Towards Neocarzinostatin Chromophore

by

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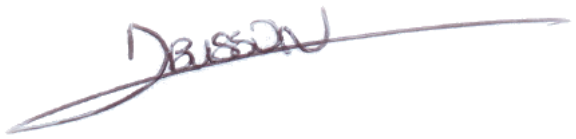
Submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

Declaration

I, Mathilde Jeanne Monique Busson, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.



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A mes grands-parents

Abstract

Neocarzinostatin chromophore (NCS-C) was the first isolated member of the enediyne family, one of the most potent family of anticancer agents ever discovered. Neocarzinostatin (NCS or holo-NCS) is a 1 : 1 non-covalent complex of a very reactive nine-membered ring epoxydiyne chromophore (NCS-C) tightly bound to a protein, apo-NCS.

Total syntheses of Myers and Hirama, and the work of Magnus and Caddick have shown the challenges involved in the synthesis of the Neocarzinostatin chromophore, and in particular its bicyclic epoxydiyne ring. This project thesis concerns evaluation of alternative approaches towards the synthesis of strained medium size rings, such as those in the Neocarzinostatin chromophore, using McMurry coupling and acyl radical chemistry.

Chapter 1 provides an introduction to the field including a discussion of the mode of action of Neocarzinostatin and a detailed evaluation of previous approaches to the Neocarzinostatin chromophore. McMurry coupling and acyl radical chemistry are also reviewed, particularly with reference to their use in strained medium ring synthesis.

Chapter 2 describes studies into aerobic hydroacylations of vinyl sulfonates in view of its application to the synthesis of NCS-C core. A broader range of aldehydes can now be used for the synthesis of β-ketosulfonates. Pentafluorophenol has been shown to have an inhibitory effect on hydroacylations of vinyl sulfonates and new conditions were developed to minimise this inhibitory effect. Preliminary mechanistic studies suggest that addition of acyl radicals to vinyl sulfonates is reversible.

Chapter 3 includes studies on different approaches to key epoxydiyne synthon of Neocarzinostatin chromophore. Whilst zinc mediated coupling to give the key epoxydiyne synthon was capricious, sulphur ylide approach gave access to disubstituted propargylic epoxides in good yields. Proof of principle for the synthesis of the key epoxydiyne *via* this method is also described.

Contents

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Last but not least, I am forever grateful to my parents and brother Tom for their unconditional love and support throughout my studies.

Abbreviations

Å: Angstrom

Ac: Acetate

acac: Acetylacetonate

AIBN: Azobisisobutyronitrile

Ala: Alanine

alk: Alkene or alkyne

apo-NCS: apo-Neocarzinostatin

app.: Apparent

Ar: Aromatic

atm.: Atmospheric

BHT: 2,6-bis(1,1-dimethyl)-4-methylphenol

Bn: Benzyl

bp: Boiling point

BPO: Benzoyl peroxide

br: Broad

Bu: Butyl

Bz: Benzoyl

C: Carbon

cat.: Catalytic

CDI: Carbonyldiimidazole

calcd: Calculated

CI: Chemical ionisation

Conv.: Conversion

Cys: Cysteine

d: Doublet

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC: 1,3-Dicyclohextlcarbodiimide

DCM: Dichloromethane

DEIPS: Diethylisopropylsilyl

DET: Diethyl tartrate

DFT : Density function theory

$(DHQD)_2PYR$: 1,4-Bis(9-*O*-dihydroquinidine)-diphenylpyrimidine

DIAD: Diisopropyl azodicarboxylate

DIBAL: Diisobutylaluminium hydride

DIPA: Diisopropylamine

DMAP: 4-Dimethylaminopyridine

DME: 1,2-Dimethoxyethane

DMF: Dimethylformamide

DMP: Dess-Martin periodinane

DNA: Deoxyribonucleic acid

DNP: 2,4-Dinitrophenol

EDG: Electron donating group

EI: Electron ionisation

EPHP: 1-ethyl-piperidine hypophosphite

epo: Epoxide

eq.: Equivalent

ES: Electrospray

Et: Ethyl

FAB: Fast-atom bombardment

FGI: Functional group interconversion

Gly: Glycine

HFB: Hexafluorobenzene

holo-NCS: see NCS

HRMS: High resolution mass spectrometry

i-Pr: *iso*-Propyl

IR: Infrared

J : coupling constant

k: kinetic rate constant

K_D: Dissociation constant

kDa: KiloDalton

LDA: Lithium diisopropylamine

LHMDS: Lithium hexamethyldisilazide

LRMS: Low resolution mass spectrometry

Lys: Lysine

M: Molar

m-CPBA: *meta*-chloroperoxybenzoic acid

Me: Methyl

MOM: Methoxymethyl

mp: Melting point

MPM: *p*-Methoxybenzyl

MS: Molecular sieves

Ms: Methanesulfonyl

N.C.: Non completed

NCS (or holo-NCS): Neocarzinostatin complex

NCS-C: Neocarzinostatin chromophore

N.I.: No isolation

nM: Nanomolar

NMR: Nuclear magnetic resonance

n-Pr: Propyl

Nu: Nucleophile

o/n: Overnight

P: Protecting group

PCB: Pentachlrobenzene

PCC: Pyridinium chlorochromate

PDB: Protein Data Bank

PE: Petrol

PFP: Pentafluorophenyl

PFPOH: Pentafluorophenol

PFPVS: Pentafluorophenyl vinyl sulfonate

PG: Protecting group

Ph: Phenyl

Phe: Phenyl

Piv: Pivaloyl

Pro: Proline

q: Quartet

quant.: Quantitative

quint.: Quintet

rpm: Rotation per minute

rt: Room temperature

s: Singlet

sat: Saturated

Ser: Serine

sept.: Septet

sext.: Sextet

SMANCS: Poly(styrene-co-maleic acid/anhydride) Neocarzinostatin

T: Time

t: Triplet

TBAF: Tetrabutylammonium fluoride

TBDPS: *tert*-Butyldiphenylsilyl

TBHP: *tert*-Butylhydroperoxide

TBS: *tert*-Butyldimethylsilyl

t-Bu: *tert*-Butyl

TCP: 2,4,6-trichlororphenyl

TDS: Thexydimethylsilyl

TES: Triethylsilyl

Tf: Triflate, trifluoromethanesulfonate

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

TLC: Thin layer chromatography

TMS: Trimethylsilyl

TTMSS: Tris(trimethylsilyl)silane

UV: Ultraviolet

V-40: 1,1'-azobis(cyclohexane-1-carbonitrile)

Z: Zusammen (cis)

μM: Micromolar

@: At

Δ: Thermal exposure

hν: Photoexcitation

Chapter 1. Introduction

1.1 The enediyne family

The enediynes have aroused a great deal of interest for being one the most potent family of anticancer agents ever discovered *in vitro*.[1,2] For example, C-1027 **1** (Figure 1) is three orders of magnitude more potent[3] than doxorubicin[4], an anticancer drug currently used to treat a wide range of cancers. Apart from the enediyne moiety (*Z*-hexa-1,5-diyn-3-ene) found within a nine- or ten-membered ring of the chromophore, members of the enediyne family tend to have a sugar and a planar aromatic ring within their structure (Figure 1). For example, C-1027 **1** contains a tetrahydropyran motif and a benzo[1,4]oxazine in addition to the key enediyne. As for Calicheamicin **2**, four sugars and a trisulfide moiety can be found along with the ten-membered enediyne ring. The mechanism of action of this class of natural products is attributed to the reactive nature of the enediyne motif, often involving DNA strand cleavage *via* radical C-H abstraction. Other fragments of the molecular scaffolds are responsible for delivery and targeting of the warhead enediyne which, in general, is activated by a triggering device, within the target cell.[5,6]

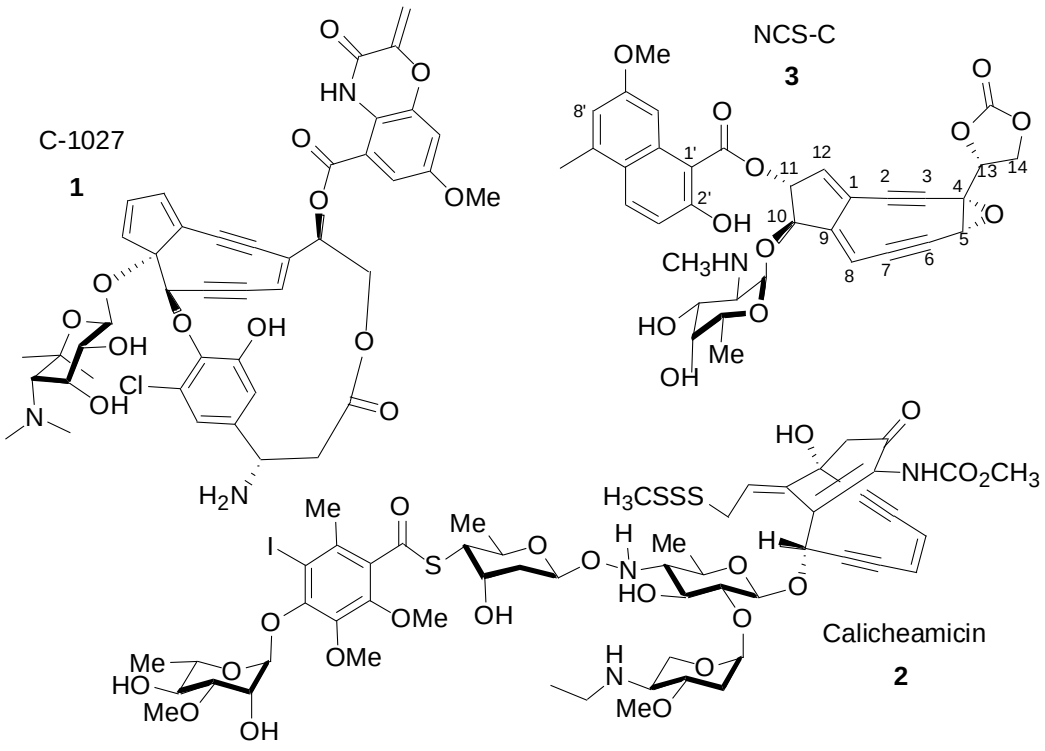

Figure 1. Examples of enediyne containing natural products

1.2 Neocarzinostatin

The protein : ligand complex Neocarzinostatin (NCS or holo-NCS) was first reported by Ishida in 1964 from a culture filtrate of *Streptomyces carzinostaticus* Var. F-41 and the ligand was the first isolated member of the enediyne family.[7] In 1966, the complementary chromophore binding protein (apo-NCS) was isolated[8] and following Maeda's studies the primary sequence of the protein was published,[9] later revised[10] and confirmed by NMR studies.[11] NCS has been employed clinically for leukemia, gastric and pancreatic cancer treatments since the mid 1970s.[12] Although Ishida already suspected a non-peptidic component to be part of NCS in 1966, it was not until 1979 that the structure of the small molecule chromophore NCS-C **3** (Figure 1), was finally reported.[13,14] A structure containing the assignment of the relative stereochemistry was published in 1985[15] and finally in 1988 Myers determined the absolute configuration of NCS-C.[16] In 1993, crystal structures of apo-NCS[17] and holo-NCS[18] were released.

1.2.1 holo-Neocarzinostatin

holo-Neocarzinostatin (holo-NCS) is a tightly bound (K_D = 0.1 nM) 1 : 1 non-covalent complex of a reactive nine-membered ring epoxydiyne chromophore, NCS-C **3** (Figure 1) and a 113 amino acid residue protein, apo-NCS (Figure 2).[19] The crystal structure of holo-NCS was reported by Myers in 1993, and is structurally very similar to that of apo-NCS, the position of Phe78 being the only noteworthy change (See 1.2.2, p 4).[18]

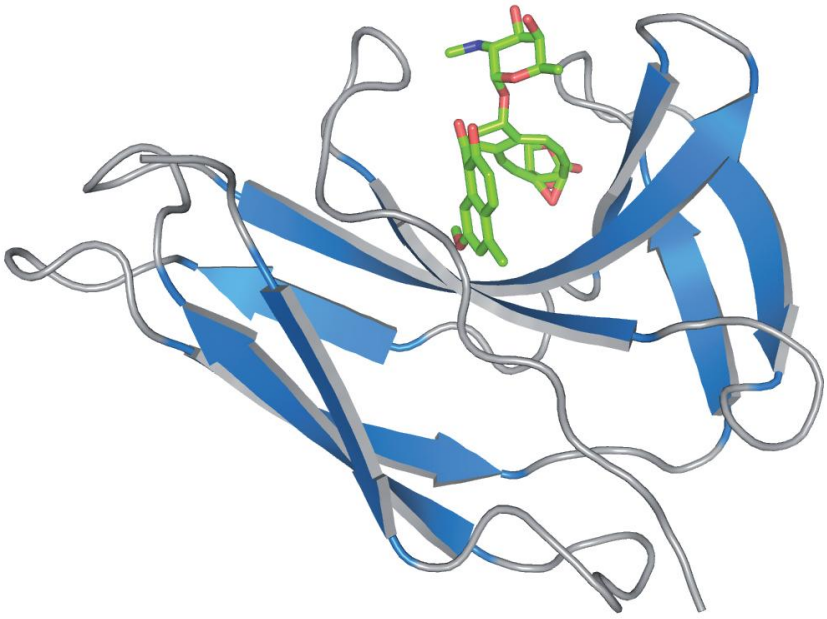

Figure 2. Structure of NCS : NCS-C bound to apo-NCS (PDB ID : 1NCO)

In the crystal structure of holo-NCS, the epoxynonadiyne ring of NCS-C was observed to be essentially planar, however the average value of the C-C≡C bond angle was 162°, demonstrating the acetylenic groups nonlinear behaviour (Figure 3). The sugar residue was found to adopt a chair conformation with the amino group orientated above C12 shielding the reactive carbon from nucleophilic attack. The two π-faces of the chromophore are sandwiched between the phenyl ring of Phe78 on face side and the phenyl ring of Phe52 and the disulfide bridge Cys37-Cys47 on the other. The naphthoate lies at the bottom of the hydrophobic binding site and forms hydrogen bonds between the carbonyl oxygen and Ser98 and between the methoxyl oxygen and Gly35. The aminosugar stacks against Phe78 and the amino group is therefore thought to be protonated, as favourable interactions between a positively charge group and the π-face of an aromatic have been observed in proteins and model systems.[18] The epoxide faces down into the hydrophobic pocket, being consequently protected from ring opening by solvent and extraneous nucleophiles. As a result of this tight binding, only 18% of the area of the free NCS-C, mainly composed of the aminosugar, the carbonate and the naphthoate hydroxyl group, is exposed to the solvent.

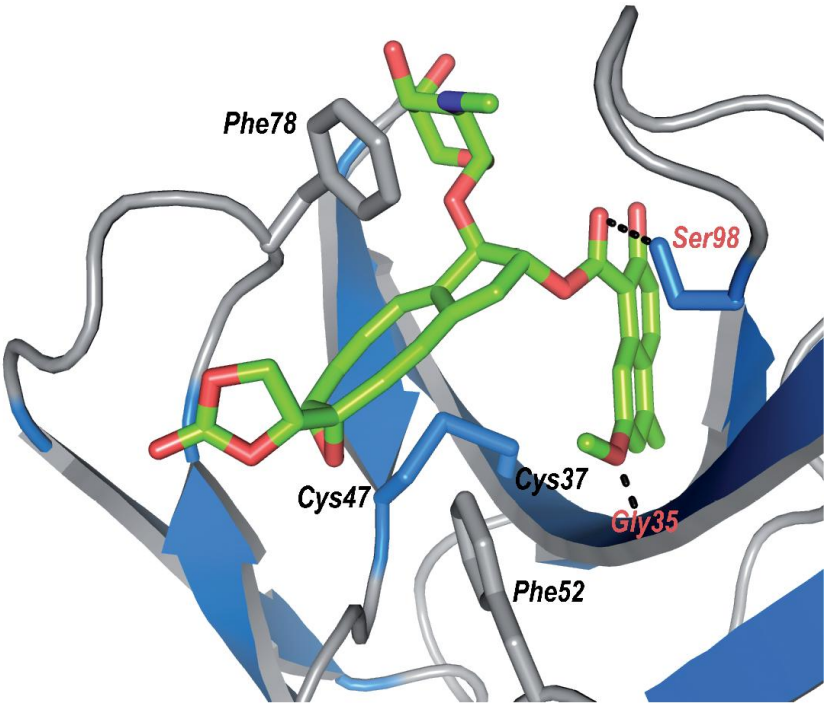

Figure 3. NCS-C binding site

1.2.2 apo-Neocarzinostatin

apo-Neocarzinostatin (apo-NCS) is a 11 kDa protein and is primarily composed of β sheets organised in two principal domains (Figure 2).[18,20] Structural determination of apo-NCS had been carried out using NMR[21,22] and X-ray crystallography.[17] The main domain of apo-NCS presents a seven-stranded antiparallel β-barrel structure whilst the smaller domain consists of two two-stranded antiparallel β-sheets and two disulfide bridges, Cys37-Cys47 and Cys88-Cys93. Unlike closely related proteins, such as actinoxanthin or macromomycin, apo-NCS also possesses a short 3_{10} helix, between Pro49 and Phe52.[18] One of the roles of apo-NCS is to protect the reactive chromophore, NCS-C, from the reaction with extraneous nucleophiles.

apo-NCS is surprisingly effective as a receptor for a number of non-natural ligands. For example, apo-NCS has been shown to bind effectively to ethidium bromide[23], the anti-tumour agent daunomycin[22], flavones[24] and naphthoates analogues of NCS-C.[25,26] In addition, Caddick had reported that apo-NCS can be used to stabilise a nitrogen mustard-naphthoate.[27] The variety of ligands accepted by the binding pocket suggests apo-NCS could become a generic drug delivery vehicle and potentially target tumours more selectively. The versatility of apo-NCS can be enhanced *via*

mutations on some of the residues in the binding site, as already characterised mutants have been shown to retain the protein scaffold.[28-30]

1.2.3 Neocarzinostatin chromophore

1.2.3.1 Structure of the Neocarzinostatin chromophore

holo-Neocarzinostatin has antibacterial activity and has been shown to be an antitumour agent.[31] The potency of the holo complex is thought to arise from the chromophore, NCS-C **3** (Figure 4).[1] Without its binding protein, NCS-C is unstable and sensitive to light, heat, basic and strongly acid pH and to reaction with nucleophiles.[32-35] NCS-C is composed of four subunits, each having a key biological role (Figure 4). The naphthoate moiety (red) plays an important part in the binding of the chromophore to the protein and also acts as a DNA intercalating agent.[36] The sugar, N-methyl-fucosamine (green), interacts with the DNA, acting as an anchor, to correctly position the active epoxydiyne core in the minor groove of DNA.[36] In addition, there is compelling evidence that the fucosamine fragment also plays a role in the activation of the chromophore.[37,38] Data described by Goldberg suggests that the principle role of the cyclic carbonate (blue) is to enable in the transport of the chromophore through nuclear and cellular membranes.[39] However, it is, in principle, the reactive epoxybicyclo[7,3,0]dodecadiyne (black) which is responsible for the cytotoxicity of NCS-C.[31]

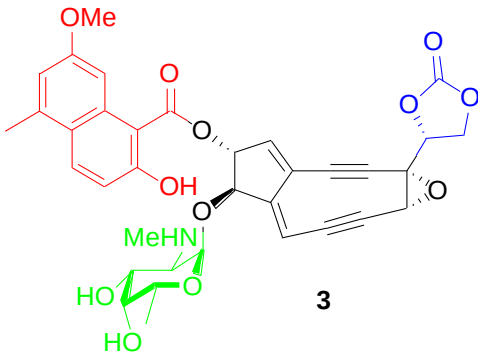

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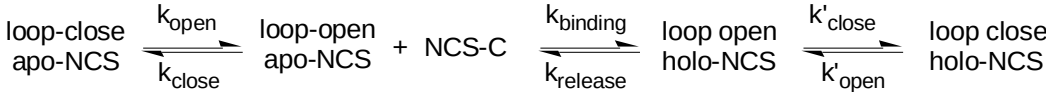
Figure 4. Structure of NCS-C

1.2.3.2 Mechanism of release of NCS-C

The site and mechanism of release of NSC-C by apo-NCS are still unclear. *In vitro* studies on agarose-bound holo-NCS, too big to enter cells, showed some of its cytotoxicity was retained.[40] It would suggest that the chromophore is able to enter the cell without the apo protein. However, Maeda reported that fluorescently labelled NCS was found in cytoplasm as well as nuclei of epithelial cells from human bladder[41] and was readily transported into eukaryotic cells.[42] Thus the exact timing of dissociation of the holo complex to give NCS-C and apo-NCS is still to be determined.

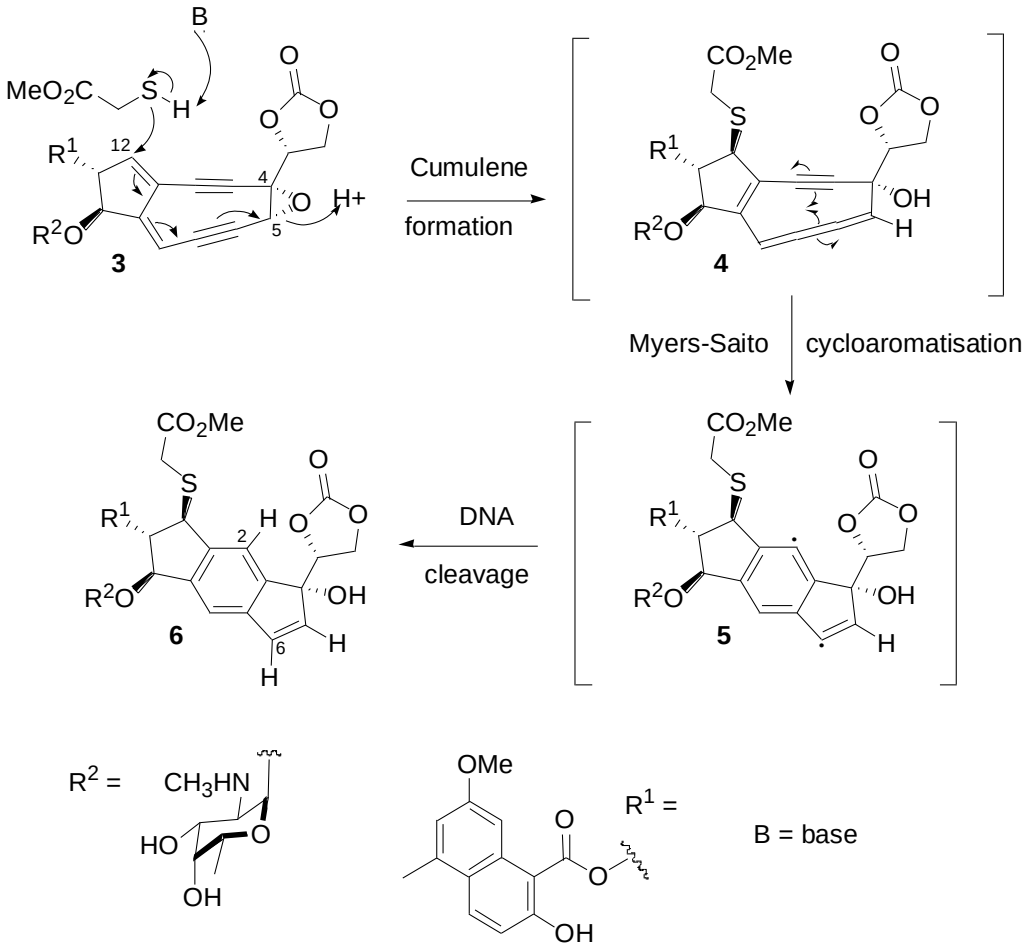
Following many studies on apo-NCS molecular dynamics[20,43], Merz recently proposed a mechanism of release of NCS-C in which loop 99-104 is proposed to be a key element (Scheme 1).[20,44]



Scheme 1. Mechanism of binding and release of NCS-C

1.2.3.3 The Myers-Saito cycloaromatisation

NCS-C **3** exists in a pro-drug state and needs activation *via* a nucleophilic attack to unveil its cytotoxicity. Myers proposed NCS-C activation mechanism at a molecular level where the activation cascade begins with the nucleophilic attack of a thiolate at C12 (Scheme 2).[45] Thiol addition leads to the opening of the C4-C5 epoxide and the formation of the highly strained cumelene **4.** Myers-Saito cycloaromatisation, an example of Bergman cyclisation, of the intermediate cumulene **4** gives rise to the indenyl biradical species **5.** Biradical **5** then cleaves DNA by hydrogen abstraction on the deoxyribose residue resulting in the formation of **6** and DNA fragments. Goldberg proposed an alternative base-catalysed thiol-independent mechanism.[46]



Scheme 2. Thiol-dependent mode of activation of NCS-C **3**

1.2.4 SMANCS

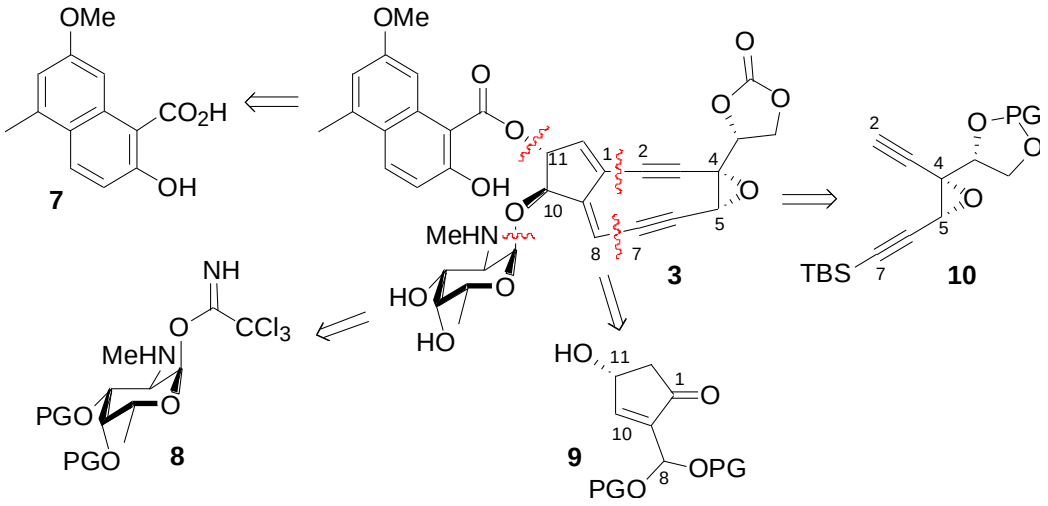
holo-NCS has aroused high interest in the scientific community for its cytotoxicity, which is greater than commonly used anti-tumour drugs such as 5-fluorouracil or adriamycin.[47] Its severe toxicity towards healthy organs, in particular bone marrow, and its short *in vivo* half-life ($t_{½} \approx 1.9$ min) has prevented a large clinical use of NCS. However, some of these limitations have been overcome by synthesising SMANCS, a polymer conjugated version of holo-NCS formed by cross-linking two chains of poly(styrene-co-maleic acid/anhydride) (SMA) to holo-NCS *via* the amino acids Ala1 and Lys20 to give SMANCS.[47] SMANCS has a significantly improved *in vivo* half-life compared to holo-NCS ($t_{½} \approx 19$ min). In addition to a 10-fold improvement in the *in vivo* half-life, SMANCS retained similar levels of activity. Even more significantly, due to its macromolecular structure, SMANCS is preferentially retained by solid tumors, increasing selectivity.[47]

1.3 Synthetic approaches to NCS-C and related enediynes

The principle challenge in the total synthesis of the enediyne class of natural products is the construction of the reactive enediyne core. A plethora of approaches towards the various subclasses of enediynes have been investigated and extensively reviewed.[48,49] Selected synthetic approaches most relevant to this thesis are discussed below. In each case, the focus of the discussion will be on the formation of the strained enediyne epoxide. Throughout the discussion of the synthetic approach, the carbon numbering for the parent natural product is employed.

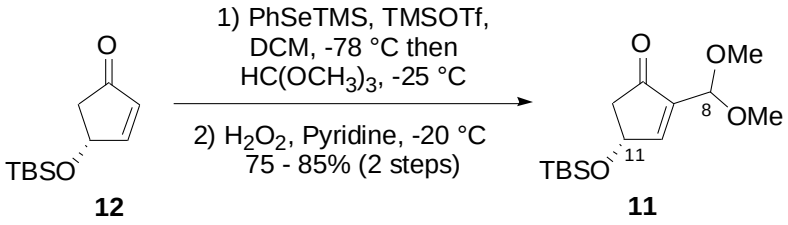
1.3.1 Myers' approach to NCS-C

In 1996, Myers reported the first total synthesis of NCS-C **3**, this remains the only total synthesis to date and relies on the formation of the C7-C8 bond to close the strained nine-membered ring.[50] The successful strategy is based on the convergent assembly of four principle fragments: naphthoate **7**; carbohydrate **8**; cyclopentenone **9**, decorated with the latent C8 aldehyde; and a suitably protected C2-C7 epoxydiyne **10** (Scheme 3).[51,52] Naphthoate **7** was synthesised from commercially available 4-bromo-3-methylanisole in six steps with moderate overall yields (40-48%),[53] while galactal sugar **8** was prepared as the activated trichloroacetimide in 10 steps from 3,4,6-tri-O-acetyl-D galactal**,** in preparation for a late stage Schmidt coupling on the C10 hydroxyl.[51]



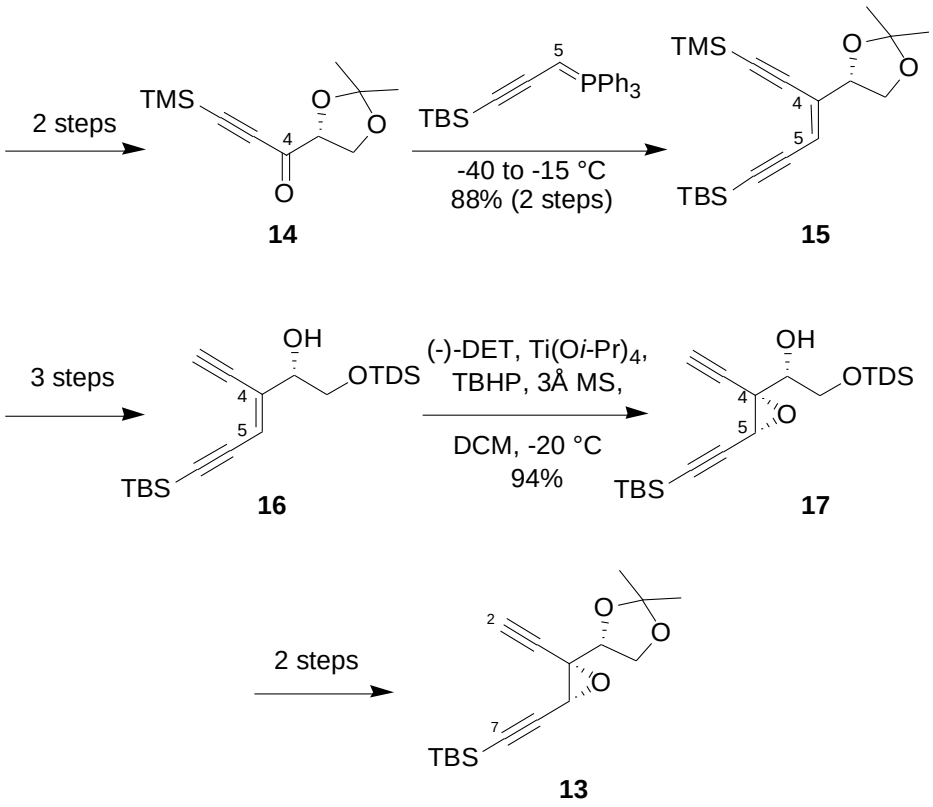
Scheme 3. Myers' strategy for synthesis of NCS-C **3**

Cyclopentenonate **11**, functionalised with both the required masked C8 aldehyde and with the C11 hydroxyl installed, was obtained in a one-pot procedure from cyclopentenone **12** *via* a careful optimisation of Noyori's method (Scheme 4).[54] Key to the success of the formation was sequential addition of trimethylsilylphenyl selenide, trimethyl orthoformate and hydrogen peroxide/pyridine to enantiopure prostaglandin intermediate to obtain cyclopentenonate **11** in good yield with C11 stereochemistry established.[55]



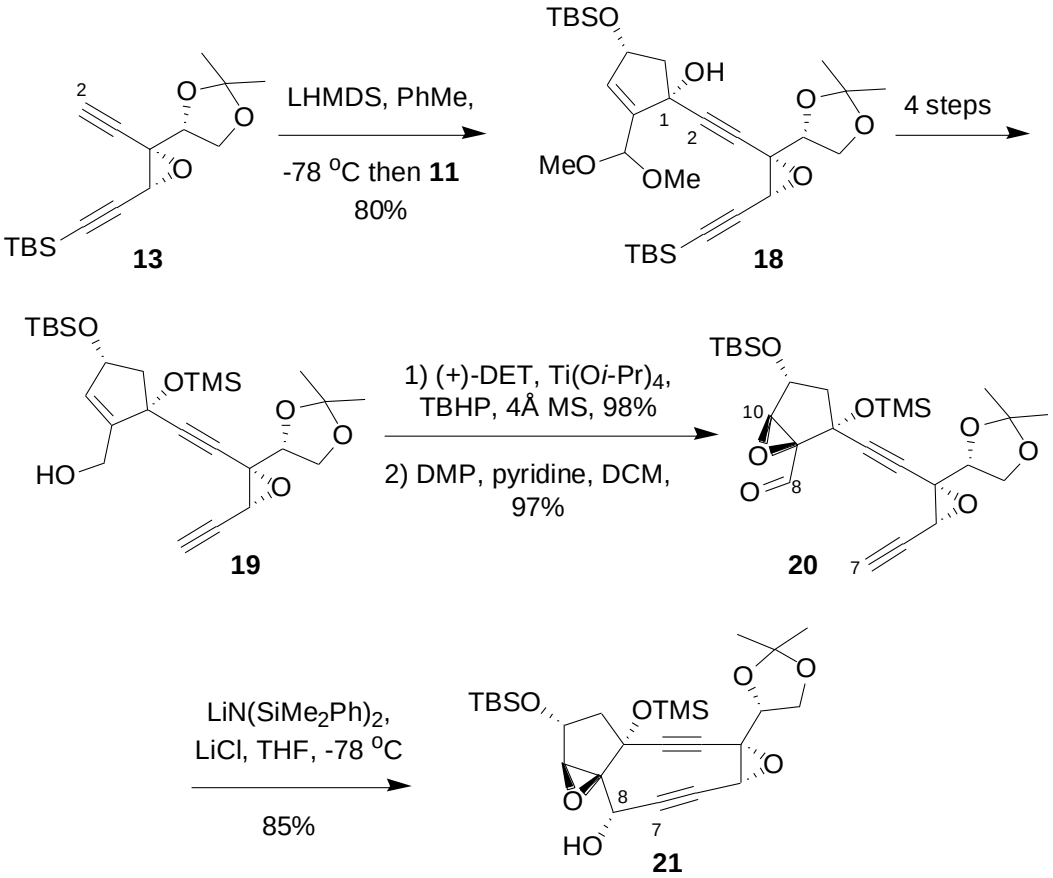
Scheme 4. Synthesis of cyclopentenone **11**

Key to Myers' successful synthesis of NCS-C **3** was construction of crucial C2-C7 epoxidyine **13** in 9 steps from D-glyceraldehyde acetonide with an overall yield of 43% (Scheme 5).[52] Myers' approach relies on a diastereoselective Wittig reaction between a C5-C7 phosphonium ylide with ketone **14** to construct the C4-C5 bond in diyne **15**, and a Sharpless asymmetric epoxidation to an allylic alcohol **16** to establish epoxydiyne **17**. Protection group manipulation afforded desired epoxydiyne **13** with differential protection on the C2 and C7 alkynyl carbons ready for further elaboration.



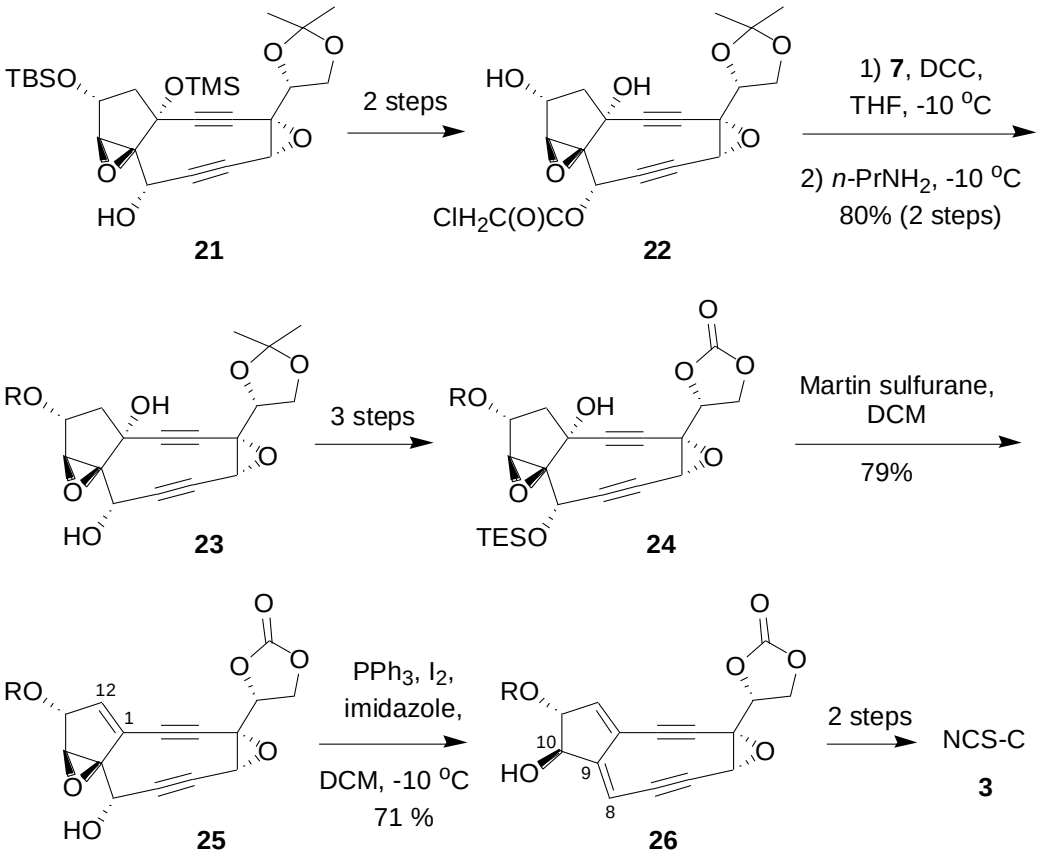
Scheme 5. Synthesis of key epoxydiyne **13**

Myers' successful union of the two fragments of the NCS-C enediyne core, cyclopentenone **11** and epoxydiyne **13**, was achieved through the construction of the key C1-C2 and C7-C8 bonds *via* diastereoselective alkyne addition to carbonyls at C1 and C8 respectively (Scheme 6). Reaction of the C2 lithiated alkyne derived from **13** with cyclopentenone **11** afforded alcohol **18** in excellent yield with good diastereocontrol.[52] The stereochemistry at C10 was established *via* diastereoselective Sharpless asymmetric epoxidation of the allylic alcohol **19**. Subsequent oxidation of the intermediate alcohol with Dess-Martin periodionane afforded key aldehyde **20** ready for subsequent ring closure. Ring closure *via* formation of C7-C8 bond, hence construction the carbon framework of the epoxydiyne core, was achieved *via* intramolecular addition of lithiated C7 alkyne onto C8 aldehyde to give alcohol **21**.



Scheme 6. Myers' synthesis of NCS-C core

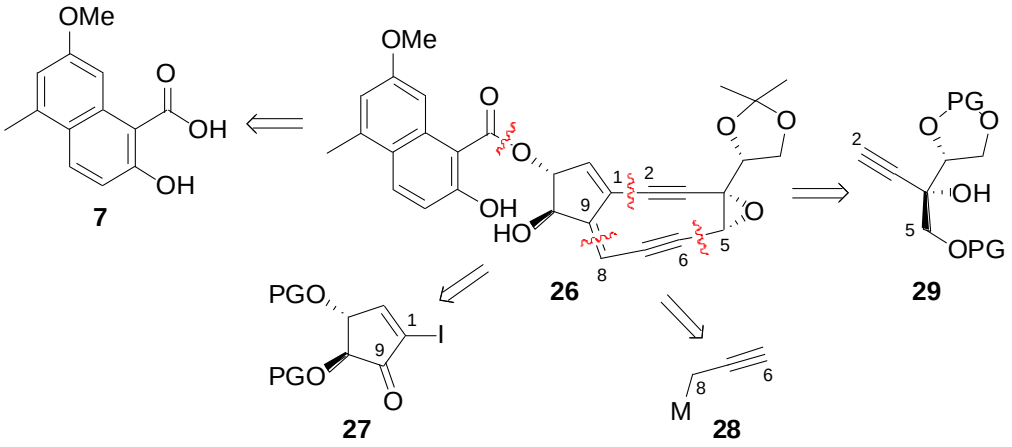
Myers' synthesis of NCS-C **3** was completed using a selective DCC-mediated esterification of alcohol **22** with naphthoate **7** to afford ester **23** (Scheme 7). Dehydration of alcohol **24** to enediyne **25**, to install the C1-C2 alkene, was achieved using Martin sulfurane. Ring opening of epoxide **25**, and subsequent dehydration, using iodine/triphenylphosphine installed the C9-C10 alkene, unveiled the C11 hydroxyl, and thus provided NCS-C aglycon **26** in a 71% yield. The synthesis was completed by Schmidt glycosylation and deprotection giving NCS-C **3** in a 1.4% overall yield over 29 linear steps.



