtained. Furthermore, TMS-protected epoxydiynes could not be obtained by treatment with DBU; a complex mixture of unknown products being generated.



Scheme 54. Preparation of the allenyl zinc bromide and synthesis of epoxydiynes.

The stereochemical outcome is in agreement with the transition state model described above with the major stereoisomer being generated from a transition state minimising the steric interactions between the alkyne and the chlorine atom. The diastereospecific cyclisation *via* an S_N2 mechanism then leads to the transfer of stereochemical integrity to the epoxydiyne products (Figure **9**).

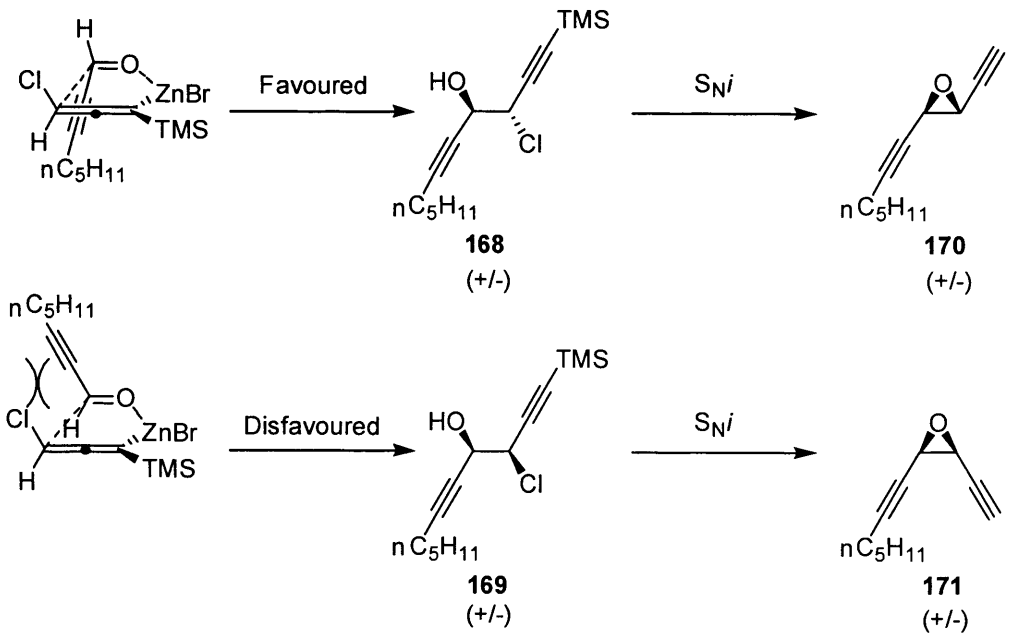


Figure 9. Chelate-type transition state for diastereoselectivity.

According to this transition state model, we postulated that propargylic ketones with a bulky α-group that is sterically more demanding than the alkyne, should preferentially lead to *trans* epoxydiynes. Furthermore, the stereochemical outcome of the addition of acetylides to erythrulose derivatives structurally similar to our synthon **35** has been investigated previously (Figure **10**).[111] Stereoselective addition of ethynyl Grignard to ketone derivatives gave *syn* and *anti*-adducts in good yield with a high level of diastereoselectivity depending on the conditions used. An α-chelation transition state involving the α-oxygen of the acetonide and a chelating agent such as Ti(*i*-PrO)$_4$ can be used to explain the observation that the major adduct is *syn* rationalised by nucleophilic addition to the *Re* side of the ketone. Alternatively, in the absence of the Ti(*i*-PrO)$_4$ the major *anti* adduct is obtained by addition to the *Si* face of the ketone. This is explained by involving a six-membered chelate involving the β-oxygen of the acetonide with the magnesium or through a Felkin-Ahn transition state.

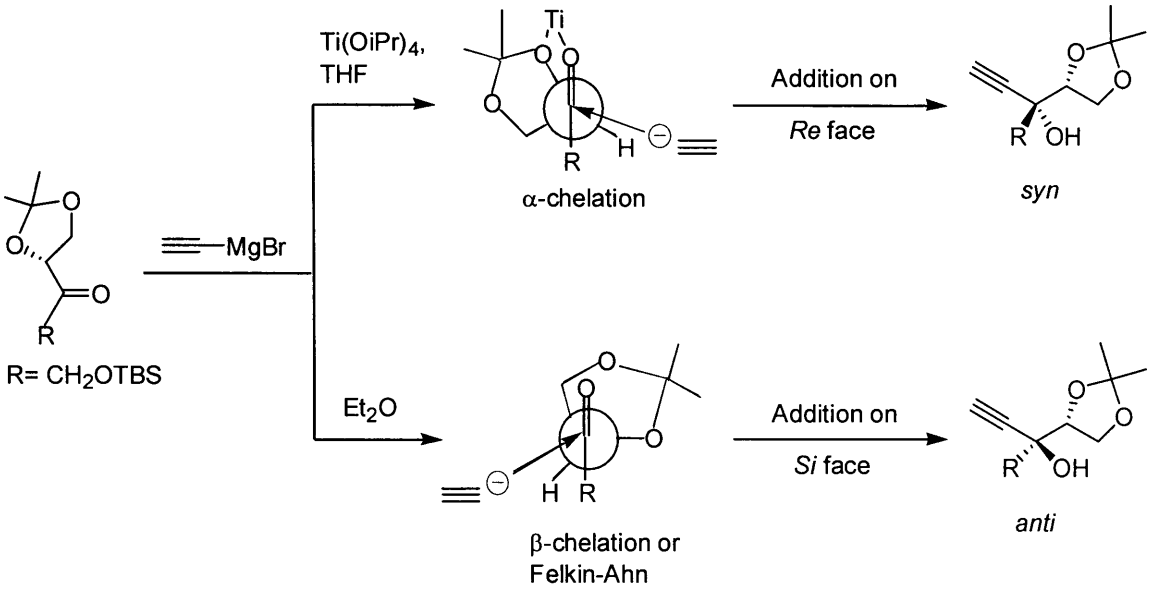


Figure 10. Proposed transition states for the diastereoselective acetylide addition to erythrulose derivative.

Building from these studies, we hoped that the chiral center which will be (*R*-*C*13) at the α-position of the ketone **35** would influence the addition of the allenyl zinc reagent to the *Si* face of the ketone to favour the formation of the alcohol with the required *R*-stereochemistry at *C*4. This can be rationalized by proceeding *via* a β-chelation transition state involving the zinc or non-chelation Felkin-Ahn transition state (Figure **11**).

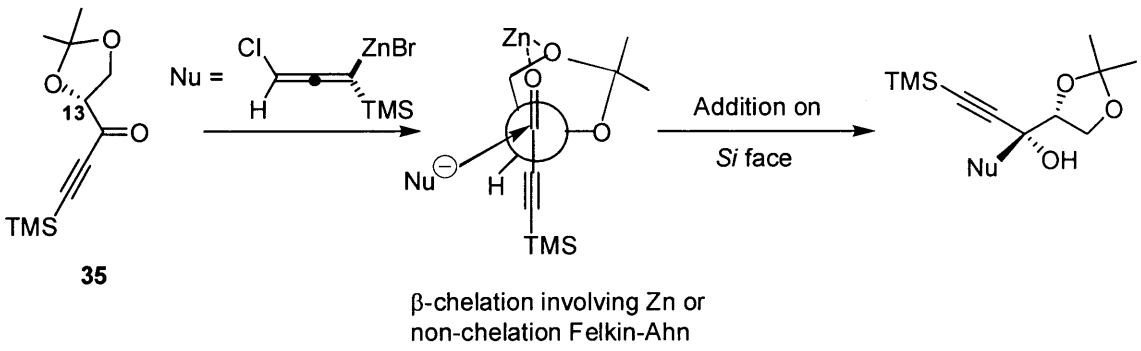
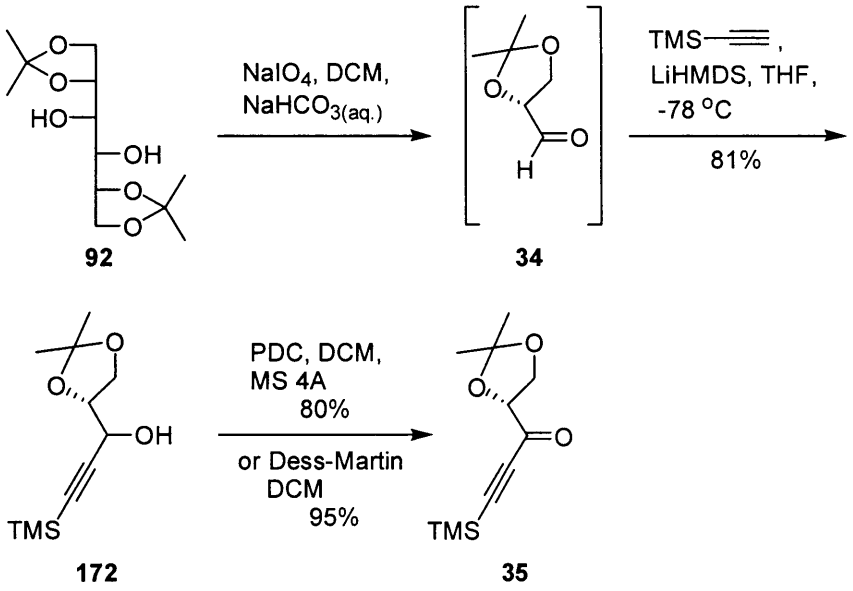


Figure 11. Proposed transition state for the stereoselective nucleophilic attack.

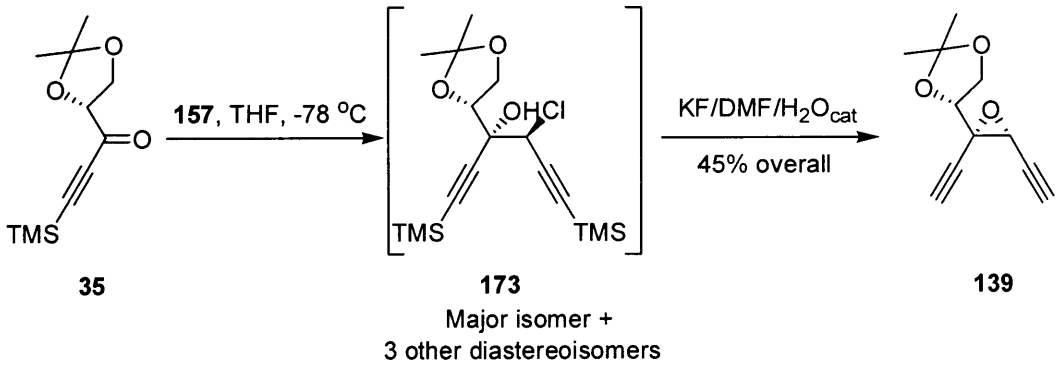
To test this, the propargylic ketone **35** was initially prepared from the commercially available chiral D-mannitol derivative **92** (Scheme **55**). Oxidative cleavage of **91** with sodium periodate followed by addition of lithium (trimethylsilyl)acetylide to D-glyceraldehyde acetonide **34** led to diastereoisomeric propargylic alcohols **172** as a

mixture in a 1.2:1 ratio and in 75% yield over 2 steps. Oxidation with pyridinium dichromate or Dess-Martin periodinane gave the required ketone **35** in 84% or 95% yield respectively. Dess-Martin periodinane is easier to handle and far less toxic than PDC but more expensive for scale-up purpose.



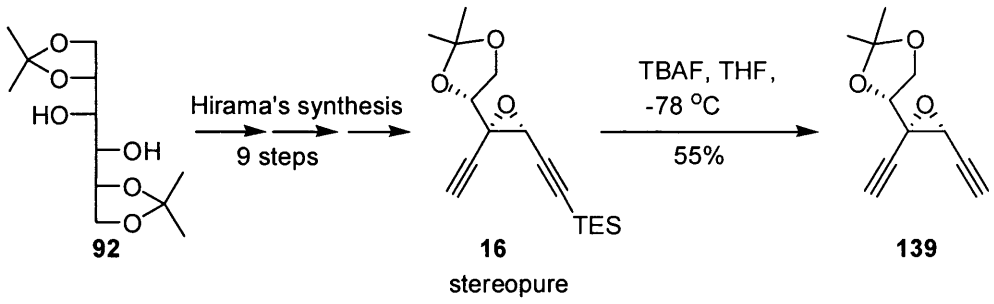
Scheme 55. Synthesis of the chiral propargylic ketone.

A colleague, Dr Baker then carried out the addition of the allenyl zinc reagent **157** to **35**.[107] From four possible stereoisomers obtainable in this reaction, one major chlorohydrin **173** was observed from NMR analysis of the crude mixture. Subsequent treatment with KF led to the removal of both silyl groups and cyclisation, to give a mixture of diastereoisomeric epoxydiynes of which only **139** was cleanly isolable in a moderate yield (Scheme **56**).



Scheme 56. Epoxydiyne synthesis *via* stereoselective condensation.

The stereochemistry of this product was confirmed by comparison with the work of Hirama.[47] Baker followed the synthesis of Hirama to give the epoxydiyne **16**, and subsequent removal of the TES group yielded the epoxydiyne **139**, which had identical spectroscopic properties. Thus the stereochemical outcome of this two-step sequence matched the desired stereochemistry of the epoxydiyne moiety of NCS-C (Scheme **57**).



Scheme 57. Confirmation of the stereochemistry.

Encouraged by this result, we extended this protocol to unsymmetric trisubstituted epoxydiynes. To date, only Myers and Hirama have reported the synthesis of such epoxydiynes and used **39**[51] and **16**[47] respectively as valuable intermediates for their studies towards the total synthesis of NCS-C (Figure **12**).

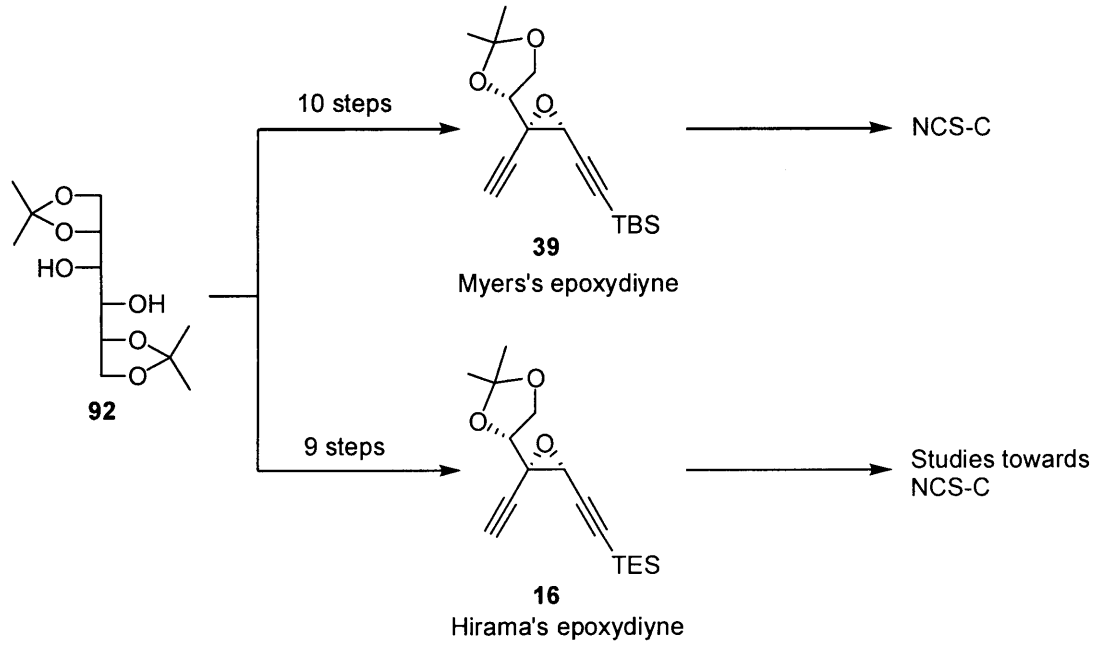
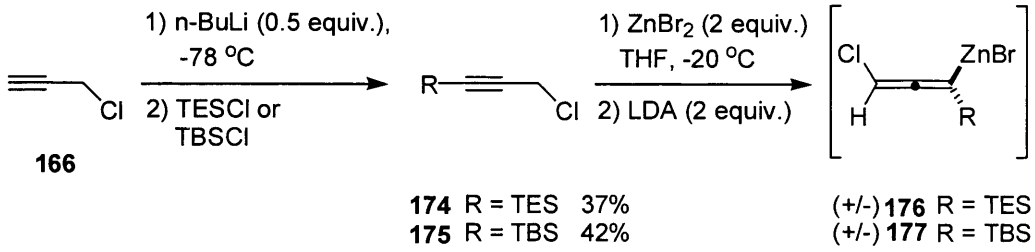


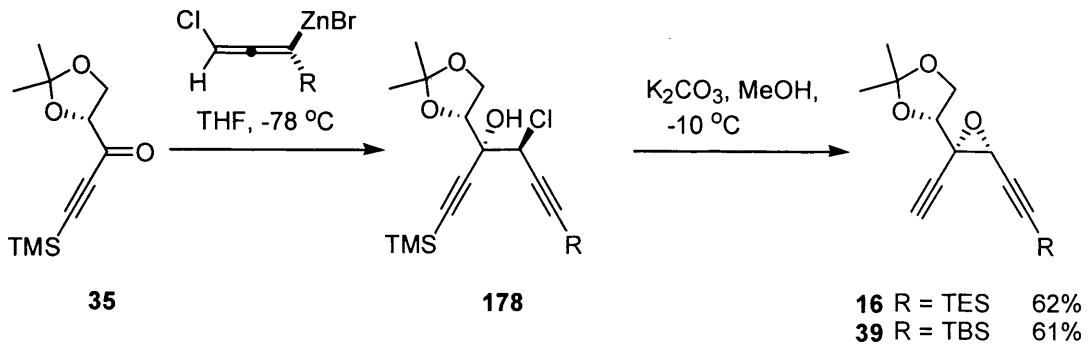
Figure 12. Stereochemical structure of Myers and Hirama epoxydiynes.

We therefore attempted to synthesise **39** and **16** to provide a new and general access to epoxydiynes previously reported in the literature. The appropriate TES and TBS-protected propargyl chlorides **174** and **175** were made using the same procedure as for the preparation of **156**. Subsequent treatment with zinc bromide and LDA afforded the reactive organozinc reagents **176** and **177** (Scheme **58**).



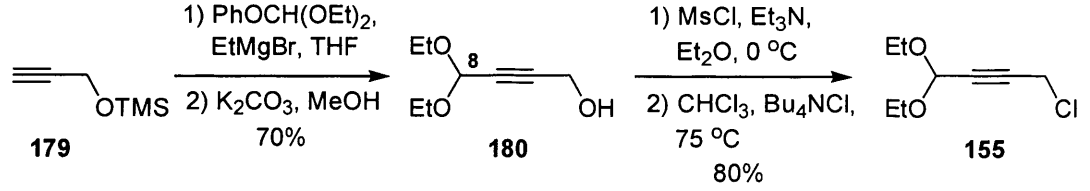
Scheme 58. Preparation of the allenyl zinc bromide reagents.

The addition of the corresponding allenyl zinc compounds **176** and **177** respectively to the propargylic ketone gave one major chlorohydrin **178** from NMR analysis of the crude mixture. In each case again the isolation and characterisation of the chlorohydrins could not be achieved due to their instability. Subsequent treatment of this mixture with potassium carbonate in methanol at low temperature led to selective TMS-removal and concomitant ring closure affording a mixture of epoxydiynes of which the major product **16** and **39** respectively, was cleanly isolable in good yield (Scheme **59**). The other diastereoisomers were present in complex mixtures thus preventing the determination of reliable diastereoisomeric ratios. The stereochemistry of the isolated epoxydiynes were the same as those reported by Hirama and Myers. In the latter case the completion of the synthesis of NCS-C with **39** unambiguously confirmed the stereochemistry. Furthermore comparison of the α_D of **39** and **16** with the literature suggested that no racemisation of ketone **35** occurred under the basic conditions of the addition.



Scheme 59. Diastereoselective synthesis of key unsymetric epoxydiynes.

As mentioned above, our general strategy toward the NCS-C has been to include the *C*8 carbon in the epoxydiyne synthon. To do this using the allenyl zinc methodology required an appropriately substituted propargylic chloride. **155** was prepared from the commercially available propargyloxytrimethysilane **179**. Functionalisation using diethylphenyl orthoformate with ethyl magnesium bromide to include the *C*8 followed by immediate desilylation afforded the propargyl acetal **180** in good yield after distillation.[112] Mesylation immediately followed by substitution with TBAC gave the functionalised propargylic chloride **155** in good yield which was of sufficient purity after work-up (Scheme **60**).



Scheme 60. Synthesis of the required propargyl chloride.

The application of the allenyl zinc method to such a fragment appears very challenging. In the presence of a strong base **155** could isomerise into cumulene **182** with ethoxide elimination. Alternatively, deprotonation at *C*8 would lead to the undesired allenyl zinc **183**. The latter could lead to another cumulene **184** with loss of chloride. Due to the products obtained, it is thought that **181** is formed in the presence of zinc bromide/LDA *via* deprotonation occurring in the α-position to the chlorine at *C*5, likely due to steric bulk considerations. No cumulene degradation was observed (Figure **13**).

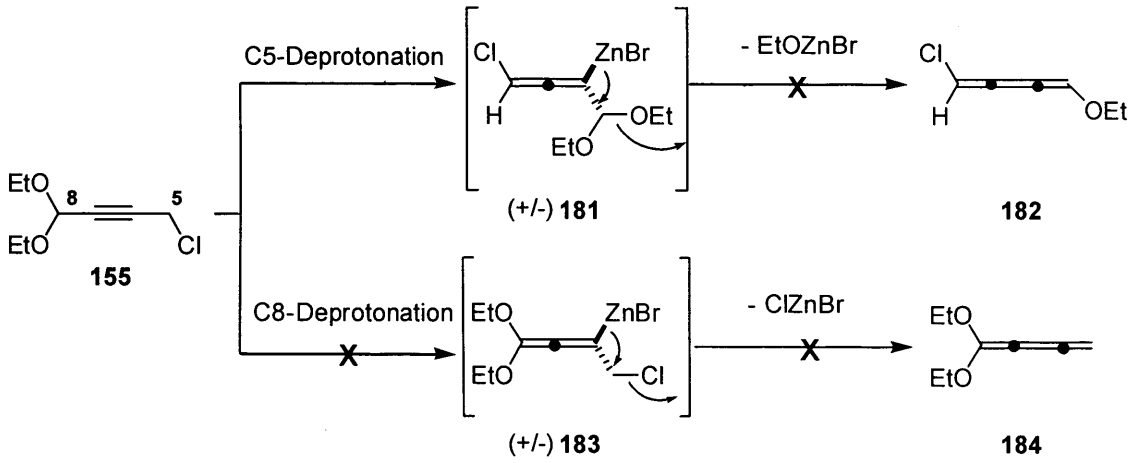
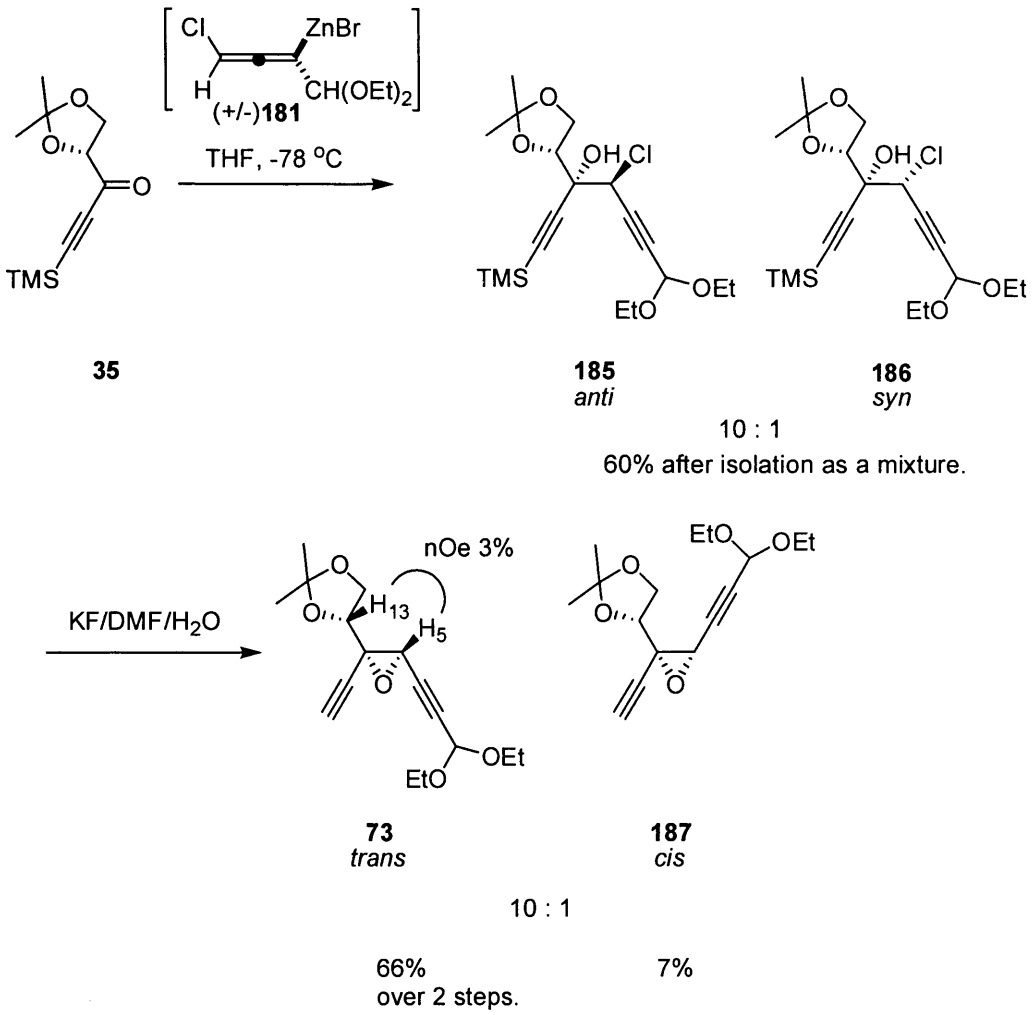


Figure 13. Possible behaviour of the propargyl chloride.