Scheme 7. Completion of Myers' total synthesis of NCS-C **3**

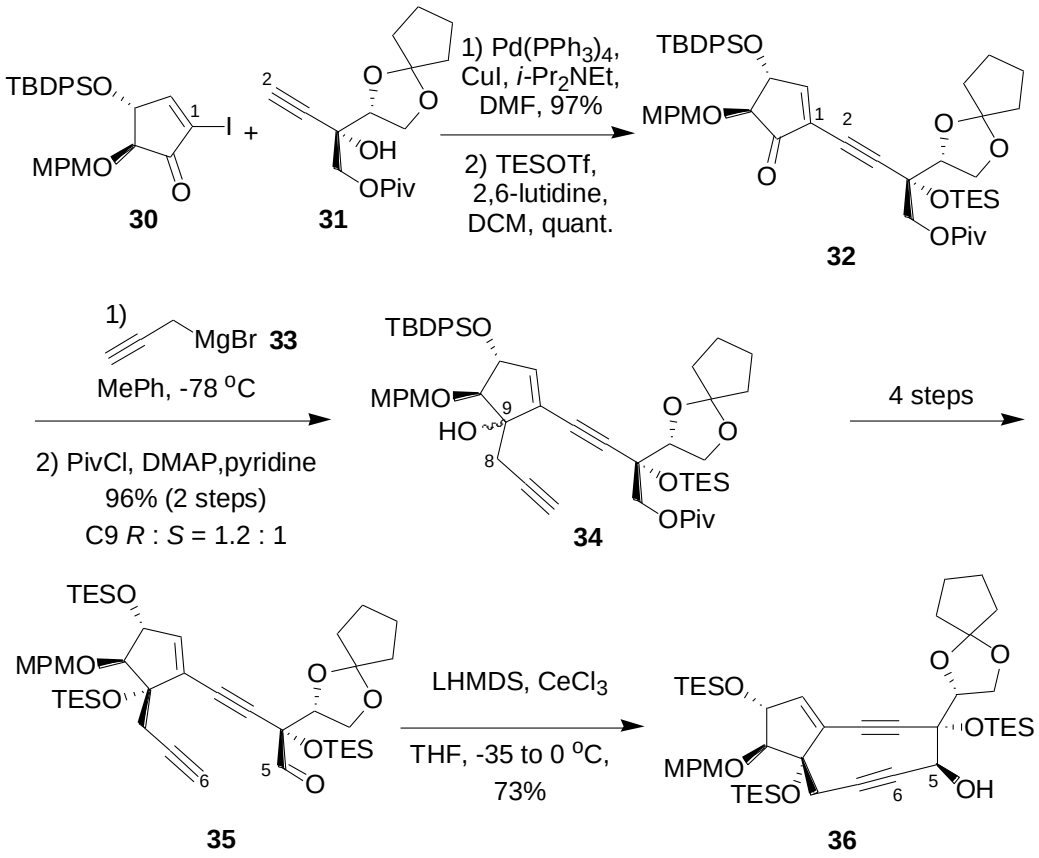
1.3.2 Hirama's approach to NCS-C aglycon

Hirama reported the formal total synthesis of NCS-C aglycon **26** in 2006 employing a convergent assembly of functionalised cyclopentenone **27**, propargylic metal species **28** and alkyne **29** relying on a stereoselective intramolecular acetylide-aldehyde cyclisation to form the C5-C6 bond and close the nine-membered ring of the enediyne core (Scheme 8).[56]



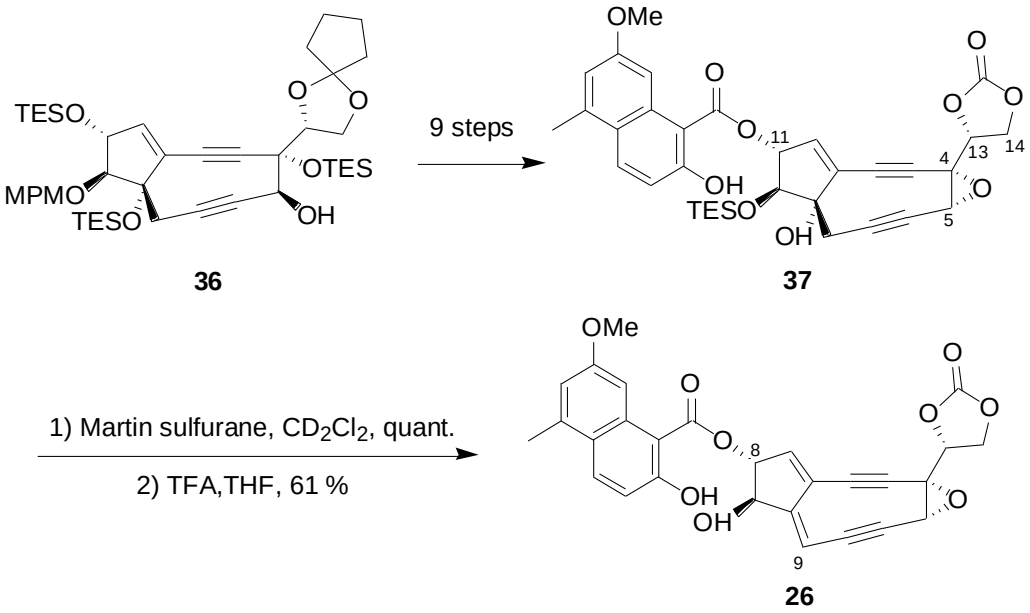
Scheme 8. Hirama's strategy for synthesis of NCS-C alygcon **26**

In Hirama's approach to the NCS-C core, the synthesis of cyclopentenone fragment **30** with differentiable protecting groups on the C10 and C11 hydroxyls was achieved in 12 steps from methyl D-glucopyranoside in an 11% overall yield (Scheme 9).[57] Protected polyol **31** could be prepared in 8 steps from D-isoascorbic acid in an 24 % overall yield.[58] The construction of the nine-membered ring was initiated with the formation of the C1-C2 bond using a Sonogashira coupling between iodocyclopentenone **30** and alkyne **31** to afford enyne **32** in an excellent yield.[58] Grignard addition of propargylmagnesium bromide **33** to ketone **32** resulted in formation of the C8-C9 bond in the resultant tertiary alcohol **34**, after reprotection with pivaloyl chloride, as a 1.2 : 1 mixture of epimers at C9 which could be readily separated. Further protecting group manipulations and oxidation provided key cyclisation precursor **35**. In a similar fashion to the approach of Myers' (See section 1.3.1, p 8), the intramolecular cyclisation of the metalated alkyne (C6) onto a carbonyl (C5) was used to construct the carbon skeleton of the NCS-C core and, thus, generate tertiary alcohol **36** in an excellent yield as a single diastereoisomer.



Scheme 9. Hirama's total synthesis of NCS-C diyne scaffold

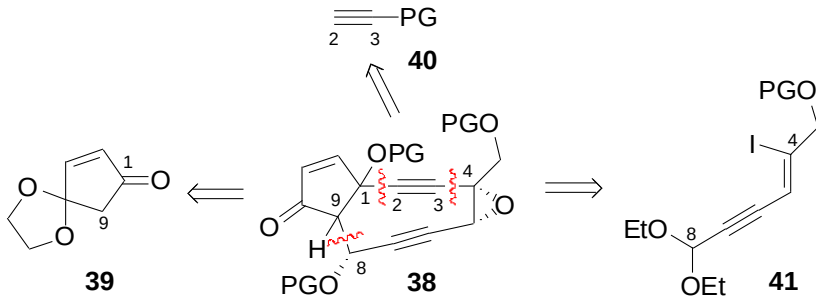
Hirama completed the synthesis of NCS-C aglycon **26** from alcohol **36** using a mesylation-desilylation-base-mediated ring closure to install the C4-C5 epoxide, condensation of the naphthoate fragment onto the C11 hydroxyl and installation of the C13-C14 carbamate to give advanced intermediate alcohol **37** (Scheme 10). In an analogous fashion to the approach adopted by Myers, Hirama relied on the dehydration of tertiary alcohol **37** using Martin's sulfurane to install the C8-C9 alkene followed by a deprotection to afford NCS-C aglycon **26** in a 0.2% overall yield in 32 linear steps.



Scheme 10. Completion of Hirama's total synthesis of NCS-C aglycon

1.3.3 Magnus' approach to NCS-C

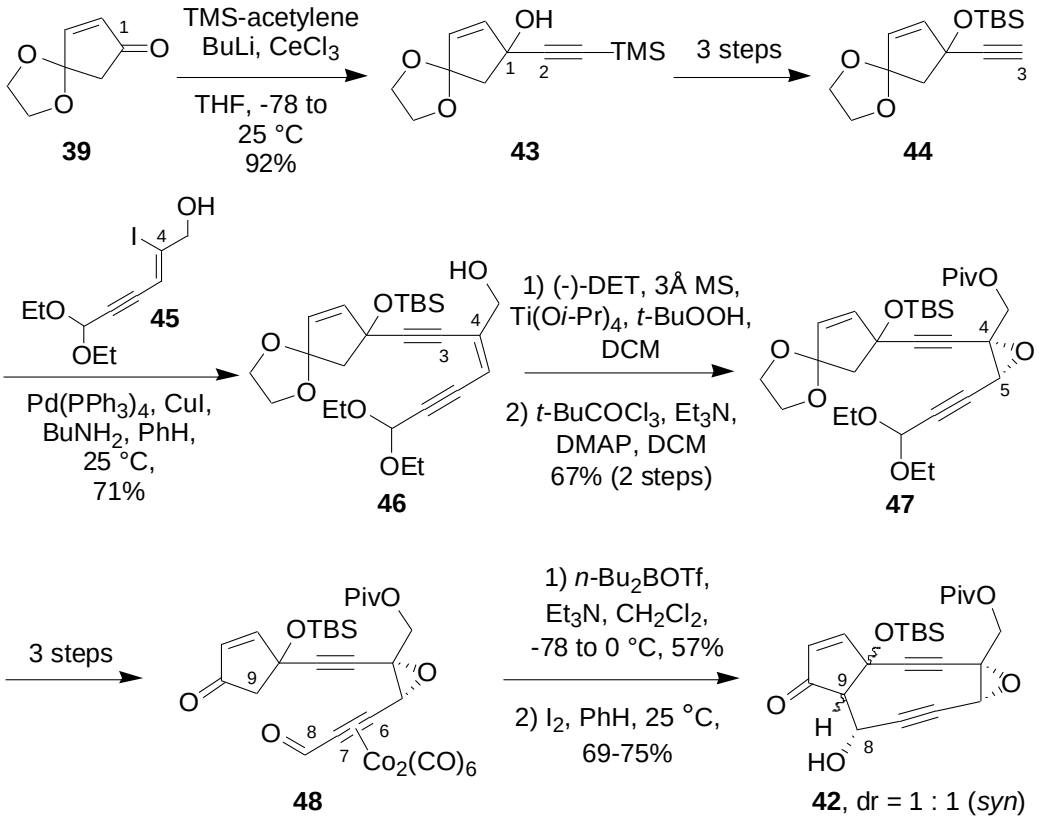
Magnus published the synthesis of a bicycle-enediyne NCS-C core **38** employing convergent assembly of cyclopentenone **39**, acetylene **40** and enyne **41** (Scheme 11)**.**[59] The strategy relies on an intramolecular aldol reaction to form C8-C9 bond and close the nine-membered enediyne ring assisted by η^2 complexation of the C6-C7 alkyne to cobalt.



Scheme 11. Magnus' approach to the NCS-C core

Magnus' synthesis of NCS-C core **42** was initiated with reaction of cyclopentenone **39** with trimethylsilylacetylene to form the C1-C2 bond and give cyclopentene **43** in excellent yield (Scheme 12). Multiple protection/deprotection steps gave alkyne **44** with the C3 alkynyl carbon unmasked. Formation of the C3-C4 bond was readily achieved through the coupling of iodoalkene **45**, available in two steps from commercial starting materials, to alkyne **44** *via* Sonogashira coupling to afford key

diynene **46**. Sharpless asymmetric epoxidation on alkene **46** installed the C4-C5 epoxide in epoxydiyne **47**. Subsequent C8 aldehyde **48** was unveiled after complexation of the sterically least encumbered alkyne C6-C7, with cobalt. Ring closure and formation of the C8-C9 bond *via* an intramolecular aldol reaction was catalysed by the addition of *n*-Bu_2BOTf and provided the NCS-C epoxydiyne carbon skeleton as a 1 : 1 mixture of *syn* diastereoisomers (C1-C9). Oxidative decomplexation of the C6-C7 cobalt gave **42** as a mixture of separable C1-C9 diastereoisomers.

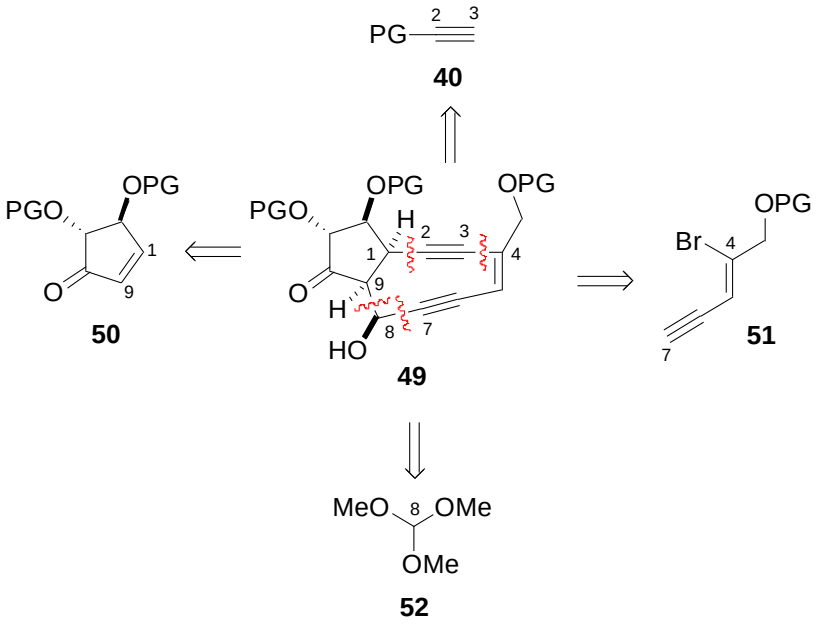


Scheme 12. Magnus' synthesis of bicyclic enediyne NCS-C core **42**

1.3.4 Caddick's approach

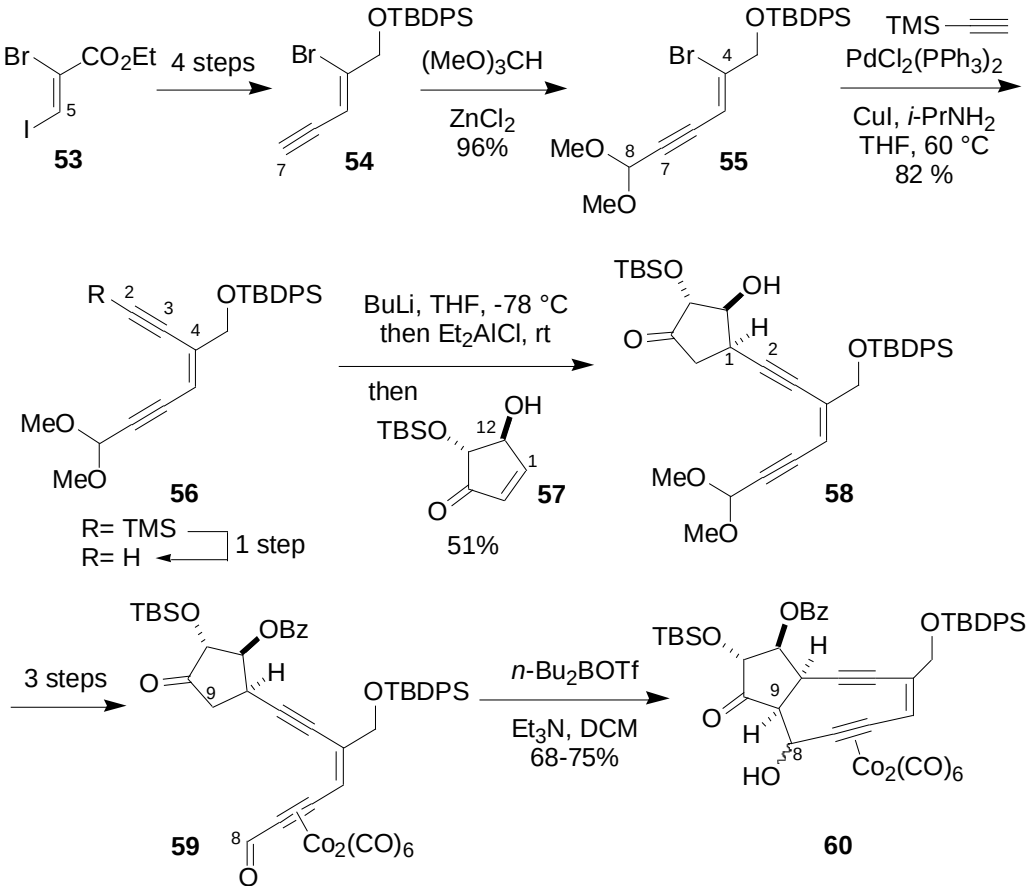
Caddick has made significant progress toward the NCS-C core *via* a number of distinct, but related, approaches.[60-67] The most successful reported approach towards advanced model system **49** relies, in an analogous fashion to that described by Magnus (See 1.3.3, p 15), on an intramolecular aldol reaction. Having the C6-C7 alkyne complexed to cobalt, closure of the strained nine-membered ring is realised through formation the C8-C9 bond (Scheme 13). The cyclisation precursor was

constructed from four fragments: cyclopentenone **50**, C2-C3 alkyne **40**, C4-C7 vinyl bromide **51** and C8 from trimethylorthoformate **52**.



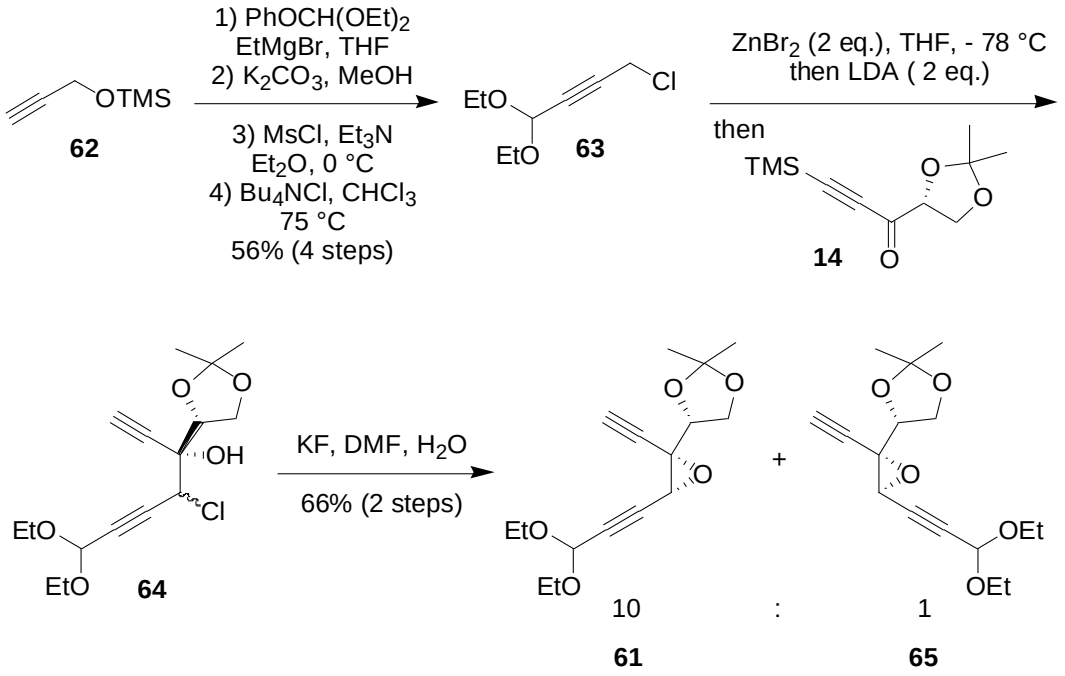
Scheme 13. Caddick's approach to the NCS-C core

Caddick's synthesis of the NCS-C core begins with the installation of the C6-C7 alkyne *via* selective Sonogashira coupling of the more reactive C5 iodide of bisvinyl halide **53** with TMS-acetylene (Scheme 14).[63] Subsequent manipulations gave the required vinyl bromide fragment **54**. Functionalisation of vinyl bromide **54** with trimethylorthoformate **52** in the presence of zinc dichloride gave acetal **55** and installed C8 on the enediyne fragment. The C2-C3 fragment was introduced via Sonogashira coupling of the C4 bromide **55** with TMS-acetylene in good yield. Key to the novelty of Caddick's approach is the formation of the C1-C2 in ketone **58**, *via* a stereoselective conjugate addition reaction of an alkynyl aluminium species derived from alkyne **56** with cyclopentenone **57**.[63,64] Cyclopentenone **57** can be accessed in 7 steps from furfuryl alcohol in good yield. Further manipulations including cobalt complexation of the C6-C7 alkyne furnished aldehyde **59**. Treatment of aldehyde **59** with di-*n*-butylboron and triethylamine gave product **60** essentially as a diastereoisomer mixture with a 10 : 1 ratio of epimers at C8.



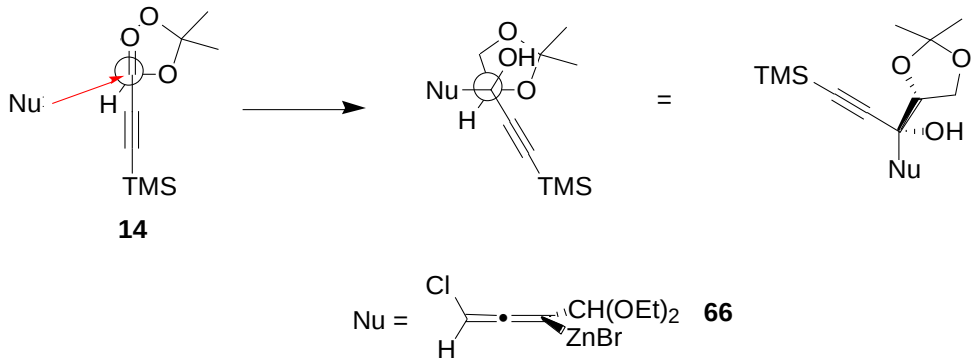
Scheme 14. Caddick conjugate addition/aldol approach toward the NCS-C core

Although Caddick had successfully synthesised the NCS-C core *via* a conjugate addition/aldol approach (Scheme 14), the synthesis of the diyne portion was long winded, lacked C14 and the C4-C5 epoxide which proved impossible to install at an advanced stage. Therefore, an alternate synthesis of the epoxydiyne fragment of NCS-C was developed.[66,67]



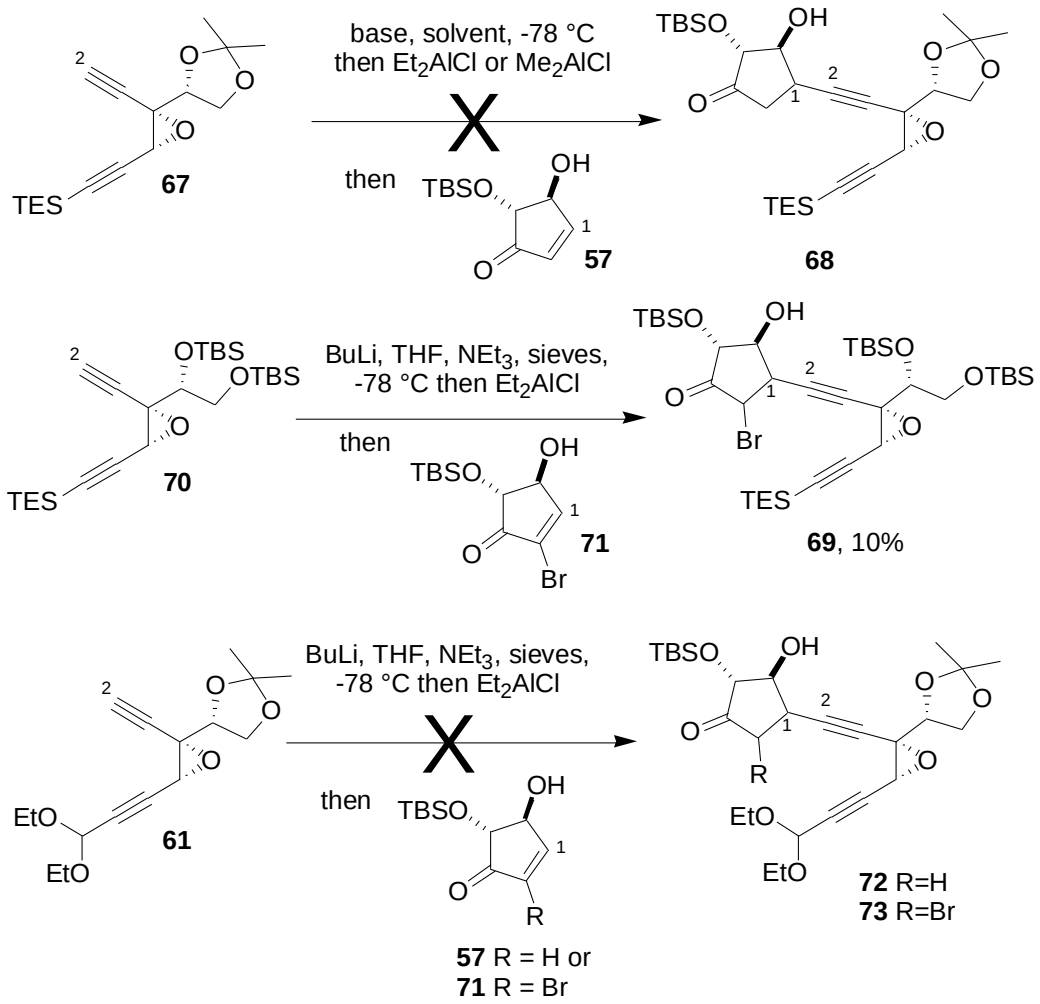
Scheme 15. Route to epoxydiyne **61** *via* allenyl zinc reaction

Synthesis of epoxydiyne **61** started with the conversion of TMS-protected propargyl alcohol **62** to chloride **63** in two sequential two-step one-pot procedure (Scheme 15). Deprotonation of propargyl chloride **63**, in the presence of $ZnBr_2$, gave the corresponding allenyl zinc reagent which was coupled to propargyl ketone **14**, synthesised according to Hirama's procedure,[68] to provide a mixture of chlorohydrins **64**, epimeric at C5, in a 10 : 1 ratio. Chlorohydrins **64** were directly converted into the desired C2-C8 epoxydiynes **61** and **65**, *via* reaction with KF in DMF, conserving the established 10:1 ratio of epimers at C5, the desired epimer being the major product. Baker and Caddick proposed that the selectivity of the reaction of the allenyl zinc **66**, derived from deprotonation of the propargylic chloride **63**, with the propargylic ketone **14** can be rationalised *via* a Felkin-Anh model (Scheme 16).[66] In that, approach of the nucleophile to ketone **14** preferentially occurs on the sterically least encumbered *Re* face of ketone **14**.



Scheme 16. Proposed transition state for addition of allenyl zinc **66** to ketone **14**

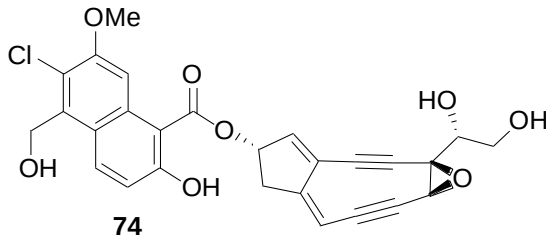
The aluminium assisted conjugate addition of epoxydiynes to key cyclopentenone **57** to construct the C1-C2 bond was thoroughly studied by Thominet.[69] Initial investigations were carried out with the epoxydiyne **67**, synthesised in an analogous manner to epoxydiyne **61** (Scheme 15), which contains all the correct stereochemistry at C4, C5 and C13 but is crucially lacking C8. Conjugate addition of diyne **67** to cyclopentenone **57**, following the conditions successful for the addition of model enediynes, BuLi in THF at -78 °C followed by addition of the alkynaluminium reagent, was unsuccessful.[61] Further attempts varying the solvent (THF, toluene, Et_2O), the base (*n*-BuLi, LDA) and the alkynaluminium reagent (Et_2AlCl or Me_2AlCl) were investigated without success. However, upon replacement of the C13-C14 acetonide with TBS silyl ethers and addition of triethylamine and molecular sieves, formation of Michael adduct **69** could be observed on reaction of epoxydiyne **70** with brominated cyclopentenone **71**, albeit in 10% yield (Scheme 17). Unfortunately, these modest results could not be reproduced upon the reaction of key epoxydiyne **61** containing the C8 acetal with cyclopentenone **57** or **71** to obtain adduct **72** or **73**. Application of Schwartz's conditions ($Ni(acac)_2$/DIBAL/BuLi, Me_2AlCl) lead to decomposition of epoxydiyne **61**,[70] whereas zinc-mediated Michael addition afforded no reaction, with only starting material recovered.[71] Finally, the use of Nilsson's conditions (alkynyl copper/TMSI) were also unsuccessful.[72]



Scheme 17. Michael addition of epoxydiynes with cyclopentenones

1.3.5 Synthesis of N1999-A2

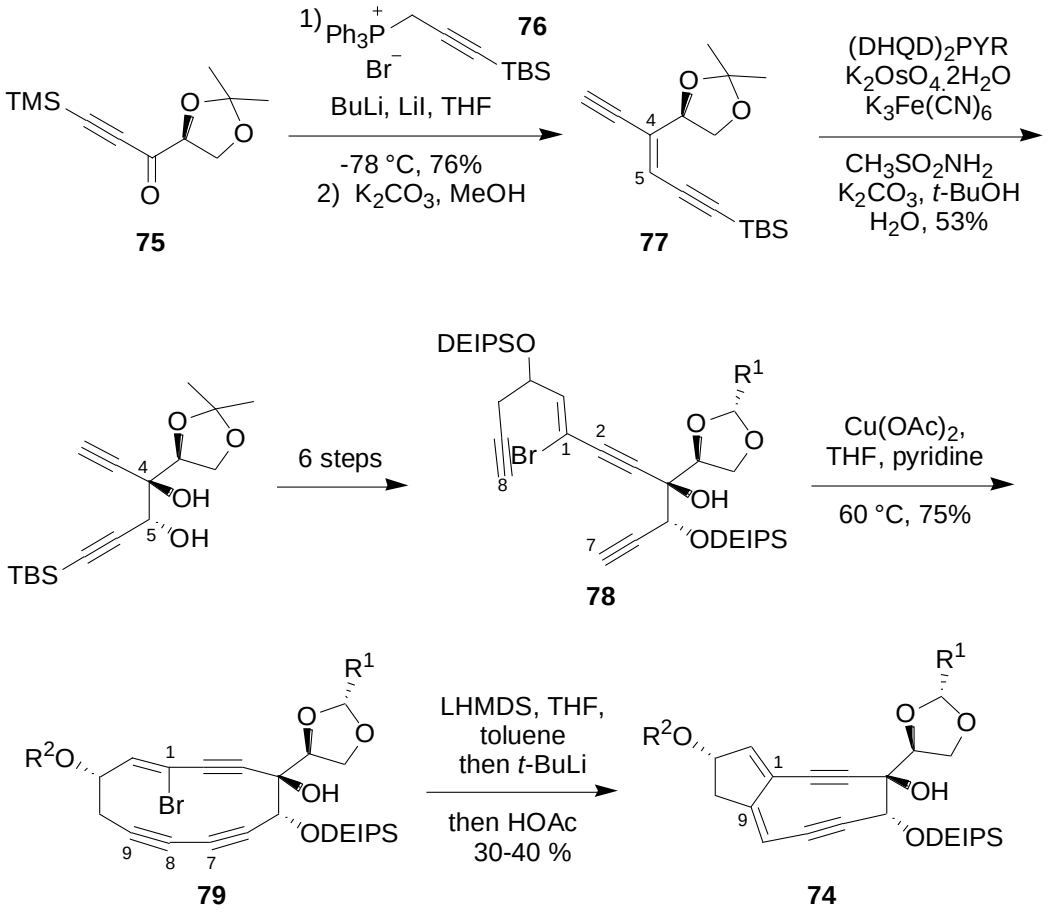
N1999-A2 **74** is an enediyne that has been isolated from *Streptomyces Sp*. AJ9493 and exhibits anti-tumour and anti-bacterial properties (Figure 5).[73] It possesses the nine-membered enediyne ring similar to NCS-C chromophore but lacks the C10 amino-sugar residue, has no C13-C14 carbonate and possesses the opposite stereochemistry at both the C4-C5 epoxide and the C13 hydroxyl. Both Hirama[74] and Myers[75] have described total syntheses of N1999-A2. Hirama adopted an almost identical strategy for the synthesis of N1999-A2 as for NCS-C aglycon **26** (See 1.3.2, p 12), therefore his synthesis will not be discussed further. However, Myers'strategy for the synthesis of N1999-A2 differed significantly from his approach to NCS-C **3** (See 1.3.1, p 8).



74

Figure 5. Structure of N1999-A2

Myers proposed a convergent total synthesis of the N1999-A2 core by achieving a transannular cyclisation at C1-C9 (Scheme 18). Wittig reaction of propargylic ketone **75**, prepared in two steps from (S)-glyceraldehyde acetonide,[50] with phosphonium salt **76** formed the C4-C5 bond and gave exclusively the (Z)-olefin **77**. Diastereoselective dihydroxylation of alkene **77** using Sharpless' conditions, installed the C4 stereocentre in good yield. Subsequent manipulations including installation of the C1-C2 bond by Sonogashira coupling gave triyne **78** in 6 steps. The completion of the synthesis of the N1999-A2 core was achieved *via* sequential cyclisation of linear triyne **78** to generate the C7-C8 bond, under modified Eglinton conditions, to give cyclic enetriyne **79**, containing a 12-membered ring. Subsequent transannular cyclisation of triyne **79**, and formation of the C1-C9 bond, afforded the bicyclic core of N1999-A2 **74**.



Scheme 18. Myers' approach to N1999-A2 **74**

Work of Myers, Hirama, Magnus and Caddick has shown the inherent challenges which exist in the total synthesis of NCS-C. In particular the bicyclic epoxydiyne which, much like many medium-sized rings, offers the greatest challenge with regards to synthesis. In this project, evaluation of alternatives approaches for the synthesis of medium size rings using McMurry coupling and acyl radical chemistry is proposed.

1.4 Cyclisation methods

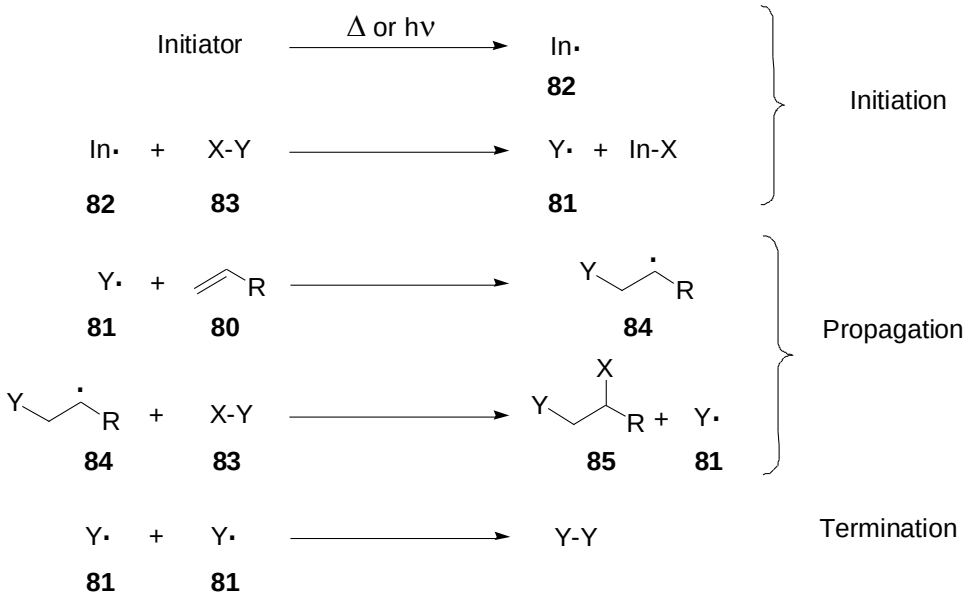
The synthesis of rings is of particular interest for organic chemists because of their prevalence in synthetic and natural products. Many methods exist, and have been employed, to synthesise rings of all sizes, such as the Diels-Alder reaction,[76] ring-closing metathesis,[77,78] Nazarov cyclisation,[79] Dieckmann condensation[80] and many others. Of particular relevance for this project is the use of McMurry reaction or acyl radical chemistry for the synthesis of medium sized ring systems.

1.4.1 Radical chemistry

1.4.1.1 Introduction

Pioneering studies of free radical chemistry were carried out by Gomberg in 1900 while working on reactions of chlorotriphenylmethane with metals.[81] However, the impact of this discovery was not grasped until Kharasch's work on the addition of bromine radicals to alkenes in 1933.[82]

Radicals are species with a single unpaired electron. Reactions of radicals proceed *via* a chain process which is composed of three steps: initiation; propagation and termination (Scheme 19).[83] For example, the reaction of alkene **80** with radical **81** begins with the formation of initial radical **82** by homolytic bond fission or fragmentation of an initiator upon thermal exposure or photochemical excitation. Radical **82** then reacts with a non-radical species **83** to subsequently form radical **81**, often called the chain carrier, whose role is to propagate the chain process. Addition of radical **81** to alkene **80** generates radical **84**, which then reacts with molecule **83** to form compound **85** and regenerate chain carrier **81** for another cycle of propagation. Radical reactions are, in general, terminated by recombination of two chain carriers **81**.

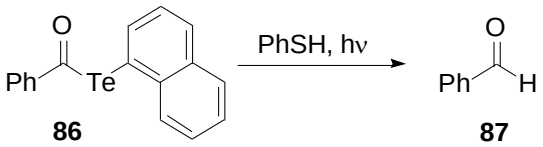


Scheme 19. Radical chain process

Many radical initiators exist, among which azobisisobutyronitrile (AIBN), diacyl peroxides, and triethylborane/oxygen, are the most commonly employed.[84,85] Trialkyltin radicals are the most widely used chain carriers.[86] Nevertheless, due to the toxicity of tin wastes, alternative non-tin based chain carrier have been developed, such as 1-ethyl-piperidine hypophosphite (EPHP)[87] and tris(trimethylsilyl)silane (TTMSS).[88]

1.4.1.2 Acyl radical chemistry

Acyl radicals have been widely used and reviewed in depth by Chatgilialoglu, Crich and Ryu.[89] Acyl radicals can be generated from a variety of substrates including aldehydes, acyl chlorides, telluro- and selenoesters. For example, photolysis of naphthyl telluride ester **86** generated subsequent acyl radical which gave benzaldehyde **87** after abstraction of a proton from benzothiol (Scheme 20).[90]

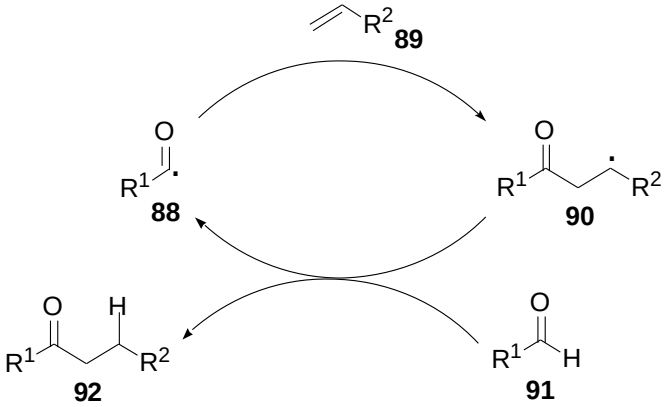


86 **87**

Scheme 20. Synthesis of benzaldehyde **87** *via* photolysis of telluroester **86**

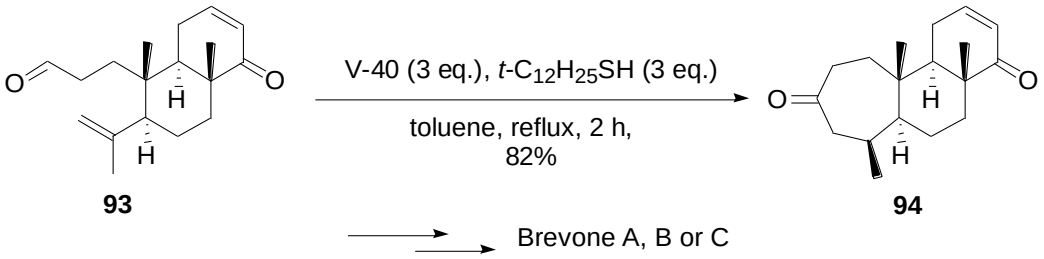
1.4.1.2.1 Hydroacylations via acyl radicals

The hydroacylation of an alkene by an aldehyde to form an unsymmetrical ketone has attracted much attention, as the reactivity of the aldehyde is reversed and it reacts as a nucleophile.[89] One method to affect alkene hydroacylation is *via* the addition of an acyl radical to a suitably functioned substrate. Addition of acyl radical **88** to alkene **89** generates adduct radical **90**. Radical **90** can then propagate the chain, if suitably polarity matched, by abstraction of an aldehydic proton of **91** to give an unsymmetrical ketone **92** and regenerate acyl radical **88**.