The allenyl zinc reagent **181** condensed to the propargylic ketone **35** in a diastereoselective manner affording two inseparable chlorohydrins **185** and **186** in a *anti*:*syn* / 10:1 ratio after purification. In that case the two chlorohydrins could be isolated in only 60% yield after purification. Traces of the two other diastereoisomers were also just visible by NMR but only in negligible quantities. Subsequent treatment of this mixture with KF in DMF led to the separable desilylated epoxydiynes **73** and **187** in a *trans*:*cis* / 10:1 ratio from which our key synthon **73** was isolated in 66% over two steps. The stereochemistry of the epoxydiynes was confirmed by NMR experiments allowing the stereochemistry of the chlorohydrins to be deduced.



Scheme 61. Diastereoselective synthesis of a key epoxydiyne intermediate toward Neocarzinostatin.

It is worth noting that no cyclisation of chlorohydrins resulting from the addition to propargylic aldehydes (e.g. **188**) proceeded in the presence of KF/DMF/H_2O or K_2CO_3/MeOH. In contrast chlorohydrins resulting from the addition to the propargylic ketone readily cyclised in these two conditions. This difference in reactivity can be explained by the Thorpe-Ingold effect.[113] In the case of the more substituted chlorohydrin **185**, the α angle is smaller than the α angle for the chlorohydrin **188**. The acetonide group repels and forces the hydroxyl group closer to the *C*4-*C*5 bond. Therefore the cyclisation demands less entropy loss to cyclise (Figure **14**).

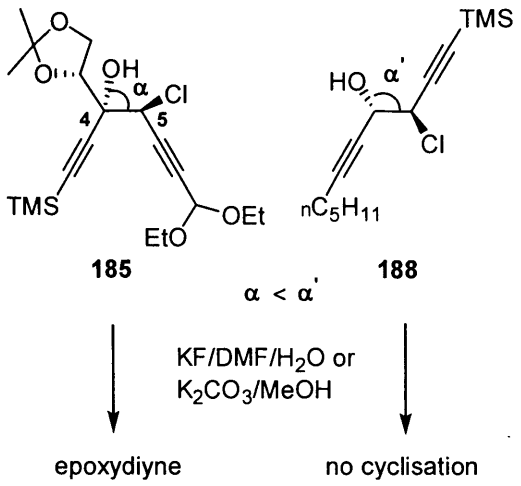
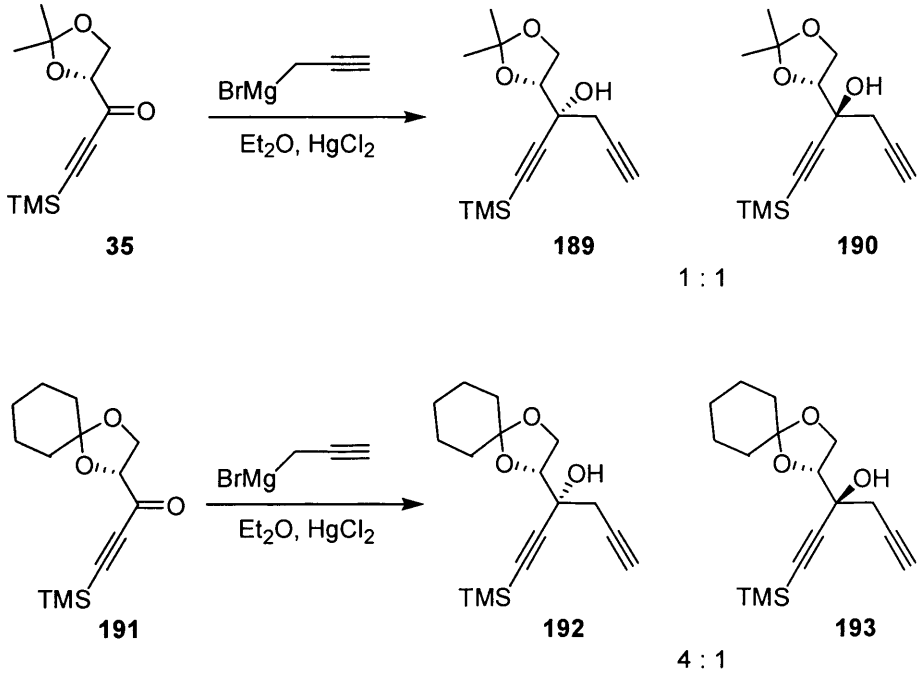


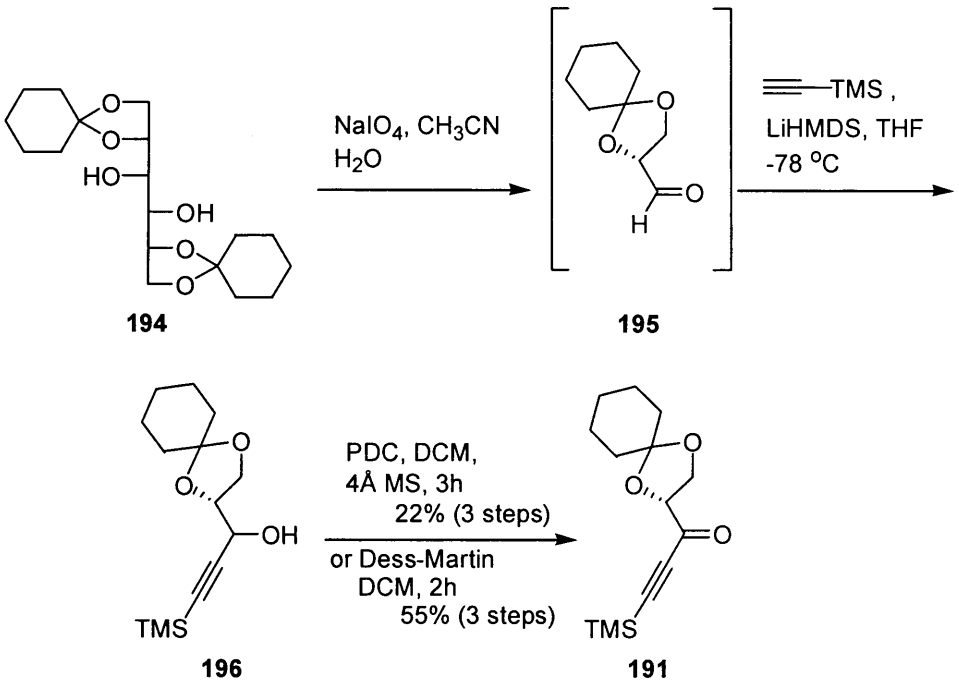
Figure 14. Illustration of the Thorpe-Ingold effect.

To try to further improve the diastereoselectivity of the transformation, the cyclohexylidene ketal was used in place of the isopropylidene group. A bulkier protected group might influence the stereochemical addition to the adjacent carbonyl group of our key propargylic ketone **35**. The cyclohexyl ketal was chosen as Britton found that the addition of propargyl Grignard with **191** gave a better diastereoselectivity 4:1 in favour of the required *R* stereochemistry at the *C*4 carbon compared to 1:1 with **35** (Scheme **62**).[90]



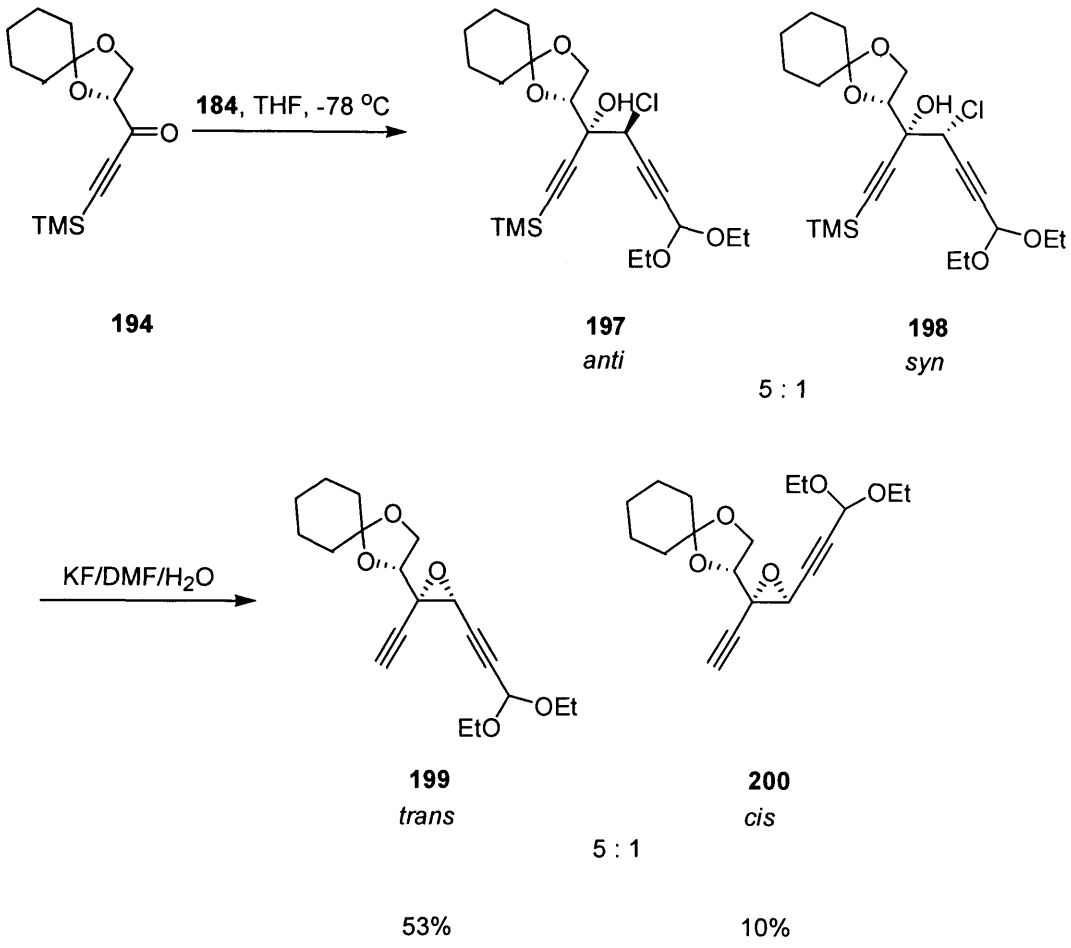
Scheme 62. Influence of the cyclohexylidene ketal group on the diastereoselectivity.

Thus **191** was made from the commercially available D-mannitol derivative **194** (Scheme **63**). The same sequence was applied as in the case of **35**. In this sequence, the oxidation with PDC proved difficult. and the propargylic ketone **191** was isolated in 22% overall yield. Eventually, **191** was obtained in 15 h and in 55% overall yield by employing 2.5 equivalents of Dess-Martin periodinane.



Scheme 63. Synthesis of the required propargylic ketone.

The chlorohydrin formation (**197** and **198**) proceeded with good diastereoselectivity (*anti/syn*: 5/1) and subsequent cyclisation with concomitant desilylation afforded diastereoisomeric epoxydiynes **199** and **200** (*trans*:*cis* / 5:1) from which the required product was isolated in 53% overall yield (Scheme **64**). Surprisingly, a bulkier group at the α-position to the ketone does not seem to influence the stereocontrol of the reaction.



Scheme 64. Diastereoselective synthesis of the key epoxydiyne.

2.5.4 Conclusions

The development of a general strategy for a synthesis of epoxydiynes has proven to be extremely difficult due to the formation of unstable intermediates which could not be processed to the fully elaborated epoxydiyne. After considerable investigations, we finally found that the addition of allenyl zinc bromide to propargylic ketones and aldehydes provides an expeditious entry to stereochemically pure epoxydiynes. For our particular project the ability to introduce the *C*8 portion required for NCS-C is particularly useful. It is noteworthy that the present protocol provides a very simple synthetic route to other functionalised epoxidiynes which have previously found use in the synthesis of NC-C. Epoxydiynes can be prepared in order to test our Michael/aldol sequence.

2.6 Michael Addition Studies

The Michael addition reaction of organometallic species to α-β-unsaturated carbonyls represents a powerful method for carbon-carbon bond formation. Organocopper reagents are the most widely used for Michael addition of alkyl and alkenyl groups to cyclic or acyclic α-β enones.[114] Alkynylcopper reagents have rarely been employed[68] [115] as copper does not readily transfer the alkynyl group to the conjugated system due to the strength of the alkynyl-Cu(I) bond.[116] Pappo *et al.* found that 1,4-addition of organoaluminium acetylenic reagents **201** to cyclic enone **202** gave **203** with chirality transfered from the free hydroxyl group.[67c] The hydroxyl group chelates the organoaluminium species and then the alkynyl group is transferred in a diastereoselective manner from the aluminium in a 1,4 fashion *via* a possible five-membered ring transition state intermediate (Figure **15**).

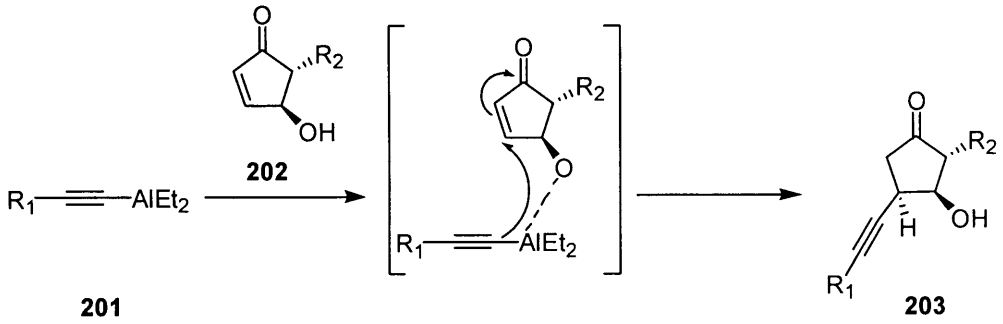
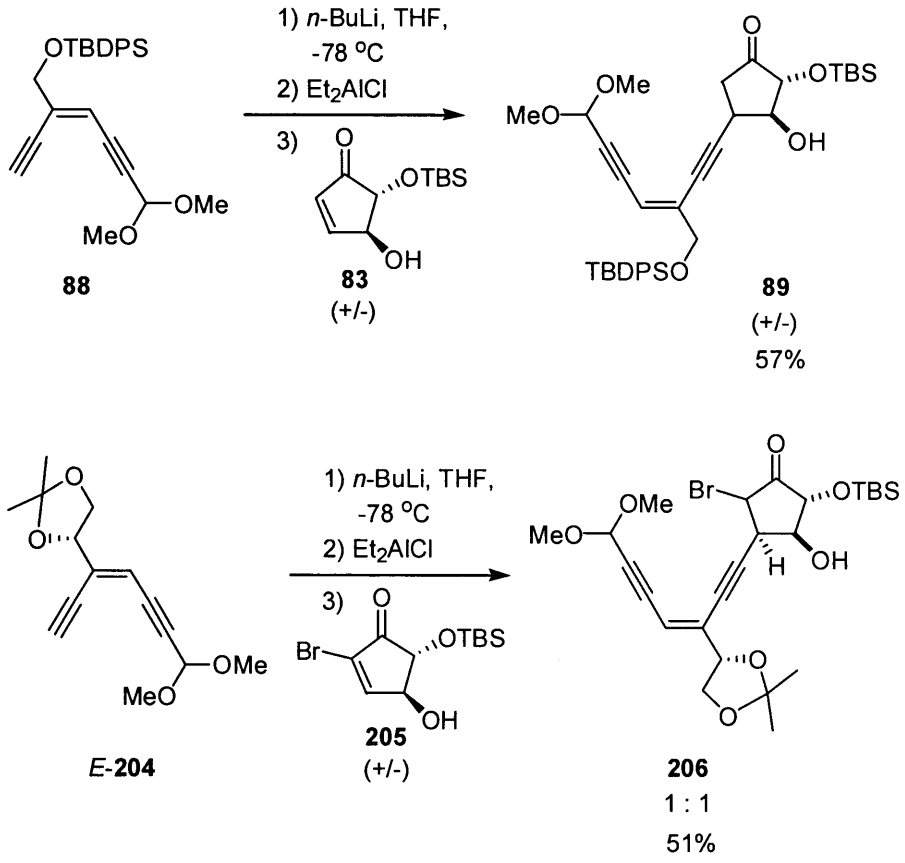


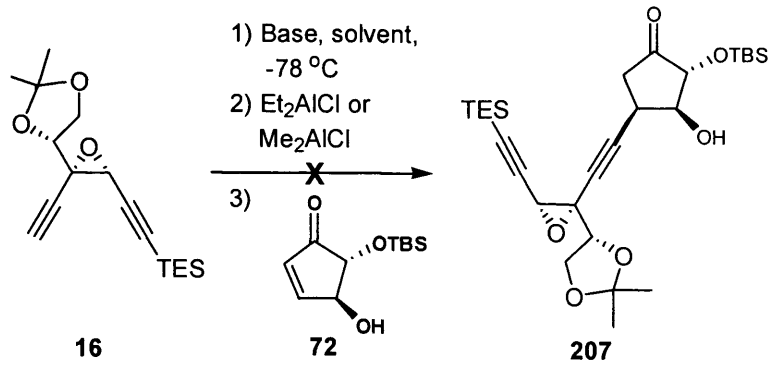
Figure 15. Diastereoselective Michael addition.

Inspired by Pappo's work,[67c] Caddick *et al.* have optimised the Michael addition of the enediyne **88** with the enone **83** to give **89** (Scheme **65**). The organoaluminium reagent was prepared by treating **88** with *n*-BuLi followed by transmetalation using Et_2AlCl. The method has also been extended to the related-NCS-C enediyne **204** and the brominated enone **205** to give **206** in a moderate yield as a 1:1 mixture of diastereoisomers.[79]



Scheme 65. Michael addition.[79]

We then decided to test the diastereoselective aluminium-catalysed Michael addition under the conditions reported by Caddick *et al.*[75] This reaction was initially investigated using the epoxydiyne **16** and the cyclopentenone **72** (Scheme **66**) . The alkynylaluminium reagent was prepared from the starting epoxydiyne **16** using 1.0 equiv. of *n*-BuLi at -78 °C followed by addition of 1.3 equiv. of Et_2AlCl. The reaction was then stirred for 1 h at rt. Addition of the cyclopentenone **72** to the alkynylaluminium reagent at -40 °C failed to give the cycloadduct **207** (Table **9**, entry **1**). Carrying out the reaction in Et_2O (entry **2**) or toluene (entry **3**) also proved to be unsuccessful. The same result was observed employing Me_2AlCl (Entry **4**), LDA (Entries **5-6**) or increasing the temperature to 0 °C or rt (Entries **7-10**).

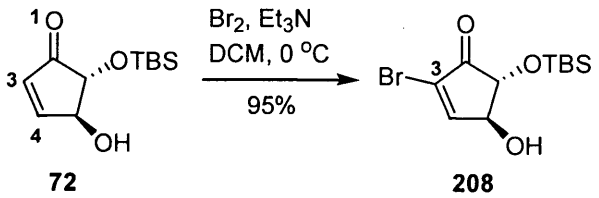


Scheme 66. Attempted Michael addition.

Entry	Reagent	Base	Solvent	T	Results
1	Et_2AlCl	*n*-Buli	THF	-40 °C	No reaction
2	Et_2AlCl	*n*-Buli	Et_2O	-40 °C	No reaction
3	Et_2AlCl	*n*-Buli	Toluene	-40 °C	No reaction
4	Me_2AlCl	*n*-Buli	THF	-40 °C	No reaction
5	Et_2AlCl	LDA	THF	-20 °C	No reaction
6	Me_2AlCl	LDA	THF	-20 °C	No reaction
7	Et_2AlCl	*n*-Buli	THF	0 °C	No reaction
8	Me_2AlCl	*n*-Buli	THF	0 °C	No reaction
9	Et_2AlCl	*n*-Buli	THF	rt	No reaction
10	Me_2AlCl	*n*-Buli	THF	rt	No reaction

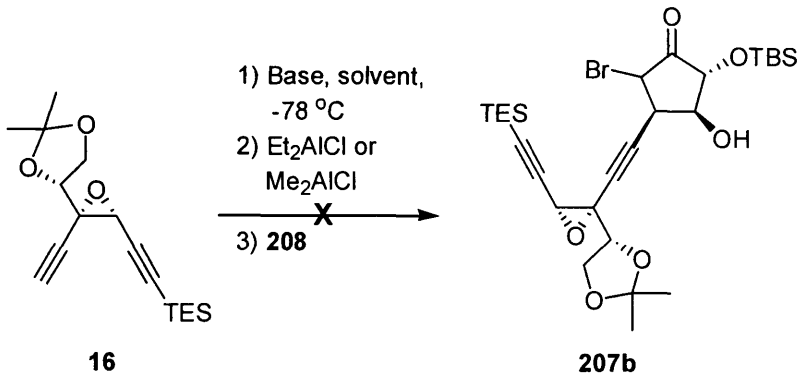
Table 9. Attempted Michael addition.

We postulated that the *C*4 position of **72** was not activated enough towards nucleophiles. We then envisaged activating *C*4 through bromination of **72** at *C*3 under basic conditions (Scheme **67**).



Scheme 67. Cyclopentenone bromination under basic conditions.

However, when the brominated cyclopentenone **208** was used under the same conditions as for **72**, no reaction was observed and both starting materials were recovered quantitatively (Table **10**, entries **1-10**).



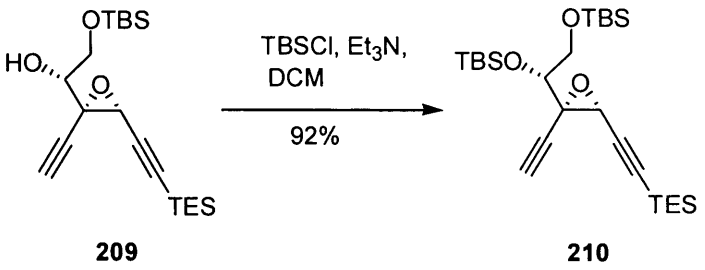
16 **207b**

Scheme 68. Attempted Michael addition.

Entry	Reagent	Base	Solvent	T	Results
1	Et_2AlCl	*n*-Buli	THF	-40 °C	No reaction
2	Et_2AlCl	*n*-Buli	Et_2O	-40 °C	No reaction
3	Et_2AlCl	*n*-Buli	Toluene	-40 °C	No reaction
4	Me_2AlCl	*n*-Buli	THF	-40 °C	No reaction
5	Et_2AlCl	*n*-Buli	THF	0 °C	No reaction
6	Me_2AlCl	*n*-Buli	THF	0 °C	No reaction
7	Et_2AlCl	*n*-Buli	THF	rt	No reaction
8	Me_2AlCl	*n*-Buli	THF	rt	No reaction
9	Et_2AlCl	LDA	THF	-20 °C	No reaction
10	Me_2AlCl	LDA	THF	-20 °C	No reaction

Table 10. Optimisation studies.

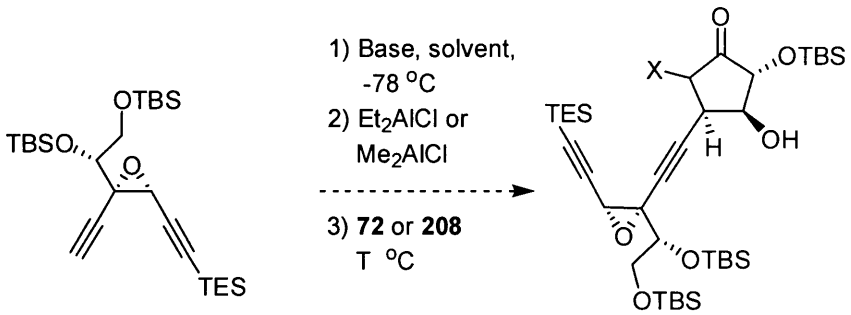
We decided to vary the protecting group of **16** at *C*13-*C*14 as we thought the acetonide represented a problem for the reaction to succeed. We chose to protect the diol moiety through silylation. By following the synthesis of Hirama to give the epoxydiyne **16**,[80] Baker within the Caddick group made the intermediate **209** which we thought would represent a valuable substrate for the silylation. Thus, silylation of **209** under basic conditions led to **210** in high yield (Scheme **69**).



209 **210**

Scheme 69. Silylation of epoxydiyne.

210 was then submitted to the Michael addition conditions with the cyclopentenones **208** and **72** respectively (Scheme **70**). However, no reaction was observed using the same conditions previously described (See table **9** and **10**) and both starting materials were recovered quantitatively (Table **11**, entry **1-10**). We assumed that the alkynyl aluminium species was not nucleophilic enough towards the cyclopentenones. We then decided to increase the basicity by using Et_3N and some molecular sieves to trap water. We were pleased to observe the Michael adduct **212** as a single diastereoisomer by using these conditions. **211** Was not detected and **72** was recovered quantitatively.



210

211 X=H
212 X=Br

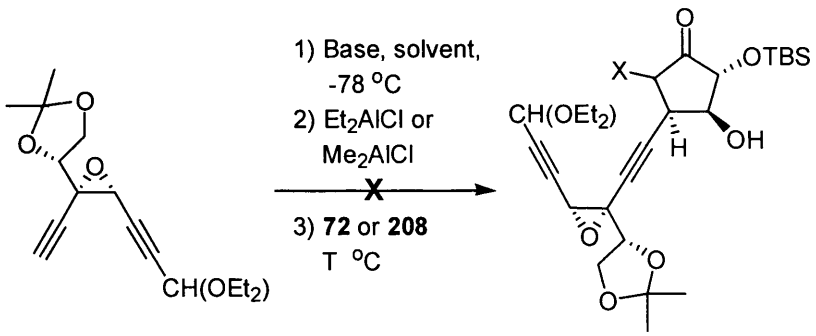
Scheme 70. Attempted Michael addition.

Entry[a]	Reagent	Base	Solvent	T	Results
1	Et_2AlCl	*n*-Buli	THF	-40 °C	No reaction
2	Et_2AlCl	*n*-Buli	Et_2O	-40 °C	No reaction
3	Et_2AlCl	*n*-Buli	Toluene	-40 °C	No reaction
4	Me_2AlCl	*n*-Buli	THF	-40 °C	No reaction
5	Et_2AlCl	*n*-Buli	THF	0 °C	No reaction
6	Me_2AlCl	*n*-Buli	THF	0 °C	No reaction
7	Et_2AlCl	*n*-Buli	THF	Rt	No reaction
8	Me_2AlCl	*n*-Buli	THF	Rt	No reaction
9	Et_2AlCl	LDA	THF	-20 °C	No reaction
10	Me_2AlCl	LDA	THF	-20 °C	No reaction
11*	Me_2AlCl	*n*-Buli	THF	-20 °C	10% **212**, no reaction using **72**
12*	Et_2AlCl	*n*-Buli	THF	-20 °C	No reaction

[a]: Cyclopentenone **72** and **208** was used for each entry.

Table 11. Optimisation studies.

We decided to screen the conditions for the Michael addition using our key intermediate **73** and cyclopentenones **72** and **208** (Scheme **71**). Unfortunately, conjugate addition under the conditions previously described proved unsuccessful (Table **12**, entries **1-12**). We found that **73** decomposed using *n*-BuLi/Et_2AlCl or *n*-BuLi/Me_2AlCl (Entries **1-8**). The use of the LDA/Et_2AlCl system partially solved the problem of decomposition. We decided then to increase the amount of **73** to 4 equiv. but no product was observed (Entries **13-14**). Adding a Lewis acid such as $BF_3.Et_2O$ during the reaction (Entry **15**) failed to give **213** and **214** respectively, even by increasing the temperature (Entries **16-17**). Corey *et al.* have reported that complete reaction of trimethysilylacetylene with Me_2AlCl takes 5h at 10 °C. Unfortunately, we found that the alkynylaluminium decomposed at room temperature under these conditions (Entry **18**).



73

213 X=H
214 X=Br

Scheme 71. Attempted Michael addition.

Entry[a]	AlCl reagent	Base	Solvent	T	Results
1	Et_2AlCl	*n*-Buli	THF	-40 °C	No reaction
2	Et_2AlCl	*n*-Buli	Et_2O	-40 °C	No reaction
3	Et_2AlCl	*n*-Buli	Toluene	-40 °C	No reaction
4	Me_2AlCl	*n*-Buli	THF	-40 °C	No reaction
5	Et_2AlCl	*n*-Buli	THF	0 °C	No reaction
6	Me_2AlCl	*n*-Buli	THF	0 °C	No reaction
7	Et_2AlCl	*n*-Buli	THF	rt	No reaction
8	Me_2AlCl	*n*-Buli	THF	rt	No reaction
9	Et_2AlCl	LDA	THF	-20 °C	No reaction
10	Me_2AlCl	LDA	THF	-20 °C	No reaction
11	Me_2AlCl	*n*-Buli/Et_3N /Sieves 4Å	THF	rt	No reaction
12	Et_2AlCl	*n*-Buli/Et_3N /Sieves 4Å	THF	rt	No reaction
13[b]	Et_2AlCl	LDA	THF	0 °C	No reaction
14[b]	Me_2AlCl	LDA	THF	0 °C	No reaction
15[c]	Et_2AlCl	LDA	THF	-40 °C	No reaction
16[c]	Et_2AlCl	LDA	THF	-20 °C	No reaction
17[c]	Et_2AlCl	LDA	THF	rt	No reaction
18[d]	Me_2AlCl	LDA	THF	rt	No reaction

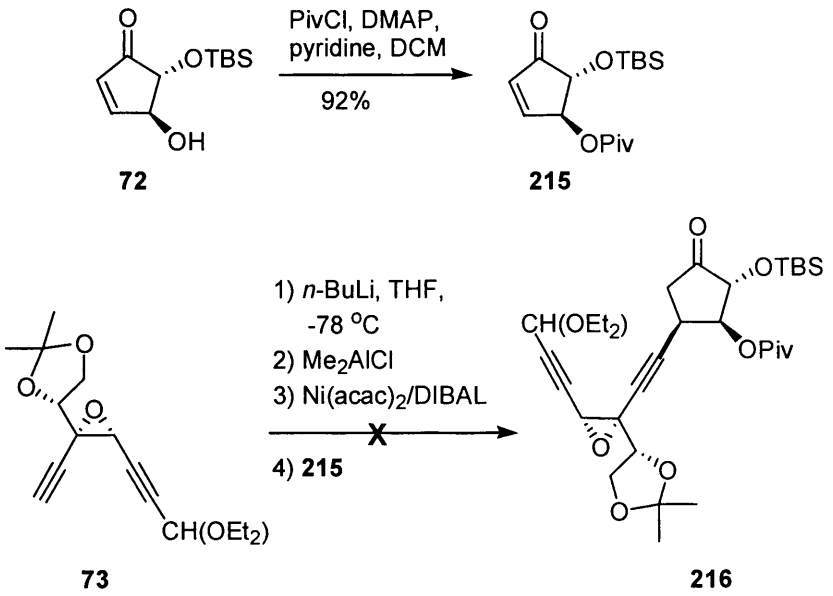
[a] : Cyclopentenones **72** or **210** were used for each entry. [b]: 4 equiv. of the epoxydiyne **73** was used. [c]: Addition of $BF_3.Et_2O$. [d]: Organometallic reagent stirred for 5h at 10°C.

Table 12. Attempted Michael addition.

We assumed that the alkynylaluminium might not be generated efficiently or that the oxygen atoms of the diol *C*13/*C*14 might coordinate the organoaluminium reagent making it inactive towards the conjugate addition.

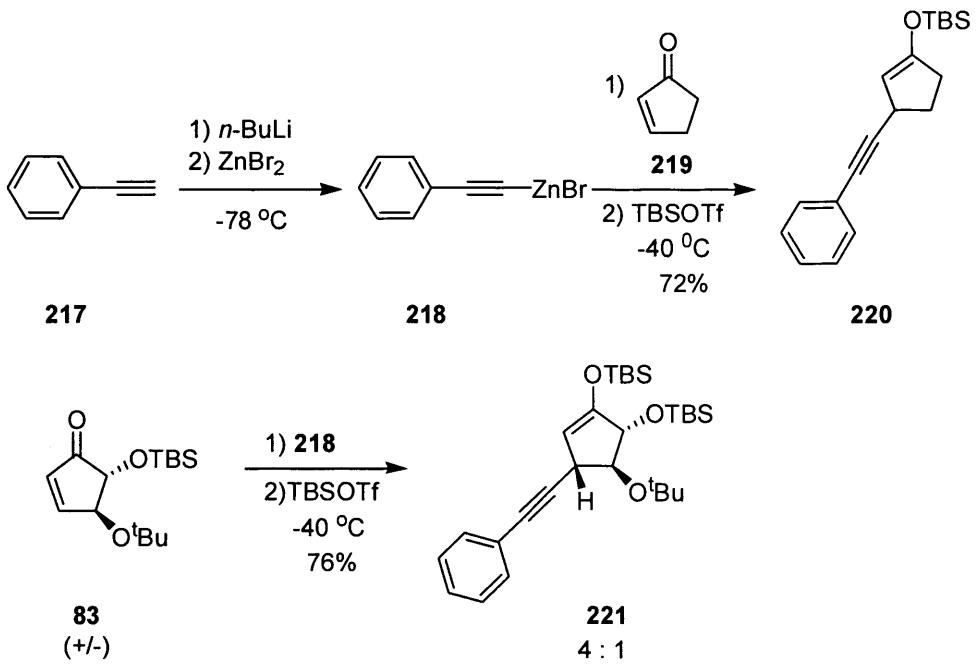
Facing these disappointing results, we turned to alternative methods for conjugate addition. Schwartz *et al.* have reported the conjugate addition of alkynyl groups to cyclic α,β-enones using organoaluminium reagents in the presence of Ni(I), generated

in situ by a reduction of $Ni(acac)_2$ with DIBAL.[67a,b] We decided to apply this method to the cyclopentenone **215** (Scheme **72**). **215** was prepared by reacting **72** with pivaloyl chloride under basic conditions in good yield. **215** was then reacted with epoxydiyne **73** under Schwartz' conditions. Unfortunately, **216** was not detected and only **215** was recovered quantitatively. **73** was found to decompose under these conditions.



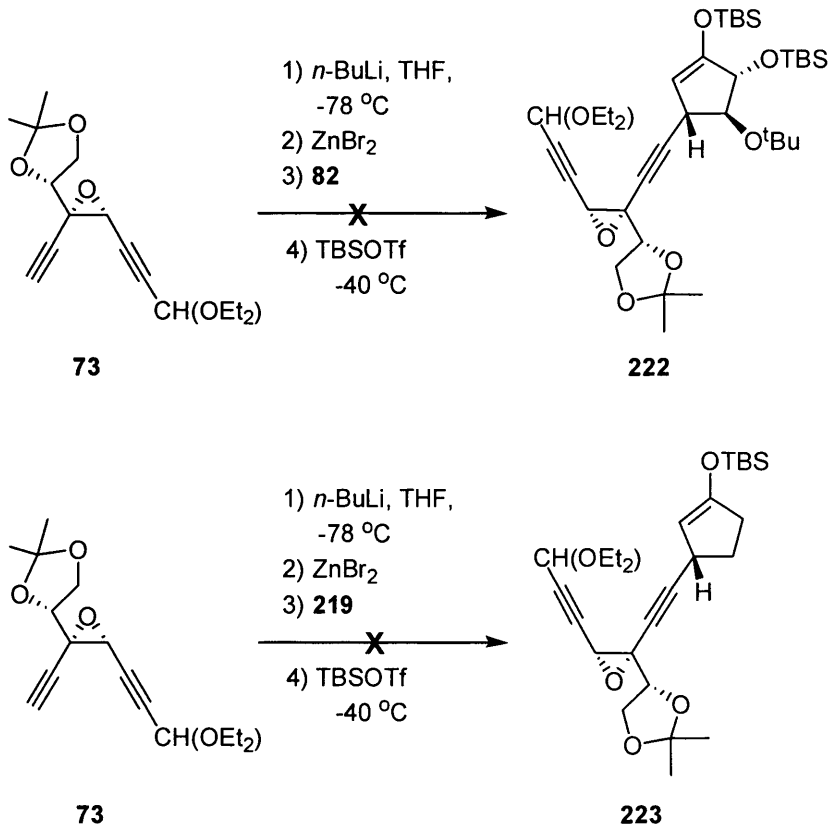
Scheme 72. Attempted conjugate addition.

Another method has been reported using alkynylzinc reagents.[66] This requires the use of an activator such as TBSOTf. The organozinc **217** is generated by deprotonation of **216** using *n*-BuLi followed by transmetalation with $ZnBr_2$. Condensation of **218** to cyclopentenone **219** lead to **220** in 72% (Scheme **73**).[66] Within the group, the conjugate addition has been achieved with the cyclopentenone **83** and phenylacetylene **218** to give **221** as a mixture of diastereoisomers in a 4:1 ratio in 56% yield (Scheme **71**).[79]



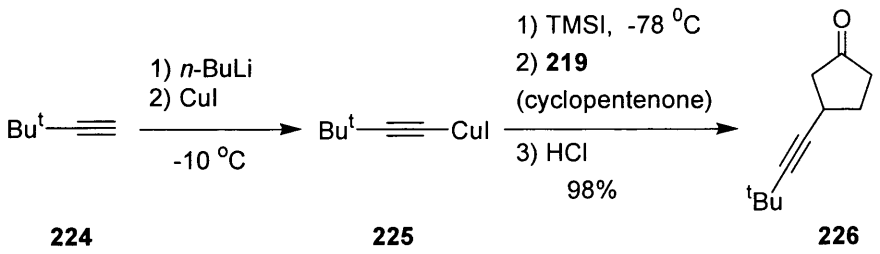
Scheme 73. Zinc-mediated Michael addition.

We then decided to apply the same conditions to the addition of **73** to **83**. **73** was treated with *n*-BuLi followed by $ZnBr_2$. Enone **83** was then added followed by TBSOTf at -40 °C. No reaction was observed however and both starting materials were recovered (**73**: 26%, **83**: 52%). We also applied the same conditions using the cyclopentenone **219** but without any success (Scheme **74**).



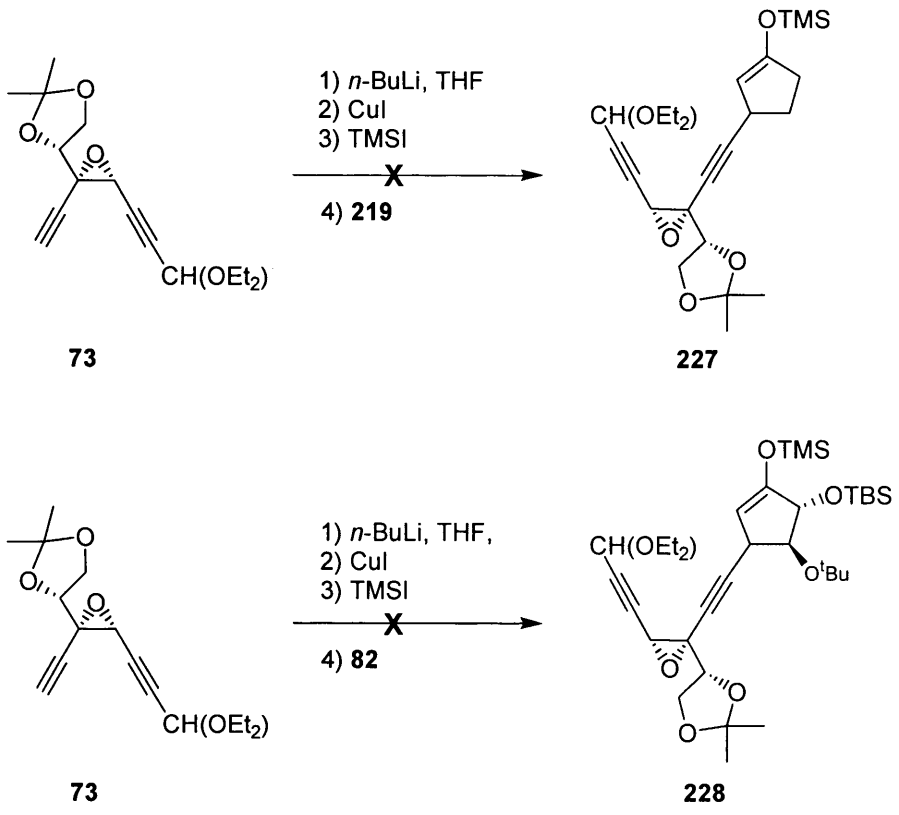
Scheme 74. Attempted zinc-mediated Michael addition.

Nilsson *et al.* have achieved the conjugate addition of alkynylcopper reagents to cyclic enones using TMSI as promoter.[68] Conjugate addition of **224** to cyclopentenone **225** using the conditions reported has been achieved by Dr Baker (Scheme **75**).[117] **224** was treated with *n*-BuLi followed by CuI at low temperature to give **225**. TMSI was then added and the mixture was reacted with **219** to give **226** in high yield after hydrolysis.[117]



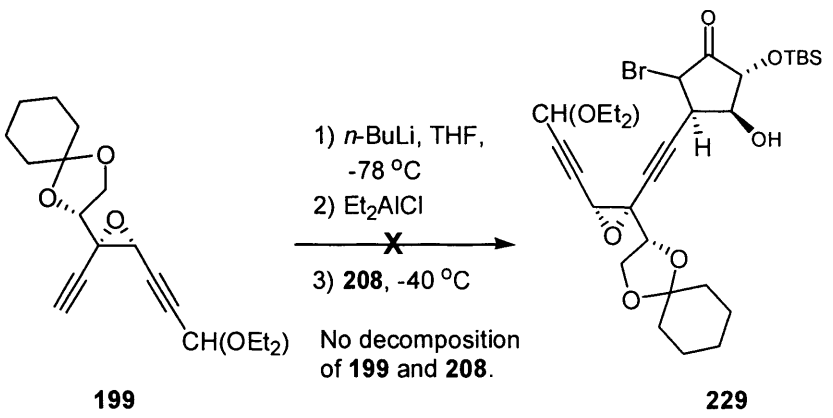
Scheme 75. Copper-mediated Michael addition.

We then applied these conditions to **73** and the enones **219** and **82** (Scheme **76**). We decided to apply a basic work-up as reported by Nilsson *et al.*[68] in order to obtain the TMS enol-ether product as we thought the hydrolysis of **227** or **228** *via* desilylation would decompose under aqueous acidic conditions (HCl 3M).[68] No product was detected however and **73** could not be recovered in either case.



Scheme 76. Attempted copper-mediated Michael addition.

Lastly we decided to retry the aluminium-catalysed Michael addition with a epoxydiyne more stable towards acidic conditions. The epoxydiyne **199** protected as its cyclohexylidene ketal at *C*13-*C*14-diol was chosen. The conjugate addition was then submitted to the original conditions reported by Caddick *et al.* (Scheme **79**).[75] Unfortunately no product was observed carrying out the reaction at -40 °C but both starting materials were recovered quantitatively solving the stability problem when making the organoaluminium reagent. Unfortunately, we were unable to carry out any further investigations on this reaction due to time constraints.



Scheme 79. Attempted Michael addition.

The first priority of future work towards the NCS-C would be to test the aluminium-mediated conjugate addition with **199**. **199** may require a longer exposure to Et_2AlCl or Me_2AlCl to be generated efficiently.[118] Once this goal is achieved, the cobalt-mediated aldol reaction would be tested.[75]

2.7 Future work and alternative strategies

2.7.1 Intramolecular Michael addition

Having experienced problems with the intermolecular Michael addition, another approach to generating the macrocycle of NCS-C would be to carry out the conjugate addition intramolecularly. The *C*8-*C*9 bond would first be formed through a Baylis-Hillman reaction followed by a Michael addition leading to the core of NCS-C (Figure **16**).

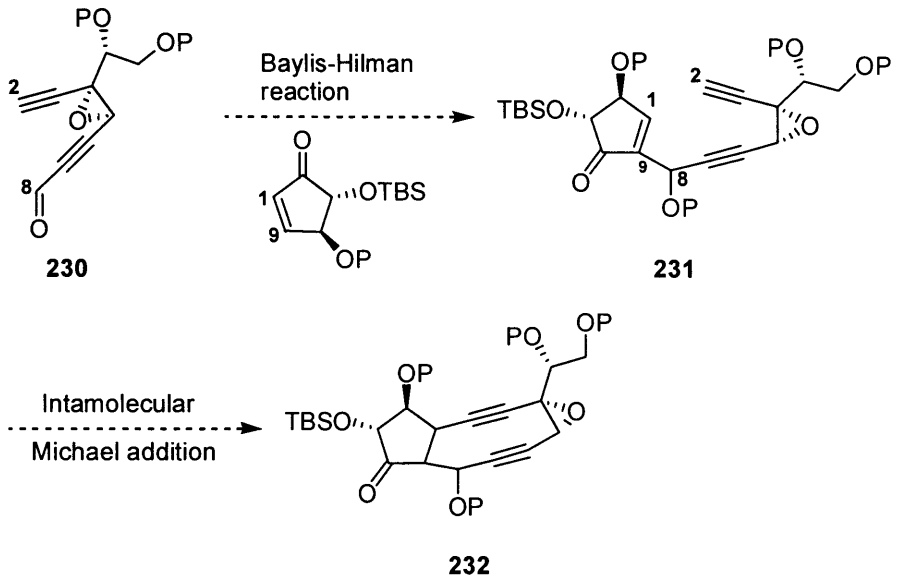


Figure 16. Baylis-Hillman/Michael sequence.

In order to carry out the conjugate addition intramolecularly, another alternative would be to introduce a linker-bearing epoxydiyne **233** on the free alcohol of **234**. The resulting substrate **235** would be processed through a Michael addition to give **236**. The linker would be cleaved under conditions that do not degrade the product and the aldol reaction would be tested affording **237** (Figure **17**).