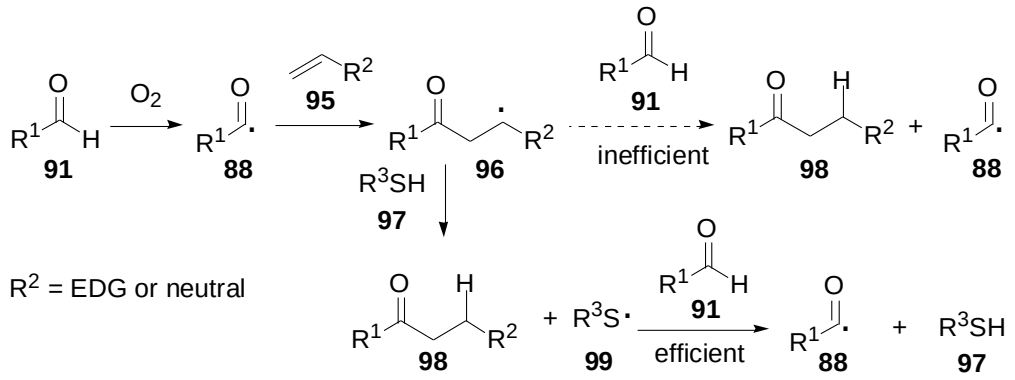


Scheme 21. Hydroacylation *via* acyl radicals

Many examples of the addition of acyl radicals to a variety of alkenes and enones have been reported.[89] For example, Shishido reported the use of an acyl radical cyclisation in his synthesis of Breviones A, B and C (Scheme 22).[91] The acyl radical derived from aldehyde **93** by use of radical initiator V-40 (1,1'-azobis(cyclohexane-1-carbonitrile)) selectively attacks the alkene over enone to form seven-membered ring **94**. In this example, *tert*-dodecanethiol was used as a polarity reversal catalyst. Acyl radicals tend to add more favourably to electron poor alkenes. For electron neutral and rich alkene **95**, abstraction of the aldehydic proton from nucleophilic radical **96** is inefficient (Scheme 23). However, abstraction of proton from thiol **97** by nucleophilic radical **96** happens readily providing ketone **98** and electrophilic thiyl radical **99**, well polarity matched to abstract the aldehydic proton and propagate the chain.



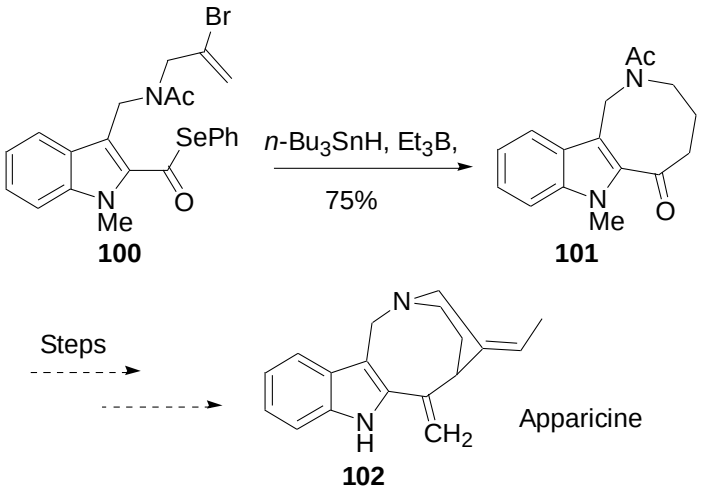
Scheme 22. Use of acyl radical cyclisation *en route* to Brevione A, B or C



Scheme 23. Use of thiols as polarity reversal catalyst in hydroacylation of alkenes

1.4.1.2.2 Use of acyl radical in synthesis of medium-sized rings

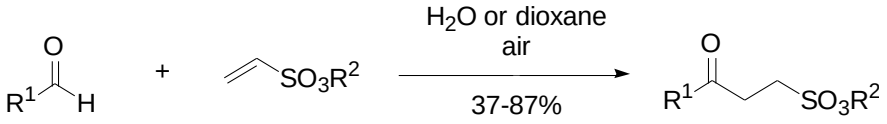
Acyl radicals have been widely used for cyclisation reactions and reviewed in depth by Chatgilialoglu, Crich and Ryu.[89] Radical cyclisation is a well-established method for the synthesis of five and six-membered rings, however approaches for medium-sized rings are still limited. Recently, Bennasar reported a *8-endo-trig* cyclisation with an acyl radical derived from selenoester **100** to form tricyclooctanone **101**, a sub-unit of Apparicine **102** (Scheme 24).[92]



Scheme 24. Use of acyl radical cyclisation for the synthesis of medium-sized ring intermediate **101**

1.4.1.2.3 New mild method of hydroacylation of vinyl sulfonates

Recently Caddick reported a mild and selective method of hydroacylation of vinyl sulfonates **103** with a variety of simple alkyl aldehydes **91** to give ketosulfonates **104** (Scheme 25).[93-95] Caddick suggests the hydroacylation proceeds *via* interception of the acyl radical generated during auto-oxidation of aldehyde **91** by the highly electron deficient vinyl sulfonate **103**. Thus, hydroacylation of vinyl sulfonate **103** proceeds in the presence of ony two reactants, solvent and air, and affects a clean, atom economic hydroacylation. More recently Caddick has expanded the range of acceptors to sulfones, unsaturated esters and azo-dicarboxylates (Scheme 25).

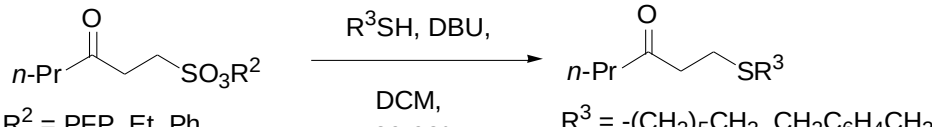


91 **103** **104**

R^1 = alkyl, R^2 = TCP, PFP, Ph, Et

Scheme 25. Hydroacylation of vinyl sulfonates **103** with aldehydes **91**

This method allows not only access to novel β-ketosulfonates compounds but also to synthetically useful enones, *via* efficient in-situ elimination.[94] Caddick has shown that treatment of β-ketosulfonates **105** with DBU in the presence of thiols gave sulphides **106** in good to excellent yields, *via* an elimination-addition sequence (Scheme 26).



R^2 = PFP, Et, Ph
105

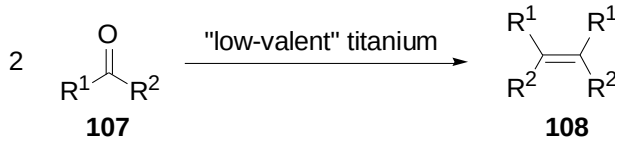
R^3 = $-(CH_2)_5CH_3$, $CH_2C_6H_4CH_3$
106

Scheme 26. *In situ* elimination-thiolation of β-ketosulfonates **105**

1.4.2 The McMurry coupling

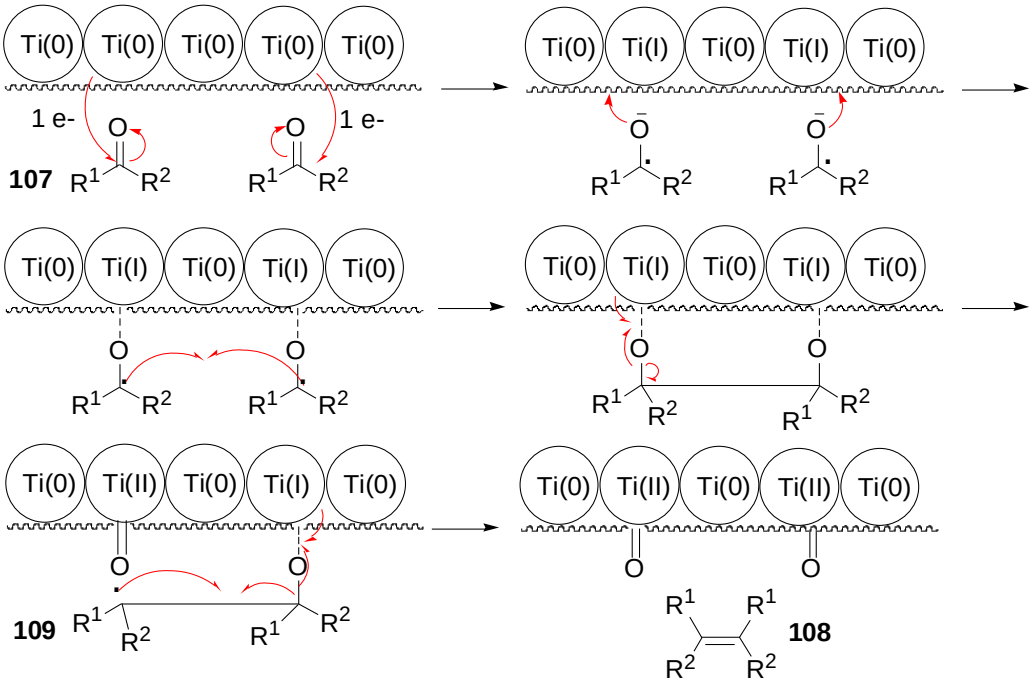
1.4.2.1 Introduction

The McMurry coupling is a reductive dimerisation of aldehydes or ketones **107** in the presence of low-valent titanium, to yield olefins **108** (Scheme 27).[96] Low-valent titanium can be prepared *via* a range of methods; $TiCl_3/LiAlH_4$, $TiCl_3$/Zn-Cu, $TiCl_3(DME)_2$/Zn-Cu being the most commonly employed.



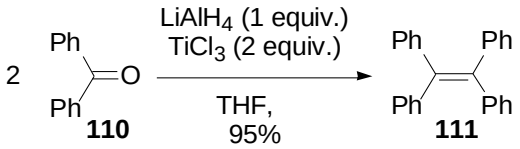
Scheme 27. The McMurry coupling

This carbonyl coupling reaction takes place in two steps; first a reductive dimerisation of the aldehyde or ketone **107** to form the C-C bond, then a deoxygenation of 1,2-diolate **109** intermediate to yield olefin **108** (Scheme 28). The first step is similar to a pinacol reaction and is not unique to titanium. Titanium-induced deoxygenation of pinacolates takes place by coordination of the pinacolate to the surface of a small Ti(0) particle, followed by a stepwise cleavage of the C-O bonds, to form the desired π-bond and an oxide-coated titanium surface.[96]

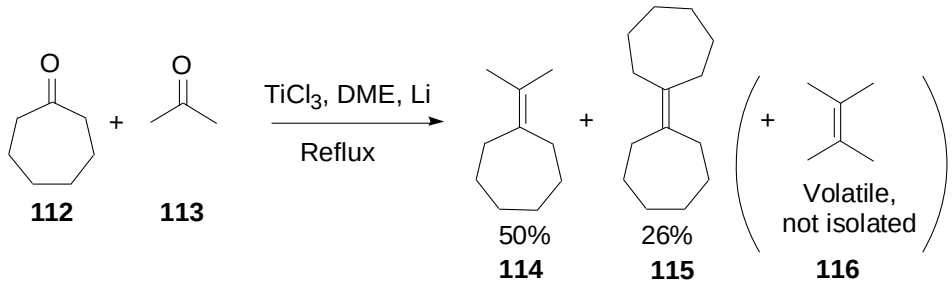


Scheme 28. Mechanism of the McMurry coupling

One of the earliest examples of McMurry coupling is the dimerisation of benzophenone **110** to give 1,1,2,2-tetraphenylethylene **111** (Scheme 29).[97] When two different carbonyls are reacted together, a roughly statistical mixture of the possible alkenes is obtained.[96,98] For example, McMurry observed that when mixing cycloheptanone **112** and acetone **113**, a roughly statistical mixture of ispropylidenecycloheptane **114**, bicycloheptylidene **115** and tetramethylethylene **116** was obtained; tetramethylethylene **116** being volatile was not isolated (Scheme 30).[99] Thus, the intermolecular coupling is limited in its use and McMurry couplings are mostly employed to affect intramolecular cyclisation.

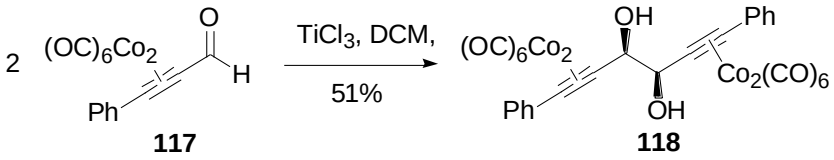


Scheme 29. Dimerisation of benzophenone **110** under McMurry conditions



Scheme 30. Statistical mixture in an intermolecular McMurry coupling

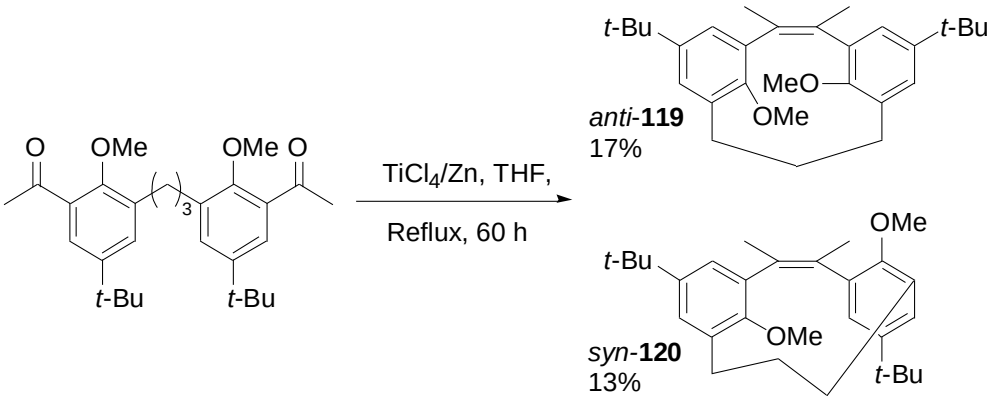
The McMurry conditions are often used for the first step of the reaction, *i.e.* the pinacol reaction.[100-102] Of particular interest is the pinacol coupling of cobalt-complexed propargylic aldehyde **117** to give *syn* diol **118** in moderate yield (Scheme 31).[103]



Scheme 31. Pinacol coupling of cobal-complexed propargylic aldehyde **117**

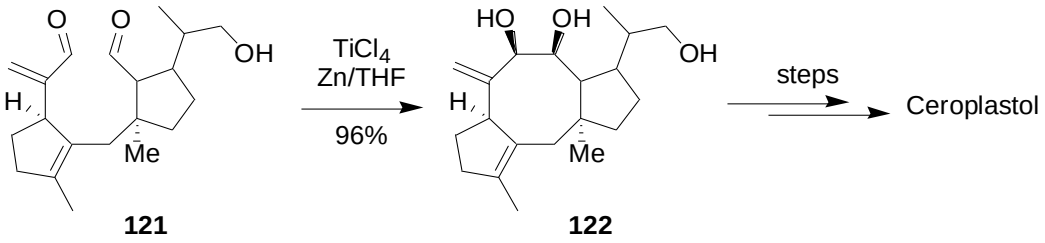
1.4.2.2 Use of McMurry couplings in the synthesis of strained medium-sized rings

McMurry conditions have been widely employed for the synthesis of strained medium-sized rings.[96,101,104-112] For example, Yamato used a McMurry coupling in his synthesis of distorted eleven-membered metacylophanes *anti*-**119** and *syn*-**120** (Scheme 32).[111]



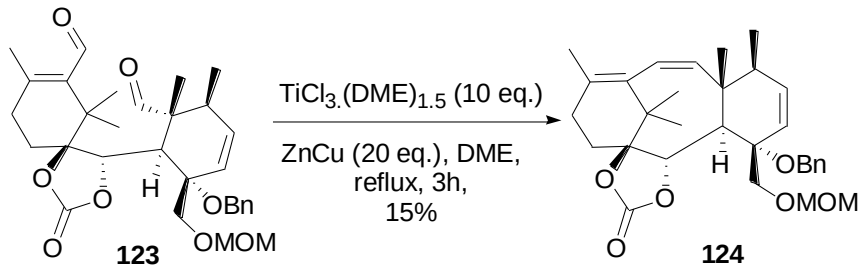
Scheme 32. Synthesis of highly strained medium rings *via* McMurry coupling

Since its discovery, the McMurry coupling has been used in numerous total syntheses.[96,98,100-102,113-119] Even polyoxygenated compounds, which are particularly challenging due to the high affinity of low-valent titanium for oxygen, have been used as substrates for these reactions. A variety of ring sizes have been explored, from five-membered to seventy-two-membered rings;[96,119] illustrating the powerful and flexible nature of this method. Of particular note is the use of a McMurry coupling by Kato in the construction of the eight-membered central ring of Ceroplastol (Scheme 33).[120] Intramolecular pinacol coupling of diketone **121** gave tricyclic intermediate **122** in excellent yield. During his studies on Taxol, Nicolaou reported a McMurry coupling of diketone **123** forming a highly polyoxygenated ten-membered ring **124** (Scheme 34).[110]



121 **122**

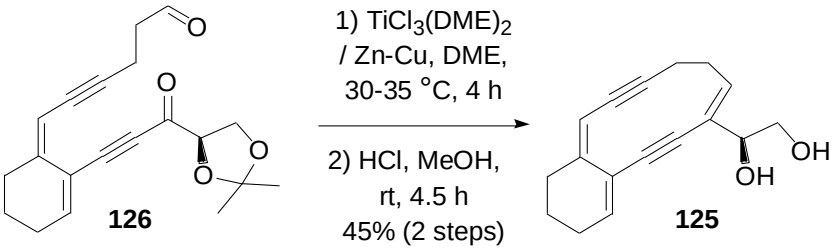
Scheme 33. Synthesis of Ceroplsatol intermediate **122** using the McMurry coupling



123 **124**

Scheme 34. Synthesis of polyoxygenated medium-sized Taxol intermediate **124**

Of particular interest is Brückner's synthesis of a model enediyne **125** based on Neocarzinostatin chromophore.[112] Treatment of keto aldehyde **126** under the McMurry conditions afforded a strained eleven-membered dienediyne **125**, forming a 6/11 bicyclic core, in 30% yield (Scheme 35).



Scheme 35. Brückner's synthesis of eleven-membered dienediyne **125**

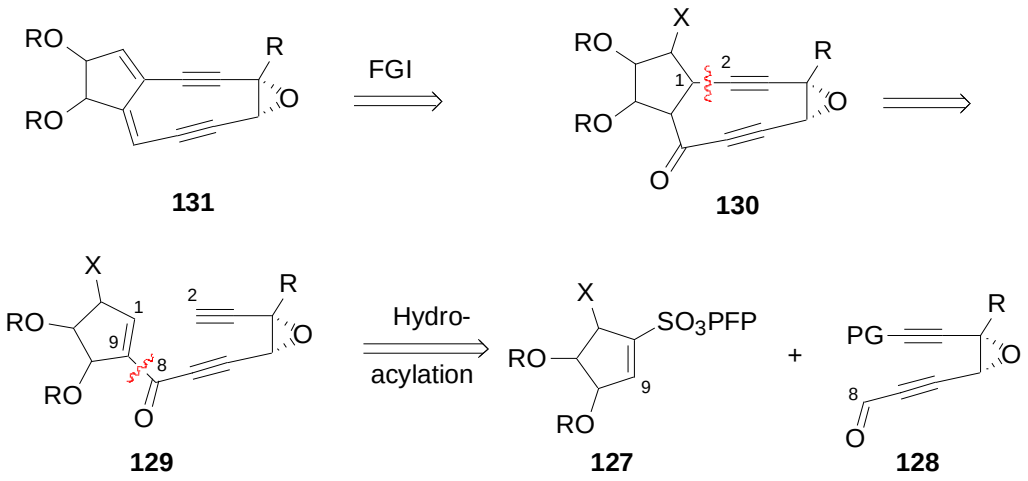
1.5 Aims for the project and retrosynthetic analysis

Different approaches have been adopted to close the enediyne ring of Neocarzinostatin chromophore. Addition of a lithiated alkyne onto an aldehyde has been used by both Myers[50] and Hirama[56] to close the enediyne ring and form the C7-C8 and C5-C6 bond respectively. Adopting an approach similar to that previously employed by Magnus and Caddick (See 1.3.3 and 1.3.4, p 15 and 16), but incorporating novel strategies for the ring closure of the nine-membered ring enediyne epoxide would provide interesting novel approaches to NCS-C core. Considering that both McMurry coupling and acyl radical additions to alkenes have been used to construct complex natural product scaffolds (See 1.4.1.2.2 and 1.4.2.2, p 27 and 31), both strategies were to be evaluated. Installation of the naphthoate and the sugar moeities of NCS-C have been reported previously by Hirama and Myers and do not represent the key synthetic challenge of this complex natural product. Therefore, the target for this project is a suitably differentially protected NCS-C enediyne epoxide lacking both the naphthoate and the sugar portions of the natural product NCS-C.[51,52]

1.5.1 Acyl radical approach

Work carried out within the Caddick group led to the discovery of a new method of hydroacylation (See 1.4.1.2.3, p 28).[93-95] It was therefore decided to investigate the use of this acyl radical method as a means to cyclise the enediyne ring. The hydroacylation/elimination of an appropriately substituted vinyl sulfonate, **127**, with a functionalised aldehyde, **128**, would provide an alternate route for the construction of the NCS-C C8-C9 bond and derive the intermediate ketone **129** (Scheme 36). Subsequent construction of the C1-C2 bond, **130**, could be affected *via* an aluminium assisted conjugate addition/cyclisation[69] of C2 onto C1, perhaps with additional

cobalt complexation[59] of either C2-C3 or C6-C7 alkynes to relieve ring strain, to close the desired nine-member ring enediyne core. Subsequent reduction and elimination sequences should derive the intact NCS-C enediyne epoxide **131**. However, the factors governing the aerobic hydroacylation of vinyl sulfonates are not completely understood. Therefore, the initial focus of this project will evaluate the feasibility of the use of such a reaction for construction of more complex molecular architectures than those described by Caddick to date. In addition, further insight into the mechanism of this complex process will be sought.

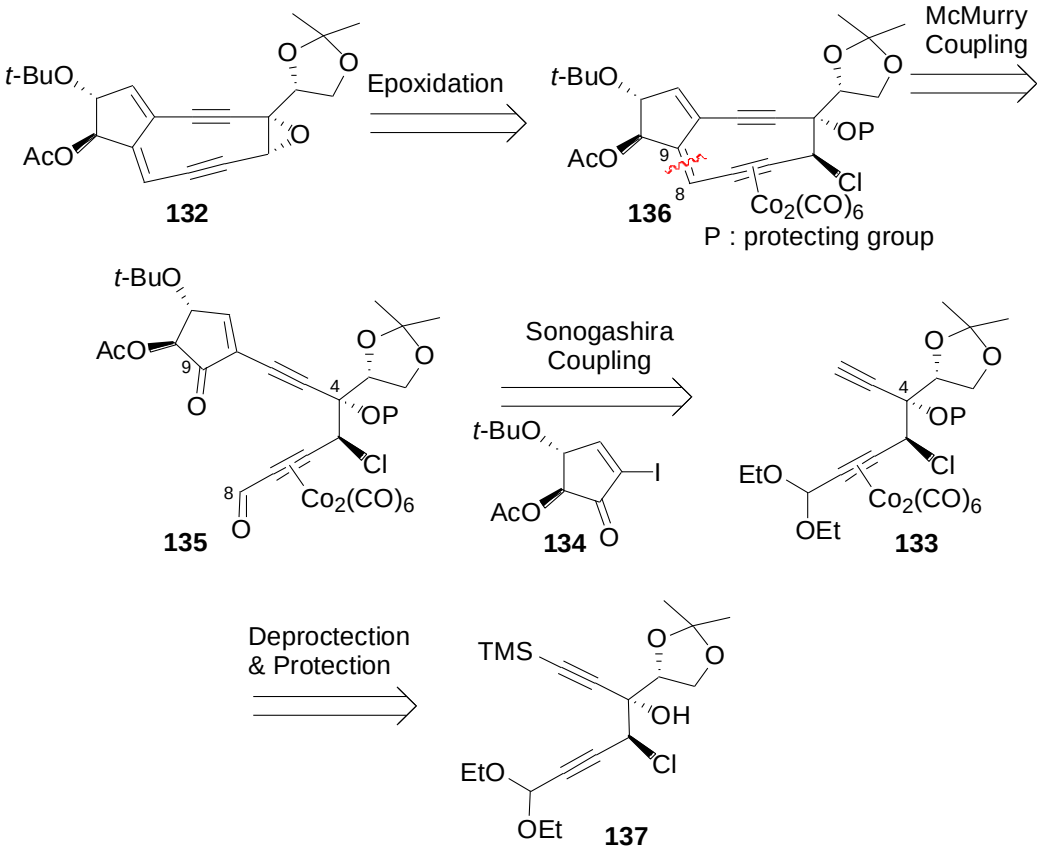


Scheme 36. Retrosynthetic analysis for the synthesis of epoxydiyne **131** *via* the acyl radical approach

1.5.2 McMurry coupling approach

Thominet's work on the rapid construction of the C2-C8 fragment of NCS-C from relatively simple building blocks provides access to the advanced intermediate **61** for the completion of the synthesis of NCS-C core (See 1.3.4, p 16).[69] However, intramolecular Michael additions of this advanced epoxydiyne to induce the formation of the C1-C2 bond appeared to be non-trivial. Among the other possible routes, the combination of a Sonogashira reaction between diyne **133** and iodocyclopentenone **134**, to construct the C1-C2 bond, in an analogous fashion to Hirama,[56] and an intramolecular McMurry coupling with adduct **135** (Scheme 37) is highly convergent and would generate the NCS-C core **136** in a short manner. McMurry couplings are known to be efficient for synthesising strained medium rings, including very strained ones.[96] Therefore, McMurry coupling was identified as an ideal methodology to close the nine-membered ring *via* formation of the C8-C9

bond. However, given the intolerance of the McMurry reaction for oxygenated functionalities, in particular epoxides, a modified approach using Thominet's intermediate **137** was conceived (Scheme 37).

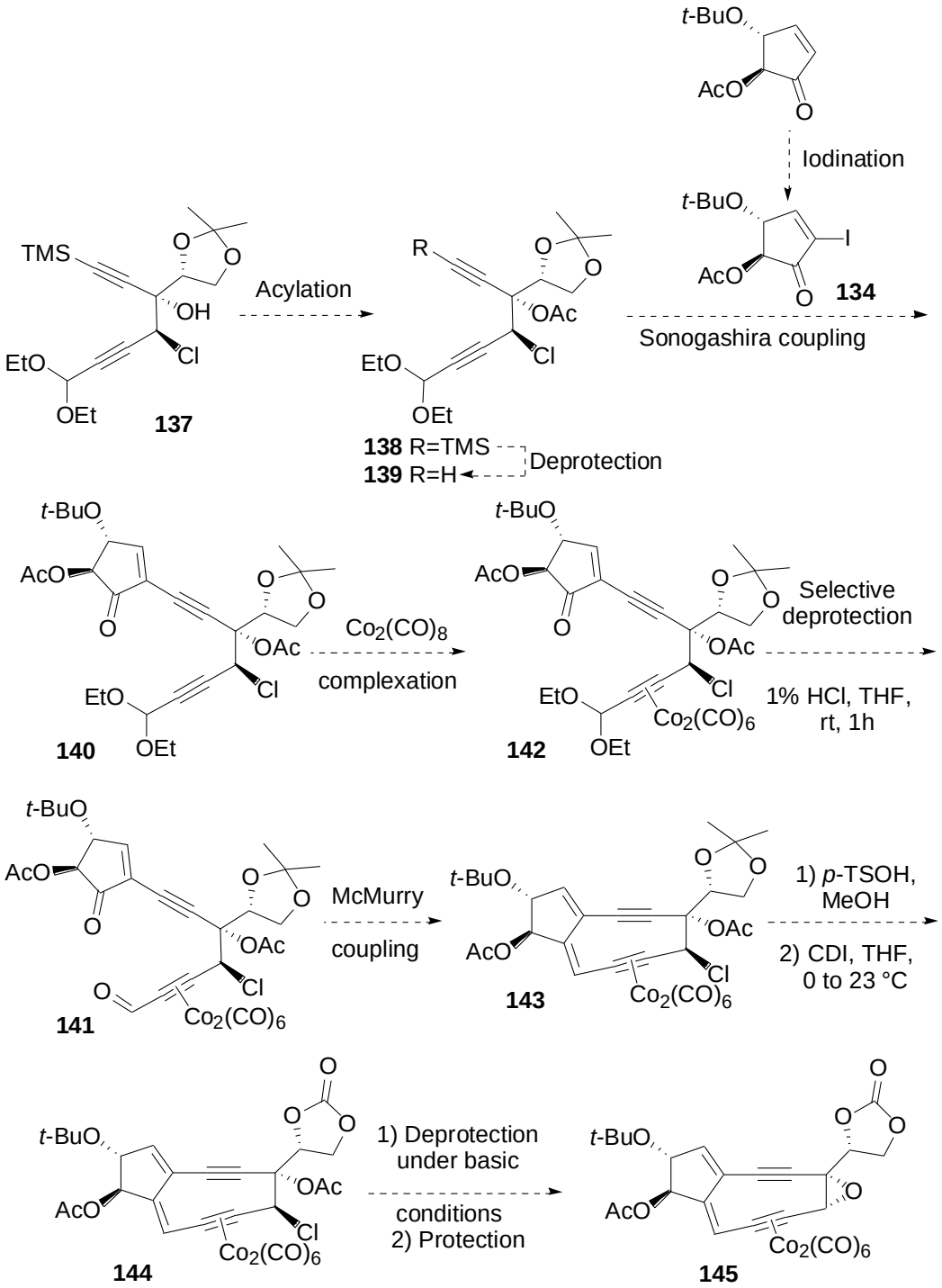


Scheme 37. Retrosynthetic analysis for the synthesis of epoxydiyne **132** *via* the McMurry approach

It is envisaged that protection of C-4 alcohol as an acetate to give **138** would prevent undesired epoxide formation in later steps (Scheme 38).[56] Sonogashira coupling between free alkyne **139** and iodonated cyclopentenone **134** should provide diyne **140**.[56] Selective deprotection of terminal acetal[121] and cobalt complexation[59] should afford cobalt-complexed diyne **141**, although the order of reaction to provide **141** from **142** may be reversed if selectivity of complexation and deprotection is enhanced. Should the selective acetal deprotection fail to work, the route would need to be modified. Replacement of the acetal by a protected alcohol, which would then be deprotected and oxidised immediately prior to the McMurry coupling, would be a suitable alternative.

Cobalt-complexation of the C6-C7 alkyne should assist the first step of the McMurry coupling of keto aldehyde **141**, *i.e.* the pinacol reaction (See 1.4.2.2, p 31), by both stabilising the coupling intermediate and by bringing the aldehyde closer to the ketone, as the coordinated alkyne is severely bent.[103]

Removal of the dioxolane protecting group in cyclic diyne **143** would be followed by installation of the carbonate to give intermediate **144**. Deprotection of the alcohol **144** under basic conditions is hoped to readily provide epoxide **145**; providing competitive epoxidation, resulting from the carbonate group leaving, does not occur.



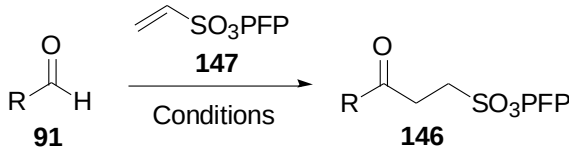
Scheme 38. NCS-C strategy via McMurry cyclisation

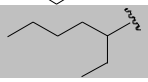
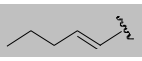
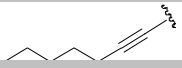
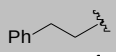
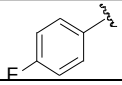
Chapter 2. Studies on the aerobic hydroacylation of vinyl sulfonates

2.1 Hydroacylation of vinyl sulfonates

Modern organic synthesis requires the elaboration of novel and efficient methods to construct complex molecules. C-C bond formation still represents a challenge in total synthesis and many methods have been developed focusing on the use of catalysts, as they tend to offer enhanced atom-economy and minimal waste.[122] Nevertheless, those methods require the preparation of a modified substrate whose functional group will undergo a chemical reaction to provide the desired product. An attractive alternative is to use the C-H activation, in particular with transition metal catalysis.[123-125] However, many selectivity issues have been encountered for the C-H activation step, often relying on local directing groups to provide selectivity.[126-128]

Recently Caddick reported mild and selective methods for preparation of 1,4-keto-sulfonates **146** *via* radical hydroacylation of pentafluorophenyl vinyl sulfonate (PFPVS) **147** with aldehydes **91** (Table 1).[93-95,129,130] Only simple alkyl aldehydes **91** (Table 1, Entries 1-6) were reported to be effective in aerobic hydroacylation of PFPVS **147** in moderate to excellent yield. The hydroacylation of PFPVS **147** did tolerate all simple alkyl aldehydes **91**; indeed, some had very little or no reactivity (Table 1, Entries 7-9). In the particular case of hydrocinnamaldehyde (Table 1, Entry 10), reaction of hydroacylation proceeded to some extent but no pure product could be isolated, as ketosulfonate (R = - CH_2CH_2Ph) could not be separated from its corresponding enone generated upon elimination of ketosulfonate on silica. 4-Fluorobenzaldehyde (Table 1, Entry 11) was the only aromatic aldehyde to show some reactivity towards hydroacylation of PFPVS **147** and the corresponding ketosulfonate was isolated, albeit in low yield. Using water as a solvent enabled the number of equivalents of aldehyde **91** to be reduced from 5 (Method A) to 2 (Method B and C). Hydrogen peroxide was found to have a limited impact on yield and reaction times, therefore method C (aldehyde **91** (2 eq.), PFPVS **147** (1 eq.), water, 300 rpm, 21 °C) is the preferred method for hydroacylation of PFPVS **147**.



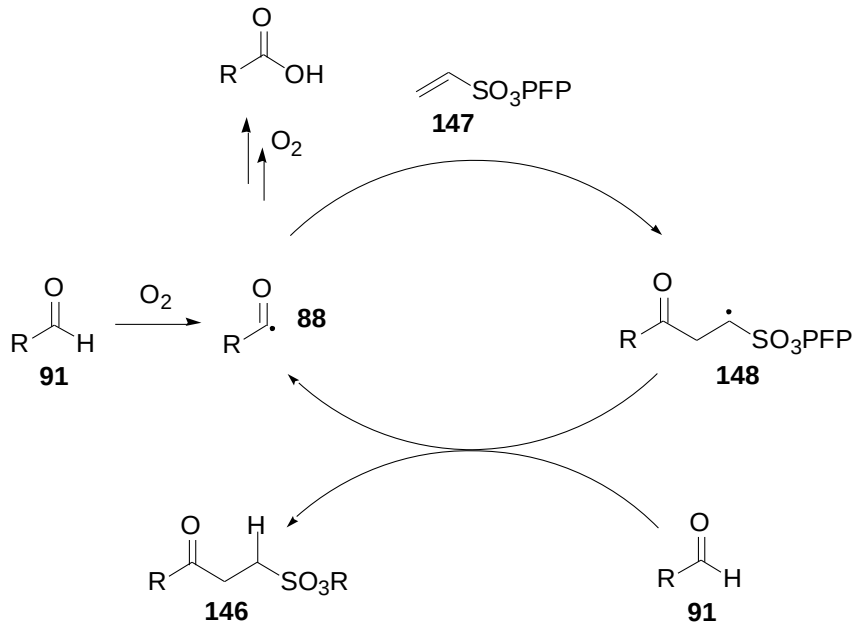
Entry	R	Method A		Method B		Method C	
		T(h)	Yield(%)	T(h)	Yield(%)	T(h)	Yield(%)
1		1	65	1	84	3	78
2		3	58	1	56	3	40[a]
3		3	47	1	79	3	74
4		1	69	1	87	3	83
5		-	-	2	66	6	62
6		3	5[b]	3	58[c]	-	-
7		3	38	168	0	-	-
8		24	12	-	-	-	-
9		168	0	-	-	-	-
10		18	0[d]	-	-	-	-
11		18	40[e]	-	-	-	-

Method A : Aldehyde (5 eq.) and PFPVS (1 eq.) were stirred in 1,4-dioxane at 300 rpm at 21 °C; Method B : Aldehyde (2 eq.), PFPVS (1 eq.) and H_2O_2 (5 mol%) were stirred in water at 300 rpm at 21 °C; Method C : Aldehyde (2 eq.) and PFPVS (1 eq.) were stirred in water at 300 rpm at 21 °C

[a]: only 60% conversion; [b]: PFP 3,3-dimethylbutane-1-sulfonate isolated (53%); [c]: PFP 3,3-dimethylbutane-1-sulfonate isolated (28%); [d]: could not be isolated from its corresponding enone; [e]: PFP 2-[1,4]dioxane-ethane-1-sulfonate isolated (20%)

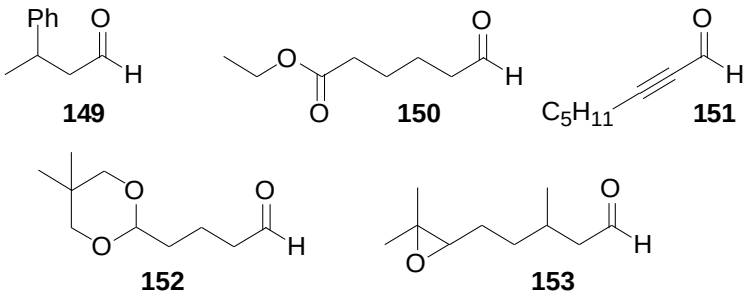
Table 1. Hydroacylation of pentafluorophenyl vinyl sulfonate (PFPVS) **147** with aldehydes **91**

The precise mechanism for the formation of 1,4-keto-sulfonates **146** is yet unknown. This transformation is thought to commence by the molecular oxygen induced conversion of aldehyde **91** to acyl radical **88**, as for the auto-oxidation of aldehydes (Scheme 39). This radical **88** can then undergo addition to electron-poor alkene **147** and form adduct radical **148**, which can then abstract an aldehydic proton to form 1,4-keto-sulfonate **146** and re-generate acyl radical **88**.[130]



Scheme 39. Postulated mechanism for hydroacylation of PFPVS **147**

Prior to investigating the application of aerobic hydroacylation to the total synthesis of NCS-C enediyne epoxide **131** (See 1.5.1, p 33), further understanding of the effect of aldehyde structure on the outcome of vinyl sulfonate hydroacylation was required. Therefore, investigations into hydroacylation of vinyl sulfonates with aldehydes bearing additional functionality were initiated in order to provide insight into the feasibility of this approach for natural product synthesis. Thus, aldehydes **149**-**153** (Scheme 40) were selected as they bear functional groups that are likely to be present in the mid/late stage steps in the total synthesis of NCS-C, *e.g.* ester, acetal, epoxide and alkyne. In addition, the relatively simple model system 3-phenylbutanal **149** was chosen (Scheme 40). Additional mechanistic insight would also assist in the development of protocols for hydroacylation employing more complex substrates.