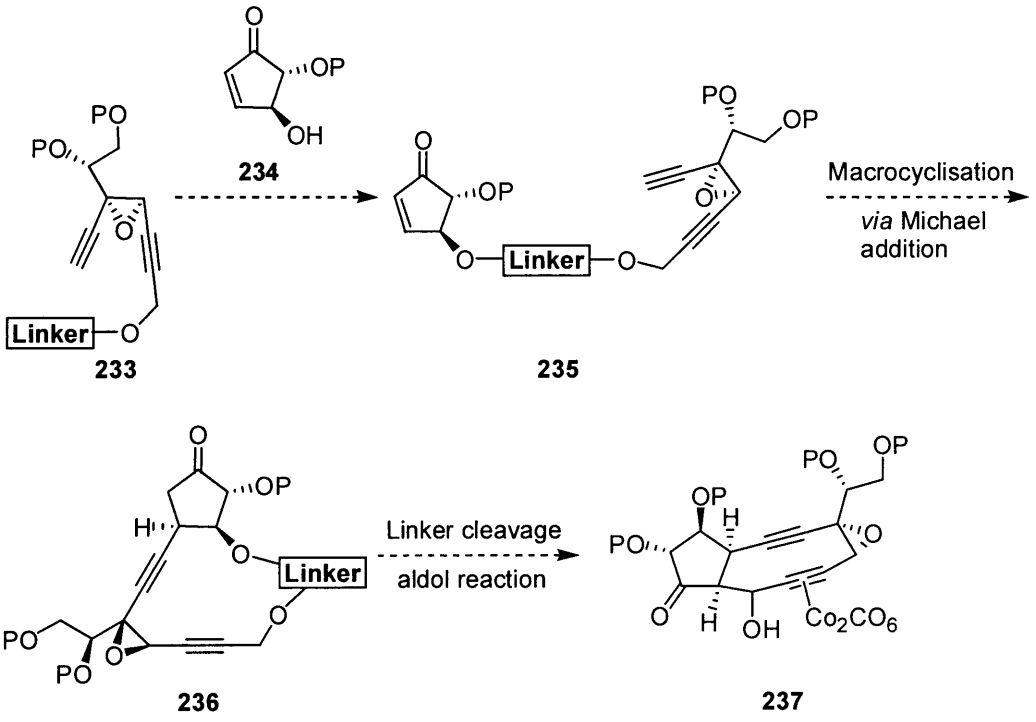
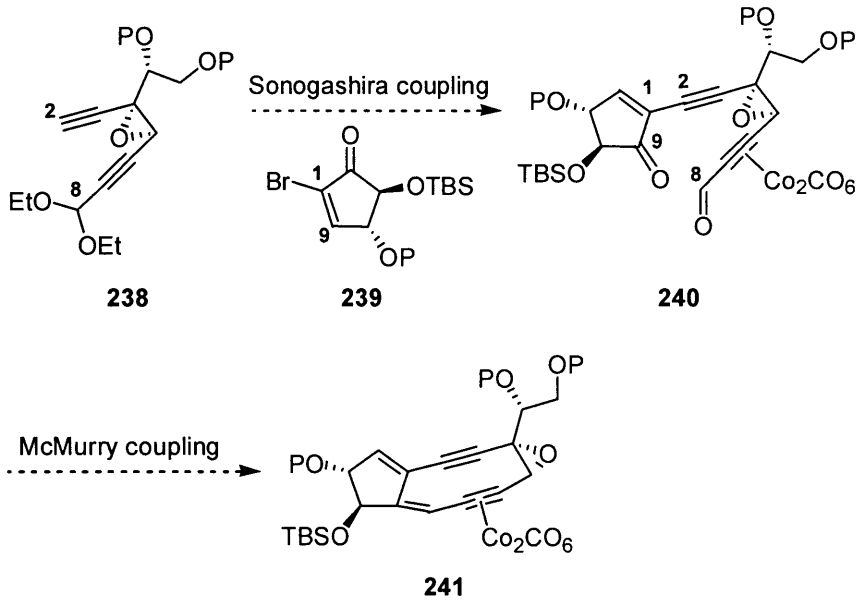


Figure 17. Intramolecular Michael /aldol sequence.

2.7.2 Other strategies

Our synthons would be coupled using other approaches to give the core of NCS-C. The first sequence involves a Sonogashira coupling between **238** and **239** at *C*1-*C*2 to give **240**. This would be followed by a macrocyclisation through a McMurry coupling affording **241** (Figure **18**).



238 **239** **240** **241**

Figure 18. Sonogashira/McMurry coupling.

The second sequence requires the synthesis of the synthon **242**. **242** would be coupled to the cyclopentenone **239** *via* a Sonogashira coupling followed by phosphorane preparation to give the Wittig precursor **243**. **244** would then be generated by mean of a Wittig olefination (Figure **19**).

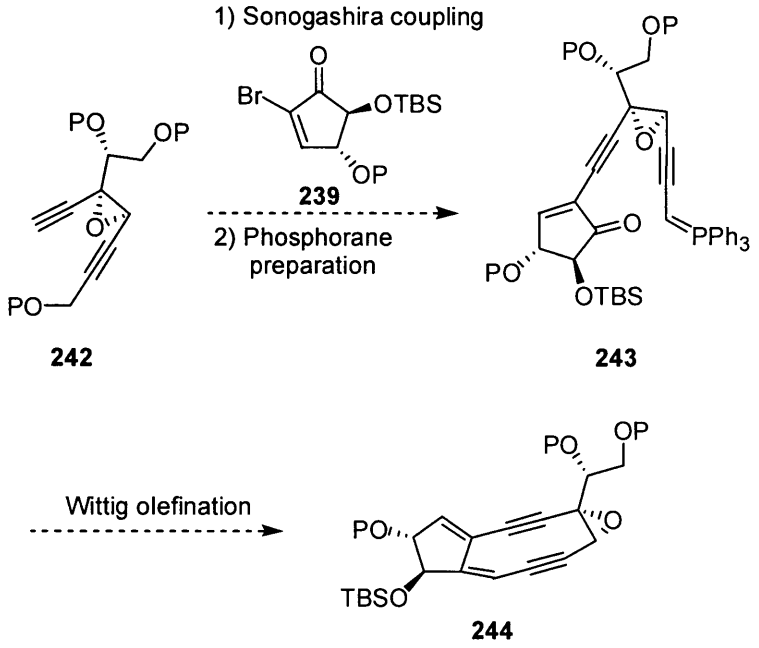


Figure 19. Wittig/Sonogashira sequence.

2.7.3 Model study towards the Kedarcidin chromophore

Kedarcidin chromophore is another antitumour antibiotic whose structure is related to NCS-C.[63] In the proposed strategy, it is anticipated to test the useful application of the allenyl zinc reaction to form the *C*8-*C*9 bond (Figure **20**). Inspired by Hirama et al.[18] conditions, Sonogashira coupling of **245** with **246** would lead to the adduct **247**. **247** would then react with **155** in a Darzens-type reaction to give **248**. Finally, the *C*4-*C*5 double bond would be generated by a Barbier-Grignard reaction followed by elimination to afford the core structure **249** of the Kedarcidin chromophore.

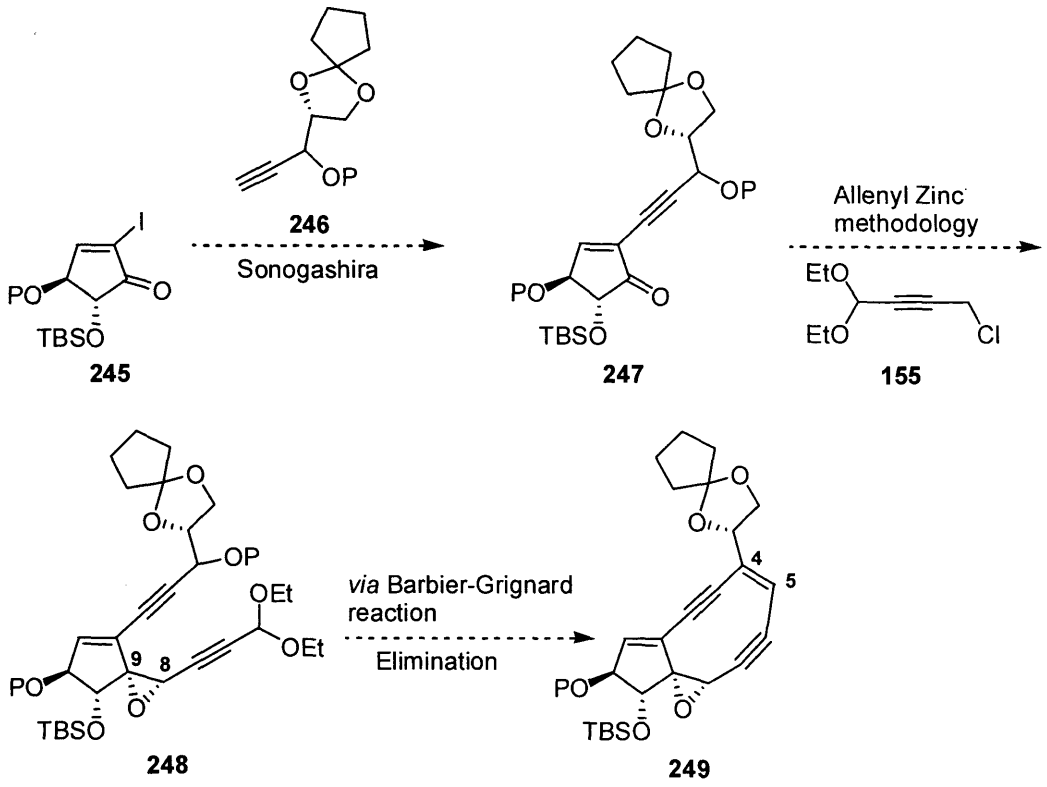


Figure 20. Model study towards the kedarcidin chromophore.

3 CONCLUSIONS

The development of a general and new strategy towards epoxydiynes proved to be extremely difficult. Our early strategies were built from the work of Myers, Hirama and Bruckner and turned to be rather long and linear. They led to the generation of unstable intermediates which could not be processed to the fully elaborated epoxydiyne **73**. After considerable investigation studies, a concise and convergent approach to epoxydiynes was discovered and applied efficiently on a multi-gram scale. This involves a diastereoselective addition of an allenyl zinc bromide to propargylic ketone/aldehyde followed by epoxide formation. From this method, known epoxydiynes have been successfully synthesised with the correct stereochemistry in good overall yield. Our sequence required only five steps from the D-mannitol derivative compared to Myers (10) and Hirama (9). The allenyl zinc protocol allowed the diastereoselective synthesis of our fully elaborated synthon **73**. This enabled us to release *C*2 and incorporate *C*8, key sites of our Michael/aldol strategy. Michael addition did not prove successful with our key epoxydiyne partly due to stability problem. However, the epoxydiyne **199** prove to be stable in the aluminium-catalysed conjugate addition. The next priority of the project should be to test this synthon for Michael addition studies. In their total synthesis of the NCS-C, Myers and Hirama have showed that the choice of specific protecting groups is critical for the success of a reaction. Owing to the flexibility of our new method, epoxydiynes with different protecting group can now be readily available enabling us to screen them for Michael addition studies or to pioneer alternative convergent strategies towards the core structure of the NCS-C. Studies are underway to complete the total synthesis of the NCS-C.

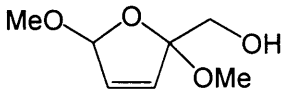
4 EXPERIMENTAL

General procedures:

Melting points were obtained using a Gallenkamp variable heater. Optical rotations were measured on a PolaAr 2000 polarimeter. Infrared spectra were recorded on a SHIMADZU FT-IR 8700 spectrometer. Data were presented as frequency of absorption (cm^{-1}). Proton and carbon NMR were measured on Bruker AMX300 spectrometer, or a Bruker AMX400 spectrometer or a Bruker AVANCE500 spectrometer. Chemical shifts were expressed in parts per million (δ) and are referenced to the residual solvent peak ($CHCl_3$, 7.26 and C_6D_5H, 7.15). The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet and br, broad. Coupling constants are recorded in Hertz. ^{13}C NMR chemical shift were referenced to resonances of the NMR solvent. Low and high resolution mass spectra were obtained from the mass spectroscopy service at Swansea. Flash chromatography was carried out on silica gel (32-70μm). Thin layer chromatography was performed on aluminium plates pre-coated with Merck silica gel 60 F_{254} and was visualised by exposure to UV and/or exposure to potassium permanganate or anisaldehyde followed by heating. Dimethyl (diazomethyl)phosphonate was visualised by exposure to iodine. All reactions were performed in flame-dried round bottom flasks and under positive pressure of argon unless otherwise noted. Commercial reagents and solvents were used as received with some exceptions. THF, Et_2O, CH_3CN and DCM were distilled through alumina column from an anhydrous engineering apparatus. Methanol was distilled from magnesium turnings and iodine. DMF was distilled from calcium hydride under reduced pressure. Hexamethyldisilazane, diisopropylamine, triethylamine, *n*-propylamine, diisopropylethylamine, dichloroethane were distilled from calcium hydride at 760 torr. Lithium hexamethyldisilazide (1M in THF/Hexanes) and lithium diisopropylamine (1M in THF/hexanes) were freshly prepared by the addition of *n*-butyllithium (freshly titrated) respectively to a solution of hexamethyldisilazide and diisopropylamine in THF. The molarity of n-BuLi (Acros) was determined by titration using dry [(1S)-endo]-(-)-Borneol and fluorene as indicator. $ZnBr_2$ 99.999% was purchased from Aldrich. $ZnBr_2$ (98%) from Aldrich was oven-dried prior to use. Furfuryl alcohol was distilled under reduced pressure from Na_2CO_3 and stored over molecular sieves 4Å. Molecular sieves 4Å was flame-

activated under reduced pressure at 10^{-3} Mbar. Ti (IV) isopropoxide was purchased from Fluka and distilled under reduced pressure at 10^{-3} Mbar and stored in a drybox. D-(-)-diethyl tartrate was distilled under reduced pressure at 10^{-3} Mbar and stored under argon. Anhydrous *tert*-butyl hydroperoxide (TBHP) was prepared as described: 2 L of aqueous 70% TBHP and 2 L of DCM were shaken twice in a separating funnel. The organic phase was transferred to a 5 L round bottom flask equipped with a condenser and few boiling chips. The mixture was gently refluxed using a heating mantle for 5 days. Water and DCM were distilled out and periodically DCM was added to maintain the volume constant in the flask (ca. 2.5 L). The solution was transferred to high density polyethylene bottle and stored over 250 g of activated molecular sieves 4Å at 4 °C. **CAUTION: EXPLOSIVE; heating must be done in a hazard laboratory and behind a blast shield.** The molarity of TBHP was determined by iodometric titration. Tetrakis(triphenylphosphine)palladium(0) purchased from Strem Chemicals, Inc. and Lipase AK "Amano" 20 purchased from Amano Enzyme Inc. were both stored at -20 °C.

2-Hydroxymethyl-2,5-dimethoxy-3,4-dihydrofuran 78[72b]



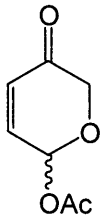
A solution of bromine (136.9 g, 860 mmol) in methanol (239 mL) was slowly added to a stirred solution of furfuryl alcohol (70.4 g, 718 mmol) in a mixture of dry Et_2O (239 mL) and methanol (239 mL) at -40 °C. Stirring was then continued for a further 2 hours at -40 °C. The resulting light yellow solution was saturated with gaseous ammonia at -70 °C to pH 8 and allowed to warm to ambient temperature. The resulting yellow suspension was filtered, removing ammonium bromide and concentrated *in vacuo*. Further filtration removed the white solid formed upon concentration of the yellow oil. The oil was diluted in benzene (500 mL) and filtered through neutral alumina. Evaporation of the solvent yielded **78** (102.6 g, 91%) as a yellow oil which was seen to be of sufficient purity for use in further stages.

νmax (cm^{-1}) 3473, 2988, 2837, 1632;

^1H (300MHz, $CDCl_3$) δ_H 6.04 (d, 1H, *J* 4.7, CH_{alkene}), 5.93 (dd, 1H, *J* 4.7, 0.9, CH_{alkene}), 5.48 (d, 1H, *J* 0.9, CHOMe), 3.69-3.52 (m, 2H, CH_2OH), 3.38 (s, 3H, CH_3), 3.09 (s, 3H, CH_3), 1.95 (br s, 1H, OH);

^{13}C (75MHz, $CDCl_3$) δ_C 132.2 (CH), 131.3 (CH), 112.9 (CH), 107.3 (CH), 66.6 (CH_3), 56.2 (CH_3), 50.4 (CH_2).

6-Acetoxy-2,3-dihydro-6H-pyrano-3-one 79[72b]



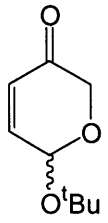
To 2-hydroxymethyl-2,5-dimethoxy-3,4-dihydrofuran **78** (71.4 g, 0.72 mol) in THF (700 mL) and H_2O (25 mL) cooled to 0 °C was added triflic acid (16.6 g, 0.11 mol) producing a dark colouration. The reaction mixture was stirred at 0 °C for 3 h, after which time acetic anhydride (292 g, 2.86 mol) and sodium acetate (235 g, 2.86 mol) were added. The reaction was allowed to warm to room temperature and stirred for 18 h, after which time the resulting orange solution was filtered under vacuum to remove any residual solid. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (500 mL) and additional solid $NaHCO_3$ (30 g) until effervescence ceased. The mixture was extracted in Et_2O (2 x 1 L), dried over magnesium sulfate, filtered and concentrated *in vacuo* (cold bath) to yield an orange oil. Flash column chromatography eluting with EtOAc (15%)/PE gave the desired product **79** (77.4 g, 69%) as a yellow oil.

νmax (cm^{-1}) 2979, 1707, 1700, 1630, 1264, 998;

^1H (300 MHz, $CDCl_3$) δ_H 6.95 (dd, 1H, *J* 11.1, 3.6, CH_{alkene}), 6.47 (d, 1H, *J* 11.1, CH_{alkene}), 6.32 (d, 1H, *J* 3.6, CHOAc) 4.51 (d, 1H, *J* 17.4, CH_2), 4.23 (d, 1H, *J* 17.4, CH_2), 2.15 (s, 3H, CH_3);

^{13}C (75 MHz, $CDCl_3$) δ_C 193.8 (C=O), 169.9 (C=O), 142.7 (CH), 129.2 (CH), 87.0 (CH), 67.8 (CH_2), 21.3 (CH_3).

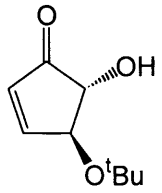
6-^{t}Butoxy-2,3-dihydro-6H-pyrano-3-one 80[72b]



A 1 M solution of tin (IV) chloride in DCM (6 mL, 6 mmol) was slowly added to a stirred solution of 6-acetoxy-2,3-dihydro-6H-pyrano-3-one **79** (17.6 g, 113 mmol) in dichloroethane (10 mL) and *tert*-butanol (53 mL, 550 mol). Stirring was continued at ambient temperature for 5 h, at which point the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (150 mL). The resulting mixture was extracted with ethyl acetate (500 mL), washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and H_2O (40 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with EtOAc (10%)/PE afforded the title compound **80** (17.1 g, 89%) as a colourless liquid.

vmax (cm^{-1}) 3056, 2979, 1707, 1630, 1392, 1266, 998;
^1H (300 MHz, $CDCl_3$) δ_H 6.64 (dd, 1H, *J* 10.2, 3.4, CH_{alkene}), 5.95 (d, 1H, *J* 10.2, CH_{alkene}), 5.33 (d, 1H, *J* 3.4, CHO*t*-butyl), 4.39 (d, 1H, *J* 16.9, CH_2), 3.91 (d, 1H, *J* 16.9, CH_2), 1.17 (s, 9H, $C(CH_3)_3$);
^{13}C (75 MHz, $CDCl_3$) δ_C 195.9 (C=O), 146.6 (CH), 127.6 (CH), 88.3 (CH), 74.7 (C), 66.5 (CH_2), 28.9 (3 x CH_3).

***trans*-[4-(1,1-Dimethylethoxy)-5-(hydroxy)]-2-cyclopenten-1-one 81**[84]

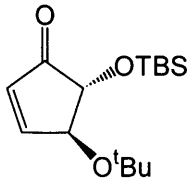


(+/-)

A stirred solution of pyranone **80** (42 g, 0.25 mol) in DMF (700 mL) and Et_3N (16 mL, 1.20 mol) was heated at 80 °C for 24 h. The black reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (30%)/PE gave the title compound **81** (32.8 g, 78%) as a white solid.

νmax (cm^{-1}) 3430, 2979, 1719, 1615, 1393, 1266, 922;
^1H NMR (300 MHz, $CDCl_3$) δ_H 7.28 (dd, 1H, *J* 6.1, 1.8, CH_{alkene}), 6.18 (d, 1H, *J* 6.1, CH_{alkene}), 4.56-4.53 (m, 1H, C*H*OH), 4.03 (d, 1H, *J* 2.2, CHO*t*-butyl), 3.42 (br s, 1H, OH), 1.25 (s, 9H, $C(CH_3)_3$);
^{13}C NMR (75 MHz, $CDCl_3$) δ_c 205.5 (C=O), 161.5 (CH), 131.3 (CH), 80.7 (CH), 76.4 (CH), 75.1 (C), 28.2 (3 x CH_3).

***trans*-[4-(1,1-Dimethylethoxy)-5-[[(1,1dimethylethyl)dimethylsilyl]oxy]]-2-cyclopenten-1-one 82**[84]

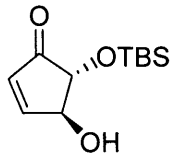


(+/-)

To the alcohol **81** (10.4 g, 61.2 mmol) stirring in DCM (240 mL) at 0 °C was added TBSCl (13.85 g, 92.0 mmol) followed by portionwise addition of imidazole (6.20 g, 92.0 mmol) after 10 minutes. The mixture was stirred for 2 h, after which time it was quenched with a saturated aqueous solution of NH_4Cl (50 mL) and extracted with DCM (2 x 100 mL). The organics were washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (2%)/PE afforded **82** (17.0 g, 97%) a colourless oil.

vmax (cm^{-1}) 2931, 2887, 2858, 1729, 1619, 1587, 1473;
^1H (300 MHz, $CDCl_3$) δ_H 7.19 (dd, 1H, *J* 6.3, 1.6, CH_{alkene}), 6.07 (d, 1H, *J* 6.3, CH_{alkene}), 4.5 (d, 1H, *J* 1.2, CHOTBS), 4.07 (d, 1H, *J* 2.9, CHO*t*Bu), 1.24 (s, 9H, $C(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si);
^{13}C (75 MHz, $CDCl_3$) δ_c 203.3 (C=O), 160.0 (CH), 132.3 (CH), 81.7(CH), 77.6 (CH), 75.3 (C), 28.8 (3 x CH_3), 26.2 (3 x CH_3), 18.8 (C), -3.8 (CH_3), -4.7 (CH_3);
HRMS $(M+H)^+$ cald. for $C_{15}H_{29}O_3Si$ 285.1886, found 285.1886.

***trans*-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]]-4-hydroxy]-2-cyclopenten-1-one 83**[84]



(+/-)

To a stirring solution of cyclopentenone **82** (17.0 g, 59 mmol) in DCM (170 mL) at -78 °C, was added a 1 M solution of $TiCl_4$ (66 mL, 66 mmol) over 5 min. The reaction was stirred for a further 5 min. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL), extracted with DCM (3 x 150 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with EtOAc (20%)/PE afforded **83** (11.6 g, 85%) as a white crystalline solid.

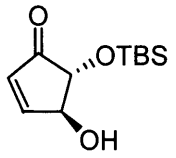
vmax (cm^{-1}) 3443, 2985, 2927, 2855, 1741, 1593, 1470, 1361, 1283, 1260, 1141, 1117, 1063, 1038, 871, 839, 774, 725;

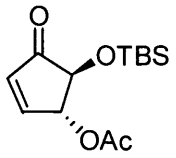
^1H (300MHz, $CDCl_3$) δ_H 7.18 (dd, 1H, *J* 6.3, 1.9, CH_{alkene}), 6.04 (dd, 1H, *J* 6.3, 1.2, CH_{alkene}), 4.60-4.56 (m, 1H, CHOTBS), 3.96 (d, 1H, *J* 2.7, C*H*OH), 2.16-2.14 (br. s, 1H, OH), 0.78 (s, 9H, $C(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$);

^{13}C (75MHz, $CDCl_3$) δ_c 203.0 (C=O), 158.9 (CH), 133.0 (CH), 82.7 (CH), 78.0 (CH), 26.2 (3 x CH_3), 18.8 (C), -4.1 (CH_3), -4.7 (CH_3);

HRMS $(M+H)^+$ cald. for $C_{11}H_{21}O_3Si$ 229.1260, found 229.1260.

(4S,5R)-4-Hydroxy-5-^{t}butyldimethylsilyloxy-cyclopenten-1-one 72 and (4R,5S)-4-acetoxy-5-^{t}butyldimethylsilyloxy-cyclopenten-1-one 84[74]





To **83** (5 g, 21.9 mmol) in benzene (20 mL), was added lipase Amano AK (3.57 g) followed by vinyl acetate (40 mL). The reaction was stirred at 34 °C for 15 h then filtered under reduced pressure and concentrated *in vacuo*. Flash column chromatography eluting with EtOAc (20%)/PE resulted in **72** (2.5 g, 50%) as a white solid and **84** (2.9 g, 49%) as a colourless oil.

72:

α_D^{22} +118 (*c* 1.14 in $CHCl_3$);

vmax (cm^{-1}) 3443, 2985, 1741;

^1H (300MHz, $CDCl_3$) δ_H 7.18 (dd, 1H, *J* 6.3, 1.9, CH_{alkene}), 6.04 (dd, 1H, *J* 6.3, 1.2, CH_{alkene}), 4.60-4.56 (m, 1H, CHOTBS), 3.96 (d, 1H, *J* 2.7, C*H*OH), 2.16-2.14 (br s, 1H, OH), 0.78 (s, 9H, $C(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$);

^{13}C (75MHz, $CDCl_3$) δ_C 203.0 (C=O), 158.9 (CH), 133.0 (CH), 82.7 (CH), 78.0 (CH), 26.2 (3 x CH_3), 18.8 (C), -4.1 (CH_3), -4.7 (CH_3).