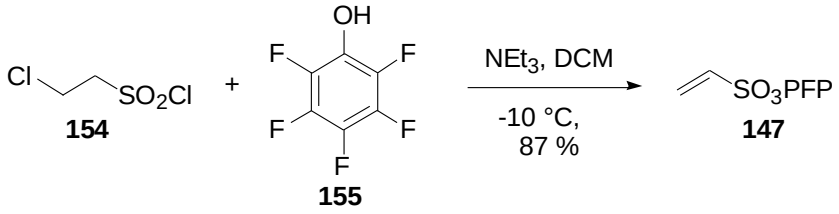


Scheme 40. Aldehydes **149**-**153** chosen for the investigation of aldehyde structure on vinyl sulfonate hydroacylation

2.2 Synthesis of ketosulfonates

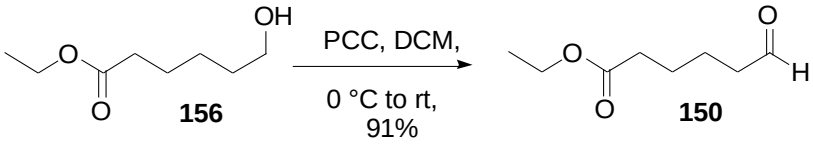
2.2.1 Synthesis of substrates

Synthesis of pentafluorophenol vinyl sulfonate (PFPVS) **147** was readily achieved by treatment of 2-chloroethane sulfonyl chloride **154** by pentafluorophenol (PFPOH) **155** under basic conditions, in excellent yield (Scheme 41).[93] Key to the success of subsequent radical chemistry (See 2.2.2, p 42 and 2.2.3, p 44) was to utilise dichloromethane, in place of diethyl ether, for purification steps. This avoided contamination of PFPVS **147** with radical inhibitor 2,6-bis(1,1-dimethyl)-4-methylphenol (BHT) which was present in commercial diethyl ether.[130]



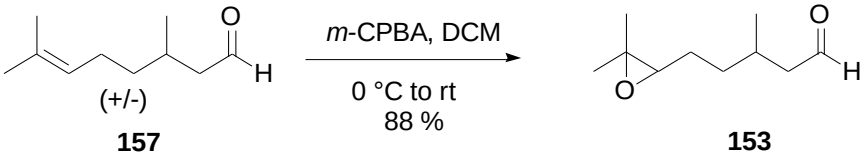
Scheme 41. Synthesis of PFPVS **147**

Oxidation of commercially available ethyl-6-hydroxy-hexanoate **156** by pyridinium chlorochromate gave the corresponding aldehyde **150** in 91% yield (Scheme 42).



Scheme 42. Synthesis of aldehyde **150**

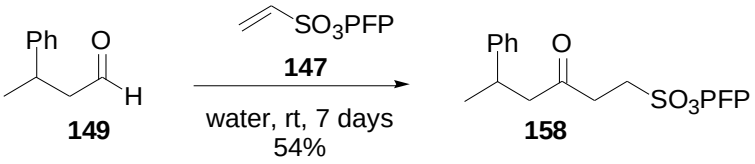
Epoxidation of (+/-)-citronellal **157** with *m*-CPBA afforded epoxyaldehyde **153** in excellent yield (Scheme 43).



Scheme 43. Synthesis of epoxyaldehyde **153**

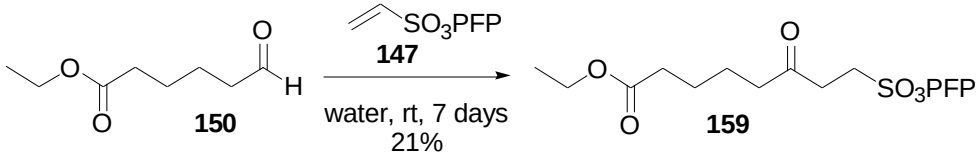
2.2.2 Hydroacylation of vinyl sulfonates with functionalised aldehydes

With the substrates in hand, investigations into the scope of the hydroacylation reaction of PFPVS **147** started with 3-phenylbutanal **149** (2 eq.). The reaction was notably slow compared to those employing alkyl aldehydes (See Table 1, p 39),[93,94] and reached complete conversion after 7 days to give, ketosulfonate **158** in a moderate yield (Scheme 44). In order to prevent the formation of elimination products, *i.e.* the corresponding enone of ketosulfonate **158**, a rapid flash chromatography protocol was used with careful control of solvent gradient. Isolation of pure ketosulfonate **158** in reasonable yield was achieved.



Scheme 44. Synthesis of ketosulfonate **158**

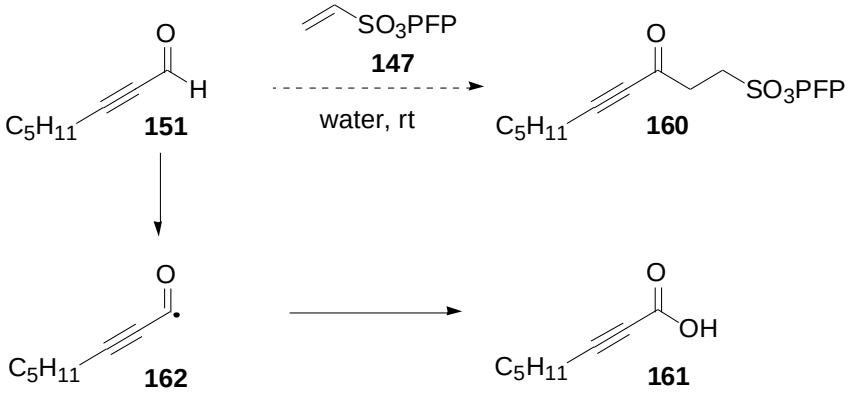
Addition of aldehyde **150** (2 eq.) to PFPVS **147** gave ketosulfonate **159** in 21% yield (Scheme 45). As for 3-phenylbutanal **149** (Scheme 44), hydroacylation was slow and required a prolonged reaction time of 7 days to achieve a desirable conversion of 95%. Ketosulfonate **159** was isolated in low yield principally because the product needed to be crystallised directly from the reaction mixture in order to isolate pure product.



Scheme 45. Synthesis of ketosulfonate **159**

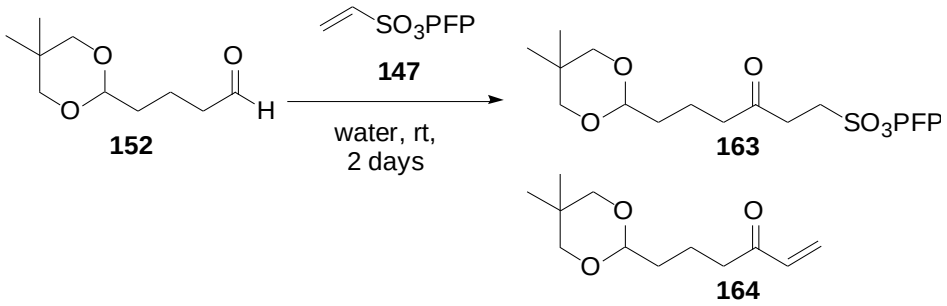
Of particular note is the reactivity of octynal **151**, relevant because of its similarity to the likely precursor **128** to be used in the proposed synthesis of NCS-C enediyne epoxide **131** (See 1.5.1, p 33). Even after 14 days, no trace of ketosulfonate **160** was observed in the crude ^{1}H NMR of the reaction mixture (Scheme 46). However, partial oxidation of 2-octynal **151** to its corresponding acid **161** was observed, suggesting acyl radical **162** was formed, but prefententially reacted with molecular

oxygen to generate acid **161** rather than with PFPVS **147** to generate ketosulfonate **160** (See Scheme 39, p 40).



Scheme 46. Reaction of aldehyde **151** with PFPVS **147**

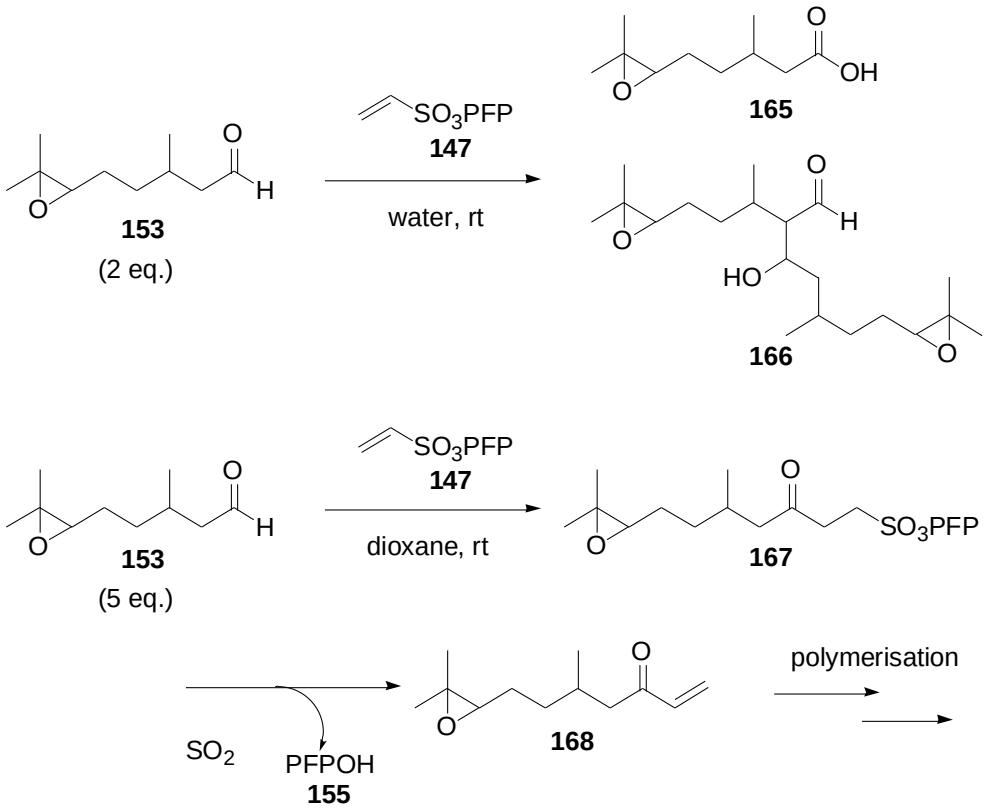
Hydroacylation of PFPVS **147** with aldehyde **152** (2 eq.), bearing a terminal acetal, proceeded in excess of 95% conversion, after 2 days at room temperature (Scheme 47). Despite clear evidence in the crude ^{1}H NMR for the formation of the expected hydroacylation product **163** in 42% yield, appearance of 2 triplets at 3.13 and 3.75 ppm, no pure product could be obtained. Although the presence of desired ketosulfonate **163** was evident after chromatographic purification, it could not be separated from α,β-unsaturated ketone **164**.



Scheme 47. Synthesis of ketosulfonate **163**

Addition of the acyl radical derived from epoxyaldehyde **153** to vinyl sulfonates **147** was evaluated under two sets of reaction conditions. When hydroacylation of PFPVS **147** was carried out with 2 equivalents of aldehyde **153** in water, oxidation of epoxyaldehyde **153** to acid **165** and the formation of the aldol product **166** were both observed in the crude ^{1}H NMR. Formation of acid **165** suggests an acyl radical is formed under reaction conditions. However, the formation of aldol product **166** and further oxidation to acid **165** would indicate these side reactions are favoured over

addition to vinyl sulfonate, in water. Hydroacylation of PFPVS **147** with epoxyaldehyde **153** (5 eq.) in dioxane did not give ketosulfonate **167**. However, the presence of pentafluorophenol (PFPOH) **155** in the crude ^{1}H NMR would indicate that ketosulfonate **167** was formed and reacted further to give enone **168** and PFPOH **155**. Enone **168** has most likely polymerised, which could explain the many impurities observed in the crude NMRs.



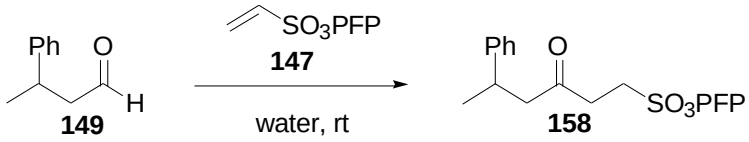
Scheme 48. Attempted hydroacylation of PFPVS **147** with epoxyaldehyde **153**

The aldehydes 3-phenylbutanal **149**, 6-oxo-hexanoic acid ethyl ester **150**, octynal **151**, aldehyde **152**, and epoxyaldehyde **153** were much less reactive than alkyl aldehydes.[93,94] It was speculated this might be attributed to contamination by PFPOH **155**, as phenols are known to be radical inhibitors.[131] Therefore, an investigation into the role of PFPOH inhibition of the aerobic radical hydroacylation was embarked upon.

2.2.3 Investigation into inhibition of aerobic hydroacylation

Reaction of 3-phenylbutanal **149** (2 eq.) with PFPVS **147** 'on water' had previously led to the isolation of ketosulfonate **158** in only moderate yield (Scheme 44, p 42).

Repeatition of this reaction using NMR standards (DMF, formic acid) highlighted the significant discrepancy between the conversion of PFPVS **147** and the yield of ketosulfonate **158** (Table 2). This large discrepancy can be explained by the observation of significant quantities of PFPOH **155** as a side product. It was also noted that PFPOH **155** was only observed in the crude ^{1}H NMR after an extractive work-up (CH_2Cl_2) was employed. In contrast, when the reaction mixture was directly concentrated under vacuum, as in the original protocol (See Table 1, p 39), no PFPOH **155** was observed in the crude ^{1}H NMR and it is likely PFPOH **155** was removed by the evaporation process.



Entry	T (day)	Conv. **149** (%)	Yield **158** (%)
1[a]	1	84[c]	34[c]
2[b]	2	94[c]	39[c]
3[b]	3	97[d]	44[d]

[a]: evaporation of reaction mixture; [b]: extractive work-up; [c]: determined by integration of ^{1}H NMR with formic acid (1 eq.) as standard; [d]: determined by integration of ^{1}H NMR with DMF (1 eq.) as NMR standard

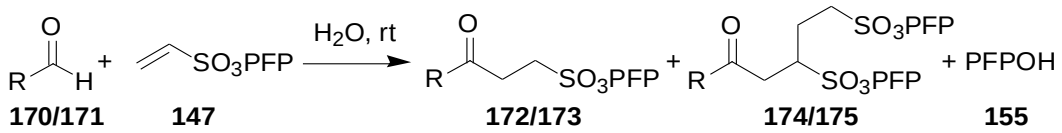
Table 2. Monitoring of addition of 3-phenylbutanal **149** to PFPVS **147**

The likely source of PFPOH **155** was considered to be from hydrolysis of either PFPVS **147** or the ketosulfonate **158**. To gain some greater insight into the likely source of the PFPOH **155**, PFPVS **147** was stirred in water (4 days), acidic (1 M AcOH/H_2O, 21 days) or peracidic conditions (1 M *meta*-chloroperoxybenzoic acid (*m*-CPBA)/H_2O, 5 days). In all the cases, PFPVS **147** was stable and no PFPOH **155** could be detected using ^{19}F NMR. Similar results were obtained when hexanal derived ketosulfonate **169** was stirred at room temperature in either an acidic (1 M AcOH/H_2O, 2 days) or peracidic solution (1 M *m*-CPBA/H_2O, 2 days). In both cases, ketosulfonate **169** was unchanged, and no PFPOH **155** was detected by ^{19}F NMR.

The evidence led us to speculate that PFPOH **155** may originate from a radical intermediate generated during the hydroacylation of PFPVS **147**. In order to evaluate this hypothesis, a protocol to enable effective monitoring of the production of the PFPOH **155** in the reaction mixture was designed.

To this end, butanal **170** (2 eq.) was stirred with PFPVS **147** 'on' water for 6 h and the reaction mixture was diluted directly with (neutralised) $CDCl_3$ and passed through an ISOLUTE filtration column (Standard grade, single fritted reservoir 15 mL, polyethylene frit, 10 μm porosity), in order to reduce the water content. Observation of PFPOH **155** in the crude ^{19}F NMR strongly indicated that the formation of PFPOH **155** occurred during the reaction.

As PFPOH **155** had been hypothesised to have an inhibitory effect; the difference in reactivity seen for a range of simple alkyl aldehydes in the hydroacylation of PFPVS **147** (Table 1, p 39) was believed to be related to the amount of PFPOH **155** generated during the reaction. To this end, accurate assessment of the quantity of PFPOH **155** produced in the reaction mixture for different aldehydes, *i.e*. butanal **170** and hydrocinnamaldehyde **171**, was carried out through NMR studies (Table 3). For this study, hexafluorobenzene (HFB) was first chosen as a ^{19}F NMR standard. However, it created an emulsion, which led to inconsistent results. Therefore, since ketosulfonates **172** and **173** and PFPVS **147** are stable to the hydroacylation reaction conditions, the total quantity of ketosulfonate **172** or **173**, double addition product **174** or **175**, PFPOH **155** and unreacted PRPVS **147** was approximated to the initial quantity of PFPVS **147**. Considering hydrocinnamaldehyde derived ketosulfonate **173** had never been isolated, due to its fast rate of elimination, NMR results were based on comparison with trichloro-ketosulfonate equivalent NMR shifts.[93] It appeared the amount of PFPOH **155** produced for hydrocinnamaldehyde **171** was higher than for butanal **170**. The reaction of PFPVS **147** with hydrocinnamaldehyde **171** (Table 1, Entry 10, p 39) had previously been observed not to be as efficient as the one with butanal **170** (Table 1, Entry 1, p 39), leading to think the PFPOH **155** produced during the reaction might be, at least partially, inhibiting the process.



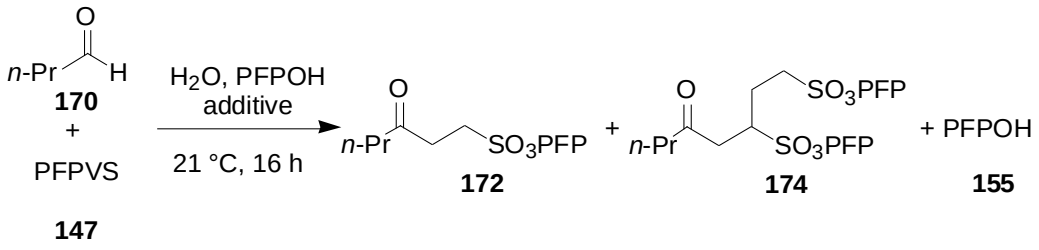
170/171 **147** **172/173** **174/175** **155**

Entry	R	T (day)	Conv. **147** (%)	Yield (%) **172/172**	**174/175**	**155**
1	**170**	1	99	73	16	12
2	Ph **171**	3	54	25	<1	28

Table 3. Study of PFPOH **155** produced for butanal **170** and hydrocinnamaldehyde **171**

To gain further evidence for the inhibitory effect of PFPOH **155** on the reaction, PFPVS **147** was incubated with butanal **170** and PFPOH **155** (Table 4). In the absence of added PFPOH **155**, reaction of PFPVS **147** with butanal **170** proceeded smoothly to 90% conversion in 2.5 h under standard conditions (**170** (2 eq.), 21 °C, H_2O (1 mL/mmol)) (Table 4, Entry 1). Addition of 0.5 eq. of PFPOH **155** completely suppressed the reaction (Table 4, Entry 4) whereas addition of 0.02 eq. of PFPOH **155** did not significantly inhibit the reaction (Table 4, Entry 2). Addition of 0.1 eq. of PFPOH **155** reduced the yield of ketosulfonate **172** and the conversion of PFPVS **147** dropped to 64% after 2.5 h (Table 4, Entry 3). Deprotonation of PFPOH **155** to give the corresponding phenoxide should suppress the ability of PFPOH **155** to act as a radical inhibitor and hence restore the reactivity of butanal **170** with PFPVS **147** without the presence of PFPOH **155**. A range of bases were evaluated for their ability to restore the reactivity of butanal **170** with PFPVS **147** (Table 4, Entries 5-10). Surprisingly, potassium carbonate was found to completely suppress hydroacylation of PFPVS **147** with butanal **170** (Table 4, Entry 7). In the presence of either pyridine (Table 4, Entry 8) or the mixture sodium bicarbonate/tetrabutylammonium chloride (Table 4, Entry10), conversion of PFPVS **147** was low and no ketosulfonate **172** was observed. However, in both cases, careful examination of the crude ^{1}H NMR clearly indicated formation of a small amount (8-10%) of the ester derived from conjugate addition of butyric acid to PFPVS **147** (See Scheme 49, p 49). Sodium phosphate (Table 4, Entry 6) at first looked promising and appeared to restore the initial reactivity of the hydroacylation reaction; however, upon repetition no consistent results could be obtained. Pleasingly, sodium bicarbonate (20 mol%) (Table 4, Entry 5) appeared relatively efficient at restoring the initial reactivity (Table 4, Entry 1) as

the reaction proceeded to a 76% conversion of PFPVS **147** and yielded ketosulfonate **172** in 43%. However, a 40 mol% addition of sodium bicarbonate to the reaction mixture significantly reduced the yield and conversion of the reaction (Table 4, Entry 9). Having established its effect on a reaction mixture containing extra PFPOH, an optimal amount of sodium bicarbonate (20 mol%) was added to the reaction of PFPVS **147** and butanal **170**, in an attempt to improve the hydroacylation (Table 4, Entry 11). A slight improvement on both conversion (92%) of PFPVS **147** and yield (55%) of ketosulfonate **172** was then seen. The effect of sodium bicarbonate on the addition of butanal **170** to PFPVS **147** seems to be relatively slight, probably due to the fact the control reaction already has a good conversion of PFPVS **147** and a reasonable yield for ketosulfonate **172**.



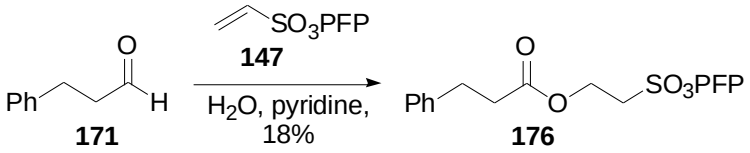
Entry	PFPOH (eq.)	Additive	(eq.)	Conv.[a] **170** (%)	Yield[a] (%) **172**	**174**	**155**
1	-	-	-	90	54	8	17
2	0.02	-	-	87	52	10	25
3	0.10	-	-	64	32	5	32
4	0.50	-	-	5	0	0	47
5	0.10	$NaHCO_3$	0.20	76	43	8	30
6	0.10	NaH_2PO_4	0.20	81/16	47/9	8/0	31/20
7	0.10	K_2CO_3	0.20	<1	0	0	0
8	0.10	Pyridine	0.20	22	0	0	19
9	0.10	$NaHCO_3$	0.40	25	4	0	18
10	0.10	$NaHCO_3$ TBAB	0.20 0.12	12	0	0	18
11	-	$NaHCO_3$	0.20	92	55	8	19

[a]: Determined by integration of ^{1}H NMR with pentachlorobenzene (PCB) (0.2 eq.) as standard

Table 4. Effect of addition of PFPOH **155** and additives on hydroacylation of PFPVS **147** by butanal **170**

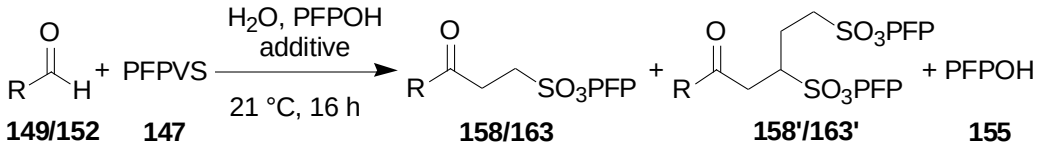
The effect of bases on hydroacylation of PFPVS **147** was further investigated by examining a less reactive aldehyde, hydrocinnamaldehyde **171**, as it was envisaged that sodium bicarbonate might have a greater effect on less reactive aldehydes.

However, due to its poor reactivity, no consistent results could be obtained with hydrocinnamaldehyde **171**. Stirring PFPVS **147** with hydrocinnamaldehyde **171** in the presence of pyridine (20 mol%) led to exclusive formation of ester **176**, in small yield (Scheme 49). This result is in correlation with the ester derived from conjugate addition of butyric acid to PFPVS **147** observed to a smaller extent for butanal **170** (See Table 4, Entries 8 & 10). Formation of ester **176** is thought to proceed *via* deprotonation of the hydrocinnamaldehyde derived acid by pyridine and subsequent addition of the resulting carboxylate to PFPVS **147**.

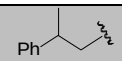
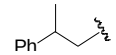
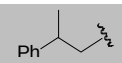
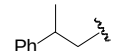
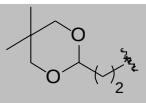
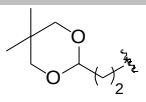


Scheme 49. Formation of ester **176**

Investigations into the inhibitory effect of PFPOH **155** were then extended by examinating the reaction of 3-phenylbutanal **149** (Table 5). PFPOH **155** inhibited the reaction (Table 5, Entry 2) to a greater extent than for butanal **170** (Table 4, Entry 3). As previously seen for butanal **170**, addition of 20 mol% of sodium bicarbonate induced a slight improvement on both conversion of PFPVS **147** and the yield of β-ketosulfonate **158**. However, no improvement was observed on addition of aldehyde **152** to PFPVS **147** (Table 5, Entries 5-6). The effect of addition of 20 mol% of sodium bicarbonate to the reaction mixture of addition of aldehyde to PFPVS is therefore inconclusive.



149/152 **147** **158/163** **158'/163'** **155**

Entry	R	PFPOH (eq.)	Additive	(eq.)	Conv.[a] **147** (%)	Yield[a] (%) **158/163**	**158'/163'**	**155**
1	 **149**	-	-	-	97	50	4	26
2	 **149**	0.10	-	-	50	19	2	37
3	 **149**	0.10	$NaHCO_3$	0.20	0	0	0	16
4	 **149**	-	$NaHCO_3$	0.20	97	56	6	27
5	 **152**	-	-	-	92	57	8	18
6	 **152**	-	$NaHCO_3$	0.20	81	44	6	21

[a]: Determined by integration of ^1H NMR with PCB (0.2 eq.) as standard

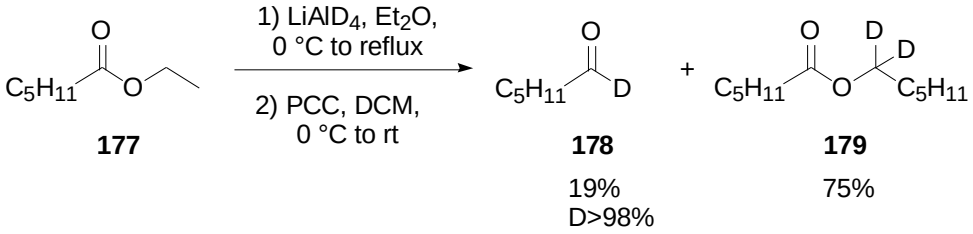
Table 5. Effect of addition of PFPOH **155** and additives on hydroacylation of PFPVS **147** by 3-phenylbutanal **149** and aldehyde **152**

2.3 Mechanistic studies

The problems encountered in the methodology study (See 2.2.3) highlighted the importance of extending the mechanistic understanding of the hydroacylation of PFPVS by aldehydes. Based on the assertion that PFPOH is inhibiting the reaction and that it is most likely generated during the radical process, the likely source of PFPOH is from the radical adduct **148** (See Scheme 39, p 40). Therefore, an increased understanding of the factors affecting the rate of consumption of adduct radical **148** may provide opportunities to modulate the rate of the second propagation step, **148** to **146**, and hence increase reaction yields for more challenging aldehydes. A sequence of labelling experiments was undertaken in order to provide further evidence for the source of the abstracted hydrogen.

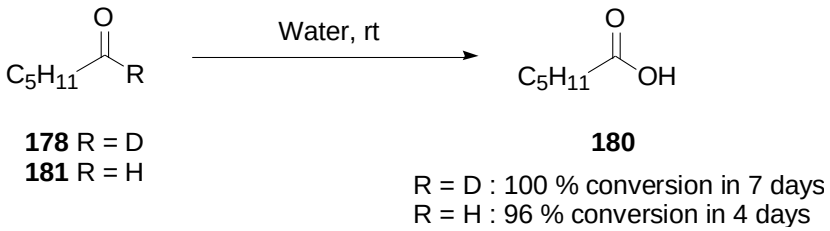
2.3.1 Substrate synthesis and auto-oxidation

Reduction of ethyl hexanoate **177** by lithum aluminium deuteride gave corresponding deuterated alcohol which was then oxidised by PCC to give deuteriohexanal **178**, in a low yield (Scheme 50). The reaction was complicated by the formation of the undesired deuterated hexyl hexanoate **179** as the main product.[132]



Scheme 50. Synthesis of deuteriohexanal **178**

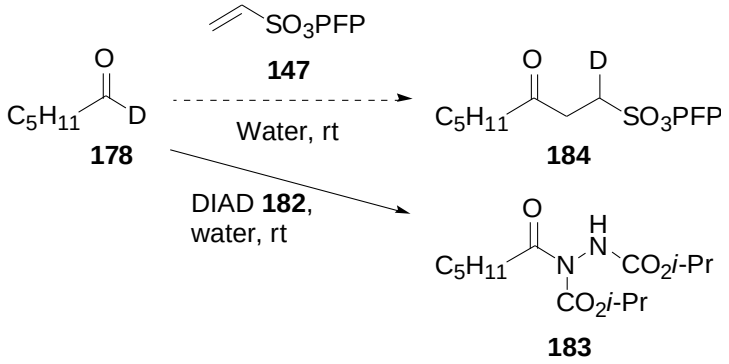
Only aldehydes oxidising to their corresponding acids were reported to add to PFPVS.[94] Therefore, the oxidation of deuteriohexanal **178** to hexanoic acid **180** was evaluated and compared to the oxidation of hexanal **181** to hexanoic acid **180** (Scheme 51). The auto-oxidation rates of hexanal **181** (2 M, water, room temperature) and deuteriohexanal **178** (1.3 M, water, room temperature) were determined, in a side by side experiment, by NMR integration of the α protons. The auto-oxidation rates were comparable, the oxidation of hexanal **181** to hexanoic acid **180** being only modestly faster than the corresponding reaction with deuteriohexanal **178**. Oxidation of deuteriohexanal **178** to hexanoic acid **180**, hence production of subsequent acyl radical, suggests the feasibility of addition of deuteriohexanal **178** to PFPVS.



Scheme 51. Auto-oxidation rates of hexanal **181** and deuteriohexanal **178**

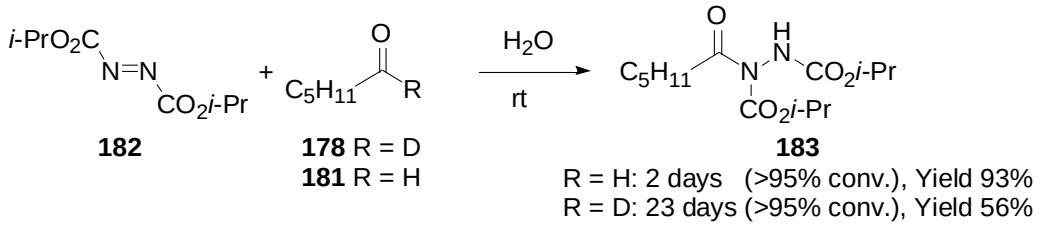
2.3.2 Hydroacylation of PFPVS with deuteriohexanal

Deuteriohexanal **178** was submitted to hydroacylation conditions 'on' water but no reaction was observed (Scheme 52). After 3 days at room temperature, NMR of reaction mixture showed both starting materials unconsumed; interestingly, no trace of oxidation of deuteriohexanal **178** to its corresponding acid was observed. Diisopropyl azodicarboxylate (DIAD) **182** (1 eq.)**,** a more efficient radical acceptor for aerobic radical hydroacylation than PFPVS **147**, was then added to the reaction mixture. Hydrazide biscarboxylate **183** seemed to be very slowly formed, which would suggest formation of the radical derived from deuteriohexanal **178** does indeed occur but is poorly propagated by vinyl sulfonate **147**.



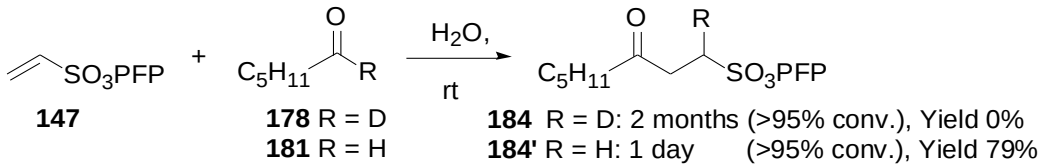
Scheme 52. Attempted synthesis of deuterated ketosulfonate **184**

In order to ascertain whether aerobic hydroacylation with deuterated hexanal **178** was feasible, DIAD **182** was incubated with deuteriohexanal **178** (0.8 eq.) or hexanal **181** (0.8 eq.) under standard reaction conditions (water, room temperature) in side by side experiments (Scheme 53). As expected, complete consumption of DIAD **182** was observed after 2 days at 21 °C in the presence of hexanal **181**. However, reaction between deuterohexanal **178** and DIAD **182** was extremely slow and afforded a much reduced isolated yield for hydroacylation product **183**.



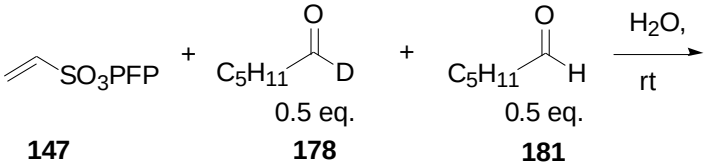
Scheme 53. Addition of hexanal **181** and deuteriohexanal **178** to DIAD **182**

The addition of deuteriohexanal **178** to PFPVS **147** was compared to the addition of hexanal **181** to PFPVS **147** in side by side experiments (Scheme 54). Even after 2 months, no trace of deuterated ketosulfonate **184** was evident by ^{1}H NMR; however, as expected, complete conversion of PFPVS **147** in the presence of hexanal **181** was observed within 24 h. After 2 months, 88% of PFPVS **147** could be recovered from the reaction between PFPVS **147** and deuterated hexanal **178** with some PFPOH **155** also observed in the reaction mixture (11%), suggestive of the formation of a small amount of ketosulfonate **184** followed by decomposition. Given that the formation of acyl radical occurs at a comparable rate for both hexanal **181** and deuteriohexanal **178**, abstraction of aldehydic deuterium by aduct radical appears to be much slower than abstraction of aldehydic proton. This would seem to suggest that abstraction of aldehydic proton, *i.e.* conversion of **148** to **146**, is the rate determining step (See Scheme 39, p 40).

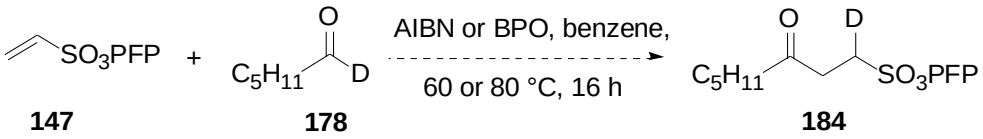


Scheme 54. Addition of hexanal **181** and deuteriohexanal **178** to PFPVS **147**

Competitive addition of hexanal **181** and deuteriohexanal **178** to PFPVS **147** was inconclusive (Scheme 55). Some ketosulfonate was formed but it was unclear whether the product was deuterated. In an attempt to synthesise a reference sample of deuterioketosulfonate **184** for direct comparision, an alternative route for the synthesis of **184** was attempted. PFPVS **147** was stirred with deuteriohexanal **178** (2 eq.) in benzene with either azobisisobutyronitrile (AIBN) or benzoyl peroxide (BPO), as radical initiator, at 60 or 80 °C, but no deuterioketosulfonate **184** could be observed in the crude ^{1}H NMR of the reaction mixture.



Scheme 55. Competitive addition of hexanal **178** and deuteriohexanal **181** to PFPVS **147**



147 **178** **184**

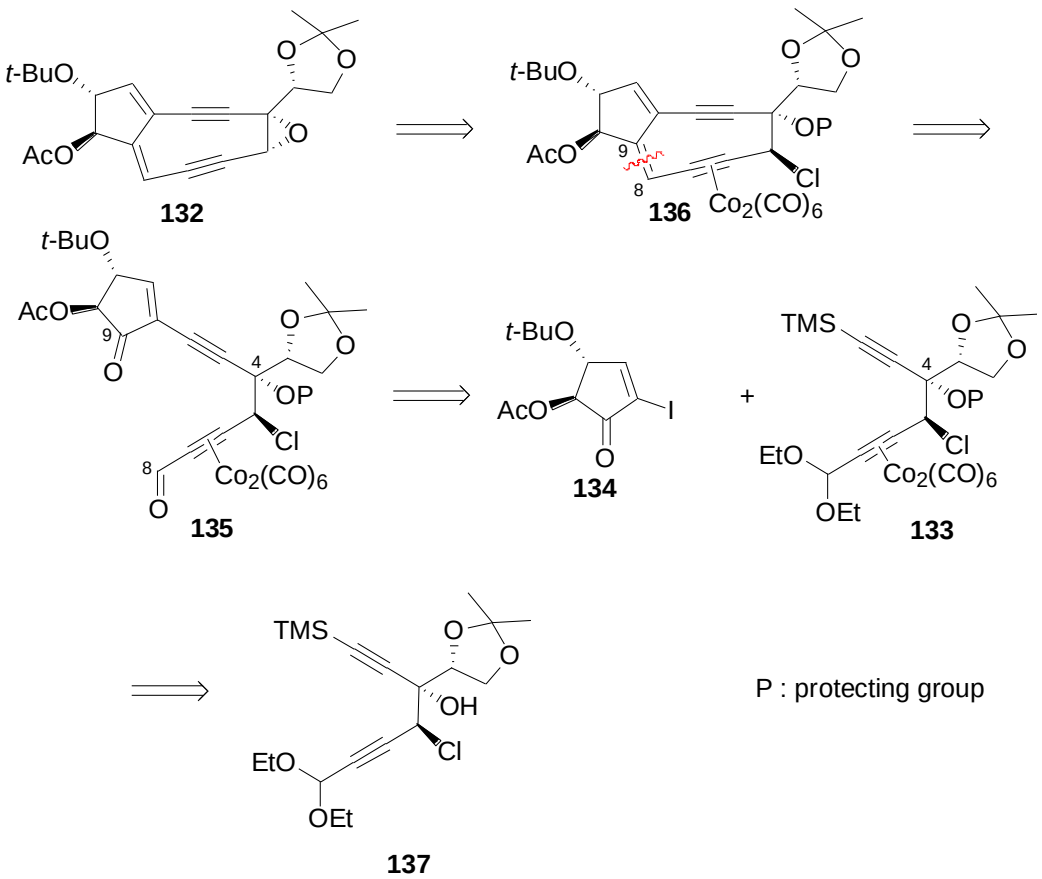
Scheme 56. Attempted syntheses of deuterioketosulfonate **184**

2.4 Conclusion

The range of aldehydes, which can be used in the hydroacylation of vinyl sulfonates in the presence of water using air as radical initiator, has been broadened. Moreover, it has been demonstrated that pentafluorophenol (PFPOH), produced within the reaction mixture, can have an inhibitory effect on the hydroacylation of vinyl sulfonates. A new set of conditions has been identified, which provides opportunities to minimise this undesirable inhibitory effct. Preliminary results would tend to indicate that the addition of acyl radicals to vinyl sulfonates is reversible.

Chapter 3. Synthesis of epoxydiyne synthon

The total syntheses of NCS-C **3** have been described by Myers[50] (See 1.3.1, p 8) and Hirama[56] (See 1.3.2, p 12) in 29 and 32 steps respectively. In our proposed alternative approach, the combination of a Sonogashira reaction and a McMurry coupling would be highly convergent and would generate the NCS-C core in a reduced number of steps (See 1.5.2, p 34 and Scheme 57). Caddick and Thominet's work on the rapid construction of the C2-C8 fragment of NCS-C from relatively simple building blocks provides access to the advanced intermediate **137** (See 1.3.4, p 16 and Scheme 57).[69]



Scheme 57. Retrosynthetic analysis for the synthesis of epoxydiyne **132** *via* McMurry approach

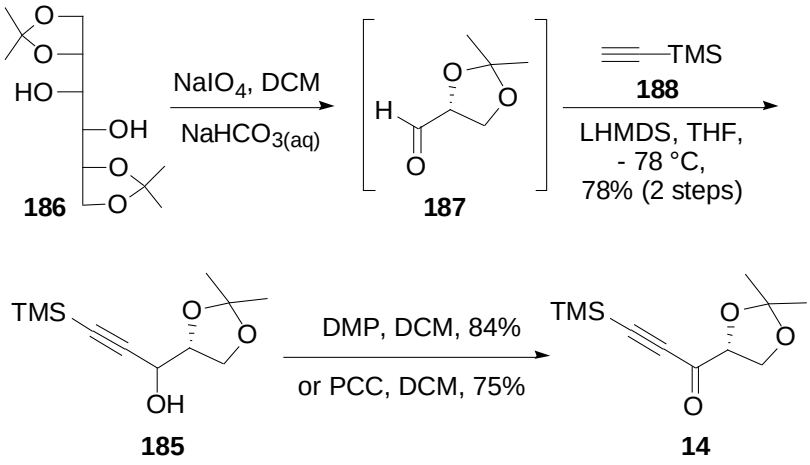
3.1 Zinc bromide coupling approach

The investigation of the synthesis of diyne synthon **135** began with synthesis of chlorohydrin **137** following the method developed by Caddick and Thominet.[66]

3.1.1 Synthesis of chlorohydrin 137

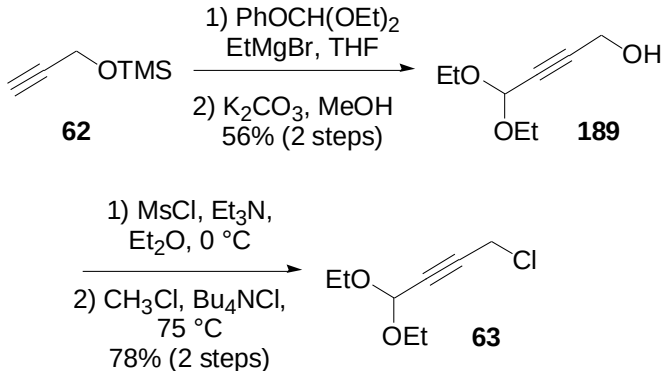
3.1.1.1 Synthesis of substrates

Alcohol **185** was obtained in a one-pot reaction from commercially available 1,2-5,6-diisopropylidene-D-mannitol **186** following Hirama's procedure (Scheme 58).[66,68] Oxidative cleavage of protected carbohydrate **186** gave aldehyde **187** which was converted directly to alcohol **185** upon addition of the organolithium derived from treatment of trimethylsilylacetylene **188** with *n*-BuLi. Ketone **14** was then obtained *via* oxidation of alcohol **185** using Dess-Martin periodinane (DMP) or pyridinium chlorochromate (PCC), giving ketone **14** from commercially available 1,2-5,6-diisopropylidene-D-mannitol **186** in three steps in an 66% overall yield.



Scheme 58. Synthesis of ketone **14**

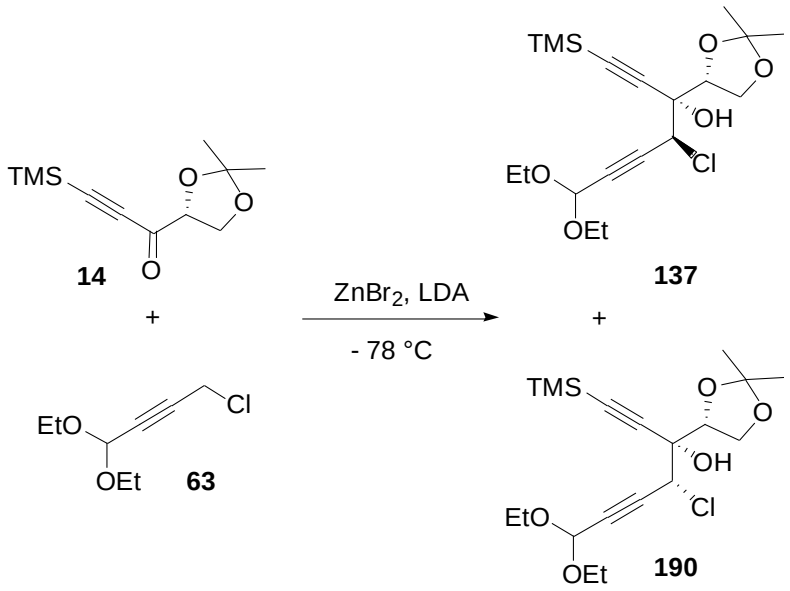
Alcohol **189** was synthesised in a two-step reaction from commercially available TMS-protected propargyl alcohol **62** (Scheme 59).[133] Contrary to that previously reported by Maddaluno, both distillation and flash chromatography were required to achieve high purity of alcohol **189**. Alcohol **189** was then converted to its mesylate and next, treated with tetrabutylammonium chloride to provide propargyl chloride **63**, thereby obtaining propargyl chloride **63** in two steps from TMS-protected propargyl alcohol **62** with an overall yield of 44%.[66]



Scheme 59. Synthesis of propargyl chloride **63**

3.1.1.2 Synthesis of chlorohydrin 137

Initial attempts to synthesise chlorohydrin **137** using the method reported by Caddick and Thominet showed the reaction between ketone **14** and propargyl chloride **63** in presence of zinc bromide to be extremely capricious (Scheme 60).[66] Freshly opened *n*-BuLi as well as thoroughly purified starting materials and zinc bromide are essential for the reactivity. However, despite repeated attempts, the reported stereoselectivity (*i.e. anti* : *syn*: 10 : 1) could not be reproduced, having either a 1 : 1 or at best a 2 : 1 mixture of diastereoisomers **137** and **190**. Zinc allene coupling will be evaluated later in more detail to understand this lack of reproducibility (See 3.1.3, p 62).

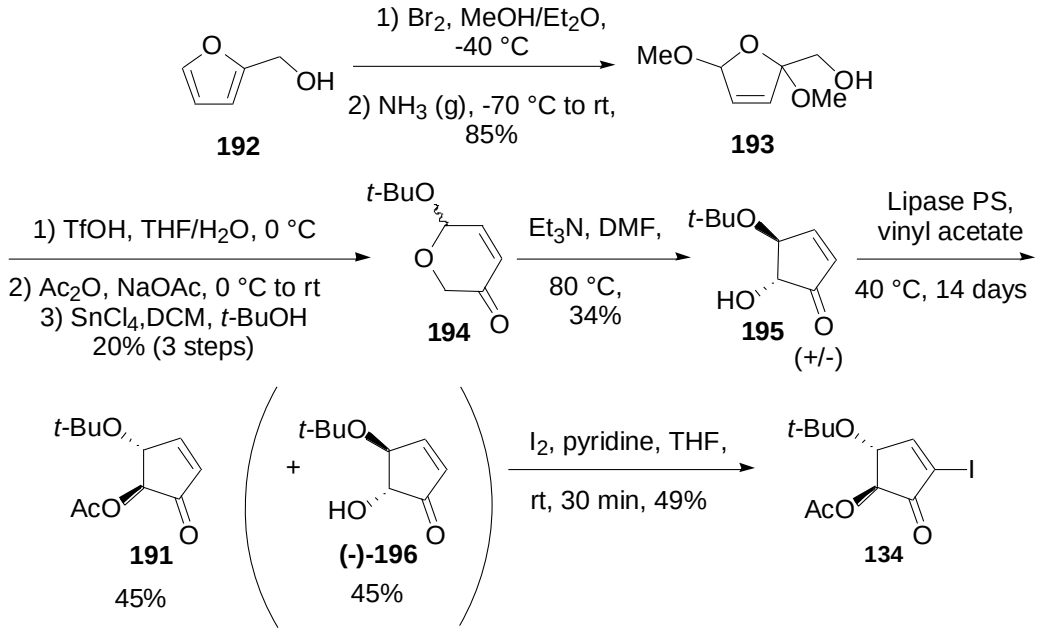


Scheme 60. Synthesis of chlorohydrins **137** and **190**

3.1.2 Studies on Sonogashira coupling

3.1.2.1 Synthesis of iodocyclopentenone 134

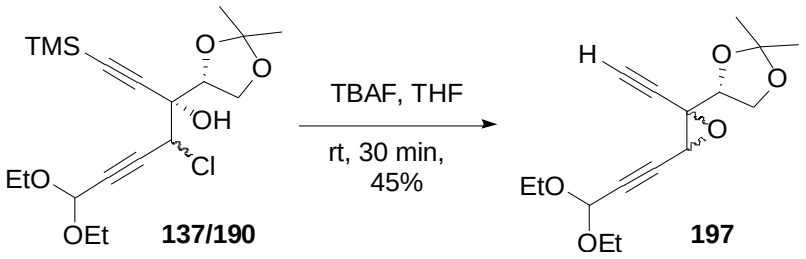
Extensive studies have established a route to cyclopentenone **191** (Scheme 61).[69] Treatment of commercially available furfuryl alcohol **192** with excess bromine in methanol followed by quenching with gaseous ammonia provided furan **193** in an excellent yield.[64] Controlled addition of bromine in methanol, close monitoring of the internal temperature and distillation of the furfuryl alcohol were found to be key elements to obtain a high yield. Acid-catalysed ring expansion followed by *in-situ* acylation gave the pyranone which was immediately converted to its corresponding *t*-Bu ether **194**.[69] Low yields were obtained due to contamination by a polymer, coming either from synthesis of furan **193** or pyranone **194**. Base-mediated ring contraction of pyranone **194** gave cyclopentenone **195** in a moderate yield.[64] Cylopentenone **195** was synthesised in four steps from furfuryl alcohol **192** with an overall yield of 6.1%. For the total synthesis of NCS-C, (1*S*,5*R*) enantionerically pure cyclopentenone **191** was required. The required asymmetric desymmetrisation of cyclopentone **191** was achieved following some work previously reported by Caddick, in which lipase mediated kinetic resolution with Amano lipase AK or PS effects selective acylation of **195** to give the desired cyclopentenone **191** whilst leaving the cyclopentenone (-)-**196** untouched.[134] Instead of the 7 reported, 14 days were necessary to allow acylation of alcohol **195** to reach completion and regular adding of vinyl acetate was necessary to enable the reaction to proceed to full conversion. For both lipases AK and PS, after 14 days, a 1 : 1 mixture of **191** and (-)-**196** was observed in the crude ^{1}H NMR. Both lipases seem to have equal efficiency for the kinetic resolution of cyclopentenone **195** but isolation was unsuccessful for lipase AK. The enantiomerically pure cyclopentenone **191** was then iodinated to provide iodocyclopentenone **134** in 49% yield.[56]



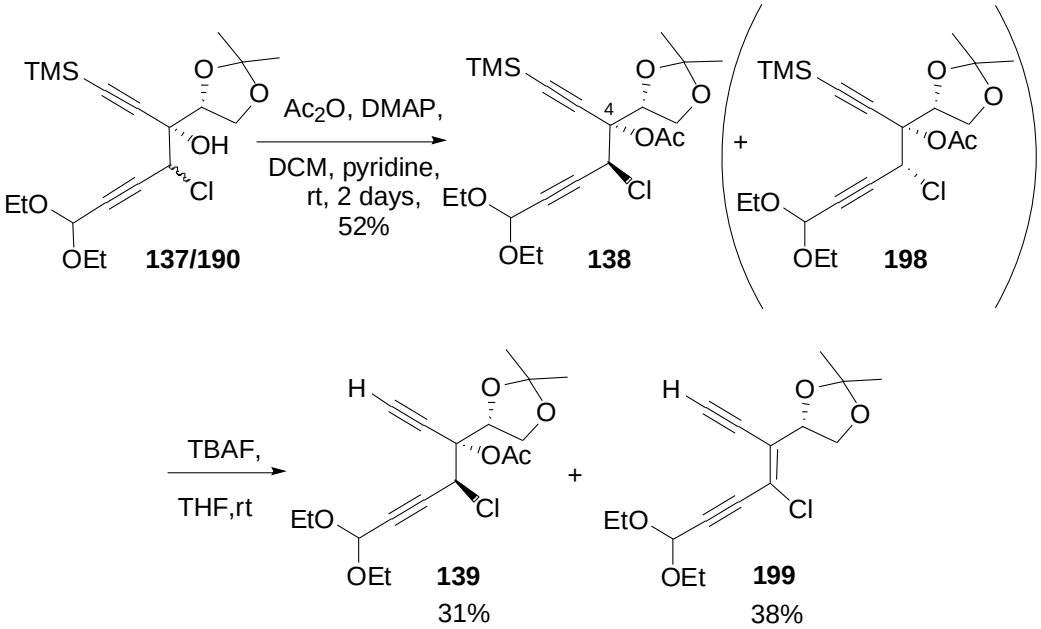
Scheme 61. Synthesis of iodocyclopentenone **134**

3.1.2.2 Synthesis of alkyne 139

Removal of the TMS group on chlorohydrins **137**/**190** with tetrabutylammonium fluoride led to formation of side product epoxide **197** (Scheme 62). Therefore, in order to allow for the successful TMS deprotection of chlorohydrins **137**/**190** the tertiary alcohol was proctected *via* acylation (Scheme 63). Pleasingly, it was discovered that the separation of the two diastereoisomers **138** and **198** was possible at this stage, enabling the pursuit of the enantiopure synthesis of NCS-C in an enantiopure form (Scheme 63). Silyl deprotection of acyl chlorohydrin **138** with tetrabutylammonium fluoride gave alkyne **139** in low yield, along with alkene **199**, presumably derived from E2 elimination of the C4 acetate. The low yield obtained in the TMS-deprotection step was due to the use of non-optimised reaction conditions; synthesising diyne **139** for the Sonogashira coupling studies (See 3.1.2.3) being the main focus. The conditions developed by Hoffmann would enable deprotection of the TMS group leaving the acetate untouched and would therefore provide a more viable method for the synthesis of NCS-C.[135]



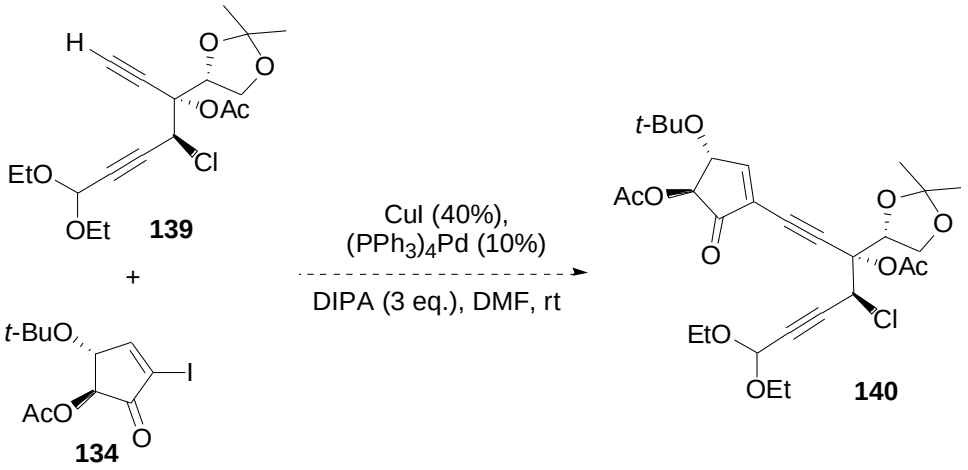
Scheme 62. Formation of side product epoxide **197**



Scheme 63. Synthesis of alkyne **139**

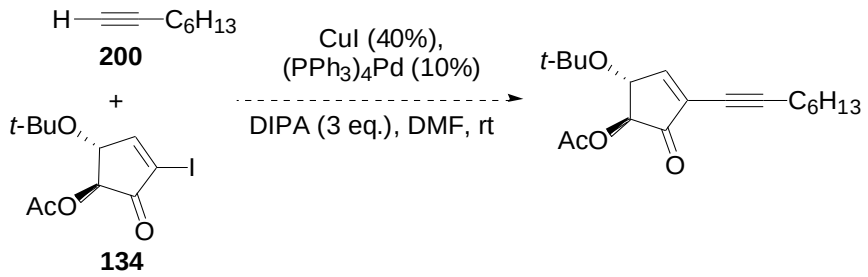
3.1.2.3 Studies on Sonogashira coupling

With a very small amount of both alkyne **139** and iodocyclopentenone **134** in hand, Sonogashira coupling to afford diyne **140** was evaluated using copper iodide, palladium tetrakis triphenylphosphine and diisopropyl amine (Scheme 64).[56] ^{1}H NMR of the crude mixture showed some unreacted iodocyclopentenone **134** and the formation of another product. The characteristic shift for the terminal alkyne was not present in this new product, suggesting consumption of alkyne **139**. Unfortunately it was not possible to determine if the new product was the expected coupling product **140** or the product from dimerisation of alkyne **139**.



Scheme 64. Sonogashira coupling between alkyne **139** and iodocyclopentenone **134**

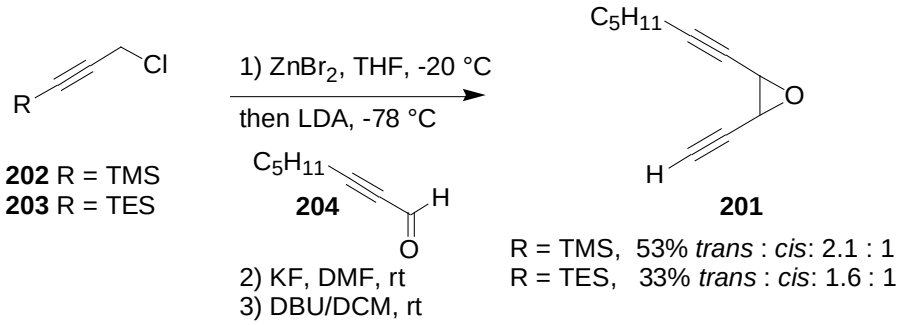
Lack of results in the Sonogashira coupling between alkyne **139** and iodocyclopentenone **134** (Scheme 64) was hypothesised to come from the low reactivity of alkyne **139**. To confirm the reactivity of iodocyclopentenone **134** in Sonogashira couplings, a test reaction was run between iodocyclopentenone **134** (0.01 mmol) and octyne **200** (Scheme 65). Flash chromatography allowed the isolation of a very small amount (< 1 mg) of a new product, in which the chemical shift for the alkenyl proton changed from 5 ppm (starting material) to 5.5 ppm, which would tend to indicate some coupling had occured. This result would suggest that Sonogashira coupling product **140** (Scheme 64) was not observed because of the low reactivity of alkyne **139**.



Scheme 65. Test reaction on iodocyclopentenone **134** reactivity in a Sonogashira coupling

3.1.3 Evaluation of model zinc allene coupling

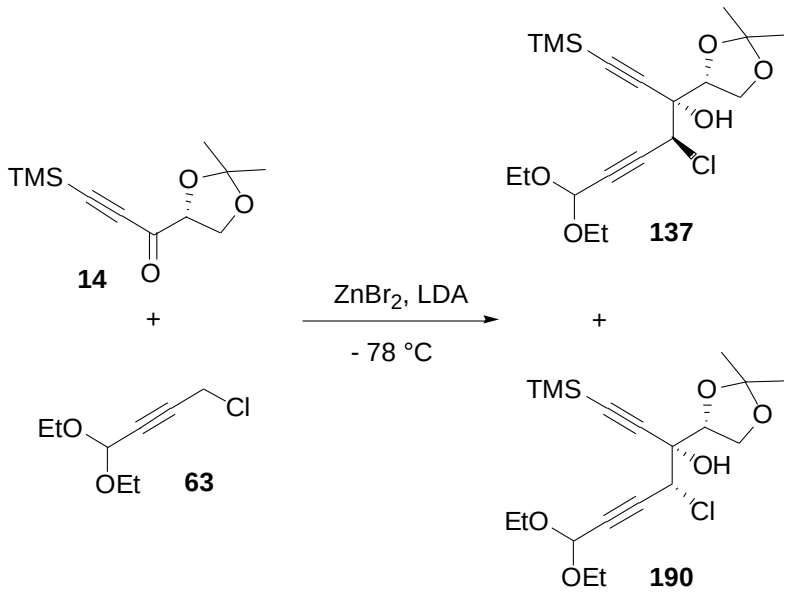
Even though chlorohydrin **137** could be synthesised (See 3.1.1.2), the low yield and stereoselectivity obtained made this step inappropriate for a total synthesis. Some further studies on the zinc allene coupling itself were therefore carried out to understand the lack of success in the coupling between propargyl chloride **63** and ketone **14** (See 3.1.1.2) and attempt to reproduce the previously reported yield and stereoselectivity.[66] In order to compare directly with known methodology, studies were carried out on epoxide **201** (Scheme 66). Propargyl chlorides **202** and **203** were synthesised *via* silylation of the corresponding free alkyne. Reaction of propargyl chlorides **202** and **203** with commercially available aldehyde **204**, redistilled immediately prior to use, pleasingly afforded the desired epoxide **201**, after desilylation and cyclisation. Key to the success was the thorough drying of zinc bromide immediately prior to use. The observed diastereoselectivity for both propargyl chlorides **202** and **203** *trans* : *cis*: 2.1 : 1 and 1.6 : 1 respectively, were in general agreement with that previously reported by Caddick (*trans* : *cis*: 1.7 : 1).[67]



Scheme 66. Synthesis of the model system **201** for zinc allene coupling evaluation

Having had some positive results with the model system **201** (Scheme 66), synthesis of chlorohydrin **137** was attempted again (Table 6). The moisture contained in the zinc bromide powder was hypothesised to be one of the causes of the lack of positive results in the zinc allene coupling. Therefore, the effect of different methods of drying, *i.e.* drying or flaming under vacuum, on the reaction was investigated. Some improvement in selectivity was observed when the zinc bromide was dried under vacuum at 120 °C overnight but in that case the yield was very low (Table 6, Entry 1). Flaming the zinc bromide did not improve the stereoselectivity but did improve the yield slightly (Table 6, Entry 2). For both entries 1 and 2 (Table 6), the mass recovery was very low, indicating either propargyl chloride **63** and/or the

chlorohydrins **137**/**190** were unstable to the work-up conditions. The stability of propargyl chloride **63** was then tested against two different work-up conditions: saturated solution of ammonium chloride solution and 0.5 M solution of ammonium chloride. Only 66% of the material was recovered when saturated ammonium chloride was used whereas a greater than 98% recovery was achieved with 0.5 M ammonium chloride solution. Following those results, new work-up conditions using a 0.5 M ammonium chloride solution were used for the following reactions (Table 6, Entries 3-4). Subsequent attempts to react propargyl chloride **63** with ketone **14** to give chlorohydrin **137** could not be reproduced, including under increased temperature (Table 6, Entry 4). The many attempts at coupling propargyl chloride **63** and ketone **14** have yet failed to reproduce the previously observed yield (60%) or stereoselectivity (*anti* : *syn*: 10 : 1).[66]



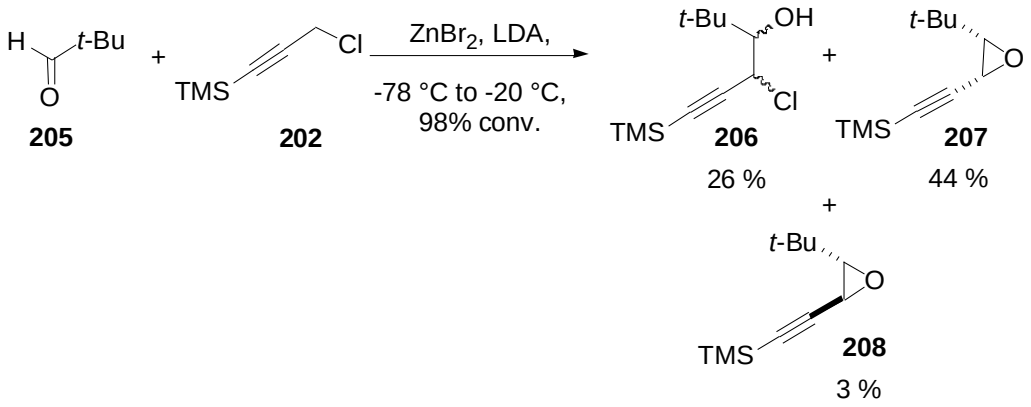
Entry	Drying method for $ZnBr_2$	Conditions (h/°C)	Work-up	Yield **137** + **190** (%)	*trans* : *cis* ratio
1	Vacuum[a]	2/-78	$NH_4Cl_{(sat)}$	12	4 : 1
2	Flamed	2 /-78	$NH_4Cl_{(sat)}$	37	2.2 : 1
3	Flamed	2/-78	0.5 M NH_4Cl	0	-
4	Flamed	1/-78 + 1/-20	0.5 M NH_4Cl	0	-

[a]: 120 °C, 18 h

Table 6. Reaction conditions for the synthesis of chlorohydrin **137**

The unsuccessful results in the synthesis of natural product chlorohydrin **137** (Table 6), using the protocol optimised with model system **201** (Scheme 66), showed that epoxide **201** was not an appropriate model for the synthesis of natural product

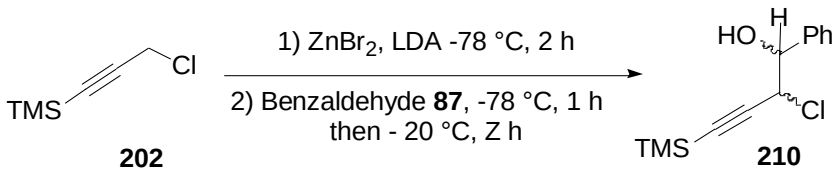
chlorohydrin **137**. Therefore, a more challenging substrate, pivalaldehyde **205**, was chosen to carry studies out with propargyl chloride **202** (Scheme 67).[136] Both starting materials were distilled prior to use and the zinc bromide was melted, instead of just dried, under vacuum for 5 min to eliminate any trace of water. Those modifications of the reaction conditions were successful and the conversion was excellent when two equivalents of pivaldehyde were used instead of one as reported by Chemla.[136] Contrary to previous reports, a substantial amount of chlorohydrin **206** cyclised to epoxides **207** and **208**, irrespective of the pH of the work-up conditions. These conditions were then applied to the reaction of ketone **14** and propargyl chloride **63** unfortunately with little success (Scheme 60, p57); at best, the *anti* : *syn* stereoselectivity in chlorohydrins **137**/**190** was estimated as 3.1 : 1 in the crude ^{1}H NMR.



Scheme 67. Test reaction with propargyl chloride **202** and pivaldehyde **205**

In order to gain greater insight into the coupling and understand the factors determining reproducibility, further studies were carried out using benzaldehyde **87** and acetophenone **209** as model systems (See Table 8). Reaction of propargyl chloride **202** with benzaldehyde **87** (Table 7) was examined in order to find effective reaction conditions for the investigation into the reactivity of propargyl chlorides **63** and **202** (See Table 8). The purity of zinc bromide and the rate of addition of LDA were envisaged to have a possible effect on conversion and diastereoselectivity of the zinc bromide coupling (Table 7). Indications were that the purity of zinc bromide did not seem to have an effect on the outcome of the reaction (Table 7, Entries 1-2), as long as it was melted under vacuum prior to its use. The rate of addition of LDA does not appear to effect the outcome of the reaction (Table 7, Entries 2-4). An extended reaction time (Table 7, Entry 5) appeared to be the solution to a high

conversion and a better diastereoselectivity, albeit not as good as previously published.[66]



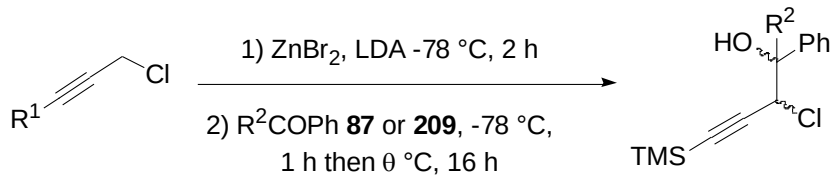
202 **210**

Entry	$ZnBr_2$ purity (%)	$Flow_{LDA}$ ($mL.h^{-1}$)	Step 2 Z (h)	Conv.[a] **87** (%)	*anti : syn* ratio
1	99.999	2	1.5	46	1.4 : 1
2	98	2	1.5	60	1.3 : 1
3	98	1.3	3	53	1.6 : 1
4	98	-[b]	16	96	3.3 : 1[c]

[a]: evaluated based on assumption benzaldehyde is stable to reaction conditions; [b]: addition of LDA in one portion; [c]: a mixture of chlorohydrin and epoxide was obtained: chlorohydrin : epoxide: 3.2 : 1; *cis* : *trans* epoxide ratio: 11.5 : 1; *anti* : *syn* chlorohydrin ratio : 3.3 : 1

Table 7. Investigation of the effect of the rate of addition of LDA and the purity of zinc bromide on the reaction between benzaldehyde **87** and propargyl chloride **202**

The reaction conditions derived from the benzaldehyde **87** and propargyl chloride **202** study (Table 7), were applied to the reactions of acetophenone **209** and benzaldehyde **87** with propargyl chlorides **63** and **202** (Table 8). It had been observed that the zinc allene coupling seemed to work better when the propargyl chloride had a TMS group on the terminal alkyne (See Scheme 66; Scheme 67, p 64; Table 7, p 65) compared with an acetal group (See Table 6, p 63). It was hypothesised that coordination of the zinc bromide to the acetal of propargyl chloride **63** could slow the reaction down and lead to the observed unsatisfactory results. Accordingly, propargyl chloride **202** seemed to be more reactive than propargyl chloride **63** (Table 8, Entries 1&3) but propargyl chloride **63** seemed to have a better diastereoselectivity than propargyl chloride **202** (Table 8, Entries 2&4). Increasing the temperature up to 0 °C did not improve either the conversion or the diastereoselectivity (Table 8, Entries 5-6). Reaction of acetophenone **209** and propargyl chloride **63** proved to be quite slow and even increasing the temperature up to room temperature did not provide an acceptable conversion (Table 8, Entry 7). Leakage of air into the reaction mixture was envisaged as being the explanation for the poor results but conducting the reaction under a flow of argon (Table 8, Entry 8) did not provide any improvement in the outcome of the reaction.



63 $R^1 = CH(OEt)_2$ **87** $R^2 = H$ **210** $R^1 = TMS$, $R^2 = H$
202 $R^1 = TMS$ **209** $R^2 = Me$ **211** $R^1 = CH(OEt)_2$, $R^2 = H$
212 $R^1 = TMS$, $R^2 = Me$
213 $R^1 = CH(OEt)_2$, $R^2 = Me$

Entry	R^1	R^2	Product	θ (°C)	Conv.[a] **87** or **209** (%)	*anti : syn* Ratio
1	TMS	H	**210**	-20	82	1.8 : 1
2	$CH(OEt)_2$	H	**211**	- 20	74	3.2 : 1
3	TMS	Me	**212**	- 20	70	2.1 : 1
4	$CH(OEt)_2$	Me	**213**	- 20	34	3.2 : 1
5	TMS	H	**210**	0[b]	68	1.9 : 1
6	TMS	Me	**212**	0[c]	72	2.1 :1
7	$CH(OEt)_2$	Me	**213**	21[d]	51	3 : 1
8[e]	TMS	H	**210**	- 20	67	1.9 : 1

[a]: evaluated based on assumption benzaldehyde and acetophenone are stable to reaction conditions; [b]: 1 h at 0° C; [c]: 2 h at 0 °C; [d]: 16 h at -20 °C then 5 h at 21 °C; [e]: Reaction done under a flow of argon

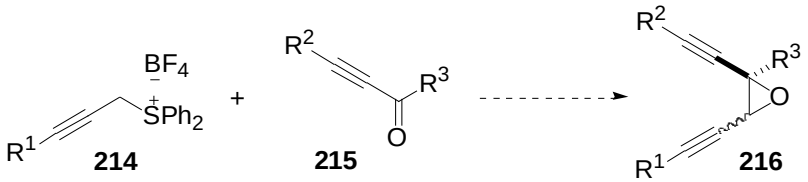
Table 8. Investigation into the reactivity of propargyl chlorides **63** and **202**

In conclusion, investigations into the zinc bromide coupling would tend to indicate that the reaction seems to be more efficient with TMS-protected propargyl chloride **202** than with acetal-protected propargyl chloride **63**, possibly due to the coordination of zinc bromide to the acetal of propargyl chloride **63**. Nevertheless, the stereoselectivity seems to be higher when acetal-protected propargyl chloride **63** is used. The reaction between propargyl chloride **63** and ketone **14** is not easily reproducible. A very time-consuming further study would be necessary to define the reasons for low yields and poor diastereoselectivity.

3.2 Sulphur ylide approach

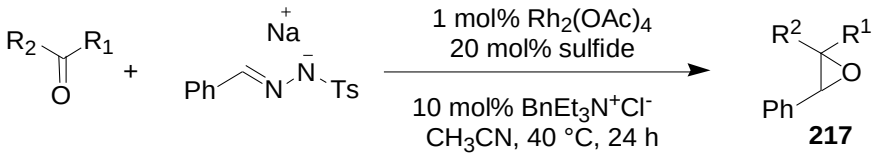
3.2.1 Aim of the sulphur ylide approach

The synthesis of the C2-C8 fragment of NCS-C *via* zinc mediated coupling of a propargylic ketone with allenyl zinc has proved unsuccessful to date. Therefore, an alternative approach *via* the conceptually similar C4-C5 bond formation, consisting of the addition of a propargylic sulphur ylide derived from salt **214** to ketone **215** to generate epoxide **216** was investigated (Scheme 68).



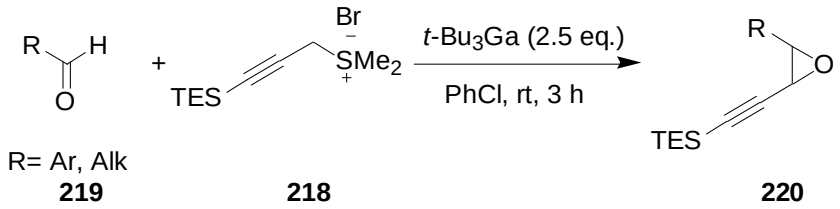
Scheme 68. Investigation of reaction of propargylic sulfonium salt **214** with propargylic ketone **215**

Presently, there are no examples of the formation of trisubstituted epoxydiynes *via* sulphur ylide chemistry. Ortiz de Montanello[137] reported a disubstituted propargylic epoxide and Wang,[138] Crandall[139] and Fujimoto[140] synthesised trisubstituted epoxides. Of particular interest, are the trisubstituted epoxides synthesised by Aggarwal under catalytic conditions (Table 9).[141] Precedent for the use of Lewis acids in the reaction of propargylic sulphur ylides **218** with carbonyls **219** provides the opportunity to increase the reactivity of unresponsive ketones (Scheme 69).[142]



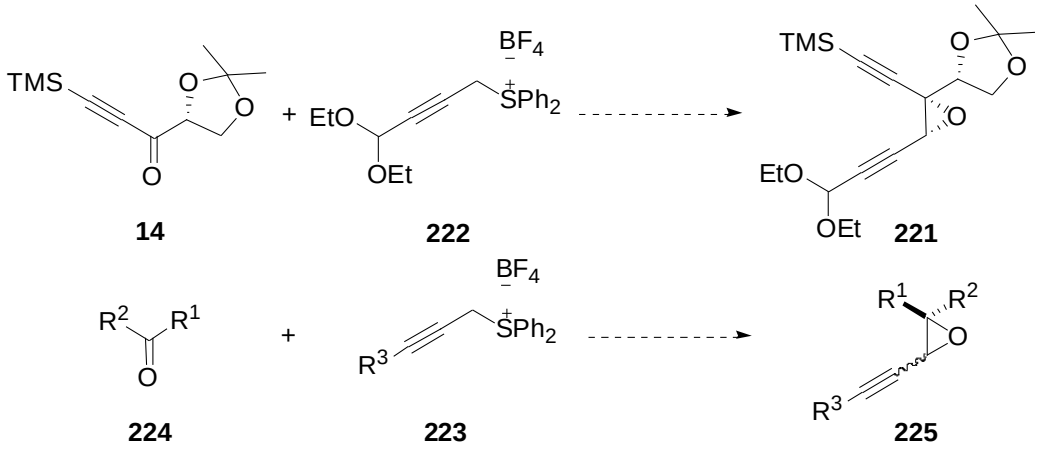
Ketone	Sulfide	Yield **217** (%)	*trans* : *cis* ratio
acetophenone	THT	15	< 2:98
p-NO_2acetophenone	THT	traces	-
acetophenone	PMS	15	< 2:98
p-NO_2acetophenone	PMS	69	< 2:98
THT: tetrahydrothiophene; PMS: pentamethylene sulphide			

Table 9. Synthesis of epoxides **217** under catalytic conditions



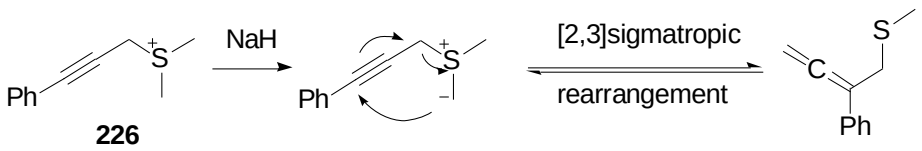
Scheme 69. Synthesis of propargylic disubstituted epoxide **220**

Work of Ortiz de Montanello,[137] Wang,[138] Crandall,[139] Fujimoto[140] and Aggarwal[141] suggests that the formation of epoxide **221** (Scheme 70) may be feasible *via* sulphur ylide chemistry. In order to evaluate the feasibility of the synthesis of the C2-C8 fragment of NCS-C **221** *via* the coupling of ketone **14** with the sulphur ylide derived from **222**, the reactivity of propargylic sulphur ylides with ketones and aldehydes, which to date has received modest attention,[142] will be investigated through reactions of ylides derived from **223** with ketones **224**.



Scheme 70. Investigation into the synthesis of propargylic trisubstituted epoxides **221** and **225** *via* sulphur ylide chemistry

The selection of diphenylsulfonium salt **222** (Scheme 70) should prevent the [2,3]sigmatropic rearrangement observed by Terada with propargylic sulfonium salt **226** (Scheme 71).[143]



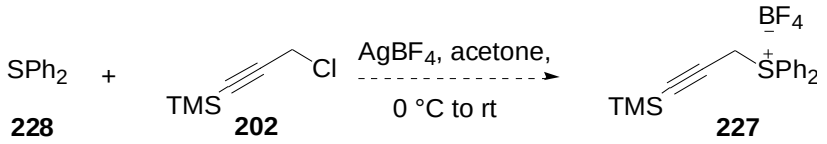
Scheme 71. [2,3]sigmatropic rearrangement of propargylic sulfonium salt **226**

3.2.2 Evaluation of sulphur ylide chemistry for the synthesis of trisubstituted epoxides

To evaluate sulphur ylide chemistry as a possible method for the synthesis of trisubstituted propargylic epoxides, in general, and epoxydiyne, in particular, new reaction conditions needed to be developed. The scarcity of trisubstituted epoxides formed *via* sulphur ylide chemistry suggests the low reactivity of ketones towards sulphur ylides and thus, suggests that the identification of new reaction conditions for trisubstituted propargylic epoxides synthesis will be challenging. Therefore, in the first instance, early investigations were carried out using more reactive propargylic aldehydes in order to find effective reaction conditions. It was envisaged that conditions identified for the synthesis of disubstituted propargylic epoxides could provide some useful insight which could be applied to the synthesis of trisubstituted propargylic epoxides and epoxydiynes.

3.2.2.1 Synthesis of disubstituted propargylic epoxides

The investigation into the synthesis of disubstituted propargylic epoxides started with production of sulfonium tetrafluoroborate salt **227**. The first attempt at synthesising sulfonium tetrafluoroborate salt **227** proved unsuccessful. This involved adapting a procedure from Dai, substituting the original propargyl bromide for the propargyl chloride **202**, it was believed the nucleophilic attack of diphenyl sulphide **228** on propargyl chloride **202** in the presence of silver tetrafluoroborate would provide the desired sulfonium tetrafluoroborate salt **227** (Scheme 72).[144]

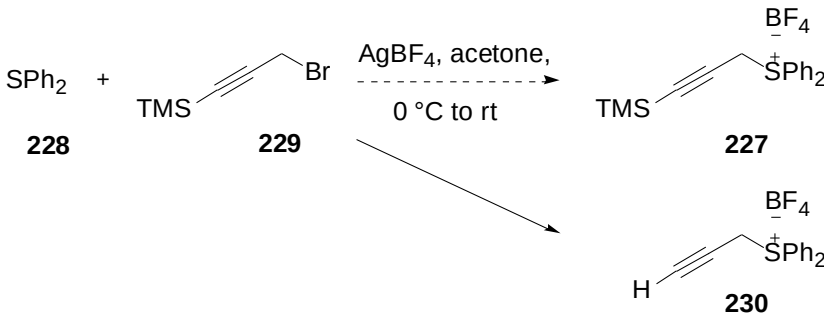


228 **202** **227**

Scheme 72. Attempted synthesis of sulfonium tetrafluoroborate salt **227** from propargyl chloride **202**

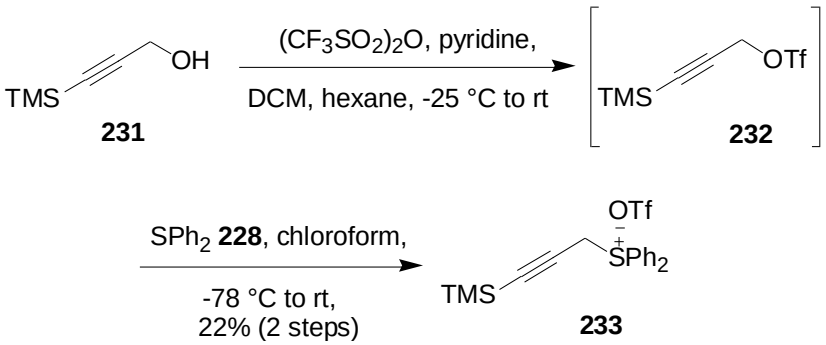
The synthesis of sulfonium salt **227** (Scheme 73) was repeated following Trost's original procedure,[144] upon which Dai's procedure was based, and having converted propargyl chloride **202** to its corresponding bromide **229**. Unfortunately, treatment of propargyl bromide **229** with diphenyl sulphide **228** gave the desilylated sulfonium

salt **230** instead of the desired sulfonium salt **227**, presumably due to the tetrafluoroborate, source of F^-, which cleaves the TMS group.