84:

α_D^{22} -155 (*c* 1.02 in $CHCl_3$);

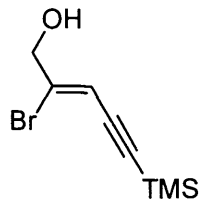
vmax (cm^{-1}) 2930, 2858, 1742, 1473, 1370;

^1H (300MHz, $CDCl_3$) δ_H 7.23 (dd, 1H, *J* 6.2, 1.7, CH_{alkene}), 6.17 (d, 1H, *J* 6.2, CH_{alkene}), 5.56-5.52 (m, 1 H, CHOAc), 4.15 (d, 1H, *J* 2.6, CHOTBS), 2.01 (s, 3H, $CH_{3acetate}$), 0.79 (s, 9H, $C(CH_3)_3$), 0.04 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$);

^{13}C (75MHz, $CDCl_3$) δ_C 203.2 (C), 171.9 (C), 157.0 (CH), 135.8 (CH), 80.5 (CH), 79.8 (CH), 27.3 (3 x CH_3), 22.5 (CH_3), 18.1 (C), -3.0 (CH_3), -3.6 (CH_3);

HRMS $(M+H)^+$ cald. for $C_{13}H_{23}O_4Si$ 271.1365, found *m/z* 271.1369.

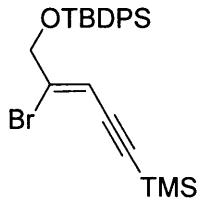
2-Bromo-5-trimethylsilanyl-pent-2-en-4-yn-1-ol 114[84]



To a solution of **87** (20.0 g, 72.6 mmol) in Et_2O (240 mL) at -78 °C was added dropwise a 1 M solution of DIBAL in toluene (145.2 mL, 145.2 mmol). The stirring was continued for 3 h at 0 °C until completion and then the reaction carefully quenched with saturated Rochelle salt solution (80 mL). The reaction mixture was stirred for a further 45 min and then extracted with Et_2O (3 x 100 mL), washed with brine (2 x 50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (10%)/PE gave the allylic alcohol **114** (16.4 g, 98%) as a colourless oil.

ν_{max} (film)/cm^{-1} 3591, 3350, 2960, 2852, 2142;
^1H NMR (300 MHz, $CDCl_3$) δ_H 6.36 (s, 1H, CH_{alkene}), 4.37-4.35 (m, 2H, CH_2), 2.11 (br. s, 1H, OH), 0.27 (s, 9H, CH_3);
^{13}C (75MHz, $CDCl_3$) δ_C 137.6 (CH_{alkene}), 110.9 (C_{alkene}), 102.3 (C), 100.8 (C), 67.8 (CH_2), 0.0 (3 x CH_3).

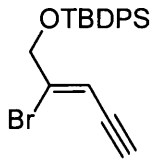
(1,1-Dimethylethyl)[(2-bromo-2-pentene-5-trimethylsilyl-4-ynyl)oxy]diphenylsilane 115[84]



To a solution of **114** (16.0 g, 69 mmol) in DMF (80 mL) at 0 °C was added successively imidazole (5.6 g, 83 mmol) and *t*-butyldiphenylsilylchloride (19.6 mL, 76 mmol). The reaction was stirred for 2 h and quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL). The reaction mixture was extracted with Et_2O (3 x 300 mL), washed with H_2O (2 x 100 mL) and brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (5%)/PE gave **115** (30.7 g, 95%) as a colourless oil.

ν_{max} (film)/cm^{-1} 3072, 2959, 2931, 2896, 2858, 2144;
^1H NMR (300 MHz, $CDCl_3$) δ_H 7.65-7.63 (m, 4H, CH_{Ar}), 7.47-7.37 (m, 6H, CH_{Ar}), 6.57 (s, 1H, CH_{alkene}), 4.31 (s, 2H, CH_2), 1.26 (s, 9H, CH_{3TBDPS}), 0.19 (s, 9H, CH_{3TMS});
^{13}C (75MHz, $CDCl_3$) δ_C 136.8 (CH_{alkene}), 136.4 (CH_{Ar}), 132.6 (CH_{Ar}), 130.2 (CH_{Ar}), 128.0 (CH_{Ar}), 109.1 (C_{alkene}), 101.4 (C), 101.3 (C), 68.0 (CH_2), 26.8 (3 x CH_{3TBDPS}), 19.4 (C_{TBDPS}), 0.0 (3 x CH_{3TMS}).

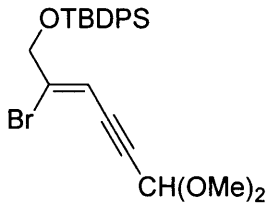
(1,1-Dimethylethyl)[(2-bromo-2-penten-4-ynyl)oxy]diphenylsilane 116[84]



To a solution of **115** (20.0 g, 42.4 mmol) in methanol (210 mL) was added K_2CO_3 (0.6 g, 4.2 mmol) and the reaction was stirred for 2 h. The mixture was concentrated *in vacuo* and then the residue was diluted with Et_2O (300 mL), washed with brine (2 x 50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (5%)/PE gave **116** (12.6 g, 75%) as a white solid.

ν_{max} (film)/cm^{-1} 3266, 2959, 2931, 2882, 2858, 2197;
^1H NMR (300 MHz, $CDCl_3$) δ_H 7.58-7.56 (m, 4H, CH_{Ar}), 7.41-7.30 (m, 6H, CH_{Ar}), 6.46-6.44 (m, 1H, CH_{alkene}), 4.25-4.24 (m, 2H, CH_2), 3.23 (d, 1H, *J* 2.2, CH_{alkyne}) 1.00 (s, 9H, CH_{3TBDPS});
^{13}C (75MHz, $CDCl_3$) δ_C 137.7 (CH_{alkene}), 135.8 (CH_{Ar}), 133.0 (CH_{Ar}), 130.5 (CH_{Ar}), 128.4 (CH_{Ar}), 108.5 (C_{alkene}), 83.7 (C), 80.4 (C), 68.3 (CH_2), 27.1 (3 x CH_{3TBDPS}), 19.7 (C_{TBDPS}).

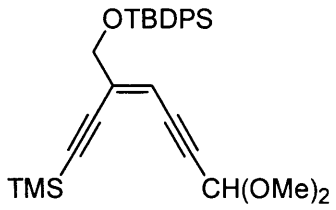
(1,1-Dimethylethyl)[(2-bromo-6,6-dimethoxy-2-hexen-4-ynyl)oxy]diphenylsilane 117[84]



A solution of **116** (10.0 g, 25 mmol) and $ZnCl_2$ (3.4 g, 25 mmol) in trimethylorthoformate (156 mL) in a Dean-Stark apparatus was heated at 160 °C for 10 h. The reaction mixture was allowed to cool to rt and then filtered through celite and washed with Et_2O (500 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography eluting with Et_2O (10%)/PE to give **117** (9.8 g, 83%) as a brown oil.

ν_{max} (film)/cm^{-1} 3082, 2955, 2931, 2892, 2828, 2225;
^1H NMR (300 MHz, $CDCl_3$) δ_H 7.58-7.55 (m, 4H, CH_{Ar}), 7.38-7.30 (m, 6H, CH_{Ar}), 6.52-6.51 (m, 1H, CH_{alkene}), 5.26 (d, 1H, *J* 1.5, $CH(OMe)_2$), 4.25 (d, 2H, *J* 1.5, CH_2), 3.37 (s, 6H, OCH_3) 0.99 (s, 9H, CH_{3TBDPS});
^{13}C (75MHz, $CDCl_3$) δ_C 137.9 (CH_{alkene}), 135.8 (CH_{Ar}), 132.9 (CH_{Ar}), 130.5 (CH_{Ar}), 128.3 (CH_{Ar}), 108.2 (C_{alkene}), 93.9 ($(MeO)_2CH$), 89.7 (C), 82.7 (C), 68.3 (CH_2), 53.1 (2 x CH_3), 27.1 (3 x CH_{3TBDPS}), 19.7 (C_{TBDPS}).

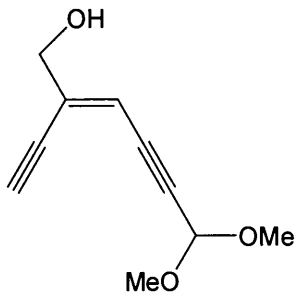
(1,1-Dimethylethyl)[(2-(2-(1,1,1-trimethylsilyl)ethynyl)-6,6-dimethoxy-2-hexen-4-ynyl)oxy]diphenylsilane 118[84]



A degassed solution of **117** (9.8 g, 20.7 mmol), *n*-propylamine (2.7 mL, 33.1 mmol) and trimethylsilylacetylene (4.4 mL, 31.0 mmol) in THF (200 mL) was added to a suspension of CuI (0.2 g, 1.8 mmol) and $(PPh_3)_2PdCl_2$ (0.6 g, 0.8 mmol) in THF (10 mL) and heated at 60 °C. The stirring was continued for 4 h and then the reaction allowed to cool to rt and quenched with a saturated aqueous solution of NH_4Cl (80 mL). The reaction mixture was extracted with Et_2O (3 x 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash chromatography eluting with (5%)/PE gave the title compound **118** (8.5 g, 80%) as a yellow oil.

ν_{max} (film)/cm^{-1} 3075, 2996, 2958, 2892, 2828, 2215;
^1H NMR (300 MHz, $CDCl_3$) δ_H 7.65-7.62 (m, 4H, CH_{Ar}), 7.45-7.35 (m, 6H, CH_{Ar}), 6.28-6.27 (m, 1H, CH_{alkene}), 5.34 (d, 1H, *J* 1.5, $CH(OMe)_2$), 4.22 (d, 2H, *J* 1.5, CH_2), 3.42 (s, 6H, OCH_3) 1.04 (s, 9H, CH_{3TBDPS}), 0.15 (s, 9H, CH_{3TMS});
^{13}C (75MHz, $CDCl_3$) δ_C 136.2 (CH_{alkene}), 135.7 (2 x CH_{Ar}), 133.1 (2 x CH_{Ar}), 130.2 (2 x CH_{Ar}), 128.2 (2 x CH_{Ar}), 128.1 (2 x CH_{Ar}), 112.7 (C_{alkene}), 103.9 (C), 100.8 (C), 93.9 ($(MeO)_2CH$), 90.1 (C), 83.8 (C), 65.3 (CH_2), 52.9 (2 x CH_3), 27.0 (3 x CH_{3TBDPS}), 19.5 (C_{TBDPS}), 0.0 (CH_{3TMS}).

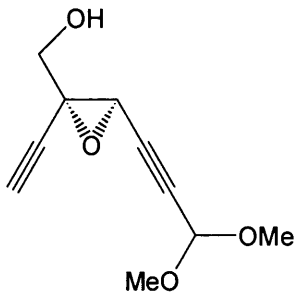
2-Ethynyl-6,6-dimethoxy-hex-2-en-4-yn-1-ol 112



To **118** (2.5 g, 8.5 mmol) in THF (15 mL) was added a 1 M solution of TBAF in THF (1.7 mL, 17.0 mmol) and the reaction was stirred for 1 h. The reaction mixture was then quenched with H_2O (5 mL) and extracted with Et_2O (2 × 10 mL), washed with brine (5 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (20%)/PE gave **112** (1.47 g, 96%) as a clear yellow oil.

ν_{max} (film)/cm^{-1} 3591, 3216, 2225, 2182, 1360;
^1H NMR (300 MHz, $CDCl_3$) δ_H 6.20 (s, 1H, CH_{alkene}), 5.42 (s, 1H, $(MeO_2)CH$), 4.33 (d, 2H, *J* 1.5, CH_2OH), 3.55 (br. s, 7H, 2 x CH_3 and H_{alkyne}), 2.41 (br. s, 1H, OH);
^{13}C (75MHz, $CDCl_3$) δ_C 128.0 (CH_{alkene}), 116.7 (C_{alkene}), 95.7 (CH_{alkyne}), 93.0 ($(MeO)_2CH$), 88.4 (C), 84.8 (C), 82.3 (C), 66.9 (CH_2), 54.9 (2 x CH_3);
HRMS $(M+H)^+$ cald. for $C_{10}H_{13}O_3$ 181.078, found *m/z* 181.081.

(2R,3S)-[3-(3,3-Dimethoxy-prop-1-ynyl)-2-ethynyl-oxiranyl]-methanol 119



To a suspension of activated powdered molecular sieves 4Å (1.3 g) in DCM (3.5 mL) cooled at -25 °C was added Ti(*i*-PrO)$_4$ (0.65 mL, 2.20 mmol) and D-(-)-diethyl tartrate (0.38 mL, 2.20 mmol) and the reaction mixture was stirred for 30 min. A prepared solution of 5.2 M of *tert*-butyl hydroperoxide in DCM (7 mL, 37.8 mmol) was added dropwise and the reaction was stirred for 10 min. The enediyne **111** (2.0 g, 11.0 mmol) was added dropwise then the reaction mixture was allowed to warm to -6 °C and stirred for 96 h. The reaction was quenched with a saturated solution of sodium thiosulfate (25 mL) and diluted with Et_2O (25 mL). The resulting precipitate was filtered through celite and washed with Et_2O (200 mL). The filtrate was extracted with Et_2O (3 x 50 mL), washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (10%)/PE gave the enantiomer **119** (200 mg, 10%) as a colourless oil.

α_D^{22} +21.1 (*c* 1.0 in $CHCl_3$);

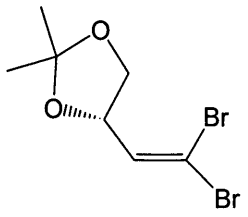
ν_{max} (film)/cm^{-1} 3425, 2202, 1630;

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.13 (s, 1H, $(MeO)_2CH$), 3.90 (d, 1H, *J* 13.0, C*H*$_2$OH), 3.79 (d, 1H, *J* 13.0, C*H*$_2$OH), 3.70 (s, 1H, H_{alkyne}), 3.30 (s, 6H, CH_3), 2.45 (s, 1H, CH_{epoxy}), 1.80 (br. s, 1H, OH);

^{13}C (75MHz, $CDCl_3$) δ_C 93.2 ($(MeO)_2CH$), 81.3 (C), 80.1 (C), 77.0 (C), 76.2 (CH_{alkyne}), 62.3 (CH_2), 57.9 (C_{epoxy}), 53.1 (2 x CH_3), 48.3 (CH_{epoxy});

HRMS $(M+NH_4)^+$ cald. for $C_{10}H_{16}NO_4$ 214.1079, found *m/z* 214.1080.

(4S)-4-(2,2-Dibromo-vinyl)-2,2-dimethyl-[1,3]-dioxolane 131[89]



To a solution of 1,2-5,6-diisopropylidene-D-mannitol **92** (25.0 g, 95 mmol) in DCM (350 mL) and aqueous sodium bicarbonate (4 mL) was added portionwise sodium periodate (41.2 g, 190 mmol) over 20 min. Then the reaction mixture was stirred for 2 h and filtered through a pad of magnesium sulfate. DCM was then evaporated under vacuum (cold bath) to give the D-glyceraldehyde acetonide **34**.

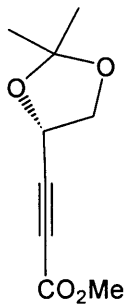
Meanwhile, to a solution of carbon tetrabromide (25.3 g, 77 mmol) in DCM (100 mL) at 0 °C, was added triphenylphosphine (40.3 g, 154 mmol). The reaction mixture was stirred for 30 min and a solution of **34** (24.7 g, 190 mmol) in DCM (250 mL) was added over a period of 30 min. Stirring was continued for 1 h and the suspension was then poured into PE (2 L) giving a precipitation of an orange/brown semi-crystalline mass. The supernatant liquid was decanted, and the resulting solid was washed with Et_2O (100 mL) and PE (100 mL). The filtrate was concentrated *in vacuo* to give an oil contaminated with triphenylphosphine oxide. Flash column chromatography eluting with Et_2O 3%/PE gave the vinyl dibromide **131** (7.09 g, 75%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.53 (d, 1H, *J* 7.6, CH_{alkene}), 4.72 (t, 1H, *J* 6.5, C*H*CH_2), 4.18 (dd, 1H, *J* 8.4, 6.3, CHC*H*$_2$), 3.68 (dd, 1H, *J* 8.4, 6.5, CHC*H*$_2$), 1.42 (s, 3H, CH_3), 1.38 (s, 3H, C*H*$_3$);

^{13}C (75MHz, $CDCl_3$) δ_C 137 (CH), 110.0 (C), 92.6 (CBr), 76.1 (CH), 68.0 (CH_2), 26.6 (CH_3), 25.6 (CH_3);

HRMS $(M+H)^+$ cald. for $C_7H_{11}O_2{}^{79}Br_2$ 284.91258, found *m/z* 284.91248.

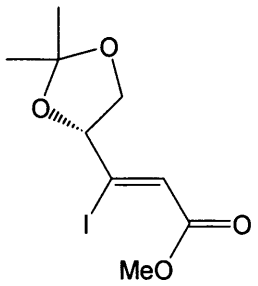
(4S)-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-propynoic acid methyl ester 120[89]



To a solution of dibromide **131** (10.0 g, 35.0 mmol) in THF (170 mL) at -78 °C was added *n*-BuLi (32.0 mL of a 2.3 M solution in hexanes, 73.4 mmol) over 30 min. The stirring was continued for 2 h and then methyl chloroformate (5.4 mL, 69.9 mmol) was added slowly. After stirring for 30 min, the reaction was warmed to rt and quenched with a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with Et_2O (3 x 150 mL), washed with brine (75 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (10%)/PE gave the title compound **120** (5.1 g, 79%) as a colourless oil;

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.80 (1H, dd, *J* 6.5, 5.5, C*H*CH_2), 4.18 (1H, dd, *J* 8.3, 6.5, CHC*H*$_2$), 4.02 (1H, dd, *J* 8.3, 5.5, CHC*H*$_2$), 3.77 (3H, s, CH_{3Ester}), 1.48 (3H, s, CH_3), 1.37 (3H, s, C*H*$_3$);
^{13}C (75MHz, $CDCl_3$) δ_C 153.4 (C=O), 111.2 (C), 84.8 (C), 76.7 (C), 69.2 (CH_2), 64.9 (CH), 52.8 (CH_3), 26.0 (CH_3), 25.7 (CH_3);
m/z 185 ($M+H^+$, 7%), 157, 137, 129, 111, 97, 83, 69, 61.

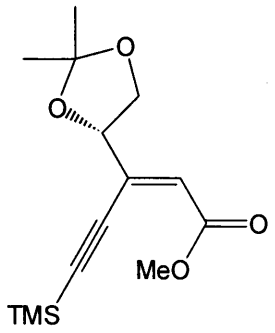
(4R)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-iodo-acrylic acid methyl ester 121



To a solution of **120** (1.00 g, 5.4 mmol) in acetonitrile (120 mL) at 175 °C was added sodium iodide (1.22 g, 8.1 mmol) and acetic acid (0.52 mL, 8.6 mmol). The stirring was continued for 90 min at this temperature and the reaction mixture was carefully poured into a mixture of a saturated solution of $NaHCO_3$ (50 mL) and Et_2O (150 mL). The resulting suspension was extracted with Et_2O (3 x 100 mL), washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (10%)/PE gave the vinyl iodide **121** (1.23 g, 95%) as a yellow oil.

α_D^{22} +40.1 (*c* 1.01 in $CHCl_3$);
ν_{max} (film)/cm^{-1} 2988, 2950, 2880, 1732, 1630, 1455, 1434, 1377;
^1H NMR (300 MHz, $CDCl_3$) δ_H 6.87 (d, 1H, *J* 1.6, CH_{alkene}), 4.74 (t, 1H, *J* 6.8, C*H*CH_2), 4.34 (dd, 1H, *J* 8.6, 6.8, CHC*H*$_2$), 3.81 (dd, 1H, *J* 8.6, 6.8, CHC*H*$_2$), 3.76 (s, 3H, CH_{3Ester}), 1.47 (s, 3H, CH_3), 1.40 (s, 3H, CH_3);
^{13}C (75MHz, $CDCl_3$) δ_C 164.8 (C=O), 123.2 (CH_{alkene}), 118.5 (C_{alkene}), 111.7 (Me_2C), 82.9 (CH), 69.9 (CH_2), 51.7 (CH_{3ester}), 26.0 (CH_3), 25.8 (CH_3);
HRMS $(M+H)^+$ cald. for $C_9H_{14}O_4I$ 312.99368, found *m/z* 312.99371.
Anal. Cald for CH: C, 34.64; H, 4.20. Found: C, 34.37; H, 4.21.

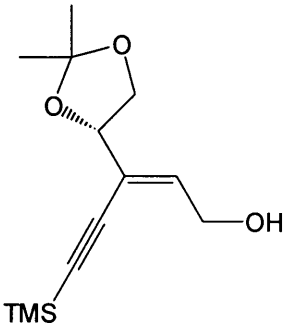
(4S)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-5-trimethylsilanyl-pent-2-en-4-ynoic acid methyl ester 127[47,86]



A degassed solution of **121** (3.0 g, 9.60 mmol), Et_3N (4.0 mL, 28.80 mmol) and trimethylsilylacetylene (1.9 mL, 13.50 mmol) in acetonitrile (75 mL) was added to a suspension of CuI (183 mg, 0.96 mmol) and $Pd(PPh_3)_4$ (555 mg, 0.48 mmol) in acetonitrile (10 mL) at rt. The reaction was continued for 2 h and a mixture of saturated aqueous solution of NH_4Cl (20 mL) and Et_2O (100 mL) was added. The reaction mixture was extracted with Et_2O (3 x 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (10%)/PE gave the title compound **127** (2.5 g, 91%) as a yellow oil.

α_D^{22} +32.6 (*c* 1.01 in $CHCl_3$);
^1H NMR (300 MHz, $CDCl_3$) δ_H 6.37 (d, 1H, *J* 1.5, CH_{alkene}), 4.61 (dt, 1H, *J* 6.8, 1.5, C*H*CH_2), 4.25 (dd, 1H, *J* 8.5, 6.8, CHC*H*$_2$), 3.92 (dd, 1H, *J* 8.5, 6.8, CHC*H*$_2$), 3.74 (s, 3H, CH_{3Ester}), 1.45 (s, 3H, CH_3), 1.41 (s, 3H, C*H*$_3$), 0.23 (s, 9H, SiC*H*$_3$);
^{13}C (75MHz, $CDCl_3$) δ_C (ppm) 165.2 (C=O), 136.9 (CH), 123.7 (C), 110.9 (C), 109.0 (C), 99.4 (C), 77.7 (CH), 69.1 (CH_2), 51.4 (CH_3), 26.2 (CH_3), 25.8 (CH_3), -0.4 (3 x CH_3);
HRMS $(M+H)^+$ cald. for $C_{14}H_{23}O_4Si$ 283.13656, found *m/z* 283.13657.

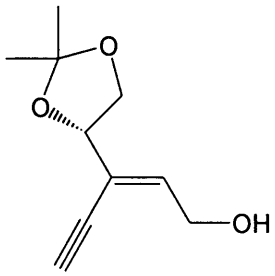
(4S)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-5-trimethylsilanyl-pent-2-en-4-yn-1-ol 132[47,86]



To a solution of **127** (2.5 g, 8.7 mmol) in THF (35 mL) at –78 °C was added dropwise a 1 M solution of DIBAL in toluene (21.8 mL, 21.8 mmol). The stirring was continued for 3 h until completion and then the reaction quenched with saturated Rochelle salt solution (10 mL). The reaction mixture was stirred for further 45 min and then extracted with Et_2O (2 x 30 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (40%)/PE gave the allylic alcohol **132** (2.2 g, 98%) as a yellow oil.

α_D^{22} +29.6 (*c* 2.07 in $CHCl_3$);
^1H NMR (300 MHz, $CDCl_3$) δ_H 6.25 (t, 1H, *J* 6.4, CH_{alkene}), 4.49 (t, 1H, *J* 6.8, C*H*CH_2), 4.40 (d, 2H, *J* 6.4, C*H*$_2$OH), 4.14 (dd, 1H, *J* 8.3, 6.8, CHC*H*$_2$), (dd, 1H, *J* 8.3, 6.8, CHC*H*$_2$), 1.62 (br. s, 1H, OH), 1.46 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 0.20 (s, 9H, CH_3Si);
^{13}C (75MHz, $CDCl_3$) δ_C 138.8 (CH), 123.7 (C), 110.2 (C), 103.0 (C), 99.2 (C), 78.0 (CH), 68.9 (CH_2), 61.3 (CH_2), 26.5 (CH_3), 26.2 (CH_3), 0.00 (3 x CH_3);
HRMS $(M+H)^+$ cald. for $C_{13}H_{23}O_3Si$ 255.1416, found *m/z* 255.1415.