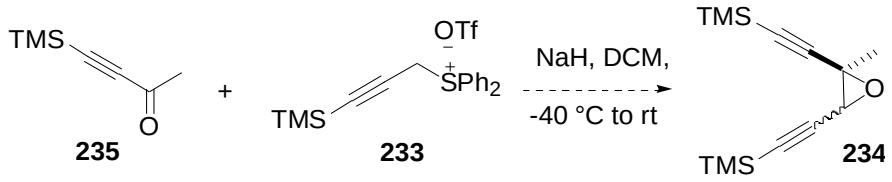
Scheme 73. Attempted synthesis of sulfonium tetrafluoroborate **227**

To circumvent the deprotection of TMS group by the presence of BF_4^-, the tetrafluoroborate counterion was replaced by the triflate ion. Treatment of commercially available propargyl alcohol **231** with triflic anhydride provided triflate **232**, which was not isolated and the crude mixture was taken on into the next step. Nucleophilic attack of diphenyl sulphide **228** on triflate **232** gave the desired sulfonium triflate salt **233**, albeit in low yield (Scheme 74).



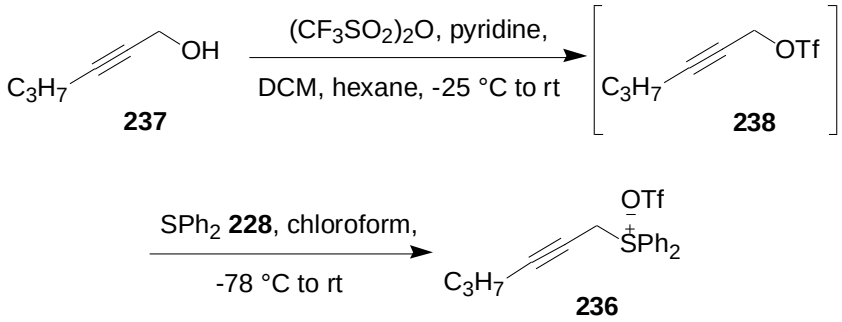
Scheme 74. Synthesis of sulfonium triflate salt **233**

The conditions developed by Solladié-Cavallo and Diep-Vohuule were applied without further optimisation, to the synthesis of epoxydiyne **234** from propargylic ketone **235** and propargylic sulfonium salt **233** (Scheme 75).[145] It is possible that partial TMS deprotection followed by rearrangement might explain the lack of results observed. Submitting each starting material separately to the reaction conditions suggested that the side products observed in the crude NMR might be derived from the sulfonium salt.



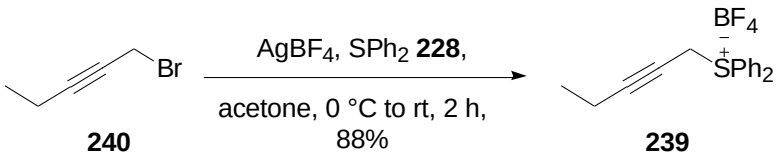
Scheme 75. Attempted synthesis of epoxide **234**

To circumvent the problems encountered in the previous attempts, the TMS group was exchanged for an alkyl group. Following the same reaction conditions as for synthesis of sulfonium salt **233** (Scheme 74), synthesis of sulfonium triflate salt **236** was then attempted from propargyl alcohol **237**, *via* triflate **238** (Scheme 76). A reaction occurred but isolating any product proved to be impossible.



Scheme 76. Attempted synthesis of sulfonium triflate salt **236**

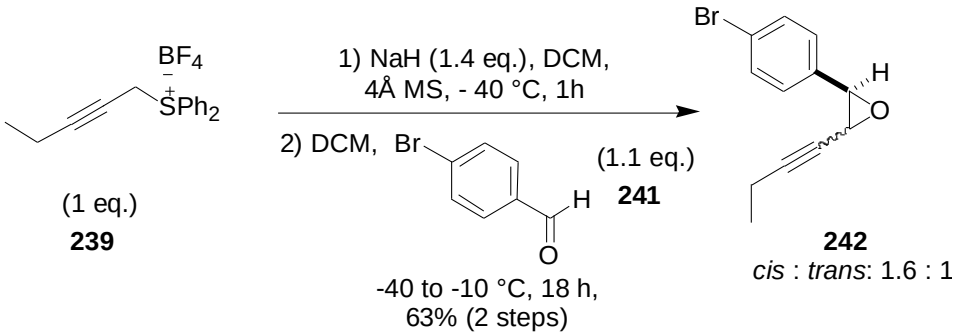
Due to complications involved in product isolation, the triflate counterion was abandoned and the original tetrafluoroborate ion was revaluated, as the triflate counterion was no longer required in the absence of a TMS group. Following Trost's procedure, sulfonium tetrafluoroborate salt **239** was synthesised from propargyl bromide **240** in good yield (Scheme 77).



Scheme 77. Synthesis of tetrafluoroborate salt **239**

Pleasingly it was discovered that the reaction of sulfonium tetrafluoroborate salt **239** with *p*-bromobenzaldehyde **241** (Scheme 78) gave the desired product **242** in good yield (Scheme 78). Lowering the temperature to -78 °C did not improve the stereoselectivity. Various attempts at -20 and -10 °C did not result in an increase in yield. Even though epoxide **242** could be obtained in a reasonable yield of 63%, the

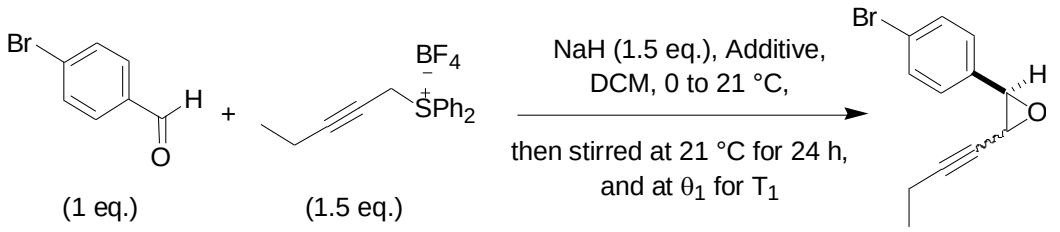
rather long reaction time (18 h) suggested that this protocol was likely to be impractical for less reactive ketones.



Scheme 78. Synthesis of epoxide **242**

Thus, new simpler reaction conditions, *i.e.* a one-pot reaction, were studied (Table 10).[146] Solvents, Lewis acids, temperature and reaction time were investigated for their effect on the stereoselectivity and the yield of the reaction. Addition of sulfonium tetrafluoroborate salt **239** to *p*-bromobenzaldehyde **241** *via* the new method gave the desired epoxide **242** with a slightly lower yield than with the previous method (54%), with a similar stereoselectivity (*cis* : *trans*: 1.6 : 1) (Table 10, Entry 1) but a longer reaction time of 24 h. Replacing dichloromethane for tetrahydrofuran as the solvent (Table 10, Entry 2) saw a small improvement in the yield (60%). Silver bromide (Table 10, Entry 3) and lithium bromide (Table 10, Entry 4) were found to be tolerated by the reaction but had little to no effect on the *cis* : *trans* ratio. Tetrahydrofuran was replaced with dichloromethane in order to avoid polymerisation of tetrahydrofuran in the presence of trifluoroborane, tin tetrachloride or silver triflate. Surprisingly, addition of boron trifluoride or tin tetrachloride at room temperature (Table 10, Entries 5-6) led to a sharp decrease in the conversion of aldehyde **241** (15-39% conversion). Notably, addition of tin tetrachloride to the reaction mixture led to exclusive formation of the *trans* epoxide (*cis* : *trans*: 1 : 18) (Table 10, Entry 6). Increasing the temperature and the reaction times (Table 10, Entries 7-8) gave good conversion of aldehyde **241**, in the presence of boron trifluoride or tin tetrachloride; however low yields (0-17%) were observed which could be explained by the decomposition of the epoxide **242** in the presence of hard Lewis acids. The addition of softer Lewis acids, *e.g.* silver triflate and dysprosium triflate (Table 10, Entries 9-10), was tolerated in the addition of

sulfonium tetrafluroborate salt **239** to *p*-bromobenzaldehyde **241** but had no significant effect on the stereoselectivity or yield.



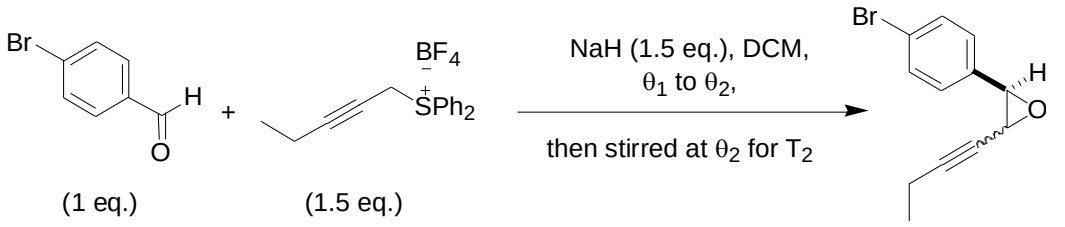
(1 eq.) **241** (1.5 eq.) **239** **242**

Entry	Additive		Conditions		Conv. **241**	Yield **242**	*cis* : *trans*
		(eq.)	θ_1(°C)	T_1(h)	(%)	(%)	ratio
1	-	-	-	-	100[d]	54	1.6 : 1
2[a]	-	-	-	-	100[d]	60	1 : 1
3[a]	AgBr	0.1	-	-	88[e]	63	1 : 1
4[a]	LiBr	0.1	-	-	89[e]	56	1.4 : 1
5	$BF_3.OEt_2$	0.2	-	-	39[e]	N. I.	1.5 : 1
6	$SnCl_4$	0.2	-	-	15[e]	N. I.	1 : 18
7[b]	$BF_3.OEt_2$	0.2	40	7	70[d]	17	1.6 : 1
8[b]	$SnCl_4$	0.2	40	7	93[d]	0	-
9[b,c]	AgOTf	0.2	21	7	100[d]	61	1.5 : 1
10[b,c]	$Dy(OTf)_3$	0.2	21	7	82[d]	36	1.4 : 1

[a]: THF instead of DCM; [b]: stirred 16 instead of 24 h; c: stirred at 0 instead of 21 °C for 24 h; [d]: determined by integration of ^{1}H NMR with DMF (1 eq.) as standard; [e]: evaluated based on the assumption aldehyde **241** is stable to reaction conditions; N.I.: No isolation

Table 10. Optimisation of reaction conditions for the synthesis of epoxide **242**

Having observed Lewis acids produced no significant effect, the impact of temperature was evaluated (Table 11). In an attempt to increase the *cis* : *trans* ratio, the temperature of the reaction mixture was lowered to -20 °C (Table 11, Entry 2) and -78 °C (Table 11, Entry 3). Pleasingly, the reaction was complete in a much shorter time, 8 h instead of 24, and good yields were achieved but with no impact on the stereochemical outcome. Lowering the temperature of the reaction mixture had no effect on the stereoselectivity. It was rationalised that the reactivity of *p*-bromobenzaldehyde **239** permitted no control on the *cis* : *trans* ratio. Having found easy reaction conditions and obtained good yields for the synthesis of disubstitued propargylic epoxides; focus was then placed on the synthesis of trisubstitued propargylic epoxides, for which it was hoped the less reactive propargylic ketones might allow more scope for stereocontrol.



(1 eq.) **241** (1.5 eq.) **239** **242**

Entry	Conditions			Conv.[a]	Yield[a]	*cis* : *trans*
	θ_1(°C)	θ_2(°C)	T_2(h)	**241** (%)	**242** (%)	ratio
1	0	21	24	100	54	1.6 : 1
2	-20	-20	8	100	66	1.6 : 1
3	-78	-78	8	98	63	1.5 : 1

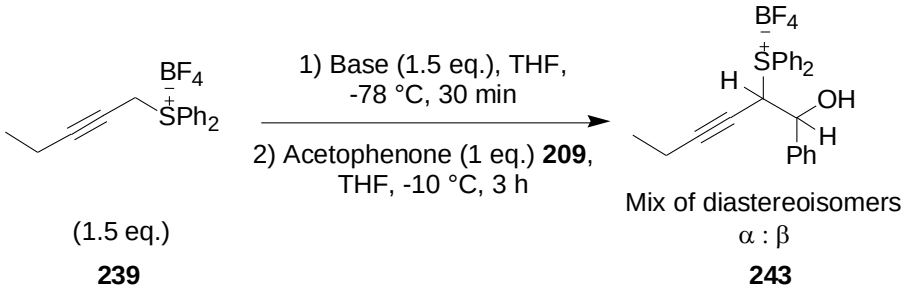
[a]: determined by integration of ^{1}H NMR with DMF (1 eq.) as standard

Table 11. Study of the effect of temperature of the synthesis of epoxide **242**

3.2.2.2 Synthesis of trisubstituted propargylic epoxides

The optimised reaction conditions for the synthesis of disubstituted propargylic epoxides were applied to the reaction of sulfonium salt **239** with acetophenone **209** (Table 12). Pleasingly, preliminary studies revealed the reaction to be complete in 30 min at -78 °C. However, addition of the sulphur ylide to a less reactive acetophenone **209** required a higher temperature, -10 °C. A range of bases and both basic and acidic work-up were investigated to assess their impact on the reaction of sulfonium salt **239** with acetophenone **209**. Use of sodium hydride as a base (Table 12, Entries 1-2) saw consumption of acetophenone **209** but did not yield any product. Hexamethyldisilazide bases (Table 12, Entries 3-8) were also investigated. No epoxide formation could be observed upon addition of sulfonium salt **239** to acetophenone **209** in the presence of base, despite increasing the temperature and using different work-up conditions. Instead of the desired epoxide, a very polar product was observed, which did not move from the Thin Layer Chromatography baseline, suggesting a salt. It was isolated as a mixture of diastereoisomers α and β, whose δ(C*H*SPh_2^+) are 3.53 and 3.30 ppm in the crude ^{1}H NMR, consistent with CH shifts for the proposed open structure **243**.[147] Conversion of acetophenone **209** ranged from good (61-63%) in the presence of NaHMDS (Table 12, Entries 5-6) to complete in the presence of LiHMDS (Table 12, Entries 7-8). However, only moderate yields of products **243** were observed in the case of LiHMDS (44-49%) (Table 12, Entries 7-8). Stereoselectivity for **243** was lower and reversed in the presence of LiHMDS (α : β: 1 : 1.2) (Table 12, Entries 7-8) compared to NaHMDS

(α : β: 4.2/4.6 : 1) (Table 12, Entries 3-4) and KHMDS (α : β: 2.3 : 1) (Table 12, Entries 5-6). Even though the stereoselectivity was higher when KHMDS was employed, the yields obtained were too low to use KHMDS in a general protocol for propargylic trisubstituted epoxides. Therefore, LiHMDS was chosen for the rest of the study, as high conversion and acceptable yields were obtained, even though stereoselectivity was low. The low reactivity of acetophenone **209** combined with the impossibility of obtaining the epoxides makes acetophenone **209** a poor model system for the investigation of the synthesis of trisubstituted propargylic epoxides. Considering the ease of access to the natural product ketone **14** (Scheme 70), subsequent investigations were carried out with this substrate.



(1.5 eq.)

239

243

Entry	Base	Work-up	Conv.[a] **209** (%)	Yield[a] **243** (%)	Ratio α : β
1	NaH	NH_4Cl(sat)	45	0	-
2	NaH	MeOH	78	0	-
3	KHMDS	NH_4Cl(sat)	76	8	2.3 : 1
4	KHMDS	MeOH	85	7	2.3 : 1
5	NaHMDS	NH_4Cl(sat)	63	20	4.6 : 1
6	NaHMDS	MeOH	61	17	4.2 : 1
7	LiHMDS	NH_4Cl(sat)	100	49	1 : 1.2
8	LiHMDS	MeOH	100	44	1 : 1.2

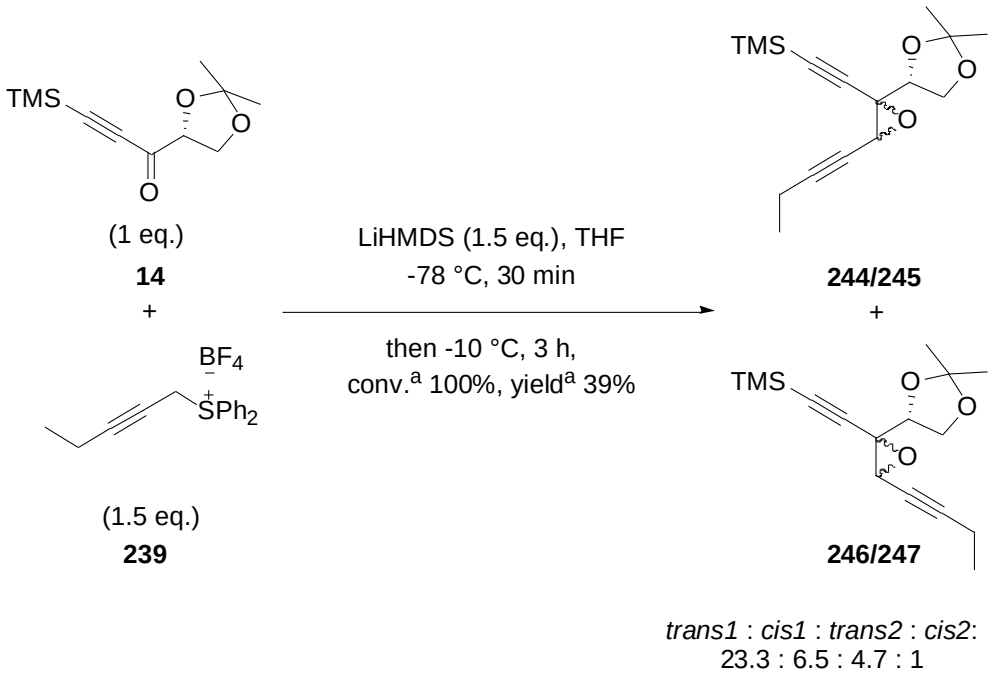
[a]: determined by integration of ^{1}H NMR with DMF (1 eq.) as standard; α: product whose δ(C*H*SPh_2^+) = 3.53 ppm; β: product whose δ(C*H*SPh_2^+) = 3.30 ppm

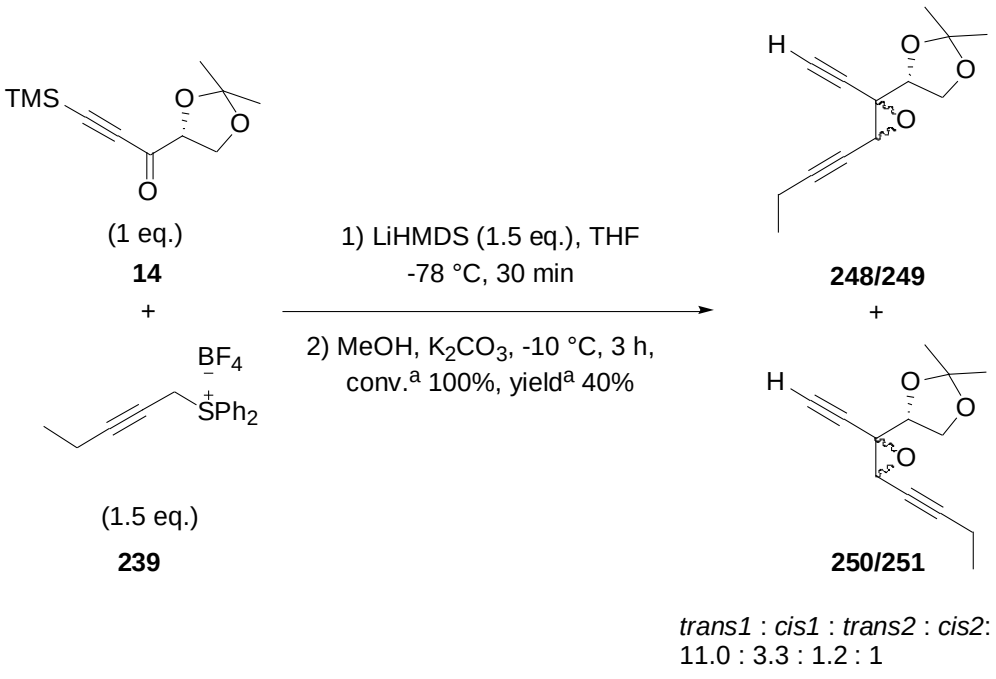
Table 12. Attempt syntheses of trisubstituted propargyl epoxides

3.2.3 Synthesis of epoxydiyne via sulphur ylide chemistry

The previously optimised reaction conditions (See 3.2.2.2) were applied to the reaction of the natural product ketone **14** with sulfonium salt **239** (Scheme 79). Pleasingly, complete conversion of ketone **14** and formation of the expected epoxides **244**-**247** and **248**-**251** were observed, albeit in moderate yield. Partial desilylation was observed when ketone **14** was reacted with sulfonium salt **239**. Considering deprotection of the TMS group in epoxydiyne **138** is needed prior to the

Sonogashira coupling between iodocyclopentenone **134** and epoxydiyne **139** (See 1.5.2, p 34), combination of the deprotection step with epoxide formation in one pot, in a similar approach to that reported by Caddick and Thominet, was evaluated (Scheme 79).[66] In order to determine the relative configuration of the formed epoxides, NMR studies, and DFT calculations, were carried out on the desilylated epoxides **248**-**251**.[148] The geometries of the most preferred conformation for each possible configuration were calculated *via* molecular mechanics (Figure 6). To distinguish *trans*- (***T*^{1}**-***T*^{2}**) and *cis*-configuration (***C*^{1}**-***C*^{2}**), the stereospecificity of ^3J(C9,H25)-couplings was used. The predicted values of these coupling constants at were 0.3 Hz (***T*^{1}**), 0.4 Hz (***T*^{2}**), 2.1 Hz (***C*^{1}**) and 2.4 Hz (***C*^{2}**). One of the diastereoisomers was available pure (**α**), whereas three others (**β**, **γ** and **ε**) were in a mixture (**β : γ : ε**: 4.0 : 1.3 : 1.0). Proton-coupled ^{13}C NMR spectra and two-dimesional heteronuclear *J*-resolved (^{1}H,^{13}C)-spectra were measured with selective irradiation of proton H25 of each diastereoisomer in order to determine experimental values of ^3J(C9,H25)-couplings. These were 0.8±0.2 Hz (**α**), 2.2±0.1 Hz (**β**), 0.9±0.2 Hz (**γ**) and 2.4±0.1 Hz (**ε**). Thus, the measured values suggest that the two triple bonds in **α** (= *trans1*) and **γ** (= *trans2*) are in the *trans*-configuration, whereas in **β** (= *cis1*) and **ε** (= *cis2*) are in the *cis*-configuration. The ratio of four diastereoisomers for sylilated epoxides **244**-**247** were extrapolated from these calculations.





[a]: determined by integration of ^{1}H NMR with DMF (1 eq.) as standard

Scheme 79. Syntheses of epoxydiynes **244-247** and **248-251**

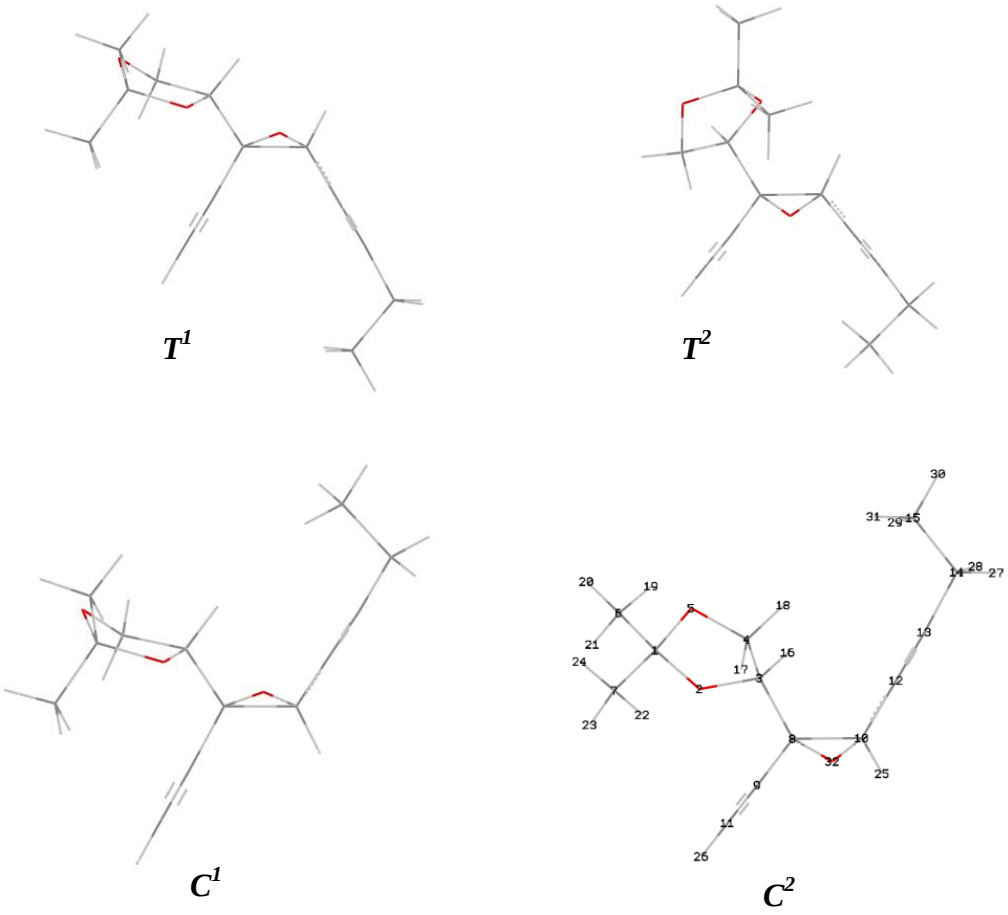
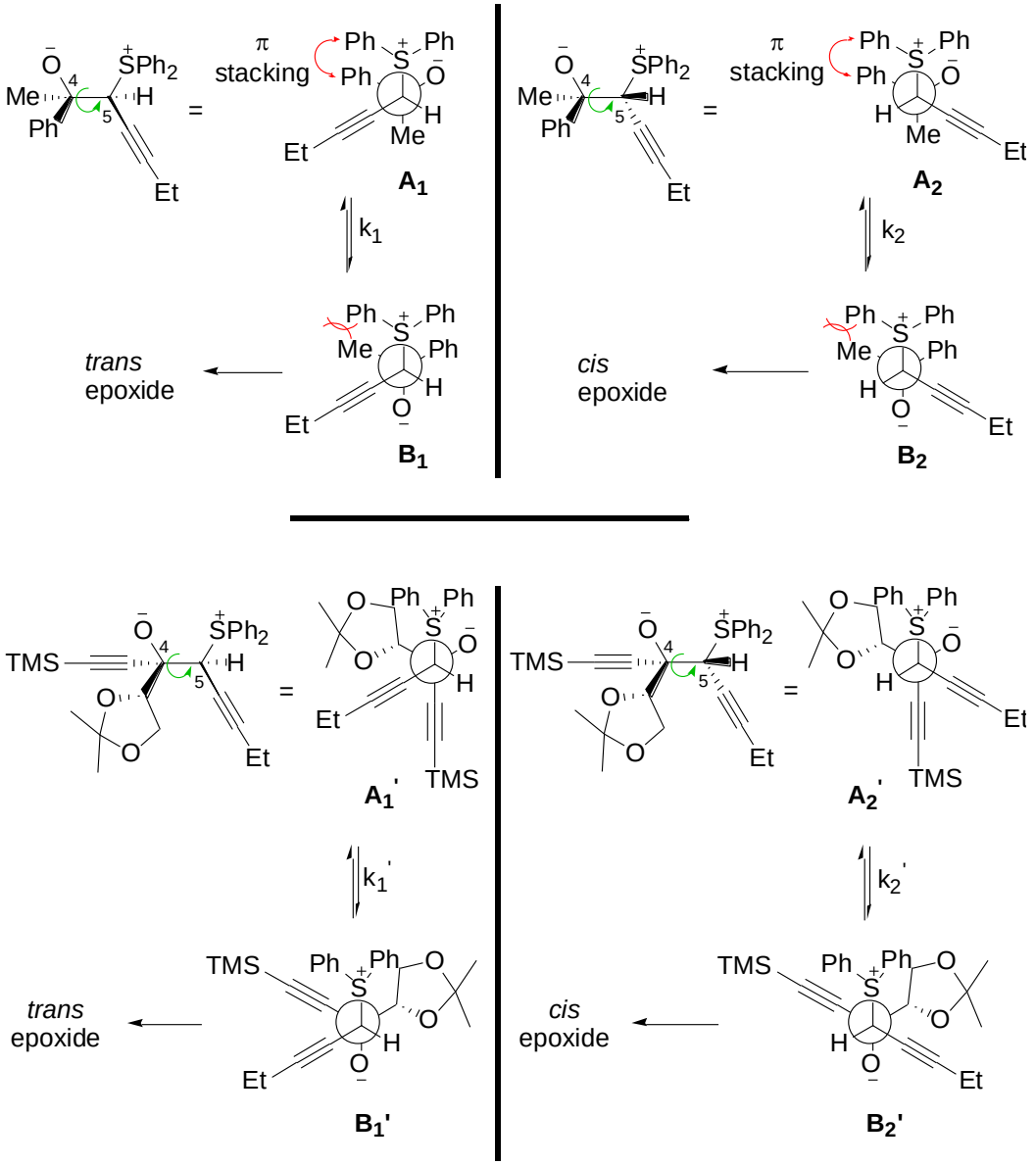


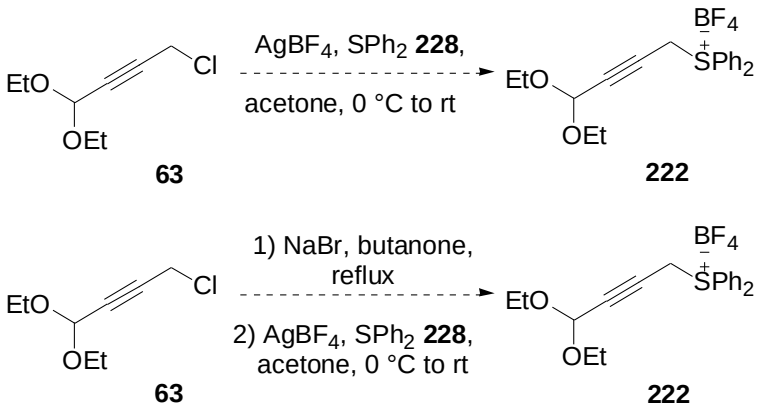
Figure 6. Optimised geometries of the preferred conformations of *trans* (***T*^{1}** and ***T*^{2}**) and *cis* (***C*^{1}** and ***C*^{2}**) isomers

The significant difference in reactivity between acetophenone **209** (See 3.2.2.2, Table 12) and natural product ketone **14** was hypothesised to arise from the rate of rotation of bond C4-C5 in the rate determining step (Scheme 80). For the epoxide to be formed, the diphenyl sulfonium group needs to be antiperiplanar to the C4 oxygen. For acetophenone **209**, π stacking between one phenyl from acetophenone and one phenyl from the diphenyl sulfonium group in open intermediates $\mathbf{A_1}$ and $\mathbf{A_2}$ combined with sterics hinderance between the methyl group and the diphenyl sulfonium group in open intermediates $\mathbf{B_1}$ and $\mathbf{B_2}$, might favour equilibrium towards open intermediates $\mathbf{A_1}$ and $\mathbf{A_2}$, hence impeding epoxide formation. For natural product ketone **14**, reduced impediment to rotation about the C4-C5 bond results in relatively facile formation of epoxides.



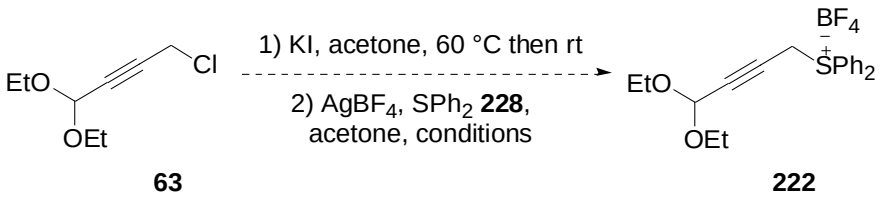
Scheme 80. Rate determining step in epoxide formation

Having obtained positive results with sulfonium salt **239** and natural product ketone **14**, the synthesis of natural product sulfonium salt **222** (See Scheme 70, p 68) was initiated in order to synthesise epoxydiyne **221**. Synthesis of natural product sulfonium salt **222** (Scheme 81) was attempted from propargyl chloride **63** (See Scheme 59, p 57). However, propargyl chloride **63** was not reactive enough and therefore was converted to its corresponding propargyl bromide before being converted to natural product sulfonium salt **222**. The six equivalents of diphenyl sulphide used in order for the reaction to proceed made the isolation of pure sulfonium salt **222** impossible.



Scheme 81. Attempted syntheses of natural product sulfonium salt **222** *via* propargyl bromide

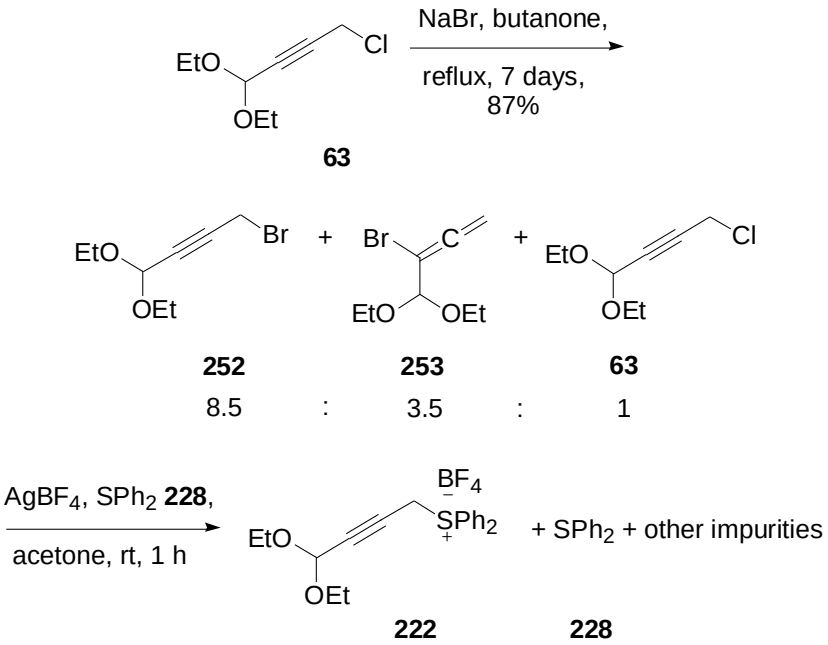
Propargyl chloride **63** was then converted to its corresponding iodide (Scheme 82). It was believed the more reactive propargyl iodide would simplify the protocol and minimise contamination of sulfonium salt **222**. Rapid deprotection of the acetal function was observed even at low temperature. Alterations such as the addition of sodium bicarbonate, the absence of silver tetrafluoroborate or conducting the reaction under stoichiometric conditions did not result in isolation of clean sulfonium salt **222.** Being very capricious, the conversion of propargyl iodide to natural sulfonium salt **222** was therefore abandoned.



Scheme 82. Attempted syntheses of natural product sulfonium salt **222** *via* propargyl iodide

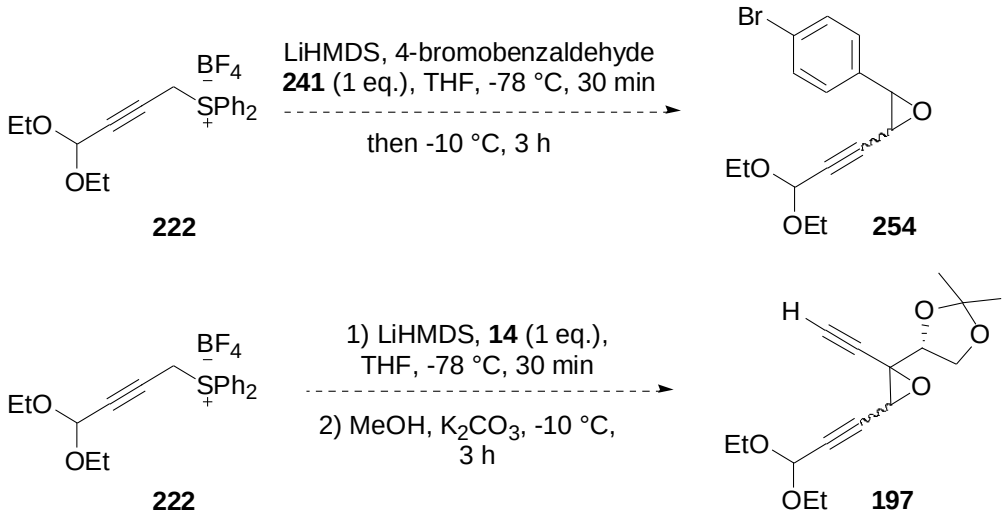
Because of the difficulties of obtaining natural product sulfonium salt **222** *via* propargyl iodide, studies reverted to the use of propargyl bromide. A minor quantity of contamination of the sulfonium salt **222** with diphenyl sulphide **228** (See Scheme 81) was deemed acceptable as it is also produced in the following step, *i.e.* epoxide formation. Treatment of propargyl chloride **63** by sodium bromide under reflux gave an inseparable mixture of propargyl bromide **252**, bromoallene **253** and propargyl chloride **63** in a 8.5 : 3.5 : 1 ratio (Scheme 83). Pleasingly, this mixture was completely converted to natural product sulfonium salt **222** at the following step, using only two equivalents of diphenyl sulphide **228**. No sulfonium salt containing

an acetal function has been reported; natural sulfonium salt **222** is therefore the first example, despite being contaminated by diphenyl sulphide.



Scheme 83. Synthesis of natural product sulfonium salt **222**

The reactivity of crude sulfonium salt **222** towards both 4-bromobenzaldehyde **241** and natural product ketone **14**, was then evaluated. However, treatment of crude sulfonium salt **222** with LiHMDS followed by addition of 4-bromobenzaldehyde **241** or ketone **14**, gave no trace of epoxides **254** or **197**. Complete consumption of ketone **14** was observed, however 4-bromobenzaldehyde **241** did not seem to have reacted. The presence of impurities in sulfonium salt **222** might explain the lack of reactivity of the sulfonium salt.



Scheme 84. Attempted syntheses of epoxydiynes **197** and **254**

In conclusion, sulphur ylide chemistry proved a valid method to access epoxydiynes **244-251**, albeit in moderate yields. Synthesis of natural product epoxydiyne **197** has not yet been achieved due to difficulties in obtaining pure natural product sulfonium salt **222**.

3.3 Conclusion

The reaction between propargyl chloride **63** and ketone **14** to access natural product chlorohydrin **137** *via* zinc bromide coupling (Scheme 60, p57) was found to be very capricious. An investigation into the zinc bromide coupling did not provide unambiguous reasons for the low yields and lack of diastereoselectivity. An alternative approach, *via* sulphur ylides, was designed. It gave access to disubstituted propargylic epoxides in good yields (Table 11, p74). Syntheses of trisubstituted epoxides were found to be more challenging and could only be isolated in moderate yield in the particular case of natural product ketone **14** (Scheme 79, p77). Difficulties in obtaining pure natural product sulfonium salt **222** prevented further evaluation of this approach for the synthesis of the desired epoxydiyne **197** (Scheme 84).

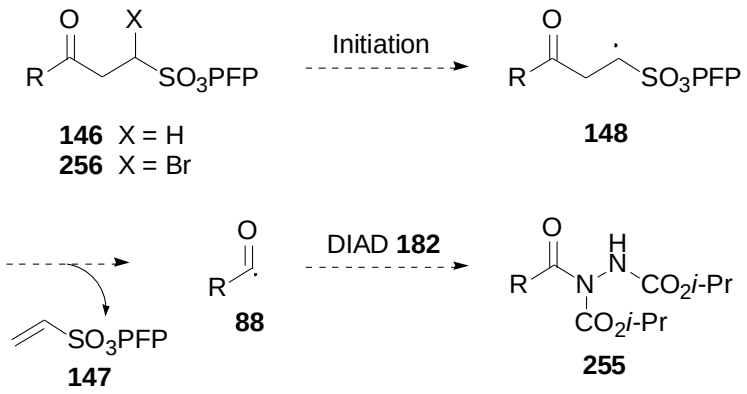
Conclusions and Further Work

The enediyne family of natural products, of which Neocarzinostatin is a member, has raised much interest from the scientific community since its discovery. Much work has been undertaken to synthesise the unusual bicyclic enediyne core, responsible for the anticancer activity. Of particular note are the total syntheses of Myers and Hirama, as well as work from Magnus. This thesis explored two novel strategies to access NCS-C core, based around acyl radical chemistry and the McMurry coupling.

Caddick recently reported a mild and selective method for the preparation of 1,4-ketosulfonates *via* radical hydroacylation of pentafluorophenyl vinyl sulfonate with simple alkyl aldehydes. In view of the application of this new method to the synthesis of NCS-C core, this thesis has broadened the scope of aldehydes which can be used for hydroacylation of this bifunctional acceptor. Moreover, pentafluorophenol has been demonstrated to have an inhibitory effect on the hydroacylation of PFPVS and modified conditions have been investigated to minimise this effect. Mechanistic studies have delivered more insight into the aerobic hydroacylation reaction of vinyl sulfonate and preliminary results suggest the addition of acyl radicals to vinyl sulfonates may be reversible.

Access to the key epoxydiyne synthon for the McMurry approach to NCS-C core has proved to be very challenging. Synthesising intermediate chlorohydrins *via* zinc bromide coupling was very capricious and the yield and stereoselectivity reported could not be reproduced. Investigation into the zinc bromide coupling suggested the intractability of this approach could be due to the coordination of zinc bromide to the acetal of propargyl chloride **63**; however no definite explanation could be obtained. An alternative approach to the key epoxydiyne, *via* sulphur ylide mediated epoxidation has been designed. This new method gave access to disubstituted propargylic epoxides in good yields from aldehydes and trisubstituted propargylic epoxides from ketones. However, difficulties in obtaining pure sulfonium salts hampered further evaluation of this approach for the synthesis of the desired key epoxydiyne.

Future work on the hydroacylation of PFPVS should focus on developing further mechanistic studies in order to understand and elucidate suitable conditions for hydroacylation of substituted vinyl sulfonates (Scheme 85). For example, if radical **148** is produced in the presence of DIAD **182** then isolation of the product **255** would provide some evidence for reversibility of intermolecular acyl radical addition to vinyl sulfonates. The increased aldehyde versatility has shown potential for the application of this aerobic hydroacylation as a key C-C bond forming reaction in complex synthesis method. However, the scope of the aldehydes and vinyl sulfonates needs to be further enlarged. For example, reactions involving vinyl sulfonates such as **257** and aldehydes such as **258** should be investigated (Figure 7).



Scheme 85. Study of reversibility of addition of acyl radicals to vinyl sulfonates

Figure 7. Model systems for NCS synthesis *via* aerobic hydroacylation

Future work on the McMurry route should begin with optimisation of the sulfonium salt, both in terms of synthesis and reactivity, to allow evaluation of the sulphur ylide approach towards the key NCS epoxydiyne. Additionally, a general method to access trisubstituted propargylic epoxydiynes could be developed. Considering the difficulties the C8 acetal brought in the synthesis of key chlorohydrins and epoxydiynes, alternative protecting group strategies at this position should be evaluated, such as dithianes or silyl protection of the equivalent alcohol. Further work in the total synthesis of NCS-C core **145** includes evaluation of the C1 to C2 Sonogashira coupling and the C8 to C9 intramolecular McMurry coupling to form the NCS nine membered ring.

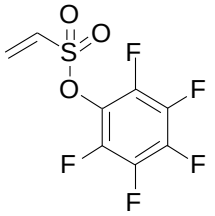
Experimental

General Experimental

All reactions were done in flame-dried round bottom flasks and under positive pressure of argon unless otherwise stated. Commercial reagents and solvents were used as received unless otherwise stated. THF and Et_2O were dried through alumina column. The ISOLUTE filtration columns (Standard grade, single fritted reservoir 15 mL, polyethylene frit, 10 μm porosity) were provided by International Sorbent Technology. Diisopropylamine was distilled on calcium hydride under argon. *n*-butyllithium was titrated with (-)-endo-Borneol and fluorene. Thin layer chromatography was done on aluminium plates pre-coated with Merck silica gel 60 F_{254} and was developed by exposure to UV and /or exposure to potassium permanganate or DNP followed by heating. Flash chromatography was carried out on silica gel (32-70 μm). Proton, carbon and fluorine NMR were obtained on Bruker AMX 300, AMX 400, AMX 500 or AMX 600 spectrometers, at 400, 500 or 600 Hz for the ^{1}H NMR, 125 or 150 Hz for the ^{13}C NMR and 282 Hz for ^{19}F NMR. Chemical shifts (δ) are expressed in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used to describe the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet and br, broad. Coupling constants are given in Hertz (Hz). Low and high resolution mass spectra were obtained from the mass spectroscopy service of University College London using a VG70-SE or MAT 900 XP spectrometer. Infrared spectra were recorded on a a Perkin Elmer Spectrum 100 opertaing in ATR mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected. Due to the broadness of the ^{13}C NMR signals in the pentafluorophenyl moiety these peaks have not been assigned.

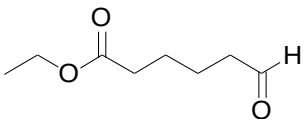
Experimental for Chapter 2

Ethenesulfonic acid pentaflorophenyl ester 147[93]



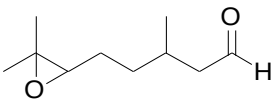
To a solution of pentafluorophenol **155** (2.12 g, 11.5 mmol) and 2-chloroethane sulfonyl chloride **154** (1.2 mL, 11.5 mmol) in DCM (30 mL) at -10 °C was added dropwise a solution of triethylamine (3.5 mL, 25 mmol) in DCM (30 mL). The reaction was further stirred at -10 °C for 30 min after addition. The reaction mixture was then washed with $NaHCO_{3(sat)}$ (x 3), a 2 M solution of HCl (x 3), and brine, dried ($MgSO_4$). Solvent was then removed under vacuum. The crude mixture was purified by flash chromatography (0-20% DCM/PE) to afford PFP vinyl sulfonate **147** as a white solid (2.7 g, 9.8 mmol, 87 %). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 6.80 (1H, dd, *J* = 16.5, 9.8 Hz, C*H*), 6.55 (1H, dd, *J* = 16.5, 0.8 Hz, CH_2), 6.34 (1H, dd, *J* = 9.8, 0.8 Hz, CH_2); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 133.3 (*C*H_2), 131.9 (*C*H); **^{19}F NMR** (282 MHz; $CDCl_3$) δ -150.9 (2F, dd, *J* = 25.4, 8.5 Hz), -155.4 (1F, app. t, *J* = 22.6 Hz), -161.3-(-161.1) (2F, m).

6-oxo-hexanoic acid ethyl ester 150[149]



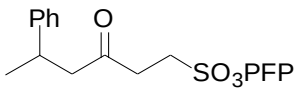
To a solution of pyridinium chlorochromate (8.1 g, 37 mmol) in DCM (40 mL) at 0 °C was added dropwise a solution of ethyl-6-hydroxy-hexanoate **156** (4.1 mL, 25 mml) in DCM (10 mL). The reaction mixture was then stirred at room temperature for 2 h. It was then diluted with Et_2O and passed through a plug of celite. It was rinsed throroughly with Et_2O and solvent was removed under vacuum to afford ester **150** as a pale yellow oil (3.60 g, 22.8 mmol, 91%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 9.75 (1H, s, C*H*O), 4.11 (2H¸ q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 2.44-2.45 (2H, m, C*H*$_2$), 2.27-2.32 (2H, m, C*H*$_2$), 1.62-1.65 (4H, m, (C*H*$_2$)$_2$), 1.24 (3H, t, *J* = 7.1 Hz, C*H*$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 202.3 (*C*HO), 173.5 (*C*(O)), 60.6 (*C*H$_2$), 43.6 (*C*H$_2$), 34.1 (*C*H$_2$), 24.5 (*C*H$_2$), 21.6 (*C*H$_2$), 14.3 (*C*H$_3$); **LRMS** (CI) 157 (76%, $[M-H]^+$), 143 (100%), 113 (28%); **HRMS** (CI) calcd for for $C_8H_{13}O_3$ 157.0865; $[M-H]^+$ 157.0865 observed

5-(3,3-dimethyloxiran-2-yl)-3-methylpentanal 153[150]

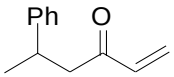


To a solution of (+/-)-citronellal **157** (14.9 mL, 83 mmol) in DCM (240 mL) was added dropwise a solution of *m*-CPBA (17.0 g, 99 mmol) in DCM (240 mL) at 0 °C. The reaction mixture was then stirred overnight at room temperature before being filtered. The filtrate was washed with $K_2CO_{3(sat)}$, water (x 3) and dried ($MgSO_4$). Solvent was removed under vacuum to afford epoxyaldehyde **153** as a transparent oil as a mixture of diastereoisomers (major : minor: 7.3 : 1). (16.7 g, 98.1 mmol, 88 %). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 9.76 (1H, s, C*H*O, *major & minor*), 2.69-2.71 (1H, m, CH_{epo}, *major & minor*), 2.44 (1H, ddd, *J* = 11.1, 5.5, 1.8 Hz, CH_2CHO, *minor*), 2.42 (1H, ddd, *J* = 11.1, 5.6, 1.9 Hz, CH_2CHO, *major*), 2.29 (1H, ddd, *J* = 7.8, 5.6, 2.4 Hz, CH_2CHO, *major*), 2.26 (1H, ddd, *J* = 8.0, 5.5, 2.5 Hz, CH_2CHO, *minor*), 2.09-2.15 (1H, m, C*H*CH_3, *major & minor*), 1.43-1.62 (4H, m, (CH_2)$_2$, *major & minor*), 1.31 (3H, s, CH_{3epo}, *major & minor*), 1.26 (3H, d, *J* = 1.8 Hz, C$H_{3epo,}$ *major & minor*), 0.99 (3H, d, *J* = 6.8 Hz, CH_3CHCH_2CHO, *major*), 0.97 (3H, d, *J* = 6.7 Hz, CH_3CHCH_2CHO, *minor*); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 202.81 (*C*(O)H), 202.75 (*C*(O)H), 64.38 (*C*H), 64.35 (*C*H), 58.5 (*C*), 58.4 (*C*), 51.1 (CH_2), 51.0 (CH_2), 33.7 (CH_2), 28.03 (C*H*), 28.02 (C*H*), 26.51 (CH_2), 26.47 (CH_2), 25.0 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 18.83 (CH_3), 18.78 (CH_3); **LRMS** (CI) 199 (65%), 185 (34%), 171 (26%, $[M]^+$), 154 (36%), 153 (94%), 135 (100%), 109 (30%); **HRMS** (CI) calcd for $C_{10}H_{19}O_2$ 171.1385; $[M]^+$ 171.1389 observed.

3-oxo-5-phenyl-hexane-1-sulfonic acid pentafluorophenyl ester 158 and 5-phenylhex-1-en-3-one 259



158



259

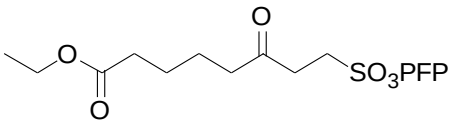
To a solution of PFP vinyl sulfonate **147** (276 mg, 1.01 mmol) in water (1 mL) in a carousel tube, 3-phenylbutanal **149** (300 μL, 2.02 mmol) was added. The reaction mixture was then stirred at room temperature at 300 rpm for 7 days. Solvent was removed under vacuum and the crude mixture was purified by flash chromatography (0-100 % DCM/PE) to afford β-ketosulfonate **158** (230 mg, 0.54 mmol, 54 %) with traces of elimination product **259**.

Data for β-ketosulfonate **158**: **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.31 (2H, t, *J* = 7.7 Hz, C*H*$_{Ar}$), 7.20-7.22 (3H, m, C*H*$_{Ar}$), 3.70 (1H, ddd, *J* = 14.9, 9.4, 5.5 Hz, C*H*$_2$SO$_3$PFP), 3.63 (1H, ddd, *J* = 14.9, 9.4, 5.5 Hz, C*H*$_2$SO$_3$PFP), 3.35 (1H, app. sext., *J* = 7.1 Hz, C*H*), 3.05 (1H, ddd, *J* = 18.4, 9.4, 5.5 Hz, C(O)C*H*$_2$CH$_2$SO$_3$PFP), 2.93 (1H, ddd, *J* = 18.4, 9.4, 5.5 Hz, C(O)C*H*$_2$CH$_2$SO$_3$PFP), 2.86 (1H, dd, *J* = 16.2, 7.3 Hz, C(O)C*H*$_2$CH), 2.76 (1H, dd, *J* = 16.2, 7.3 Hz, C(O)C*H*$_2$CH), 1.30 (3H, d, *J* = 7.0 Hz, C*H*$_3$); **^{13}C NMR*** (150 MHz; $CDCl_3$) δ 204.0 (*C*), 145.4 (*C*), 128.8 (*C*H), 126.8 (*C*H), 51.2 (*C*H$_2$), 46.9 (*C*H$_2$), 36.8 (*C*H$_2$), 35.8 (*C*H$_2$), 22.2 (*C*H$_3$); **^{19}F NMR** (282 MHz; $CDCl_3$) δ -151.5 (2F, d, *J* = 16.9 Hz), -155.3 (1F, app. t, *J* = 21.2 Hz), -161.0 (2F, app. t, *J* = 19.7 Hz); **IR** ($CHCl_3$ solution) 2964, 1721, 1519, 1495, 1453 cm^{-1}; **LRMS** (CI) 423 (38%, [M]$^{+}$), 105 (100%); **HRMS** (CI) calcd for $C_{18}H_{16}O_4SF_5$ 423.0690; [M]$^{+}$ 423.0694 observed;

Data for enone **259**: **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.28-7.31 (2H, m, C*H*$_{Ar}$), 7.18-7.23 (3H, m, C*H*$_{Ar}$), 6.31 (1H, dd, *J* = 17.6, 10.6 Hz, C*H*), 6.18 (1H, dd, *J* = 17.6, 1.0 Hz, CHC*H*$_2$), 5.79 (1H, d, *J* = 10.6, 1.0 Hz, C*H*$_2$), 3.37 (1H, app. sext., *J* = 7.0 Hz, CH$_3$C*H*), 2.91, (1H, dd, *J* = 16.1, 6.1 Hz, C*H*$_2$), 2.81 (1H, dd, *J* = 16.1, 8.2 Hz, C*H*$_2$), 1.29 (3H, d, *J* = 7.0 Hz, C*H*$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 199.8 (*C*(O)), 146.4 (*C*), 136.9 (*C*H), 128.6 (*C*H), 128.4 (*C*H$_2$), 126.9 (*C*H), 126.4 (*C*H), 48.1 (*C*H$_2$), 35.6 (*C*H), 21.9 (*C*H$_3$); **IR** ($CHCl_3$ solution) 3029, 2963, 1679, 1615, 1495, 1453 cm^{-1}.

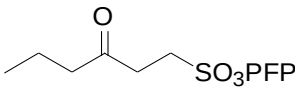
*****one aromatic CH is not seen

Ethyl-6-oxo-7-[(pentafluorophenoxy)sulfonyl]heptanoate 159



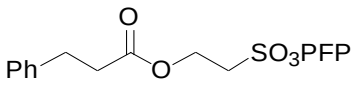
To 5,5-dimethyl-1,3-dioxane-2-butanal **150** (376 mg, 2.02 mmol) and PFP vinyl sulfonate **147** (276 mg, 1.01 mmol) in a carousel tube, water (1 mL) was added. The reaction mixture was stirred at room temperature at 300 rpm for 7 days. It was then concentrated under vacuum and the crude mixture was purified by reverse crystallisation (PE/DCM) to afford β-ketosulfonate **159** as a white solid (91 mg, 0.21 mmol, 21%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 4.13 (2H, q, *J* =7.1 Hz, C*H*$_2$CH$_3$), 3.76 (2H, t, *J* = 7.5 Hz, C*H*$_2$SO$_3$PFP), 3.14 (2H, t, *J* = 7.5 Hz, C*H*$_2$CH$_2$SO$_3$PFP), 2.56 (2H, t, *J* = 6.9 Hz, C*H*$_2$C(O)), 2.32 (2H, t, *J* = 6.9 Hz, C*H*$_2$CO$_2$CH$_2$CH$_3$), 1.61-1.70 (4H, m, (C*H*$_2$)$_2$), 1.26 (3H, t, *J* = 7,1 Hz, C*H*$_3$CH$_2$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 204.6 (*C*(O)), 173.4 (*C*(O)O), 60.5 (*C*H$_2$CH$_3$), 47.0 (*C*H$_2$SO$_3$PFP), 42.5 ((CH$_2$)$_3$*C*H$_2$C(O)), 36.1 (*C*H$_2$CH$_2$SO$_3$PFP), 34.0 (*C*H$_2$CO$_2$CH$_2$CH$_3$), 24.3 (*C*H$_2$), 23.1 (*C*H$_2$), 14.4 (*C*H$_3$); **IR** (neat) 3012, 2989, 2937, 2872, 1731, 1710, 1531, 1518 cm^{-1}; **LRMS** (ES) 455 (100%, [M+Na]$^+$), 405 (39%), 387 (24%), 367 (39%), 359 (33%); **HRMS** (ES) calcd for $C_{16}H_{17}O_6NaSF_5$ 455.0564; [M+Na]$^+$ 455.0567 observed.

Pentafluorophenyl 3-oxohexane-1-sulfonate 172[93]



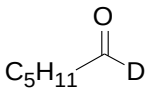
To a mixture of PFPVS **147** (295 mg, 1.1 mmol) in water (1 mL), butanal **170** (196 μL, 2.2 mmol) was added and the reaction mixture was stirred at room temperature at 300 rpm for 3 h. The reaction mixture was then concentrated under vacuum and the crude mixture was purified by flash chromatography (20-100% DCM/PE) to afford β-ketosulfonate **172** as an off-white crystalline solid (246 mg, 0.71 mmol, 66%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 3.76 (2H, t, *J* =7.5 Hz, C*H*$_2$), 3.14 (2H, t, *J* =7.5 Hz, C*H*$_2$), 2.51 (2H, t, *J* =7.3 Hz, C*H*$_2$), 1.66 (2H, sext. *J* = 7.3 Hz, C*H*$_2$), 0.95 (3H, t, *J* = 7.4 Hz, C*H*$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 205.1 (*C*(O)), 47.1 (*C*H$_2$), 44.8 (*C*H$_2$), 36.1 (*C*H$_2$), 17.3 (*C*H$_2$), 13.7 (*C*H$_3$); **^{19}F NMR** (282 MHz; $CDCl_3$) δ -151.60 (2F, m), -155.27 (1F, app. t, *J* = 21.2 Hz), -161.11-(-160.90) (2F, m).

3-phenyl-propionic acid 2-pentafluorophenyloxysulfonyl-ethyl ester 176



To a mixture of PFPVS **147** (282 mg, 1.0 mmol) in water (1 mL), pentafluorophenol **155** (12 μL, 0.10 mmol), pentachlorobenzene (255 mg, 1.0 mmol), pyridine (17 μL, 0.21 mmol) and hydrocinnamaldehyde **171** (272 μL, 2.1 mmol) were added and the reaction mixture was stirred at room temperature at 300 rpm for 1 day. $CDCl_3$, previously neutralised through basic alumina, was added to the reaction mixture. The biphasic mixture was passed through an ISOLUTE filtration column (Standard grade, single fritted reservoir 15 mL, polyethylene frit, 10 μm porosity), the organic phase was collected and the solvent removed under vacuum. The crude ixture was purified by flash chromatography (30-100% DCM/PE to 10% MeOH/DCM) to give **176** (83 mg, 0.20 mmol, 18%) and hydrocinnamaldehyde as an inseparable mixture (5.4 : 1). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.26-7.31 (2H, m, C*H*$_{Ar}$), 7.19-7.22 (3H, m, C*H*$_{Ar}$), 4.64 (2H, t, *J* = 6.1 Hz, PFPSO$_3$CH$_2$C*H*$_2$C(O)), 3.74 (2H, t, *J* = 6.1 Hz, PFPSO$_3$C*H*$_2$CH$_2$C(O)), 2.97 (2H, t, *J* = 7.7 Hz, C*H*$_2$), 2.70 (2H, t, *J* = 7.7 Hz, C*H*$_2$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 172.8 (*C*(O)), 140.1 (*C*$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.4 (*C*H$_{Ar}$), 126.4 (*C*H$_{Ar}$), 57.2 (PFPSO$_3$CH$_2$*C*H$_2$C(O)), 51.8 (PFPSO$_3$*C*H$_2$CH$_2$C(O)), 35.6 (*C*H$_2$), 30.7 (*C*H$_2$); **^{19}F NMR** (282 MHz; $CDCl_3$) δ -151.4 (2F, d, *J* = 16.9 Hz), -155.1 (1F, app. t, *J* = 22.6 Hz), -161.0-(-160.8) (2F, m); **IR** ($CHCl_3$ solution) 3029, 2936, 1743, 1604, 1518, 1497, 1471, 1454 cm^{-1}; **LRMS** (EI) 241 (43%), 184 (31%), 133 (32%), 105 (68%), 104 (62%), 91 (100%); **HRMS** (EI) calcd for $C_{17}H_{13}F_5O_5S$ 424.0404; $[M]^+$ 424.0356 observed.

1-Deuteriohexanal 178[132] and 1,1-dideuterio-hexyl hexanoate 179



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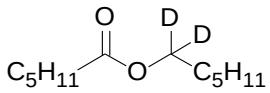


179

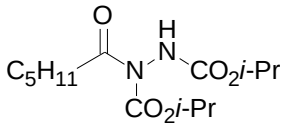
A solution of hexyl hexanoate **177** (30 mL,181 mmol) in Et_2O (275 mL) was added dropwise over 45 min to a stirred and cooled to 0 °C suspension of lithium aluminium deuteride (5 g, 119 mmol) in Et_2O (175 mL) under argon. The reaction mixture was then refluxed for 1.5 h. After allowing the reaction mixture to cool to room temperature, it was cooled down to 0 °C and cold water (200 mL) and a 10% solution of H_2SO_4 (300 mL) were added carefully. The aqueous layer was extracted with Et_2O (x 3). Combined organic layers were washed with $NaHCO_{3(sat)}$ (x 2), brine (x 2), dried ($MgSO_4$) and concentrated under vacuum to afford the crude deuterated alcohol. To a solution of pyridinium chlorochromate (63.8 g, 296 mmol) in DCM (200 mL) at 0 °C was added dropwise a solution of the crude alcohol in DCM (400 mL). The reaction mixture was further stirred at room temperature for 2 h. The reaction mixture was diluted with Et_2O and filtered through a plug of silica. It was thoroughly rinsed with Et_2O and concentrated under vacuum. The crude mixture was purified by distillation (bp = 51 °C at 78 mbar) to afford 1-deuteriohexanal **178** as transparent oil (2.28 g, 22.5 mmol, 19%). Residue of distillation was deuterated hexyl hexanoate **179** (18.1 g, 89.3 mmol, 75%).

Data for 1-deuteriohexanal **178**: **bp** = 51 °C at 78 mbar; **^{1}H NMR** (600 MHz; $CDCl_3$) δ 2.42 (2H, t, *J* = 7.4 Hz, C*H*$_2$CDO), 1.63 (2H, app. q., *J* = 7.4 Hz, CDOCH$_2$C*H*$_2$), 1.28-1.36 (4H, m, CH3(C*H*$_2$)$_2$), 0.90 (3H, t, *J* = 7.0 Hz, C*H*$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 203.1 (*C*(O)), 202.9 (*C*(O)), 202.7 (*C*(O)), 43.8 (*C*H$_2$), 31.4 (*C*H$_2$), 22.5 (*C*H$_2$), 21.9 (*C*H$_2$), 14.0 (*C*H$_3$); **IR** ($CHCl_3$ solution) 3393, 2926, 2856, 1729, 1460 cm^{-1};

Data for deuterated hexyl hexanoate **179**: **^{1}H NMR** (600 MHz; $CDCl_3$) δ 2.29 (2H, t, *J* = 7.6 Hz, C(O)C*H*$_2$), 1.58-1.64 (4H, m, (C*H*$_2$)$_2$), 1.25-1.36 (10H, m, C*H*$_2$), 0.89 (6H, td, *J* = 7.0, 2.7 Hz, C*H*$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 174.2 (*C*(O)), 64.2 (*C*D$_2$), 64.0 (*C*D$_2$), 63.9 (*C*D$_2$), 63.7 (*C*D$_2$), 63.6 (*C*D$_2$), 34.5 (*C*H$_2$), 31.6 (*C*H$_2$), 31.4 (*C*H$_2$), 28.5 (*C*H$_2$), 25.7 (*C*H$_2$), 24.8 (*C*H$_2$), 22.7 (*C*H$_2$), 22.5 (*C*H$_2$), 14.1 (*C*H$_3$), 14.1 (*C*H$_3$); **IR** ($CHCl_3$ solution) 2957, 2931, 2860, 1735, 1466 cm^{-1}; **LRMS** (CI) 203

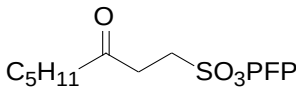
(100%, $[M+H]^+$), 117 (44%); **HRMS** (CI) calcd for $C_{12}H_{23}D_2O_2$ 203.1982; $[M+H]^+$ 203.1986 observed.

Dipropan-2-yl 1-hexanoylhydrazine-1,2-dicarboxylate 183[151]



To a solution of DIAD **182** (236 μL, 1.2 mmol) in water (0.5 mL) in a carousel tube was added hexanal **181** (120 μL, 1 mmol). The reaction mixture was stirred at room temperature at 300 rpm for 2 days. It was then concentrated under vacuum. The crude mixture was purified by flash chromatography (0-30% Et_2O/PE) to afford hydrazine **183** as a transparent oil (282 mg, 0.93 mmol, 93%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 6.57 (1H, br, N*H*), 5.03 (1H, sept., *J* = 6.3 Hz, C*H*$(CH_3)_2$), 4.97 (1H, sept., *J* = 6.3 Hz, C*H*$(CH_3)_2$), 2.89 (2H, br, C*H*$_2$C(O)), 1.65-1.68 (2H, m, $CH_3CH_2CH_2$), 1.32 (6H, d, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 1.28 (6H, br, CH(C*H*$_3$)$_2$), 0.89 (3H, t, *J* = 6.8 Hz, C*H*$_3$CH$_2$CH$_2$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 174.1 (*C*(O)), 155.2 (*C*(O)), 152.8 (*C*(O)), 72.2 (*C*H), 70.5 (*C*H), 37.2 (*C*H$_2$C(O)), 31.3 (*C*H$_2$), 24.4 (*C*H$_2$), 22.5 (*C*H$_2$), 22.0 (*C*H$_3$), 21.8 (*C*H$_3$), 14.1 (*C*H$_3$CH$_2$); **LRMS** (CI) 303 (100%), 217 (20%); **HRMS** (CI) calcd for $C_{14}H_{27}O_5N_2$ 303.1920; $[M+H]^+$ 303.1926 observed.

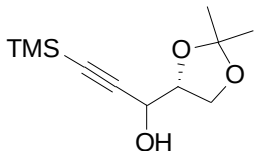
Pentafluorophenyl 3-oxooctane-1-sulfonate 184'[94]



To a mixture of PFPVS **147** (276 mg, 1.0 mmol) in water (1 mL), hexanal **181** (244 μL, 2.0 mmol) was added and the reaction mixture was stirred at room temperature at 300 rpm for 1 day. The reaction mixture was then concentrated under vacuum and the crude mixture was purified by flash chromatography (20-70% DCM/PE) to afford β-ketosulfonate **184b** as a white solid (300 mg, 0.80 mmol, 79%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 3.76 (2H, t, *J* =7.5 Hz, CH_2), 3.14 (2H, t, *J* =7.5 Hz, CH_2), 2.52 (2H, t, *J* =7.5 Hz, CH_2), 1.63 (2H, quint. *J* = 7.5 Hz, CH_2), 1.25-1.36 (4H, m, (CH_2)$_2$), 0.90 (3H, t, *J* = 7.1 Hz, CH_3); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 205.3 (*C*(O)), 47.1 (*C*H_2), 42.9 (*C*H_2), 36.0 (*C*H_2), 32.3 (*C*H_2), 23.5 (*C*H_2), 22.5 (*C*H_2), 14.0 (*C*H_3); **^{19}F NMR** (282 MHz; $CDCl_3$) δ -151.7-(-151.5) (2F, m), -155.3 (1F, app. t, *J* = 21.2 Hz), -161.1-(-160.9) (2F, m).

Experimental for Chapter 3

1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-trimethylsilanyl-prop-2-yn-1-ol 185[66]



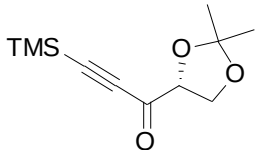
To a solution of 1,2-5,6-diisopropylidene-D-mannitol **186** (25.0 g, 95 mmol) in DCM (350 mL) and $NaHCO_{3(sat)}$ (4 mL) was added $NaIO_4$ (41.0 g, 190 mmol) over 20 min. The reaction mixture was stirred for 2 h at room temperature before being filtered through a pad of $MgSO_4$. DCM was then evaporated under vacuum in an ice-cold bath to give the D-glyceraldehyde acetonide **187** which was used directly without further purification.

A fresh 1M solution of lithium hexamethyldisilazide was made by adding *n*-BuLi (1.6 M in hexane, 112 mL, 180 mmol) dropwise to a solution of hexamethyldisilazide (38 mL, 180 mmol) in THF (30 mL) at -78 °C. It was then allowed to reach room temperature.

To a solution of trimethylsilylacetylene **188** (29 mL, 207 mmol) in THF (900 mL) was added dropwise the fresh 1M lithium hexamethyldisilazide solution at -78 °C. The reaction mixture was stirred for 1 h at this temperature before addition of D-glyceraldehyde acetonide **187** in THF (250 mL). The reaction mixture was stirred at -78 °C for 4 h before being quenched with $NH_4Cl_{(sat)}$ (150 mL). The reaction mixture was concentrated under vacuum to a volume of approximately 300 mL and was then diluted with EtOAc (300 mL). The organic phase was washed with $NH_4Cl_{(sat)}$ (250 mL) and water (250 mL) and the combined aqueous phases were extracted with EtOAc (2 x 150 mL). The combined organic phases were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude was purified by flash column chromatography (0-20% EtOAc/PE) to yield the inseparable diastereomeric propargylic alcohols **185** (major : minor: 1.5 : 1) as a pale yellow oil (16.9 g, 74 mmol, 78%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 4.50 (1H, t, *J* = 3.6 Hz, C*H*OH, *minor*), 4.32 (1H, d, *J* = 7.3 Hz, C*H*OH, *major*), 4.25 (1H, dt, *J* = 6.6, 3.6 Hz, C*H*CHOH, *minor*), 4.17 (1H, dt, *J* = 7.3, 5.4 Hz, C*H*CHOH, *major*), 4.03-4.12 (3H, m, CH_2, *major & minor*), 3.90 (1H, dd, *J* = 8.7, 5.3 Hz, CH_2, *major*),

2.36 (1H, br, O*H*, *major*), 2.24 (1H, br, O*H*, *minor*), 1.47 (3H, s, CH_3, *minor*), 1.45 (3H, s, CH_3, *major*), 1.38 (3H, s, CH_3, *minor*), 1.37 (3H, s, CH_3, *major*), 0.17 (9H, s, Si(CH_3)$_3$, *major & minor*); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 110.6 (*C*), 110.3 (*C*), 102.3 (*C*), 102.2 (*C*), 91.7 (*C*), 78.9 (*C*HOH), 77.8 (*C*HOH), 66.3 (*C*H_2), 65.2 (*C*H_2), 65.0 (CH_2*C*H), 62.9 (CH_2*C*H), 27.0 (*C*H_3), 26.4 (*C*H_3), 25.5 (*C*H_3), 25.4 (*C*H_3), -0.15 (Si(*C*H_3)$_3$); **LRMS** (CI) 229 (86%, $[M]^+$), 213 (53%), 211 (100%), 181 (59%), 171 (21%); **HRMS** (CI) calcd for $C_{11}H_{19}O_3Si$ $[M+H]^+$ 229.1260; observed 229.1265.

(*R*)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-trimethylsilanyl-prop-2-yn-1-one 14[66]

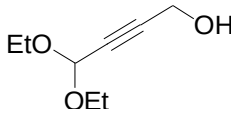


Method A: To a solution of propargylic alcohol **185** (268 mg, 1.2 mmol) in DCM (6 mL) at 0 °C was added the Dess-Martin periodinane (1.0 g, 2.4 mmol) in one portion. The reaction mixture was then stirred at room temperature for 4.5 h. The reaction was quenched with a solution of $Na_2S_2O_{3(sat)}$ (2 mL) and $NaHCO_{3(sat)}$ (2 mL). Et_2O (30 mL) was then added and the mixture was stirred for 30 min. The aqueous phase was then extracted with Et_2O (2 x 20 mL). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by flash column chromatography (25% Et_2O/PE) to afford ynone **14** as a transparent oil (222 mg, 0.98 mmol, 84%).

Method B: To a solution of pyridinium dichromate (1.6 g, 7.0 mmol) and crushed 3 Å molecular sieves in DCM (2.4 mL) was added dropwise a solution of alcohol **185** (445 mg, 2.0 mmol) in DCM (8.6 mL). The reaction mixture was stirred at room temperature for 72 h. It was then filtered through celite and washed with Et_2O. The filtrate was washed with $KHSO_{4(sat)}$ (x 3). Aqueous phase was extracted with Et_2O (x 3). Combined organic phases were washed with $NaHCO_{3(sat)}$, brine (x 2), dried ($MgSO_4$) and concentrated under vacuum to give ynone **14** as a transparent oil (332 mg, 1.47 mmol, 75%).

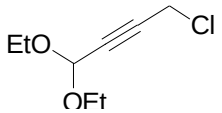
^{1}H NMR (400 MHz; $CDCl_3$) δ 4.53 (1H, dd, *J* = 7.5, 4.9 Hz, C*H*CH_2), 4.25 (1H, dd, *J* = 8.8, 7.5 Hz, C*H*$_2$), 4.16 (1H, dd, *J* = 8.8, 4.9 Hz, C*H*$_2$), 1.53 (3H, s, C*H*$_3$), 1.41 (3H, s, C*H*$_3$), 0.26 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 186.7 (*C*(O)), 112.0 (*C*), 103.7 (*C*), 99.9 (*C*), 81.0 (*C*H), 67.0 (*C*H$_2$), 26.2 (*C*H$_3$), 25.5 (*C*H$_3$), -0.8 (Si(*C*H$_3$)$_3$); **LRMS** (Positive Ion FAB) 329 (34%), 249 (40%), 227 (100%, $[M]^+$), 211 (35%), 176 (70%), 155 (36%), 154 (60%); **HRMS** (Positive Ion FAB) calcd for $C_{11}H_{19}O_3Si$ 227.1103; $[M+H]^+$ 227.1106 observed.

4,4-diethoxybut-2-yn-1-ol 189[66]



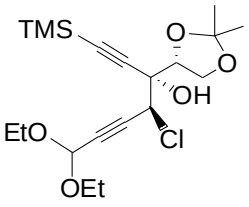
To a solution of (propargyloxy)trimethylsilane **62** (3.4 mL, 22.0 mmol) in THF (7 mL) was added a 1M solution of EtMgBr in THF (22.0 mL, 22.0 mmol). The reaction mixture was stirred for 30 min at room temperature and a solution of phenylorthoformate (3.9 mL, 20.0 mmol) in THF (3 mL) was then added. The reaction mixture was stirred at 60 °C overnight. The reaction was then quenched with $NH_4Cl_{(sat)}$ (20 mL) and H_2O (20 mL). The aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic phases were washed with 4M NaOH (3 x 10 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was then dissolved in MeOH (50 mL). K_2CO_3 (2.8 g, 20.0 mmol) was added to the mixture at 0 °C which was further stirred at the same temperature for 1 h. The reaction mixture was concentrated under vacuum and then diluted with H_20 (20 mL). The mixture was extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude was purified by flash chromatography (0-30% Et_2O/PE) to give propargyl alcohol **189** as a transparent oil (1.9 g, 11.8 mmol, 56%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.31 (1H, t, *J* = 1.4 Hz, C*H*), 4.32 (2H, d, *J* = 1.4 Hz, CH_2OH), 3.74 (2H, dq, *J* = 9.4, 7.1 Hz, CH_3CH_2O), 3.58 (2H, dq, *J* = 9.4, 7.1 Hz, CH_3CH_2O), 1.70 (1H, br, O*H*), 1.24 (6H, t, *J* = 7.1 Hz, CH_3CH_2O); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 91.3 (*C*H), 83.6 (*C*), 81.1 (*C*), 61.0 (CH_2), 51.0 (CH_2), 15.0 (CH_3); **IR** ($CHCl_3$ solution) 3419, 2977, 2931, 2893, 1720, 1624, 1446 cm^{-1}.

4-chloro-1,1-diethoxybut-2-yne 63[66]

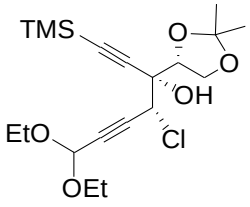


To a solution of 4,4-diethoxybut-2-yn-1-ol **189** (1.76 g, 11.1 mmol) in a mixture of Et_3N (4.65 mL, 33.4 mmol) and Et_2O (45 mL) at 0 °C was added MsCl (947 μL, 12.2 mmol) dropwise. The reaction mixture was further stirred at that temperature for 1 h. The reaction was then quenched with $NaHCO_{3(sat)}$ (20 mL). The aqueous phase was extracted with Et_2O (2 x 10 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under vacuum. The residue was dissolved in chloroform (55 mL). Bu_4NCl (6.2 g, 22.3 mmol) was added and the reaction mixture was heated up to reflux for 1.5 h. The reaction mixture was then concentrated under vacuum. The residue was dissolved in Et_2O (35 mL). The mixture was diluted with water (20 mL). Aqueous layer was extracted with Et_2O (2 x 20 mL). Combined organic phases were washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under vacuum to give propargyl chloride **63** as transparent oil (1.5 g, 8.7 mmol, 78%). The product was used without further purification. **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.30 (1H, t, *J* = 1.5 Hz, C*H*), 4.16 (2H, d, *J* = 1.5 Hz, CH_2Cl), 3.73 (2H, dq, *J* = 9.4, 7.1 Hz, CH_3CH_2O), 3.58 (2H, dq, *J* = 9.4, 7.1 Hz, CH_3CH_2O), 1.23 (6H, t, *J* = 7.1 Hz, CH_3CH_2O); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 91.2 (*C*H), 81.7 (*C*), 80.2 (*C*), 61.2 (CH_2), 30.0 (CH_2), 15.2 (CH_3); **IR** (neat) 2978, 2932, 2887, 1481, 1445 cm^{-1}.