(4S)-3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-pent-2-en-4-yn-1-ol 133



To a solution of **132** (200 mg, 0.8 mmol) in dry THF (5 mL) was added a 1 M solution of TBAF in THF (1.6 mL, 1.6 mmol) and the reaction stirred for 20 min. The reaction was poured into H_2O (2 mL). The mixture was extracted with Et_2O (3 x 15 mL) and the combined organics washed with brine (5 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O 50%/PE afforded **133** (122 mg, 85%) as a yellow oil.

α_D^{22} +17.1 (*c* 1.04 in $CHCl_3$, λ 589 nm);

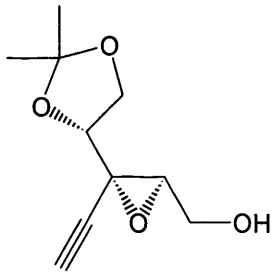
ν_{max} (film)/cm^{-1} 3411, 3284, 2987, 2940, 2882, 2361, 1457;

^1H NMR (300 MHz, $CDCl_3$) δ_H 6.33 (t, 1H, *J* 6.4, CH_{alkene}), 4.53 (dd, 1H, *J* 7.1, 6.4, C*H*CH_2), 4.42 (d, 2H, *J* 6.4, C*H*$_2$OH), 4.17 (dd, 1H, *J* 8.3, 6.4, CHC*H*$_2$), 3.90 (dd, 1H, *J* 8.3, 7.1, CHC*H*$_2$), 3.23 (s, 1H, H_{alkyne}), 1.67 (br s, 1H, OH), 1.47 (s, 3H, CH_3), 1.40 (s, 3H, CH_3);

^{13}C (75MHz, $CDCl_3$) δ_C 139.2 (CH_{alkene}), 122.6 (C), 110.2 (Me_2C), 84.8 (C), 78.1 (CH), 77.6 (CH), 68.7 (CH_2), 60.9 (CH_{2OH}), 26.3 (CH_3), 25.9 (CH_3);

HRMS $(M+H)^+$ cald. for $C_{10}H_{15}O_3$ 183.1021, found *m/z* 183.1022.

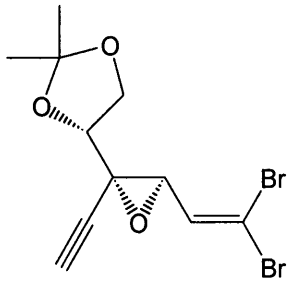
(2S,3S,4R)-[3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-ethynyl-oxiranyl]-methanol
134



To a suspension of activated powdered molecular sieves 4Å (2.3 g) in DCM (6 mL) cooled at -25 °C was added Ti(*i*-PrO)$_4$ (1.13 ml, 3.78 mmol) and D-(-)-diethyl tartrate (0.65 ml, 3.78 mmol) and the reaction mixture was stirred for 30 min. A prepared solution of 5.2 M of *tert*-butyl hydroperoxide in DCM (18 mL, 94.5 mmol) was added dropwise and the reaction was stirred for 10 min. **133** (3.447 g, 18.9 mmol) was then added dropwise and the reaction mixture was allowed to warm to -6 °C and stirred for 96 h. The reaction was quenched with a saturated aqueous solution of sodium thiosulfate (50 mL) and diluted with Et_2O (50 mL). The resultant precipitate was filtered through celite and washed with Et_2O (300 mL). The filtrate was extracted with Et_2O (2 x 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (40%)/PE gave **134** (3.2 g, 81%) as a colourless oil.

α_D^{22} +62.5 (*c* 1.1 in $CHCl_3$, λ 589 nm);
ν_{max} (film)/cm^{-1} 3452, 3271, 2987, 2921, 2889, 2119, 1377;
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.13 (dd, 1H, *J* 8.7, 6.3, C*H*$_2$CH), 4.04 (dd, 1H, *J* 8.7, 6.3, C*H*$_2$CH), 3.93 (t, 1H, *J* 6.3, CH$_2$C*H*), 3.90 (dd, 1H, *J* 12.4, 4.4, C*H*$_2$OH), 3.78 (dd, 1H, *J* 12.4, 6.2, C*H*$_2$OH), 3.28 (dd, 1H, *J* 6.2, 4.4, CH$_{epoxy}$), 2.67 (br s, 1H, OH), 2.45 (s, 1H, H$_{alkyne}$), 1.42 (s, 3H, CH_3), 1.31 (s, 3H, CH_3);
^{13}C (125 MHz, $CDCl_3$) δ_C (ppm) 110.8 (Me_2C), 77.2 (C), 76.6 (CH), 75.7 (CH$_{alkyne}$), 66.6 (CH_2), 61.7 (CH_{2OH}), 61.2 (CH$_{epoxy}$), 55.1 (C$_{epoxy}$), 26.05 (CH_3), 25.1 (CH_3);
HRMS (M+H)$^+$ cald. for $C_{10}H_{15}O_4$ 199.09703, found *m/z* 199.09602;
Anal calcd for CH: C, 60.59; H, 7.12. Found: C, 60.70; H, 7.12.

(2S,3S,4R)-4-[3-(2,2-Dibromo-vinyl)-2-ethynyl-oxiranyl]-2,2-dimethyl-[1,3]dioxolane 137



To **134** (0.50 g, 2.52 mmol) in DCM (13 mL) at 0 °C was added Dess-Martin periodinane (2.02 g, 5.04 mmol) in one portion. The stirring was continued at 0 °C for 30 min and the reaction mixture was poured into a mixture of a saturated aqueous solution of sodium thiosulfate (5 mL) and a saturated aqueous solution of $NaHCO_3$ (5 mL). Then Et_2O (100 mL) was added and the mixture stirred for 30 min. The mixture was extracted with Et_2O (3 x 50 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude epoxy-aldehyde **136** was seen to be of sufficient purity (without flash chromatography) for use in the next stage.

To a solution of carbon tetrabromide (1.68 g, 5.04 mmol) in DCM (50 mL) was added triphenylphosphine (1.32 g, 5.04 mmol) and the reaction mixture was stirred for 15 min at -78 °C. A solution of **136** and Et_3N (0.53 mL, 3.78 mmol) in DCM (30 mL) was added dropwise *via* cannula. The stirring was continued for 10 min and the reaction quenched with a saturated aqueous solution of $NaHCO_3$. The reaction mixture was extracted with DCM, washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting crude product was transferred on silica gel previously neutralised with 0.2% of Et_3N. Flash column chromatography eluting with Et_2O 10%/PE gave the epoxy-dibromoalkene **137** (0.47 g, 53%) as a colourless oil.

α_D^{22} +94 (*c* 1 in $CHCl_3$);

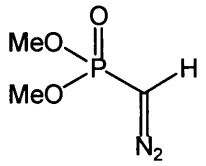
vmax (cm^{-1}) 3225, 2917, 2856, 2172, 1465;

^1H NMR (400 MHz, $CDCl_3$) δ_H 6.39 (d, 1H, *J* 7.9, CH_{alkene}), 4.15 (dd, 1H, *J* 10.4, 9.2, C*H*$_2$CH), 4.034 (dd, 1H, *J* 9.2, 5.7, CH_2CH), 4.032 (dd, 1H, 10.4, 5.7, C*H*$_2$CH), 3.78 (d, 1H, *J* 7.9, CH_{epoxy}), 2.50 (s, 1H, H_{alkyne}), 1.42 (3H, s, CH_3), 1.31 (s, 3H, CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 132.4 (CH_{alkyne}), 111.0 (Me_2C), 96.7 (CBr_2), 77.2 (C), 76.5 (C), 75.9 (CH), 66.8 (CH_2), 60.2 (CH_{epoxy}), 57.0 (C_{epoxy}), 26.2 (CH_3), 25.3 (CH_3);

HRMS $(M+H)^+$ cald. for $C_{11}H_{13}{}^{79}Br_2O_3$ 350.9231, found *m/z* 350.9230.

Dimethyl (diazomethyl)phosphonate 144[101]



To a solution of dimethyl methylphosphonate **142** (2.0 mL, 18.4 mmol) in THF (40 mL) was added a 2.3 M of a solution of *n*-BuLi in hexanes (8.0 mL, 18.4 mmol) dropwise at -78 °C and the reaction mixture was stirred for 30 min. 2,2,2-Trifluoroethyl trifluoroacetate (3.7 mL, 27.6 mmol) was added rapidly to the mixture. The stirring was continued for 15 min and warmed to rt. The reaction mixture was poured into a mixture of Et_2O (250 mL) and 3% of an aqueous solution of HCl (10 mL). The organic portion was washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and a saturated aqueous solution of NaCl (10 mL), dried over magnesium sulphate, filtered and concentrated *in vacuo* to give **143** as a pale yellow oil.

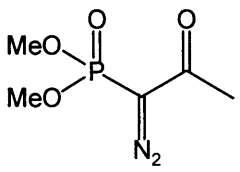
To a solution of 4-acetamidobemzenesulfonyl azide (3.97 g, 16.5 mmol) in CH_3CN (40 mL) was added the crude phosphonate **143** and the reaction was cooled to 0 °C. Et_3N (2.3 mL, 16.5 mmol) was added dropwise and the reaction was stirred for 12 h at rt. Concentration *in vacuo* gave the crude residue to which $CHCl_3$ (150 mL) was added. The mixture was filtered to remove the 4-acetamidobenzenesulfonamide which was washed with additional $CHCl_3$ (2 x 50 mL). Purification by flash coulumn chromatography eluting with EtOAc (100%) gave **144** (812 mg, 33%) as a yellow oil.

νmax (cm^{-1}) 3070, 2940, 2850, 2100, 1765, 1657;

^1H NMR (300 MHz, $CDCl_3$) δ_H 4.49 (d, 1H, $^2J_{H\text{-}P}$ 10.7 Hz, PCH); 3.74 (d, 6H, $^3J_{H\text{-}P}$ 11.5 Hz, $POCH_3$);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 59.1 ($C{=}N_2$), 53.5 (d, $^3J_{C,P}$ 5.8 Hz, OCH_3 x 2).

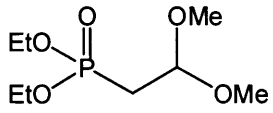
Dimethyl 1-diazo-2-oxoalkylphosphonate 146[103]



To a solution a suspension NaH (75.6 mg, 3.1 mmol) in benzene (9 mL) and THF (1.5 mL) was added dimethyl 2-oxopropylphosphonate **145** (0.42 mL, 3.0 mmol) at 0 °C and the reaction was stirred for 1 h. A solution of tosyl azide (623 mg, 3.1 mmol) in benzene (1.5 mL) was added and the reaction was warmed to rt. Stirring was continued for 2 h and the mixture filtered through celite and concentrated *in vacuo*. Purification by flash column chromatography eluting with EtOAc (50%)/PE gave **146** (467 mg, 81%).

vmax (cm^{-1}) 2950, 2849, 2221, 2120, 1736, 1652;
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.81 (d, 6H, $^{3}J_{H\text{-}P}$ 11.9 Hz, OCH_3), 2.24 (s, 3H, CH_3);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 190.3 (d, $^{2}J_{C,P}$ 3.2 Hz, C=O), 60.8 (br, $C=N_2$), 54.0 (d, $^{3}J_{C,P}$ 5.8 Hz, 2 x OCH_3), 27.5 (CH_3).

(2,2-Dimethoxy-ethyl)-phosphonic acid dimethyl ester 150



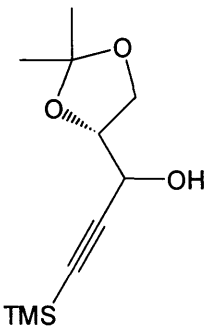
To a solution of trimethyl phosphite (10 mL, 85 mmol) was added bromo-1,1-dimethoxyethane (10 mL, 85 mmol) at 130 ^{0}C and the reaction was stirred for 2 h. Purification by flash column chromatography eluting with EtOAc (70%)/PE gave **150** as a colourless oil.

νmax (cm^{-1}) 2980, 2870;

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.63 (dd, 1H, *J* 10.9, 5.6, CH), 3.92 (q, 4H, *J* 7.15, CH_2O), 3.18 (s, 6H, CH_3O), 2.02 (dd, 2H, *J* 18.7, 5.6, CH_2P), 1.18 (t, 6H, *J* 6.8, CH_{3Et});

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 99.8 (CH), 61.5 (CH_2), 52.7 (2 x CH_3), 31.5 (CH_2), 29.7 (CH_2), 16.2 (2 x CH_3).

(4R)-2,2-Dimethyl-[1,3]dioxolane-4-yl)-3-trimethylsilanyl-prop-2-yn-1-ol 172[51a]



To a solution of 1,2-5,6-diisopropylidene-D-mannitol **92** (25.0 g, 95 mmol) in DCM (350 mL) and aqueous sodium bicarbonate (4 mL) was added portionwise sodium periodate (41 g, 190 mmol) over 20 min. Then the reaction mixture was stirred for 2 h and filtered through a pad of magnesium sulfate. DCM was then evaporated under vacum in a cold bath (28 °C) to give the D-glyceraldehyde acetonide **34**.

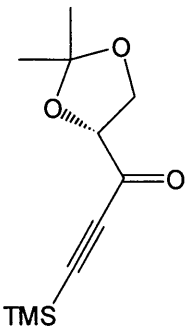
Meanwhile to a solution of trimethylsilylacetylene (32 mL, 228 mmol) in THF (900 mL) was added freshly made lithium hexamethyldisilazide (209 mL, 209 mmol) at -78 °C. The reaction mixture was stirred for 30 min and a solution of **34** (24.7 g, 190 mmol) in THF (250 mL) was added over a period of 30 min. The reaction was stirred for 30 min and quenched with a saturated aqueous solution of NH_4Cl (150 mL). The reaction mixture was concentrated *in vacuo* to a volume of approximately 300 mL and diluted with EtOAc (300 mL). The mixture was washed with a saturated aqueous solution of NH_4Cl (250 mL) and H_2O (250 mL), and the combined aqueous portions were extracted with EtOAc (150 mL). The organics were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography in EtOAc (20%)/PE afforded the inseparable diastereomeric propargylic alcohols **172** (1.2:1, 35.4 g, 81%) as a pale yellow oil.

vmax (cm^{-1}) 3434, 2990, 2962, 2252, 1456, 1374;

^1H NMR (300 MHz, $CDCl_3$) δ_H 4.33-3.71 (m, 4H, C*H*$_2$O-C*H*O-C*H*OH), 2.64 (br. s, 1H, O*H*, **major** only), 2.50 (br. s, 1H, O*H*, **minor** only), 1.28 (3H, s, CH_3), 1.21 (s, 3H, CH_3), 0.00 (s, 9H, $SiCH_3$);

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 110.8 (Me_2C), 110.4 (Me_2C), 102.7 (C), 102.6 (C), 91.7 (C), 91.6 (C), 79.1 (CH_{OH}), 78.1 (CH_{OH}), 66.5 (CH_2), 65.4 (CH_2), 65.1 (CH), 63.0 (CH), 27.1 (CH_3), 26.6 (CH_3), 25.6 (2 x CH_3), 0.4 (6 x CH_3);
HRMS $(M+NH_4)^+$ cald. for $C_{11}H_{24}NO_3Si$ 246.1520, found *m/z* 246.1517.

(4R)-1-(2,2)-Dimethyl-[1,3]dioxolan-4-yl)-3-trimethylsilanyl-propynone 35[51a]



Method A: To pyridinium dichromate (66.0 g, 175.2 mmol) and crushed 3Å molecular sieves (40 g) in DCM (150 mL) was added dropwise a solution of propargylic alcohol **172** (20 g, 87.6 mmol) in DCM (75 mL) and the reaction mixture was stirred for 4 h. Celite (40 g) was then added and the suspension was stirred for 30 min. The reaction mixture was then filtered through a plug of celite and diluted with Et_2O (400 mL). The filtrate was washed with saturated aqueous potassium hydrogen sulfate (3 x 100 mL), saturated aqueous $NaHCO_3$ (100 mL) and brine (2 x 50 mL), then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (25%)/PE afforded the ynone **35** (16.2 g, 82%).

Method B: To **172** (5.1 g, 22 mmol) in DCM (110 mL) at 0 °C was added Dess-Martin periodinane (18.2 g, 44 mmol) in one portion. The stirring was continued at rt for 6 h and the reaction mixture was poured into a mixture of a saturated aqueous solution of sodium thiosulfate (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). Then Et_2O (150 mL) was added and the mixture stirred for 30 min. The mixture was extracted with Et_2O (2 x 100 mL), washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (25%)/PE afforded the ynone **35** (4.7 g, 95%). Alternatively the crude propargylic ketone, which was seen to be of sufficient purity (without flash chromatography) for use in further stages, was stored at -20 °C in dry THF for later use.

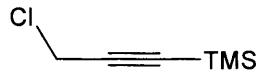
vmax (cm^{-1}) 2989, 2963, 2902, 2153, 1677, 1373;

^1H NMR (300 MHz, $CDCl_3$) δ_H 4.28 (1H, dd, *J* 7.4, 5.0, C*H*CH_2), 4.0 (1H, dd, *J* 8.8, 7.4, CHC*H*$_2$), 3.91 (1H, dd, *J* 8.8, 5.0, CHC*H*$_2$), 1.27 (3H, s, C*H*$_3$), 1.15 (3H, s, C*H*$_3$), 0.00 (9H, s, CH_3Si);

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 187.5 (*C*=O) 112.8 (C), 104.6 (C), 100.7 (C), 81.8 (CH), 67.8 (CH_2), 27.0 (CH_3), 26.3 (CH_3), 0.0 (3 x CH_3);

HRMS $(M+NH_4)^+$ cald. for $C_{11}H_{22}NO_3Si$ 244.1363, found *m/z* 244.1363.

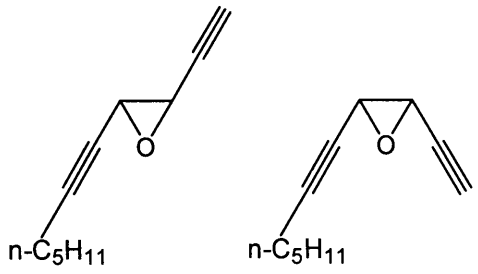
(3-Chloroprop-1-ynyl)trimethylsilane 156[107]



To propargyl chloride (5.0 mL, 69 mmol) in THF (200 mL) at -78 °C was added dropwise a 1.4 M solution of *n*-BuLi in hexane (25 mL, 35 mmol) over 2 h. TMSCl (8.8 mL, 69 mmol) was then added dropwise and the solution allowed to warm to rt and stirred for 1 h. The reaction mixture was quenched with H_2O (200 mL), then Et_2O (200 mL) was added. The aqueous layer was washed with Et_2O (2 × 200 mL) and the combined organic extracts washed with H_2O (100 mL), brine (100 mL), and dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification *via* distillation (bp 135 °C) gave **156** (4.8 g, 48%) as a colourless oil.

ν_{max}(film)/cm^{-1} 2962, 2183, 1269, 1029;
^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.13 (s, 2H, CH_2), 0.18 (s, 9H, CH_3);
^{13}C NMR (75 MHz; $CDCl_3$) δ_C 99.6 (C), 91.8 (C), 30.7 (CH_2), -0.4 (3 x CH_3).

2-Ethynyl-3-hept-1-ynyl-oxirane 170 and 171[107]



170 (+/-)

171 (+/-)

To $ZnBr_2$ (0.306 g, 1.36 mmol) in THF (1 mL) at -20 °C was added **156** (0.100 g, 0.68 mmol), then the mixture cooled to -78 °C and freshly prepared LDA (1.36 mmol) in THF (3 mL) was added. The mixture was stirred for 1 h then 2-Octynal (0.093 g, 0.75 mmol) was added. The stirring was continued for 1 h at -78 °C and the reaction was warmed to -30 °C and stirred for 45 min. The reaction was poured into a mixture of a saturated aqueous solution of NH_4Cl (5 mL) and H_2O (20 mL) and then diluted with Et_2O (50 mL). The aqueous layer was washed with Et_2O (2 × 50 mL) and the combined organic extracts washed with H_2O (20 mL), brine (20 mL), dried over magnesium sulfate and filtered. Concentration *in vacuo* gave the crude chlorohydrins **168** and **169** to which DMF (3.5 mL) was added followed by addition of KF (2.73 mmol, 0.158 g) in one portion. The reaction mixture was stirred for 1 h and then quenched with H_2O (1 mL). The mixture was extracted with Et_2O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with $CHCl_3$ (50%)/PE afforded the crude desilylated chlorohydrins.

To the crude chlorohydrins in DCM (2.5 mL) was added DBU (3.4 mmol, 0.519 g) and the reaction mixture was stirred for 2 h. The mixture was poured on silica gel previously neutralised with DBU (0.1%) in PE. Flash column chromatography eluting with $CHCl_3$ (30%)/PE resulted in the inseparable diastereoisomeric epoxydiynes **170** and **171** (42 %, *trans* / *cis*: 5 / 3). Repeated column chromatography allowed a small amount of each diastereoisomer to be isolated for analysis.

ν_{max}(film)/cm^{-1} 3298, 2956, 2933, 2871, 2860, 2237, 2171, 1460, 1398, 1315;

***trans*-epoxydiyne (major) 170:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.50 (dt, 1H, *J* 2.0, 1.7, CH_{epoxy}), 3.43 (dd, 1H, *J* 2.0, 1.7, CH_{epoxy}), 2.33 (d, 1H, *J* 1.7, H_{alkyne}), 2.19 (td, 2H, *J* 7.1, 1.7, $CH_{2propargylic}$), 1.50 (m, 2H, CH_2), 1.32 (m, 4H, CH_2), 0.89 (t, 3H, *J* 7.3, CH_3);

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 86.0 (C), 79.0 (C), 74.9 (C), 72.4 (CH_{alkyne}), 47.3 (CH_{epoxy}), 46.7 (CH_{epoxy}), 30.9 (CH_2), 27.8 (CH_2), 22.1 (CH_2), 18.6 (CH_2), 13.9 (CH_3);

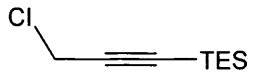
***cis*-epoxydiyne (minor) 171:**

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.54 (dt, 1H, *J* 3.8, 1.7, CH_{epoxy}), 3.50 (dd, 1H, *J* 3.8, 1.7, CH_{epoxy}), 2.43 (d, 1H, *J* 1.7, H_{alkyne}), 2.26 (td, 2H, *J* 7.1, 1.7, $CH_{2propargylic}$), 1.54 (m, 2H, CH_2), 1.38 (m, 2H, CH_2), 1.31 (m, 2H, CH_2), 0.89 (t, 3H, *J* 7.3);

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 87.7 (C), 78.2 (C), 77.2 (C), 73.9 (CH_{alkyne}), 46.6 (CH_{epoxy}), 46.1 (CH_{epoxy}), 30.8 (CH_2), 27.9 (CH_2), 22.1 (CH_2), 18.7 (CH_2), 13.9 (CH_3);

HRMS $(M+H)^+$ cald. for $C_{11}H_{15}O$ 163.11228, found *m/z* 163.11190.

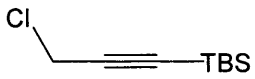
(3-Chloroprop-1-ynyl)triethylsilane 174[107]



To propargyl chloride (2.5 mL, 34.6 mmol) in THF (100 mL) at -78 °C was added a 1.4 M solution of *n*-BuLi in hexane (12.5 mL, 17.5 mmol) dropwise over 2 h. TESCl (5.8 mL, 34.6 mmol) was then added dropwise and the solution allowed to warm to rt and stirred for 1 h. The reaction mixture was quenched with H_2O (100 mL), then Et_2O (100 mL) was added. The aqueous layer was then washed with Et_2O (2 × 100 mL) and the combined organic extracts washed with H_2O (50 mL), brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with 100% PE gave **174** (2.4 g, 37%) as a colourless oil.

ν_{max}(film)/cm^{-1} 2959, 2179, 1029;
^{1}H NMR (300 MHz; $CDCl_3$) δ_H 4.15 (s, 2H, CH_2Cl), 0.99 (t, 9H, *J* 7.9, CH_3), 0.61 (q, 6H, *J* 7.8, CH_2);
^{13}C NMR (75 MHz; $CDCl_3$) δ_C 100.8 (C), 89.5 (C), 30.8 (CH_2), 7.3 (3 x CH_3), 4.1 (3 x CH_2).

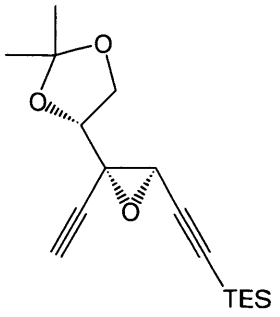
tert-Butyl-(3-Chloro-prop-1-ynyl)-dimethylsilane 175[107]



To propargyl chloride (5.0 mL, 69 mmol) in THF (200 mL) at -78 °C was added a 2.18 M solution of *n*-BuLi (16 mL, 35 mmol) dropwise over 2 h. A 2 M solution of TBSCl in THF (34.5 mL, 69 mmol)) was then added dropwise *via* cannula and the reaction was allowed to warm to rt and stirred for 1 h. The reaction was quenched with H_2O (200 mL), extracted with Et_2O (2 x 200 mL), washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with 100% PE gave 175 (5.5 g, 42%) as a colourless oil.

ν_{max} (cm^{-1}) 2916, 2198 1450, 1257, 1033, 817;
^1H NMR (300 MHz; $CDCl_3$) δ_H (300 MHz, $CDCl_3$) 4.14 (s, 2H, CH_2), 0.94 (s, 9H, $C(CH_3)_3$), 0.13 (s, 6H, CH_3);
^{13}C NMR (75 MHz; $CDCl_3$) δ_C 100.3 (C), 90.2 (C), 30.7 (CH_2), 25.9 (C), 16.4 (3 x CH_3), -4.8 (2 x CH_3).

(2S,3S,4R)-[3-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-3-ethynyl-oxyranylethynyl]triethyl-silane 16[107,47]



To $ZnBr_2$ (477 mg, 2.1 mmol) in THF (2 mL) at -20 °C was added **174** (200 mg, 1.1 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1M solution of LDA in THF (2.12 mL, 2.1 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone **35** (240 mg, 1.06 mmol) was then added quickly. Stirring was continued for 2 h at -78 °C and the reaction poured into a mixture of a saturated aqueous solution of NH_4Cl (5 mL) and H_2O (5 mL). The resulting mixture was allowed to warm to rt, extracted with Et_2O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with Et_2O (20%)/PE afforded the crude chlorohydrin.

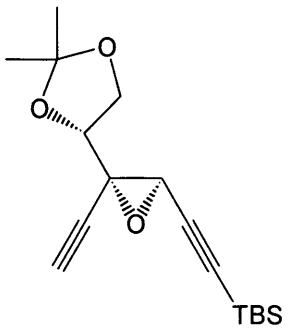
To the crude chlorohydrin in methanol (5 mL) at -10 °C was added K_2CO_3 (442 mg, 3.2 mmol). The stirring was continued for 4 h until completion and then a saturated aqueous solution of NH_4Cl (10 mL) was added. The reaction mixture was extracted with Et_2O (2 x 30 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (10%)/PE resulted in a pure epoxydiyne **16** (201 mg, 62%).

α_D^{22} +63 (*c* 1 in $CHCl_3$),
^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.21 (dd, 1H, *J* 8.6, 6.7, CHCH_2), 4.10 (dd, 1H, *J* 8.6, 6.2, CHCH_2), 4.05 (t, 1H, *J* 6.4, CHCH$_2$), 3.63 (s, 1H, H_{epoxy}), 2.47 (s, 1H, H_{alkyne}), 1.47 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 0.99 (t, 9H, *J* 7.8, CH_{3TES}), 0.61 (q, 6H, *J* 7.8, CH_{2TES});

^{13}C NMR (75 MHz, $CDCl_3$) δ_C 110.9 (C), 99.4 (C), 90.2 (C), 77.1 (C), 75.7 (CH), 75.4 (CH), 66.8 (CH_2), 57.8 (C), 49.8 (CH), 26.0 (CH_3), 25.1 (CH_3), 7.3 (3 x CH_3), 4.0 (3 x CH_2);

HRMS $(M+H)^+$ cald. for $C_{17}H_{27}O_3Si$ 307.1729, found *m/z* 307.1725.

(2S,3S,4R)-*tert*-Butyl-[3-(2,2-dimethyl-[1,3]dioxolan-4-yl)-3-ethynyl-oxyranylethynyl]dimethyl-silane 39[107,51]



To $ZnBr_2$ (238 mg, 1.06 mmol) in THF (2 mL) at -20 °C was added **175** (100 mg, 0.53 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (1.06 mL, 1.06 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone **35** (119 mg, 0.53 mmol) was then added quickly. Stirring was continued for 2 h at -78 °C and the reaction poured into a mixture of a saturated aqueous solution of NH_4Cl (5 mL) and H_2O (5 mL). The resulting mixture was allowed to warm to rt, extracted with Et_2O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with Et_2O (20%)/PE afforded a crude chlorohydrin.

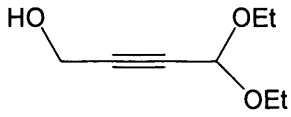
To the crude chlorohydrin in methanol (5 mL) at -10 °C was added K_2CO_3 (219 mg, 1.59 mmol). The stirring was continued for 4 h until completion and then a saturated aqueous solution of NH_4Cl (10 mL) was added. The reaction mixture was extracted with Et_2O (2 x 30 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (5%)/PE resulted in a pure epoxydiyne **39** (99 mg, 61%).

α_D^{22} +74 (*c* 1 in C_6H_6), ^1H NMR (400 MHz, C_6D_6) δ_H 3.99 (dd, 1H, *J* 8.8, 6.2, CHCH_2), 3.79 (dd, 1H, *J* 8.8, 6.6, CHCH_2) 3.64 (t, 1H, *J* 6.6, CHCH$_2$) 3.47 (s, 1H, H_{epoxy}), 1.98 (s, 1H, H_{alkyne}), 1.37 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.03 (s, 9H, $C(CH_3)_3$), 0.15 (s, 3H, CH_3), 0.14 (s, 3H, CH_3);

^{13}C NMR (100 MHz, C_6D_6) δ_C 110.7 (C), 100.5 (C), 90.6 (C), 78.1 (C), 76.7 (CH), 75.4 (CH), 66.8 (CH_2), 58.1 (C), 50.1 (CH), 26.2 (4 x CH_3), 25.4 (CH_3), 16.7 (C), -4.8 (2 x CH_3);

HRMS $(M+H)^+$ cald. for $C_{17}H_{27}O_3Si$ 307.1729, found *m/z* 307.1729.

4-Hydroxy-but-2-ynal diethyl acetal 180[112]



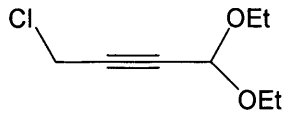
To a solution of (propargyloxy)trimethylsilane **179** (30.0 g, 234 mmol) in THF (150 mL) was added a 1 M solution of ethylmagnesium bromide in THF (234 mL, 234 mmol). The reaction was stirred for 30 min and a solution of phenyl orthoformate (41.8 g, 212 mmol) in THF (110 mL) was added. Stirring was continued for 16 h then the reaction quenched with a mixture of a saturated aqueous solution of NH_4Cl (200 mL) and H_2O (200 mL), extracted with Et_2O (2 x 200 mL), washed with NaOH (4 M solution, 3 x 100 mL) dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was then dissolved in methanol (530 mL) and K_2CO_3 (29.3 g, 212 mmol) was added at 0 °C and the mixture stirred for 10 min. The solution was concentrated *in vacuo* then H_2O (200 mL) was added. The mixture was extracted with EtOAc (3 x 150 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Distillation of the residue under vacuum (bp 88 °C; 1 mmHg) gave **180** (23.7 g, 70%) as a colourless oil.

ν_{max} (cm^{-1}) 3424, 1120;

^1H NMR (300 MHz, $CDCl_3$) δ_H 5.26 (d, 1H, *J* 1.3, $(EtO)_2CH$), 4.28 (dd, 2H, *J* 6.2, 1.3, CH_2OH), 3.70 (dq, 2H, *J* 7.2, 9.4, CH_{2Et}), 3.55 (dq, 2H, *J* 7.2, 9.4, CH_{2Et}), 2.30 (br s, 1H, OH), 1.19 (t, 6H, *J* 7.2, CH_3);

^{13}C NMR (300 MHz; $CDCl_3$) δ_C (75 MHz, $CDCl_3$) 91.6 (CH), 84.2 (C), 81.1 (C), 61.3 (CH_2), 51.1 (CH_2), 15.4 (CH_3).

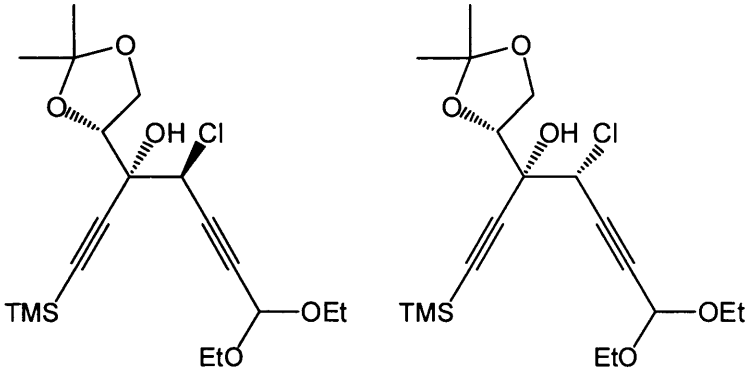
4-Chloro-1,1-diethoxy-but-2-yne 155[107]



To a solution of the alcohol **180** (10.0 g, 63 mmol) and Et_3N (26.4 mL, 190 mmol) in Et_2O (320 mL) was added dropwise methanesulfonyl chloride (5.5 mL, 70 mmol) at 0 °C. Stirring was continued for 1 h and then the reaction quenched with a saturated aqueous solution of $NaHCO_3$ (120 mL), extracted with Et_2O (2 x 60 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was dissolved in chloroform (310 mL) with tetra-n-butylammonium chloride (41.0 g, 126 mmol). The reaction was refluxed for 1 h. Concentration of the mixture *in vacuo* gave the crude residue to which Et_2O (200 mL) was added. The solution was washed with H_2O (100 mL), brine (2 x 100 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the pure propargylic chloride **155** as a yellow oil (8.9 g, 80%).

ν_{max} (cm^{-1}) 2971, 2901, 2888, 2238;
^1H NMR (300 MHz, $CDCl_3$) δ_H 5.23 (t app, 1H, *J* 1.3, $(EtO)_2CH$), 4.13 (d, 2H, *J* 1.3, CH_2Cl), 3.69 (dq, 2H, *J* 7.2, 9.3, CH_{2Et}), 3.53 (dq, 2H, *J* 7.2, 9.3, CH_{2Et}), 1.18 (t, 6H, *J* 7.2, CH_{3Et});
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 91.1 ($(EtO)_2CH$), 81.6 (C), 79.9 (C), 60.9 (2 x CH_{2Et}), 29.7 (CH_{2Cl}), 14.9 (2 x CH_{3Et});
HRMS $(M+H)^+$ cald. for $C_8H_{14}O_2Cl$ 175.0520, found *m/z* 175.0518.

(3R),(4S)-4-Chloro-3-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7,7-diethoxy-1-trimethylsilanyl-hepta-1,5-diyn-3-ol 185[107] and (3R),(4R)-4-Chloro-3-((4R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-7,7-diethoxy-1-trimethylsilanyl-hepta-1,5-diyn-3-ol 186[107]



***anti* 185** ***syn* 186**

To $ZnBr_2$ (255 mg, 1.1 mmol) in THF (2 mL) at -20 °C was added **155** (100 mg, 0.6 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (1.0 mL, 1.0 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone **35** (118 mg, 0.5 mmol) was then added quickly. Stirring was continued for 2 h at -78 °C and the reaction poured into a mixture of a saturated aqueous solution of NH_4Cl (5 mL) and H_2O (5 mL) then diluted with Et_2O (10 mL). The resulting mixture was allowed to warm to rt and filtered through celite, then extracted with Et_2O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with Et_2O (20%)/PE afforded the inseparable diastereoisomeric chlorohydrins **185** and **186** (363 mg, *anti*:*syn* 10:1, 60%) as a clear yellow oil.

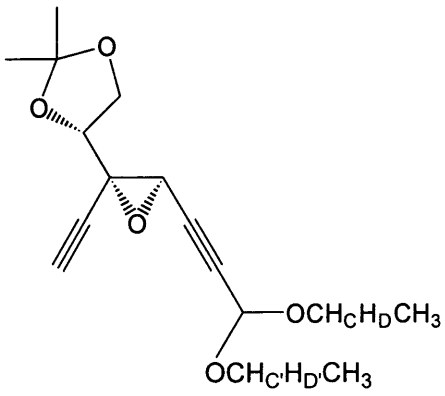
νmax (cm^{-1}) 3400, 2976, 2929, 2895, 2354, 2173, 1450;

^1H NMR (500 MHz, $CDCl_3$) δ_H 5.34 (d, 1H, *J* 1.3, $(EtO)_2CH_{syn}$), 5.32 (d, 1H, *J* 1.4, $(EtO)_2CH_{anti}$), 4.93 (d, 1H, *J* 1.4, $CHCl_{syn}$), 4.90 (d, 1H, *J* 1.4, $CHCl_{anti}$), 4.33 (dd, 1H, *J* 6.8, 5.8, $CHCH_{2anti}$), 4.32 (dd, 1H, *J* 6.8, 5.8, $CHCH_{2syn}$), 4.21 (dd, 1H, *J* 8.5, 5.8, $CHCH_{2anti}$), 4.16 (dd, 1H, *J* 8.5, 6.8, $CHCH_{2anti}$), 3.727 (dq, 1H, *J* 9.5, 7.1, $CH_{2Etanti}$), 3.722 (dq, 1H, *J* 9.5, 7.1, CH_{2Etsyn}), 3.59 (dq, 1H, *J* 9.5, 7.1, $CH_{2Etanti}$), 3.58 (dq, 1H, *J* 9.5, 7.1, CH_{2Etsyn}), 2.86 (s, 1H, OH_{anti}), 2.84 (s, 1H, OH_{syn}), 1.44 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.22 (t, 3H, *J* 7.2, CH_{3Et}), 1.21 (t, 3H, *J* 7.2, CH_{3Et}), 0.17 (s, 9H, $SiCH_3$);

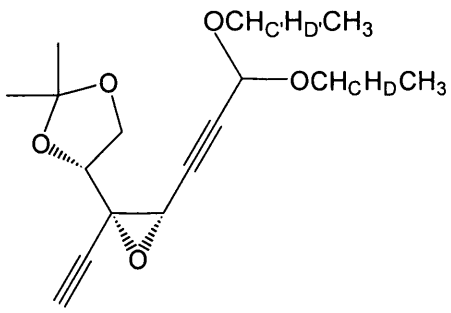
^{13}C NMR (125 MHz, $CDCl_3$) δ_C 110.4 (Me_2C_{anti}), 110.3 (Me_2C_{syn}), 101.5 (C_{anti}), 101.3 (C_{syn}), 93.6 (C_{syn}), 92.7 (C_{anti}), 90.99 ($(EtO)_2CH_{anti}$), 90.95 ($(EtO)_2CH_{syn}$), 84.1 (C_{anti}), 83.3 (C_{syn}), 80.3 (C_{syn}), 78.9 (C_{anti}), 77.6 (CH_{anti}), 76.3 (CH_{syn}), 74.9 (C_{OHanti}), 74.3 (C_{OHsyn}), 66.8 (CH_{2anti}), 66.3 (CH_{2syn}), 60.9 ($CH_{2Etanti}$), 60.8 (CH_{2Etsyn}), 60.8 (CH_{2Etsyn}) 60.9 ($CH_{2Etanti}$), 55.0 (CH_{Clanti}), 53.7 (CH_{Clsyn}), 26.2 (CH_{3anti}), 26.1 (CH_{3syn}), 25.2 (CH_{3anti}), 25.1 (CH_{3syn}), 14.914 ($CH_{3Etanti}$), 14.912 (CH_{3Etsyn}), -0.53 (3 x CH_{3anti}), -0.57 (3 x CH_{3ayn});

HRMS $(M+NH_4)^+$ cald. for $C_{19}H_{35}NO_5Cl$ 420.1968, found *m/z* 420.1970.

(2S,3S,4R)-4-[3-(3,3-Diethoxy-prop-1-ynyl)-2-ethynyl-oxyranyl]-2,2-dimethyl-[1,3]dioxolane 73[107] and 187[107]



trans **73**



cis **187**

To $ZnBr_2$ (255 mg, 1.1 mmol) in THF (2 mL) at -20 °C was added **155** (100 mg, 0.6 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (1.0 mL, 1.0 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone **35** (118 mg, 0.5 mmol) was then added quickly. Stirring was continued for 2 h at -78 °C and the reaction poured into a mixture of a saturated aqueous solution of NH_4Cl (5 mL) and H_2O (5 mL) then diluted with Et_2O (10 mL). The resulting mixture was allowed to warm to rt and filtered through celite, then extracted with Et_2O (20 mL), washed with brine (2 x 10 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude diastereoisomeric chlorohydrins.

To the crude chlorohydrins in DMF (3 ml) was added KF (263 mg, 2.0 mmol). The reaction mixture was stirred overnight and both ether (40 mL) and a saturated aqueous solution of NH_4Cl (30 mL) were added. The aqueous layer was washed with Et_2O (2 x 15 mL) and the combined organic extracts washed with H_2O (2 x 20 mL), brine (20 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with Et_2O (20%)/PE afforded the *trans*-epoxydiyne **73** (97 mg, 66%) and the *cis*-epoxydiyne **187** (10 mg, 7%).

α_D^{22} +30.2 (*c* 0.508 in $CHCl_3$, 589 nm, ***trans*-epoxydiyne**);

α_D^{22} -61.2 (*c* 1 in $CHCl_3$, 589 nm, ***cis*-epoxydiyne**);

vmax (cm^{-1}) 3201,2926, 2854, 2195, 2160,1399,1273,1210,1087;

***trans*-epoxydiyne:**

^1H NMR (500 MHz, $CDCl_3$) δ_H 5.29 (1H, d, *J* 1.1, $(EtO)_2CH$), 4.18 (1H, dd, *J* 10.8, 8.9, $CHCH_2$), 4.065 (1H, dd, *J* 10.8, 5.9, $CHCH_2$), 4.062 (1H, dd, *J* 8.9, 5.9, $CHCH_2$), 3.75 (1H, dq, *J* 9.6, 7.0, H_C), 3.73 (1H, dq, *J* 9.6, 7.0, $H_{C'}$), 3.68 (1H, dd, *J* 1.1, H_{epoxy}), 3.57 (2H, dq, *J* 9.4, 7.0, H_D and $H_{D'}$), 2.47 (1H, s, H_{alkyne}), 1.42 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.25 (3H, t, *J* 7.0, CH_{3Et}), 1.20 (3H, t, *J* 7.0, CH_{3Et});

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 111.0 (Me_2C), 91.0 ($(EtO)_2CH$), 81.8 (C), 78.8 (C), 77.0 (C), 75.6 (CH_{alkyne}), 75.4 (CH), 66.7 (CH_2) 61.1 (CH_{2Et}), 61.0 (CH_{2Et}), 57.7 (C_{epoxy}), 49.1 (CH_{epoxy}), 25.9 (CH_3), 25.0 (CH_3), 15.2 (CH_{3Et}), 15.0 (CH_{3Et});

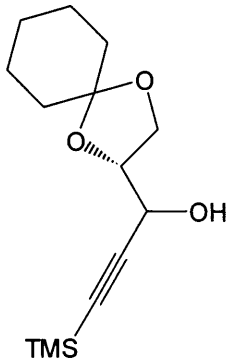
***cis*-epoxydiyne:**

^1H NMR (500 MHz, $CDCl_3$) δ_H 5.20 (1H, d, *J* 1.1, $(EtO)_2CH$), 4.12 (1H, dd, *J* 8.7, 6.3,$CHCH_2$), 4.11 (1H, dd, *J* 8.75, 6.3, $CHCH_2$), 3.98 (1H, t, *J* 6.2, $CHCH_2$), 3.71 (1H, d, *J* 1.1, H_{epoxy}), 3.64 (1H, dq, *J* 9.5, 7.0, H_C), 3.63 (1H, dq, *J* 9.5, 7.0, $H_{C'}$), 3.506 (1H, dq, *J* 9.5, 7.0, H_D), 3.502 (1H, dq, *J* 9.5, 7.0, $H_{D'}$), 2.38 (1H, s, H_{alkyne}), 1.42 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.14 (3H, t, *J* 7.0, CH_{3Et}), 1.13 (3H, t, *J* 7.0, CH_{3Et});

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 110.6 (Me_2C), 90.8 ($(EtO)_2CH$), 82.4 (C), 77.7 (C), 77.5 (C), 75.1 (CH), 73.8 (CH_{alkyne}), 66.5 (CH_2), 60.8 (CH_{2Et}), 60.7 (CH_{2Et}), 55.6 (C_{epoxy}), 51.4 (CH_{epoxy}), 25.9 (CH_3), 25.1 (CH_3), 14.8 (2 x CH_3);

HRMS $(M+NH_4)^+$ cald. for $C_{16}H_{26}NO_5$ 312.1805, found *m/z* 312.1805.

(2R)-1-(1,4-Dioxa-spiro[4.5]dec-2-yl)-3-trimethylsilanyl-prop-2-yn-1-ol 196



To a solution of 1,2-5,6-Di-O-cyclohexylidene-D-mannitol **194** (25.0 g, 73 mmol) in MeCN/H_2O (145 mL:95 mL) was added portionwise sodium periodate (31 g, 146 mmol) over 20 min and the reaction mixture was stirred for 2 h. The reaction mixture was extracted with ether, dried over magnesium sulfate and concentrated *in vacuo*. Meanwhile to a solution of trimethylsilylacetylene (24 mL, 175 mmol) in THF (900 mL) was added freshly made lithium hexamethyldisilazide (192 mL, 192 mmol) at –78 °C. The reaction mixture was stirred for 30 min and a solution of **195** (24.8 g, 146 mmol) in THF (250 mL) was added over a period of 30 min. The reaction was stirred for 30 min and quenched by the addition of saturated aqueous NH_4Cl (150 mL). The reaction mixture was concentrated *in vacuo* to a volume of approximately 300 mL and diluted with EtOAc (300 mL). The mixture was washed with a saturated aqueous solution of NH_4Cl (250 mL) and H_2O (250 mL), and the combined aqueous portions were extracted with EtOAc (150 mL). The organics were washed with brine (100 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography in EtOAc (20%)/PE afforded the inseparable diastereomeric propargylic alcohols **196** (1:1, 22.7 g, 58%) as a pale yellow oil.

νmax (cm^{-1}) 3431, 2932, 2903, 2853, 2173;

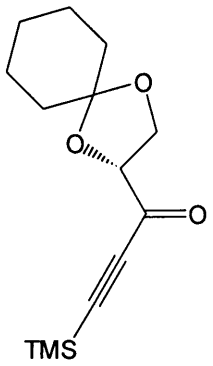
^1H NMR (300 MHz; $CDCl_3$) δ_H 4.35-3.71 (m, 4H, C*H*$_2$O-C*H*O-C*H*OH), 2.40 (1H, d, *J* 3.9, OH), 2.25 (1H, d, *J* 4.8, OH, other diastereoisomer), 1.51-1.29 (m, 10H, $CH_{2\,cyclohexyl}$), 0.01 (s, 9H, CH_3);

^{13}C NMR (75 MHz; $CDCl_3$) δ_C 111.4 ($C_{cyclohexyl}$), 111.0 ($C_{cyclohexyl}$), 102.6 (C), 102.5 (C), 91.8 (C), 91.7 (C), 78.7 (CH_{OH}), 77.7 (CH_{OH}), 66.1 (CH_2), 65.3 (CH_2), 65.0 (CH), 63.1 (CH), 36.8 ($CH_{2cyclohexyl}$), 36.2 ($CH_{2cyclohexyl}$), 35.1 ($CH_{2cyclohexyl}$), 35.0

($CH_{2cyclohexyl}$), 25.4 ($CH_{2cyclohexyl}$), 25.3 ($CH_{2cyclohexyl}$), 24.2 (2 x $CH_{2cyclohexyl}$), 24.0 (2 x $CH_{2cyclohexyl}$), 0.0 (6 x (CH_3));

HRMS $(M+H)^+$ cald. for $C_{14}H_{25}O_3Si$ 269.1567, found *m/z* 269.1570.

(2R)-1-(1,4-Dioxa-spiro[4.5]dec-2-yl)-3-trimethylsilanyl-propynone 197



Method A: To pyridinium dichromate (2.8 g, 7.5 mmol) and crushed 3Å molecular sieves (1.7 g) in DCM (7 mL) was added dropwise a solution of propargylic alcohol **196** (1.0 g, 3.7 mmol) in DCM (3.5 mL) and the reaction mixture was stirred for 4 h. Celite (2 g) was added and the suspension was stirred for 30 min. The reaction mixture was then filtered through a plug of celite and diluted with ether (100 mL). The filtrate was washed with saturated aqueous potassium hydrogen sulphate (3 x 5 mL), saturated aqueous $NaHCO_3$ (5 mL) and brine (2 x 10 mL), then dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (10%)/PE afforded the ynone **197** (0.512 g, 38%).

Method B: To **196** (5.0 g, 18.6 mmol) in DCM (93 mL) at 0 °C was added Dess-Martin periodinane (15.5 g, 37.2 mmol) in one portion. The stirring was continued at rt for 12 h and the reaction mixture was poured into a mixture of a saturated aqueous solution of sodium thiosulfate (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). Then Et_2O (150 mL) was added and the mixture stirred for 30 min. The mixture was extracted with Et_2O, washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (10%)/PE afforded the pure ynone **197** (4.6 g, 94%). Alternatively the crude propargylic ketone, which was seen to be of sufficient purity (without flash chromatography) for use in further stages, was stored at -20 °C for later use.

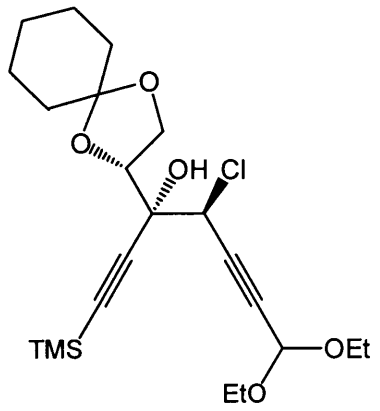
vmax (cm^{-1}) 2932, 2862, 2150, 1677, 1399, 1372;

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.33 (1H, dd, *J* 7.3, 4.6, C*H*CH_2), 4.05 (1H, dd, *J* 8.6, 7.3, CHC*H*$_2$), 3.97 ((1H, dd, *J* 8.6, 4.6, CHC*H*$_2$), 1.74-1.36 (m, 10H, $CH_{2\ cyclohexyl}$), 0.07 (s, 9H, CH_3);

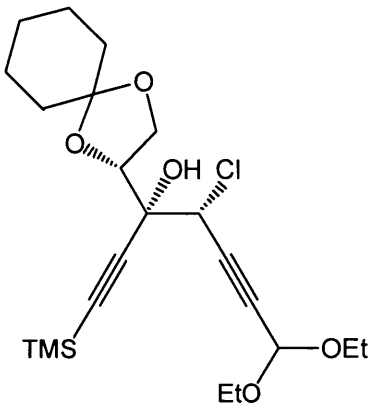
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 187.0 (*C*=O), 113.4 (*C*), 104.4 (C), 100.6 (C), 81.5 (CH), 67.5 (CH_2), 36.5 ($CH_{2cyclohexyl}$), 35.9 ($CH_{2cyclohexyl}$), 25.9 ($CH_{2cyclohexyl}$), 24.8 ($CH_{2cyclohexyl}$), 24.7 ($CH_{2cyclohexyl}$), 0.0 (3 x CH_3);

HRMS $(M+H)^+$ cald. for $C_{14}H_{23}O_3Si$ 267.1411, found *m/z* 267.1413.

(2R,3R,4S)-4-Choro-3-(1,4-dioxa-spiro[4.5]dec-2-yl)-7,7-diethoxy-1-trimethylsilanyl-hepta-1,5-diyn-3ol 197 and (2R,3R,4R)-4-Choro-3-(1,4-dioxa-spiro[4.5]dec-2-yl)-7,7-diethoxy-1-trimethylsilanyl-hepta-1,5-diyn-3ol 198



***anti* 197**



***syn* 198**

To $ZnBr_2$ (2.2 g, 9.8 mmol) in THF (9 mL) at -20 °C was added **155** (0.8 g, 4.7 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (9.3 mL, 9.3 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone **35** (1.2 g, 4.6 mmol) was then added quickly. Stirring was continued for 3 h at -78 °C and the reaction was poured into a mixture of a saturated aqueous solution of NH_4Cl (4 mL) and H_2O (50 mL), then diluted with Et_2O (150 mL). The resulting mixture was allowed to warm to rt and filtered through celite, then extracted with Et_2O (50 mL), washed with brine (2 x 30 mL), dried over magnesium sulfate, filtrated and concentrated *in vacuo*. Column chromatography eluting with Et_2O (20%)/PE afforded the inseparable diastereomeric chlorohydrins **197** and **198** (1.4 g, *anti:syn* 5/1, 59%) as a clear yellow oil.

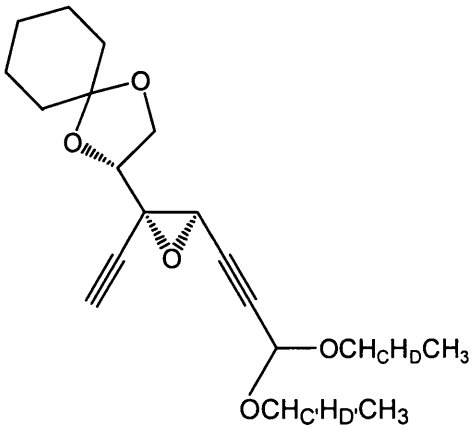
νmax (cm^{-1}) 3402, 2932, 2895, 2866, 2252, 2173, 1446, 1380, 1250;
^1H NMR (400 MHz, $CDCl_3$) δ_H 5.34 (d, 1H, *J* 1.3, $(EtO)_2CH_{syn}$), 5.32 (d, 1H, *J* 1.4, $(EtO)_2CH_{anti}$), 4.96 (d, 1H, *J* 1.3, $CHCl_{syn}$), 4.93 (d, 1H, *J* 1.4, $CHCl_{anti}$), 4.32 (dd, 1H, *J* 6.8, 5.9, $CHCH_{2anti}$), 4.30 (dd, 1H, *J* 6.8, 5.9, $CHCH_{2syn}$), 4.20 (dd, 1H, *J* 8.5, 5.9, CH_2CH_{anti}), 4.19 (dd, 1H, *J* 8.5, 5.9, CH_2CH_{syn}), 4.16 (dd, 1H, *J* 8.5, 6.8, CH_2CH_{anti}), 4.14 (dd, 1H, *J* 8.5, 6.8, CH_2CH_{syn}), 3.77-3.67 (m, 2H, CH_{2Et}), 3.53-3.64 (m, 2H, CH_{2Et}), 2.94 (s, 1H, OH_{syn}), 2.86 (s, 1H, OH_{anti}), 1.72-1.65 (m, 2H, $CH_{2cyclohexyl}$), 1.62-1.49 (m, 6H, $CH_{2cyclohexyl}$), 1.42-1.32 (m, 2H, $CH_{2cyclohexyl}$), 1.23 (t,

3H, *J* 7.0, CH_{3Etsyn}), 1.22 (t, 3H, *J* 7.1, CH_{3Etsyn}), 1.22 (t, 3H, *J* 7.1, $CH_{3Etanti}$), 1.21 (t, 3H, *J* 7.1, $CH_{3Etanti}$), 0.16 (s, 9H, $SiCH_3$);

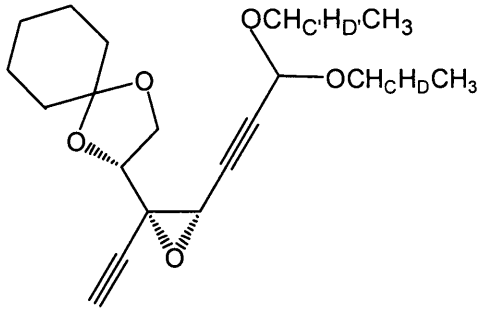
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 111.0 ($C_{cyclohexylanti}$), 110.9 ($C_{cyclohexylsyn}$), 101.8 (C_{anti}), 101.5 (C_{syn}), 93.7 (C_{syn}), 92.7 (C_{anti}), 91.1 ($(EtO)_2CH_{anti}$), 91.0 ($(EtO)_2CH_{syn}$) 84.2 (C_{anti}), 83.5 (C_{syn}), 80.4 (C_{syn}), 79.1 (C_{anti}), 77.2 (CH_{anti}), 76.1 (CH_{syn}), 75.2 (C_{OHanti}), 74.6 (C_{OHsyn}), 66.6 (CH_{2anti}), 66.1 (CH_{2syn}), 61.0 ($CH_{2Etanti}$), 60.97 (CH_{2Etsyn}), 60.94 (CH_{2Etsyn}) 60.8 ($CH_{2Etanti}$), 55.3 (CH_{Clanti}), 53.9 (CH_{Clsyn}), 35.9 ($CH_{2cyclohexyl}$), 34.9 ($CH_{2cyclohexyl}$), 25.10 ($CH_{2cyclohexyl}$), 23.8 ($CH_{2cyclohexyl}$), 23.7 ($CH_{2cyclohexyl}$), 15.0 (2 x CH_{3Et}), -0.3 (3 x CH_{3syn}), -0.4 (3 x CH_{3anti});

HRMS $(M+NH_4)^+$ cald. for $C_{22}H_{39}ClNO_5Si$ 460.2281, found *m/z* 460.2279.

(2R,3S)-2-[3-(3,3)-Diethoxy-pro-1-ynyl)-(2S)-2-ethynyl-oxiranyl]-1,4-dioxa-spiro[4.5]decane 199 and 200



***trans* 199**



***cis* 200**

To $ZnBr_2$ (2.2 g, 9.8 mmol) in THF (9 mL) at -20 °C was added **155** (0.8 g, 4.7 mmol) then the reaction was cooled to -78 °C. A freshly prepared 1 M solution of LDA in THF (9.3 mL, 9.3 mmol) was added dropwise and the reaction was stirred for 1 h. The ketone **35** (1.2 g, 4.6 mmol) was then added quickly. Stirring was continued for 3 h at -78 °C and the reaction was poured into a mixture of a saturated aqueous solution of NH_4Cl (4 mL) and H_2O (50 mL) then diluted with Et_2O (150 mL). The resulting mixture was allowed to warm to rt and filtered through celite, then extracted with Et_2O (50 mL), washed with brine (2 x 30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give the crude diastereoisomeric chlorohydrins.

To the crude chlorohydrins in DMF (30 mL) was added KF (1.9 g, 18.4 mmol). The reaction mixture was stirred overnight and both Et_2O (40 mL) and a saturated aqueous solution of NH_4Cl (30 mL) were added. The aqueous layer was extracted with Et_2O (2 x 15 mL) and the combined organic extracts washed with H_2O (2 x 20 mL), brine (20 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with Et_2O (20%)/PE afforded the *trans*-epoxydiyne **199** (953 mg, 62%) and the *cis* epoxydiyne **200** (184 mg, 12%).

α_D^{22} +30.2 (*c* 0.508 in $CHCl_3$, 589 nm, ***trans* epoxydiyne**);

α_D^{22} -61.2 (*c* 1 in $CHCl_3$, 589 nm, ***cis* epoxydiyne**);

νmax (cm^{-1}) 3205, 2940, 2841, 2180, 2160;

***trans*-epoxydiyne:**

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.30 (d, 1H, *J* 0.9, $(EtO)_2CH$), 4.19 (dd, 1H, *J* 11.0, 9.2, $CHCH_2$), 4.065 (dd, 1H, *J* 10.8, 5.9, $CHCH_2$), 4.062 (dd, 1H, *J* 8.9, 5.9, $CHCH_2$), 3.757 (dq, 1H, *J* 9.5, 7.0, CH_C), 3.750 (dq, 1H, *J* 9.5, 7.0, $CH_{C'}$), 3.71 (dd, 1H, *J* 0.9, H_{epoxy}), 3.58 (dq, 2H, *J* 9.4, 7.0, H_D and $H_{D'}$), 2.48 (s, 1H, H_{alkyne}), 1.72-1.65 (m, 2H, $CH_{2cyclohexyl}$), 1.63-1.50 (m, 6H, $CH_{2cyclohexyl}$), 1.41-1.31 (m, 2H, $CH_{2cyclohexyl}$), 1.219 (t, 3H, *J* 7.0, CH_{3Et}), 1.214 (t, 3H, *J* 7.0, CH_{3Et});

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 111.6 ($C_{cyclohexyl}$), 91.0 ($(EtO)_2C$), 81.6 (C), 78.8 (C), 77.0 (C), 75.5 (CH_{alkyne}), 75.0 (CH), 66.3 (CH_2) 61.0 (CH_{2Et}), 60.9 (CH_{2Et}), 57.8 (C_{epoxy}), 49.0 (CH_{epoxy}), 35.4 ($CH_{2cyclohexyl}$), 34.4 ($CH_{2cyclohexyl}$), 24.8 ($CH_{2cyclohexyl}$), 23.7 ($CH_{2cyclohexyl}$), 23.5 ($CH_{2cyclohexyl}$), 14.932 (CH_{3Et}), 14.931 (CH_{3Et});

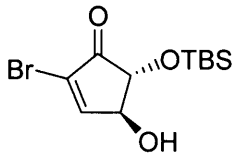
***cis*-epoxydiyne:**

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.27 (1H, d, *J* 0.9, $(EtO)_2CH$), 4.17 (1H, dd, *J* 8.7, 6.5, $CHCH_2$), 4.16 (1H, dd, *J* 8.7, 6.5, $CHCH_2$), 4.04 (1H, t, *J* 6.5, $CHCH_2$), 3.78 (1H, d, *J* 0.9, H_{epoxy}), 3.71 (1H, dq, *J* 9.4, 7.1, CH_C), 3.70 (1H, dq, *J* 9.4, 7.1, $CH_{C'}$), 3.57 (1H, dq, *J* 9.4, 7.1, H_D), 3.56 (1H, dq, *J* 9.4, 7.1, $H_{D'}$), 2.38 (1H, s, H_{alkyne}), 1.72-1.65 (m, 2H, $CH_{2cyclohexyl}$), 1.62-1.49 (m, 6H, $CH_{2cyclohexyl}$), 1.42-1.32 (m, 2H, $CH_{2cyclohexyl}$), 1.21 (3H, t, *J* 7.1, CH_{3Et}), 1.20 (3H, t, *J* 7.1, CH_{3Et});

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 111.3 ($C_{cyclohexyl}$), 90.9 ($(EtO)_2CH$), 82.4 (C), 77.9 (C), 77.7 (C), 74.7 (CH), 73.8 (CH_{alkyne}), 66.2 (CH_2), 61.0 (CH_{2Et}), 60.9 (CH_{2Et}), 55.8 (C_{epoxy}), 51.6 (CH_{epoxy}), 35.5 ($CH_{2cyclohexyl}$), 34.7 ($CH_{2cyclohexyl}$), 25.0 ($CH_{2cyclohexyl}$), 23.7 ($CH_{2cyclohexyl}$), 23.6 ($CH_{2cyclohexyl}$), 14.915 (CH_{3Et}), 14.914 (CH_{3Et});

HRMS $(M+NH_4)^+$ cald. for $C_{19}H_{30}NO_5$ 352.2118, found *m/z* 352.2118.

(4S,5R)-2-Bromo-5-(^{t}butyl-dimethyl-silanyloxy)-4-hydroxy-cyclopent-2-enone 208[72c]

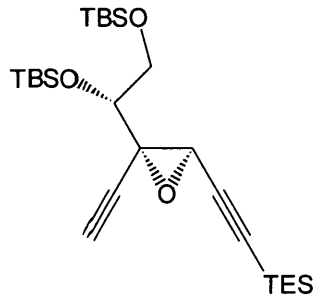


To cyclopentenone **72** (3.0 g, 13.1 mmol) in DCM (66 mL) at 0 °C was added bromine (0.75 mL, 14.4 mmol) dropwise. After 10 min Et_3N (11.41 mL, 80.0 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction was then quenched with H_2O (80 mL), extracted with Et_2O (3 x 60 mL), washed with brine (2 x 50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (15%)/PE afforded **208** (3.92 g, 97%) as a colourless oil.

νmax (cm^{-1}) 3424, 2978, 2858, 1724, 1360;
^1H (300MHz, $CDCl_3$, *J* (Hz)) δ_H (ppm) 7.50 (d, 1H, *J* 2.4, CH_{alkene}), 4.70 (m, 1H, CHOTBS), 4.20 (d, 1H, *J* 2.4, C*H*OH), 2.59 (br s, 1H, OH), 0.93 (s, 9H, $C(CH_3)_3$), 0.19 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$);
^{13}C (75MHz, $CDCl_3$) δ_C (ppm) 196.1 (C=O), 158.6 (CH_{alkene}), 125.2 (C_{Br}), 80.8 (CH_{OTBS}), 77.1 (CH_{OH}), 25.7 (3 x CH_3), 18.3 (C), -4.5 (CH_3), -5.1 (CH_3).

.

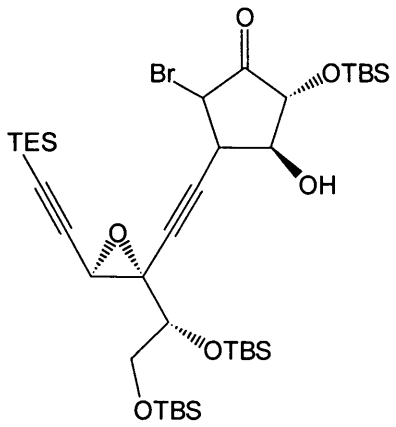
(1R,2S,3S)-2-[1,2-Bis-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-2-ethynyl-3-triethylsilanylethynyl-oxirane 210



To a solution of the epoxy-alcohol **209** (0.100 mg, 0.26 mmol) and Et_3N (0.1 mL, 0.78 mmol) in DCM (1.3 mL) was added TBSCl (78 mg, 0.52 mmol) at rt. Stirring was continued for 4 h and then the reaction quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL). The aqueous layer was extracted with Et_2O (2 x 5 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Column chromatography eluting with Et_2O (5%)/PE afforded the title compound **210** (118 mg, 92%) as a white solid.

νmax (cm^{-1}) 3280, 2960, 2929, 2882, 2183, 2127, 1463, 1369, 1256;
^1H NMR (300 MHz, $CDCl_3$) δ_H 3.89-3.73 (m, 3H, $CHCH_2$), 3.61 (s, 1H, H_{epoxy}), 2.42 (s, 1H, C≡CH), 0.99 (t, 9H, *J* 7.2, CH_{3TES}), 0.89 (s, 9H, CH_3C_{TBS}) 0.86 (s, 9H, CH_3C_{TBS}), 0.61 (q, 6H, *J* 7.2, CH_{2TES}), 0.05 (s, 12H, CH_3Si_{TBS});
^{13}C NMR (75 MHz, $CDCl_3$) δ_C 100.7 (CTES), 89.0 (C), 78.8 (C), 74.7 (CH_{alkyne}), 72.6 (CH), 65.2 (CH_2), 57.7 (C_{epoxy}), 47.7 (CH_{epoxy}) , 25.9 (3 x CH_3), 25.7 (3 x CH_3), 18.2 (C_{TBS}), 18.2 (C_{TBS}), 7.3 (3 x CH_{3TES}), 4.1 (3 x CH_{2TES}), -4.8 (2 x CH_{3TBS}), -4.9 (2 x CH_{3TBS});
HRMS $(M+Na)^+$ cald. for $C_{26}H_{50}O_3Si_3Na$ 518.3038, found *m/z* 518.3052.

(1R,2S,3S,4S,5R)-3-{2-[1,2-Bis-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-3-triethylsilanylethynyl-oxiranylethynyl}-2-bromo-5-(*tert*-butyl-dimethyl-silanyloxy)-4-hydroxy-cyclopentenone 212



To a solution of **210** (40 mg, 0.080 mmol) in THF (0.5 mL) was added a 2.3 M solution of *n*BuLi in hexanes (0.038 mL) at -78 ^{0}C. After 40 min, Et_3N (11.2 μL) was added followed by addition of a 1M solution of dimethylaluminium chloride in THF (105.0 μL) and the reaction mixture was warm at rt and stirred for 1h. A solution of enone **208** (12.5 mg, 0.040 mmol) in THF (0.3 mL) with activated molecular sieves 4Å (5 mg) was then added *via* canula to the reaction mixture at -45 ^{o}C. The reaction was stirred for 2h at this temperature and quenched with Rochelle's salt (1 mL), extracted with EtOAc (3 x 2 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (15%)/PE afforded **215** (3.2 mg, 10%) as a colourless oil.

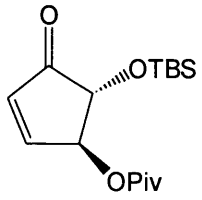
νmax (cm^{-1}) 3664, 2950, 1757, 2130, 2105;

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.36 (d, 1H, *J* 9.54, CHBr), 4.12 (m, 1H, C*H*(OTBS)$_{cyclopentanone}$), 4.02 (m, 1H, C*H*HCHOTBS), 3.88 (m, 2H, C*H*HC*H*OTBS), 3.81 (dd, 1H, *J* 4.01, 1.46, C*H*OH), 3.69 (s, 1H, H_{epox}), 3.51 (dd, 1H, *J* 9.54, 4.01, C*H*CHBr), 2.64 (s, 1H, OH), 0.97 (t, 9H, *J* 7.8, CH_{3TES}), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.878 (s, 9H, $SiC(CH_3)_3$), 0.0870 (s, 9H, $SiC(CH_3)_3$), 0.61 (q, 6H, *J* 7.8, CH_{2TES}), 0.14 (s, 3H, $CH_{3TBScyclopentanone}$), 0.12 (s, 3H, $CH_{3TBScyclopentanone}$), 0.067 (s, 12H, CH_{3TBS});

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 205.9 (C=O), 100.78 (CTES), 77.2 ($CHOTBS_{cyclopentanone}$), 76.9 (C), 76.8 (C), 76.7 (C), 75.5 (CHOH), 72.5 (CH_{diyne}), 65.4 (CH_2), 57.9 (C_{epoxy}), 48.3 (CH_{epoxy}), 47.0 (CHBr), 43.4 (CHCBr), 25.8 (3 x CH_{3TBS}),

25.6 (3 x CH_{3TBS}), 25.5 (3 x CH_{3TBS}), 18.7 (3 x C_{TBS}), 7.3 (3 x CH_{3TES}), 4.0 (3 x CH_{2TES}), -4.9 (2 x CH_{3TBS}), -5.2 (2 x CH_{3TBS}), -5.4 (2 x CH_{3TBS});
HRMS $(M+NH_4)^+$ cald. for $C_{37}H_{73}O_6NSi_4$ 818.3693, found *m/z* 818.3688.

(4S,5R)-2,2-Dimethyl-propionic acid5-(*tert*-butyl-dimethyl-silanyloxy)-4-oxo-cyclopent-2-enyl ester 215



To cyclopentenone **72** (100 mg, 0.44 mmol) in DCM (1.45 mL) at 0 °C was added Et_3N (0.122 mL, 0.88 mmol). After 10 min pivaloyl chloride (0.060 mL, 0.48 mmol) was added dropwise. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL), extracted with Et_2O (3 x 6 mL), washed with brine (2 x 1 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography eluting with Et_2O (5%)/PE afforded **215** (126 mg, 92%) as a colourless oil.

vmax (cm^{-1}) 2935, 2887, 2862, 1737, 1619, 1471;
^1H (300 MHz, $CDCl_3$) δ_H 7.30 (dd, 1H, *J* 6.2, 1.5, CH_{alkene}), 6.27 (d, 1H, *J* 6.2, CH_{alkene}), 5.61 (d, 1H, *J* 1.2, CHOTBS), 4.07 (d, 1H, *J* 2.9, CHOPiv), 1.21 (s, 9H, $C(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si);
^{13}C (75 MHz, $CDCl_3$) δ_c 201.6 (C=O), 177. 8 (C=O), 155.5 (CH), 134.0 (CH), 78.8 (CH), 78.0 (CH), 38.7 (C), 27.0 (3 x CH_3), 25.6 (3 x CH_3), 18.2 (C_{TBS}), -4.5 (CH_{3TBS}), -5.2 (CH_{3TBS});
HRMS $(M+H)^+$ cald. for $C_{16}H_{29}O_4Si$ 313.1829, found 313.1809.

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