(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 137[69] 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 190[69]



137

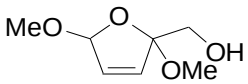


190

$ZnBr_2$ was dried under vacuum for 5 days prior to the experiment. A fresh solution of LDA was prepared by adding *n*-BuLi (1.5 M in hexane, 1.25 mL, 1.88 mmol) to a solution of diisopropylamine (265 µL, 1.88 mmol) in THF (6 mL) at -78 °C. To a solution of $ZnBr_2$ (466 mg, 2.07 mmol) in THF (4 mL) cooled down to -20 °C was added dropwise a solution of propargyl chloride **63** (200.0 mg, 1.13 mmol) in THF (4 mL) over 5 min. The reaction mixture was then cooled down to -78 °C and the freshly prepared solution of LDA was added dropwise over 45 min. The yellow reaction mixture was then stirred for 1 h at -78 °C before adding ketone **14** (213 mg, 0.94 mmol) in one portion. The reaction mixture was then stirred for 1 h at -78 °C before being poured onto a mixture of $NH_4Cl_{(sat)}$ (20 mL) and water (40 mL). It was then diluted with Et_2O (100 mL). The aqueous layer was then extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with water (x 2) and brine, dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by flash column chromatography (0-20% Et_2O/PE) to afford the inseparable mixture of chlorohydrins **137** and **190** (*anti* : *syn*: 4 : 1) as a pale yellow oil (45 mg, 0.11 mmol, 12% yield). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.35 (1H, d, *J* = 0.9 Hz, $(EtO)_2CH$, *syn*), 5.33 (1H, d, *J* = 1.2 Hz, $(EtO)_2CH$, *anti*), 4.94 (1H, d, *J* = 0.9 Hz, C*H*Cl, *syn*), 4.91 (1H, d, *J* = 1.2 Hz, C*H*Cl, *anti*), 4.32-4.34 (1H, m, C*H*CH_2, *syn & anti*), 4.22 (1H, dd, *J* = 8.5, 5.8 Hz, OCH_2, *syn & anti*), 4.16-4.19 (1H, m, OCH_2, *syn & anti*), 3.70-3.78 (1H, m, CH_2CH_3, *syn & anti*), 3.57-3.64 (1H, m, CH_2CH_3, *syn & anti*), 2.97 (br, 1H, OH, *syn*), 2.86 (br, 1H, OH, *anti*), 1.45 (3H, s, CH_3, *syn & anti*), 1.35 (3H, s, CH_3, *syn*), 1.34 (3H, s, CH_3, *anti*), 1.21-1.25 (6H, m, CH_2CH_3, *syn & anti*), 0.18 (9H, s, SiCH_3, *syn & anti*); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 110.72 (Me_2C, *anti*), 110.66 (Me_2C, *syn*), 101.6 (*C*, *anti*), 110.3 (*C*, *syn*), 94.1 (*C*, *syn*), 93.1 (*C*, *anti*), 91.25

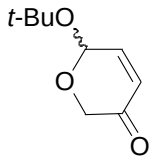
($(EtO)_2CH$, *anti*), 91.23 ($(EtO)_2CH$, *syn*), 84.5 (*C*, *anti*), 83.8 (*C*¸ *syn*), 80.4 (*C*, *syn*), 79.0 (*C*, *anti*), 77.9 (*C*H, *anti*), 76.5 (*C*H, *syn*), 75.2 (*C*OH, *anti*), 74.6 (*C*OH, *syn*), 67.1 (CH_2, *anti*), 66.6 (CH_2, *syn*), 61.23 (CH_2CH_3, *anti*), 61.16 (CH_2CH_3, *syn*), 61.14 (CH_2CH_3, *syn*), 61.09 (CH_2CH_3, *anti*), 55.3 (*C*HCl, *anti*), 54.0 (*C*HCl, *syn*), 26.52 (CH_3, *anti*), 26.45 (CH_3, *syn*), 25.48 (CH_3, *anti*), 25.42 (CH_3, *syn*), 15.2 (CH_2CH_3, *syn & anti*), -0.28 ($Si(CH_3)_3$, *anti*), -0.33 ($Si(CH_3)_3$, *anti*); **LRMS** (ES) 427 (25%), 425 (70%, $[M+Na]^+$), 359 (58%), 358 (33%), 357 (100%); **HRMS** (ES) calcd for $C_{19}H_{31}O_5NaSi^{35}Cl$ 425.1527; $[M+Na]^+$ 425.1513 observed.

(2,5-dimethoxy-2,5-dihydrofuran-2-yl)methanol 193[64]



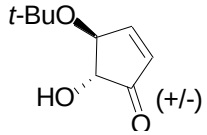
A cold solution of bromine (17.8 mL, 347 mmol) in MeOH (96 mL) was slowly added to a stirred solution of furfuryl alcohol **192** (25.0 mL, 289 mmol) in a mixture of Et_2O (96 mL) and MeOH (96 mL) at -40 °C. Stirring was continued for 2 h at -40 °C. The resulting solution was saturated with gaseous ammonia at -70 °C to pH 10-11 and allowed to warm to room temperature. The reaction mixture was concentrated under vacuum and the white solid (ammonium bromide) formed upon concentration was removed by filtration (x 2). The resulting oil was diluted in toluene (35 mL) and filtered through neutral alumina. Concentration under vacuum yielded yellow oil furan **193** as a mixture of diastereoisomers (*major* : *minor*: 4.6 : 1) (39.3 g, 246 mmol, 85%). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 6.14 (1H, dd, *J*= 1.1, 5.9 Hz, C*H*$_{alk}$, *minor*), 6.13 (1H, dd, *J*= 5.9, 1.1 Hz, C*H*$_{alk}$, *major*), 5.99 (1H, dd, *J* = 5.9, 1.2 Hz, C*H*$_{alk}$, *major*), 5.98 (1H, dd, *J* = 5.9, 1.2 Hz, C*H*$_{alk}$, *minor*), 5.75 (1H, app. t, *J* = 2.3 Hz, C*H*OMe, *minor*), 5.52 (1H, app. t, *J* = 2.3 Hz, C*H*OMe, *major*), 3.58-3.72 (2H, m, C*H*$_2$OH, *major & minor*), 3.53 (3H, s, C*H*$_3$, *major*), 3.49 (3H, s, C*H*$_3$, *minor*), 3.25 (3H, s, C*H*$_3$, *major*), 3.19 (3H, s, C*H*$_3$, *minor*); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 132.5, 132.4, 132.2, 131.4, 113.2, 112.6, 108.2, 107.5, 66.9, 66.7, 65.8, 56.5, 56.4, 51.0, 50.6, 50.2; **LRMS** (EI) 175 (29%), 159 (42%, $[M-H]^+$), 149 (25%), 143 (38%), 131 (30%), 130 (44%), 129 (100%), 127 (34%), 110 (41%), 111 (54%), 101 (95%), 99 (68%), 98 (54%), 97 (50%), 88 (32%), 85 (29%), 84 (35%), 83 (49%), 81 (40%); **HRMS** (EI) calcd for $C_7H_{11}O_4$ 159.0652; $[M-H]^+$ 159.0654 observed.

6-tert-butoxy-2H-pyran-3(6H)-one 194[64]



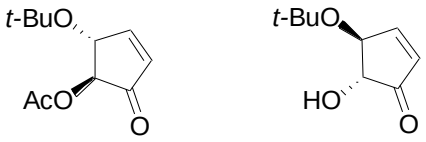
To a solution of furan **193** (41.6 g, 260 mmol) in THF (410 mL) and water (15 mL) cooled to 0 °C was added triflic acid (3.5 mL, 40 mmol). The reaction mixture was stirred at 0 °C for 3 h before adding acetic anhydride (98.0 mL, 1.04 mol) and sodium acetate (85.0 g, 1.04 mol). The reaction mixture was allowed to warm to room temperature and stirred for a further 18 h. The reaction mixture was quenched with $NaHCO_{3(sat)}$ (290 mL) and additional solid $NaHCO_3$ (17.5 g) added until the effervescence ceased. The mixture was extracted with Et_2O (2 x 600 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum (ice bath). The crude was further dried on high vacuum to afford pyranone (racemic mixture) as a brown liquid (41.0 g). A 1 M solution of tin(IV) chloride in DCM (12.7 mL, 12.7 mmol) was slowly added to a stirred solution of pyranone in DCM (23 mL) and *t*-BuOH (120 mL, 1.27 mol). The reaction mixture was then stirred at room temperature for 16 h and then quenched with $NaHCO_{3(sat)}$ (350 mL). It was extracted with EtOAc (2 x 600 mL). The combined organic layers were washed with $NaHCO_{3(sat)}$ (120 mL), water (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under vacuum. Flash chromatography (0-10% EtOAc/PE) afforded pyranone **194** (racemic mixture) as a light yellow oil (8.2 g, 48 mmol, 20%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 6.80 (1H, dd, *J* = 10.3, 3.5 Hz, C*H*$_{alk}$), 6.09 (1H, d, *J* = 10.3 Hz, C*H*$_{alk}$), 5.48 (1H, d, *J* = 3.5 Hz, C*H*O*t*-Bu), 4.53 (1H, d, *J* = 16.9 Hz, C*H*$_2$), 4.05 (1H, d, *J* = 16.9 Hz, C*H*$_2$), 1.32 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 195.5 (*C*(O)), 146.2 (*C*H$_{alk}$), 127.2 (*C*H$_{alk}$), 88.0 (*C*H), 76.1 (*C*(CH$_3$)$_3$), 66.1 (*C*H$_2$), 28.6 (*C*H$_3$); **LRMS** (CI) 331 (20%), 211 (27%), 171 (23%, $[M+H]^+$), 147 (32%), 123 (36%), 119 (32%), 115 (100%), 99 (23%), 97 (53%); **HRMS** (CI) calcd for $C_9H_{15}O_3$ 171.1021; $[M+H]^+$ 171.1021 observed.

(4S,5R)-4-tert-butoxy-5-hydroxycyclopent-2-enone 195[64]



A stirred solution of pyranone **194** (320 mg, 1.88 mmol) in DMF (5.4 mL) and triethylamine (1.1 mL, 7.7 mmol) was heated at 80 °C for 24 h. The resulting black mixture was allowed to cool to room temperature and concentrated under vacuum. Flash chromatography (50% EtOAc/PE) afforded cyclopentenone **195** as a colourless oil (107 mg, 0.63 mmol, 34%). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.33 (1H, dd, *J* = 6.1, 2.0 Hz, C(O)C*H*$_{alk}$), 6.23 (1H, dd, *J* = 6.1, 1,4 Hz, C*H*$_{alk}$), 4.57-4.59 (1H, m, C*H*OH), 4.08 (1H, d, *J* = 2.5 Hz, C*H*O*t*-Bu), 1.31 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (75 MHz; $CDCl_3$) δ 205.1 (*C*(O)), 161.6 (*C*H$_{alk}$), 131.4 (*C*H$_{alk}$), 80.7 (*C*H), 76.4 (*C*H), 75.2 (*C*), 28.2 (*C*H_3); **LRMS** (CI) 115 (20%), 114 (48%), 97 (70%), 96 (93%), 86 (87%), 84 (100%), 83 (28%); **HRMS** (CI) calcd for $C_9H_{15}O_3$ 171.1021; $[M+H]^+$ 171.1017 observed.

(1*S*,2*R*)-2-*tert*-butoxy-5-oxocyclopent-2-enyl acetate 191[134] and (4*S*,5*R*)-4-*tert*-butoxy-5-hydrocyclopent-2-enone 196[134]



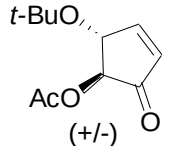
191 **196**

(4*S*,5*R*)-4-*tert*-butoxy-5-hydroxycyclopent-2-enone **195** (20 mg, 0.12 mmol) and lipase PS (78 mg) were suspended in vinyl acetate (1 mL). The reaction mixture was stirred at 40 °C for 14 days. More vinyl acetate (in 1 mL aliquots) was added through out the 14 days when the reaction mixture was dry. The reaction mixture was then filtered, rinsed with Et_20 and concentrated under vacuum. Purification by flash chromatography (10% EtOAc/PE) gave cyclopentenone **191** (11.5 mg, 0.06 mmol, 45%) and cyclopentenone **196** (10.2 mg, 0.06 mmol, 45%).

Data for cyclopentenone **191** : **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.32 (1H, dd, *J* = 6.2, 2.1 Hz, C(O)CH_{alk}), 6.27 (1H, dd, *J* = 6.2, 1.5 Hz, CH_{alk}CHO*t*-Bu), 5.02 (1H, d, *J* = 2.8 Hz, C*H*OAc), 4.83-4.85 (1H, m, C*H*O*t*-Bu), 2.17 (3H, s, CH_3C(O)), 1.25 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 199.0 (*C*(O)), 170.0 (*C*(O)O), 160.3 (*C*H), 132.7 (*C*H), 81.0 (*C*H), 75.2 (*C*), 73.8 (*C*H), 28.1 ((*C*H$_3$)$_3$), 20.6 (*C*H$_3$); **LRMS** (Positive Ion FAB) 289 (34%), 259 (23%), 257 (39%), 256 (21%), 255 (37%), 173 (48%), 156 (29%); **HRMS** (Positive Ion FAB) calcd for $C_{11}H_{17}O_4$ 213.1121; $[M+H]^+$ 213.1129 observed;

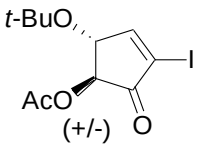
Data for cyclopentenone **196** : **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.34 (1H, dd, *J* = 6.0, 2.0 Hz, C(O)CH_{alk}), 6.25 (1H, dd, *J* = 6.0, 1.4 Hz, CH_{alk}CHO*t*-Bu), 4.58-4.59 (1H, m, C*H*O*t*-Bu), 4.08 (1H, d, *J* = 2.4 Hz, C*H*OH), 3.49 (1H, s, O*H*), 1.32 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 204.9 (*C*(O)), 161.6 (*C*H), 131.4 (*C*H), 80.9 (*C*H), 76.5 (*C*H), 75.3 (*C*), 28.3 ((*C*H$_3$)$_3$).

2-*tert*-butoxy-5-oxocyclopent-3-enyl acetate 260[134]



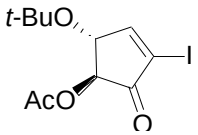
To a solution of cyclopentenone **195** (19.5 mg, 0.11 mmol) in DCM (1 mL) was added acetic anhydride (116 μL, 1.23 mmol) and DMAP (1.3 mg, 0.011 mmol). The reaction mixture was then stirred at room temperature for 16 h. The reaction was quenched with $NH_4Cl_{(sat)}$ (2 mL). The aqueous phase was extracted with Et_2O (x2). The combined organic phases were washed with water, brine, dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by flash chromatography (0-30% EtOAc/PE) to afford cyclopentenone **260** (6.2 mg, 0.03 mmol, 27%). **^{1}H NMR** (400 MHz; $CDCl_3$) δ 7.31 (1H, dd, *J* = 6.1, 2.1 Hz, C(O)CH_{alk}), 6.27 (1H, dd, *J* = 6.1, 1.4 Hz, CH_{alk}CHO*t*-Bu), 5.02 (1H, d, *J* = 2.8 Hz, C*H*OAc), 4.83-4.84 (1H, m, C*H*O*t*-Bu), 2.17 (3H, s, CH_3C(O)), 1.25 (9H, s, C(CH_3)$_3$); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 199.0 (*C*(O)), 170.0 (*C*(O)$_{Ac}$), 160.3 (*C*H), 132.7 (*C*H), 81.0 (*C*H), 75.2 (*C*), 73.8 (*C*H), 28.1 ((*C*H$_3$)$_3$), 20.6 (*C*H$_3$); **LRMS** (Positive Ion FAB) 289 (34%), 259 (23%), 257 (39%), 256 (21%), 255 (37%), 173 (48%). 156 (29%); **HRMS** (Positive Ion FAB) calcd for $C_{11}H_{17}O_4$ 213.1121; $[M+H]^+$ 213.1129 observed.

5-*tert*-butoxy-3-iodo-2-oxycyclopent-3-enyl acetate 261



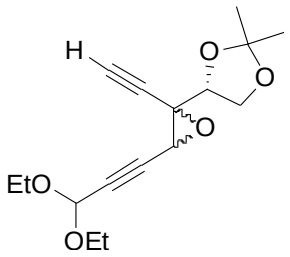
To a solution of cyclopentenone **260** (6.2 mg, 0.03 mmol) in THF (300 μL) was added pyridine (7.3 μL, 0.09 mmol) and then iodine (15.0 mg, 0.06 mmol). The reaction mixture was then stirred for 1 hour at room temperature before being quenched with $Na_2S_2O_{3(sat)}$ (1 mL) and diluted with Et_2O. The aqueous phase was extracted with EtOAc (x2). Combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by flash chromatography (0-10% Et_2O/PE) to give cyclopentenone **261** (5.0 mg, 0.01 mmol, 43%).**^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.71 (1H, d, *J* = 2.2 Hz, C*H*$_{alk}$), 5.00 (1H, d, *J* = 2.8 Hz, C*H*OAc), 4.82 (1H, t, *J* = 2.5 Hz, C*H*O*t*-Bu), 2.17 (3H, s, C*H*$_3$C(O)), 1.25 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 194.1 (*C*(O)), 169.8 (*C*(O)O), 165.7 (*C*H$_{alk}$), 101.0 (*C*H), 78.2 (*C*HOAc), 75.4 (*C*HO*t*-Bu), 28.1 (C(*C*H$_3$)$_3$), 20.5 (*C*H$_3$C(O)); **IR** (neat) 2973, 2928, 2854, 1737, 1573, 1464 cm^{-1}; **LRMS** (CI) 339 (100%, [M]$^+$), 283 (47%), 265 (38%); **HRMS** (CI) calcd for $C_{11}H_{16}O_4I$ 339.0093; [M]$^+$ 339.0096 observed; **HPLC** conditions: CHIRALPAK-AD column, hexane:*i*-PrOH 95:1, 1 mL/min, retention times: 6.07 min and 6.77 min.

(1*S*,5*R*)-5-*tert*-butoxy-3-iodo-2-oxycyclopent-3-enyl acetate 134



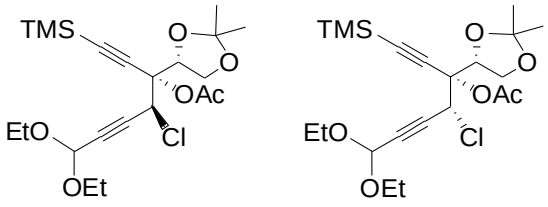
To a solution of cyclopentenone **191** (4.0 mg, 0.02 mmol) in THF (190 μL), pyridine (5 μL, 0.06 mmol) and then iodine (9.6 mg, 0.04 mmol) were added. The reaction mixture was then stirred for 1 h at room temperature before being quenched with a solution of $Na_2S_2O_{3(sat)}$ (1 mL) and diluted with Et_2O. The aqueous phase was extracted with EtOAc (x 2). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum to give cyclopentenone **134** (3.6 mg, 0.01 mmol, 49%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.70 (1H, d, *J* = 2.3 Hz, C*H*$_{alk}$), 5.00 (1H, d, *J* = 2.8 Hz, C(O)C*H*OAc), 4.81 (1H, app. t, *J* = 2.5 Hz, C*H*O*t*-Bu), 2.17 (3H, s, C*H*$_3$C(O)), 1.24 (9H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 194.0 (*C*(O)), 169.8 (*C*(O)O), 165.7 (*C*H$_{alk}$), 101.0 (*C*), 78.2 (*C*HOAc), 75.4 (*C*HO*t*-Bu), 28.0 (C(*C*H$_3$)$_3$), 20.5 (*C*H$_3$C(O)); **IR** (neat) 2925, 2854, 1737, 1574, 1463 cm^{-1}; **LRMS** (EI) 296 (36%), 283 (25%), 282 (30%), 265 (48%), 256 (20%), 240 (67%), 221 (51%), 222 (100%), 203 (23%), 204 (59%), 162 (22%), 125 (33%), 118 (59%), 113 (28%), 111 (52%), 109 (35%), 99 (84%), 98 (23%), 97 (81%), 96 (33%), 95 (51%), 91 (22%); **HRMS** (EI) calcd for $C_{11}H_{15}O_4I$ 338.0010; $[M]^+$ 338.0011 observed; **ee**: 90%, **HPLC** conditions: CHIRALPAK-AD column, hexane:*i*-PrOH 95:1, 1 mL/min, retention times: 6.11 min and 6.81 min.

(*R*)-4-((2S,3R)-3-(3,3-diethoxyprop-1-ynyl)-2-ethynyloxiran-2-yl)-2,2-dimethyl-1,3-dioxolane 197[66]



To a solution of chlorohydrins **137/190** (67 mg, 0.17 mmol) in THF (600 μL) at room temperature was added a 1M solution of TBAF in THF (190 μL, 0.19 mmol). The reaction mixture was stirred for 30 min before being quenched with $NH_4Cl_{(sat)}$ (2 mL) and diluted with Et_2O (1 mL). The aqueous phase was extracted with Et_2O (3 x 2 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by flash chromatography (25-50% EtOAc/PE) to give the mixture (*trans* : *cis:* 1.5 : 1) of epoxides **197** (23 mg, 0.08 mmol, 45%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.32 (1H, d, *J* = 0.8 Hz, $(EtO)_2CH$, *trans*), 5.29 (1H, d, *J* = 0.8 Hz, $(EtO)_2CH$, *cis*), 4.06-4.24 (3H, m, $OCHCH_2O$, *trans & cis*), 3.80 (1H, d, *J* = 0.8 Hz, CH_{epo}, *cis*), 3.71-3.79 (4H, m, CH_2CH_3, *trans & cis*), 3.71 (1H, *J* = 0.8 Hz, H_{epo}, *trans*), 3.56-3.62 (4H, m, CH_2CH_3, *trans & cis*), 2.50 (1H, s, H_{alk}, *trans*), 2.41 (1H, s, H_{alk}, *cis*), 1.53 (3H, s, CH_3, *cis*), 1.45 (3H, s, CH_3, *trans*), 1.37 (3H, s, CH_3, *cis*), 1.35 (3H, s, CH_3, *trans*), 1.21-1.25 (12H, m, CH_2CH_3, *trans & cis*); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 111.2 (*C*, *trans*), 110.9 (*C*, *cis*), 91.2 (*C*H, *trans*), 91.1 (*C*H, *cis*), 82.8 (*C*, *cis*), 81.9 (*C*, *trans*), 79.0 (*C*, *trans*), 78.0 (*C*, *trans*), 77.8 (*C*, *cis*), 75.8 (*C*H, *trans*), 75.6 (*C*H, *trans*), 75.4 (*C*H, *cis*), 74.0 (*C*H, *cis*), 66.9 (CH_2, *trans*), 66.8 (CH_2, *cis*), 61.3 (CH_2, *trans* or CH_2, *cis*), 61.2 (CH_2, *trans* or CH_2, *cis*), 61.1 (CH_2, *trans* or CH_2, *cis*), 57.9 (*C*, *trans*), 56.0 (*C*, *cis*), 51.8 (*C*H, *cis*), 49.3 (*C*H, *trans*), 26.3 (CH_3, *cis*), 26.1 (CH_3, *trans*), 25.4 (CH_3, *cis*), 25.2 (CH_3, *trans*), 15.22 (CH_3, *trans* or CH_3, *cis*), 15.16 (CH_3, *trans* or CH_3, *cis*); **LRMS** (EI) 280 (21%), 279 (95%), 249 (43%), 207 (44%), 179 (38%), 163 (27%), 145 (24%), 140 (31%), 135 (24%), 133 (26%), 123 (28%), 112 (29%), 111 (100%), 109 (29%), 103 (47%), 101 (51%), 94 (28%), 88 (37%); **HRMS** (EI) calcd for $C_{16}H_{21}O_5$ 293.1384; $[M-H]^+$ 293.1394 observed.

(3*R*,4*S*)-4-chloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-7,7-diethoxy-1-(trimethylsilyl)hepta-1,5-diyn-3-yl acetate 138 and (3*R*,4*R*)-4-chloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-7,7-diethoxy-1-(trimethylsilyl)hepta-1,5-diyn-3-yl acetate 198



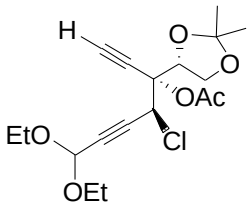
138 **198**

To a solution of chlorohydrins **137/190** (45.0 mg, 0.11 mmol) in DCM (2.5 mL) was added acetic anhydride (116 μL, 1.23 mmol) and DMAP (1.3 mg, 0.011 mmol). The reaction mixture was then stirred at room temperature for 16 h. The reaction was quenched with $NH_4Cl_{(sat)}$ (2 mL). The aqueous phase was extracted with Et_2O (x 2). The combined organic phases were washed with water, brine, dried ($MgSO_4$) and concentrated under vacuum. Products **138** and **198** were separated by flash chromatography (0-10% Et_2O/PE) and then repurified by further flash chromatography ($CHCl_3$ → MeOH (10%) $CHCl_3$) to afford major diastereosiomer **138** (21.0 mg, 0.05 mmol, 43%) and minor diastereoisomer **198** (4.4 mg, 0.01 mmol, 9%), both as pale yellow oil.

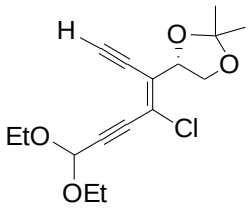
Data for diastereoisomer **138** : $[\alpha]_{D,589}^{25\ °C}$ (c = 0.948, $CHCl_3$) = -233 °.dm^{-1}.g^{-1}.cm^3; **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.51 (1H, d, *J* = 1.6 Hz, C*H*Cl), 5.31 (1H, d, *J* = 1.4 Hz, C*H*(OEt)$_2$), 4.45 (1H, app. t, *J* = 6.7 Hz, OC*H*CH$_2$O), 4.29 (1H, dd, *J* = 9.0, 7.1 Hz, OCHC*H*$_2$O), 4.14 (1H, dd, *J* = 9.0, 6.3 Hz, OCHC*H*$_2$O), 3.70-3.76 (2H, m, OC*H*$_2$CH$_3$), 3.56-3.62 (2H, m, OC*H*$_2$CH$_3$), 2.08 (3H, s, OC(O)C*H*$_3$), 1.44 (3H, s, C*H*$_3$), 1.37 (3H, s, C*H*$_3$), 1.22 (6H, td, *J* = 7.1, 3.6 Hz, C*H*$_3$CH$_2$O), 0.18 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 168.4 (*C*(O)), 110.0 (*C*), 97.2 (*C*), 96.4 (*C*), 91.2 (*C*H), 83.7 (*C*), 79.3 (*C*), 78.5 (*C*), 77.0 (*C*H), 67.5 (*C*H$_2$), 61.0 (*C*H$_2$CH$_3$), 60.8 (*C*H$_2$CH$_3$), 51.3 (*C*H), 26.2 (*C*H$_3$), 25.9 (*C*H$_3$), 21.5 (*C*H$_3$C(O)), 15.1 (CH$_2$*C*H$_3$), -0.5 (Si(*C*H$_3$)$_3$); **IR** ($CHCl_3$ solution) 2978, 2930, 1760, 1455 cm^{-1}; **LRMS** (ES) 469 (44%), 468 (30%), 467 (100%, [M+Na-H]$^+$), 281 (28%), 253 (37%); **HRMS** (ES) calcd for $C_{21}H_{33}O_6NaSi^{35}Cl$ 467.1633; [M+Na-H]$^+$ 467.1615 observed;

Data for diastereoisomer **198** : **$[\alpha]_{D,589}^{25\ °C}$** (c = 0.269, $CHCl_3$) = +810 °.dm^{-1}.g^{-1}.cm^3; **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.33 (1H, d, *J* = 1.4 Hz, C*H*$(OEt)_2$), 5.22 (1H, d, *J* = 1.4 Hz, C*H*Cl), 4.36-4.41 (2H, m, OC*H*CH_2O), 4.11 (1H, dd, *J* = 7.8, 4.8 Hz, OCHCH_2O), 3.72-3.78 (2H, m, OC$H_2$$CH_3$), 3.60-3.63 (2H, m, OC$H_2$$CH_3$), 2.10 (3H, s, OCOC$H_3$), 1.43 (3H, s, C$H_3$), 1.37 (3H, s, C$H_3$), 1.23 (6H, td, *J* = 7.1, 1.9 Hz, C$H_3$$CH_2$O), 0.18 (9H, s, Si(C$H_3$)$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 168.4 (*C*(O)), 109.6 (*C*), 97.1 (*C*), 91.2 (*C*H), 83.0 (*C*), 80.2 (*C*), 78.7 (*C*), 76.7 (*C*H), 67.9 (CH_2), 61.1 ($CH_2$$CH_3$), 60.8 ($CH_2$$CH_3$), 52.0 (*C*H), 26.3 ($CH_3$), 25.9 ($CH_3$), 21.4 ($CH_3$C(O)), 15.1 ($CH_2$$CH_3$), -0.3 (Si($CH_3$)$_3$); **IR** ($CHCl_3$ solution) 2925, 1762, 1457 cm^{-1}; **LRMS** (ES) 469 (33%), 468 (25%), 467 (91%, $[M+Na-H]^+$), 339 (38%), 283 (39%), 281 (100%), 253 (54%); **HRMS** (ES) calcd for $C_{21}H_{33}O_6NaSi^{35}Cl$ 467.1633; $[M+Na-H]^+$ 467.1613 observed.

(3*R*,4*S*)-4-chloro-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-7,7-diethoxyhepta-1,5-diyn-3-yl acetate 139 and (*S*,*Z*)-4-(4-chloro-7,7-diethyoxyhepta-3-en-1,5-diyn-3-yl)-2,2-dimethyl-1,3-dioxolane 199



139



199

To a solution of compound **138** (18 mg, 0.04 mmol) in THF (0.16 mL) was added a 1 M solution of tetrabutylammonium fluoride (44 μL, 0.04 mmol) and the reaction mixture was stirred for 1.5 h at room temperature. The reaction was quenched with $NH_4Cl_{(sat)}$ and extracted with Et_2O (x 3). The combined organic layers were washed with water, brine, dried ($MgSO_4$) and concentrated under vacuum. Products **139** and **199** were separated by flash chromatography (0-20% Et_2O/PE) and then repurified by further flash chromatography (0-10% MeOH/DCM) to afford product **139** (4.6 mg, 0.01 mmol, 31%) and product **199** (4.7 mg, 0.02 mmol, 37%).

Data for product **139** : **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.58 (1H, d, *J* = 1.4 Hz, C*H*Cl), 5.32 (1H, d, *J* = 1.4 Hz, C*H*$(OEt)_2$), 4.53 (1H, app. t, *J* = 6.6 Hz, OC*H*CH_2O), 4.31 (1H, dd, *J* = 9.1, 7.0 Hz, OCHC*H*$_2$O), 4.17 (1H, dd, *J* = 9.1, 6.4 Hz, OCHC*H*$_2$O), 3.71-3.77 (2H, m, OC*H*$_2CH_3$), 3.57-3.63 (2H, m, OC*H*$_2CH_3$), 2.76 (1H, s, C*H*$_{alk}$), 2.11 (3H, s, OC(O)C*H*$_3$), 1.46 (3H, s, C*H*$_3$), 1.39 (3H, s, C*H*$_3$), 1.22 (6H, td, *J* = 7.1, 3.7 Hz, C*H*$_3$CH$_2$O); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 168.7 (*C*(O)), 110.0 (*C*), 91.2 (*C*H), 84.4 (*C*), 78.8 (*C*), 78.5 (*C*), 77.7 (*C*), 77.3 (*C*H), 66.8 (*C*H$_2$), 61.1 (*C*H$_2$CH$_3$), 60.9 (*C*H$_2$CH$_3$), 50.8 (*C*H), 26.1 (*C*H$_3$), 25.8 (*C*H$_3$), 21.4 (*C*H$_3$C(O)), 15.1 (CH$_2$*C*H$_3$); **IR** ($CHCl_3$ solution) 3280, 2980, 2925, 1756, 1456 cm^{-1}; **LRMS** (ES) 397.1224 (36%, $[C_{18}H_{25}O_6Na^{37}Cl]^+$), 395.1240 (100%, $[C_{18}H_{25}O_6Na^{35}Cl]^+$), 327.0986 (62%),; **HRMS** (ES) calcd for $C_{18}H_{25}O_6Na^{35}Cl$ 395.1240; $[M+Na]^+$ 395.1237 observed;

Data for product **199** : **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.46 (1H, s, C*H*$(OEt)_2$), 5.07 (1H, dd, *J* = 7.2, 6.5 Hz, OC*H*CH_2O), 4.19 (1H, dd, *J* = 8.5, 6.5 Hz, OCHC*H*$_2$O), 3.93 (1H, dd, *J* = 8.5, 7.2 Hz, OCHC*H*$_2$O), 3.71-3.76 (2H, m, OC*H*$_2CH_3$ and C*H*$_{alk}$), 3.63 (2H, dq, *J* = 9.5, 7.1 Hz, OC*H*$_2CH_3$), 1.49 (3H, s, C*H*$_3$), 1.41 (3H, s, C*H*$_3$), 1.25 (6H, t, *J* = 7.1 Hz, OCH_2CH_3); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 129.4 (*C*), 121.1 (*C*), 110.6 (*C*), 96.3 (*C*), 91.4 (*C*H$(OEt)_2$), 87.4 (*C*), 78.9 (*C*), 77.7 (*C*H), 75.4 (O*C*HCH_2O), 68.0 (OCH*C*H$_2$O), 61.4 (*C*H$_2CH_3$), 26.2 (*C*H$_3$), 25.9 (*C*H$_3$), 15.1 (CH_2*C*H$_3$).

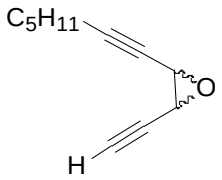
(3-chloroprop-1-ynyl)trimethylsilane 202[66]

To a solution of propargyl chloride (15 mL, 207 mmol) in THF (500 mL) at -78 °C was added *n*-BuLi (1.6 M solution in hexane, 66 mL, 105 mmol) dropwise over 1.5 h. TMSCl (26.4 mL, 207 mmol) was then added dropwise and the solution was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then quenched with water (600 mL) and diluted with Et_2O (600 mL). The aqueous phase was extracted with Et_2O (2 x 600 mL). The combined organic layers were washed with water (300 mL), brine (300 mL), dried ($MgSO_4$) and concentrated under vacuum. The product was purified by a distillation (bp = 135 °C, atm. pressure) to afford **202** as a transparent oil (9.87 g, 67.3 mmol, 64%). **bp** = 135 °C at atm. pressure. **^{1}H NMR** (400 MHz; $CDCl_3$) δ 4.13 (2H, s, CH_2Cl), 0.19 (9H, s, CH_3); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 99.7 (*C*), 91.9 (*C*), 30.8 (*C*H_2), -0.3 (*C*H_3); **IR** (neat) 2961, 2901, 2186, 1411 cm^{-1}.

(3-chloroprop-1-ynyl)triethylsilane 203[66]

To a solution of propargyl chloride (2.5 mL, 34.6 mmol) in THF (100 mL) at -78 °C was added a 2.2 M solution of *n*-BuLi (7.0 mL, 15.4 mmol) dropwise over 2 h. TESCl (5.8 mL, 34.6 mmol) was then added dropwise and the solution was allowed to warm to room temperature and stirred for a further 1 h. The reaction mixture was then quenched with water (100 mL) and diluted with Et_2O (100 mL). The aqueous phase was extracted with Et_2O (2 x 100 mL). Combined organic layers were washed with water (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under vacuum. The product was purified by flash chromatography (50% EtOAc/PE) and flash chromatography (100% PE) to afford **203** as a transparent oil (2.64 g, 14.0 mmol, 91%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 4.15 (2H, s, CH_2Cl), 1.00 (9H, t, *J* = 7.9 Hz, CH_3), 0.61 (6H, q, *J* = 7.9 Hz, CH_2); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 100.9 (*C*), 89.6 (*C*), 31.0 (*C*H_2), 7.4 (*C*H_3), 4.1 (*C*H_2); **LRMS** (EI) 161 (33%), 159 (100%), 131 (39%), 105 (22%), 103 (46%); **HRMS** (EI) calcd for $C_9H_{17}Si^{35}Cl$ 188.0783; $[M]^+$ 188.0785 observed.

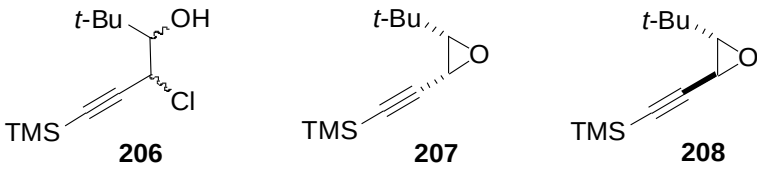
2-Ethyl-3-hept-1-ynyl-oxirane 201[66]



$ZnBr_2$ was dried at 130 °C under vacuum for at least three days prior to the reaction. A fresh solution of LDA was prepared by adding *n*-BuLi (1.6 M solution in hexane, 850 µL, 1.36 mmol) to a solution of diisopropylamine (191 µL, 1.36 mmol) in THF (3 mL) at -78 °C. To a solution of $ZnBr_2$ (306 mg, 1.36 mmol) in THF (2 mL) at -20 °C was added a solution of propargyl chloride **202** (100 mg, 0.68 mmol) in THF (1 mL) dropwise over 5 min. The reaction mixture was then cooled down to -78 °C and the freshly prepared solution of LDA was added dropwise. The reaction mixture was then stirred for 1 h at -78 °C before adding 2-octynal **204** (107 µL, 0.75 mmol) dropwise. The reaction mixture was then stirred for 2 h at -78 °C before being poured onto a mixture of $NH_4Cl_{(sat)}$ (5 mL) and water (20 mL). It was then diluted with Et_2O (50 mL). The reaction mixture was allowed to warm to room temperature. It was then extracted with Et_2O (2 x 50 mL). Combined organic phases were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated under vacuum. The crude chlorohydrins were dissolved in DMF (3.5 mL). KF (158 mg, 2.73 mmol) was added and the reaction mixture was then stirred for 1 h at room temperature. The reaction was then quenched with water (2 mL). The aqueous phase was extracted with Et_2O (2 x 50 mL) and the combined organic layers were washed with water (10 mL), brine (2 x 10 mL), dried ($MgSO_4$) and concentrated under vacuum. The crude reaction mixture was purified with a flash chromatography (50-75% $CHCl_3$/PE to 100% EtOAc) to give a mixture of crude desilylated chlorohydrins. To the crude chlorohydrins in DCM (2.5 mL) was added DBU (509 µL, 3.40 mmol) and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was poured on a flash chromatography previously neutralised with DBU(0.1%) in PE (30-100% $CHCl_3$/PE) to afford epoxide (*trans* : *cis:* 2.1 : 1) **201** as a colourless oil (58.1 mg, 0.36 mmol, 53%). Further flash chromatography (30% $CHCl_3$/PE) allowed separation of the *cis* and *trans* epoxides for characterisation. **^{1}H NMR** (500 MHz; $CDCl_3$) δ 3.54 (1H, dt, *J* = 3.6, 1.6 Hz, CH_{epo}, *cis*), 3.50 (1H, dd, *J* = 3.8, 1.7 Hz, CH_{epo}, *cis*), 3.50 (1H, app. q, *J* = 1.7 Hz, CH_{epo}, *trans*), 3.43 (1H, app. t, *J* = 1.8 Hz, CH_{epo}, *trans*), 2.43 (1H, d, *J* = 1.7 Hz, H_{alk}, *cis*), 2.33 (1H, d, *J* = 1.7 Hz, H_{alk}, *trans*),

2.25 (2H, td, *J* = 7.1, 1.6 Hz, C*H*$_{2propargyl}$, *cis*), 2.19 (2H, td, *J* = 7.2, 1.6 Hz, C*H*$_{2propargyl}$, *trans*), 1.50-1.57 (2H, m, C*H*$_2$, *cis*), 1.47-1.53 (2H, m, C*H*$_2$, *trans*), 1.36-1.42 (2H, m, C*H*$_2$, *cis*), 1.29-1.37 (4H, m, C*H*$_2$, *trans*), 1.27-1.34 (2H, m, C*H*$_2$, *cis*), 0.90 (3H, t, *J* = 7.2 Hz, C*H*$_3$, *trans*), 0.89 (3H, t, *J* = 7.3 Hz, C*H*$_3$, *cis*); **^{13}C NMR** (125 MHz; $CDCl_3$) δ 87.8 (*C*, *cis*), 86.1 (*C*, *trans*), 79.1 (*C*, *trans*), 78.3 (*C*, *cis*), 77.3 (*C*, *cis*), 75.0 (*C*, *trans*), 74.0 (*C*H$_{alk}$, *cis*), 72.5 (*C*H$_{alk}$, *trans*), 47.4 (*C*H$_{epo}$, *trans*), 46.9 (*C*H$_{epo}$, *trans*), 46.7 (*C*H$_{epo}$, *cis*), 46.2 (*C*H$_{epo}$, *cis*), 31.0 (*C*H$_2$, *trans*), 30.9 (*C*H$_2$, *cis*), 28.1 (*C*H$_2$, *cis*), 27.9 (*C*H$_2$, *trans*), 22.2 (*C*H$_2$, *cis*), 22.2 (*C*H$_2$, *trans*), 18.8 (*C*H$_2$, *cis*), 18.7 (*C*H$_2$, *trans*), 14.0 (*C*H$_3$, *cis*), 14.0 (*C*H$_3$, *trans*); **LRMS** (CI) 163 (61%, $[M+H]^+$)), 109 (21%), 107 (73%), 105 (27%), 95 (100%), 93 (77%), 91 (42%), 81 (39%), 79 (65%), 69 (22%), 67 (27%), 55 (23%); **HRMS** (CI) calcd for $C_{11}H_{15}O$ 163.1123; $[M+H]^+$ 163.1112 observed.

4-chloro-2-methyl-6-(trimethylsilyl)hex-5-yn-3-ol 206, *cis* ((3-*tert*-butyloxiran-2-yl)ethynyl)trimethylsilane 207 and *trans* ((3-*tert*-butyloxiran-2-yl)ethynyl)trimethylsilane 208[136]



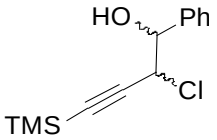
$ZnBr_2$ (957 mg, 4.25 mmol) was melted under vacuum for at least 5 min and immediately after cooling to room temperature was dissolved in dry THF (4.25 mL). A fresh solution of LDA was prepared by adding dropwise a 1.45 M solution of *n*-BuLi (2.93 mL, 4.25 mmol) to a solution of diisopropylamine (596 µL, 4.25 mmol) in THF (725 µL) at -78 °C and was then allowed to reach room temperature. The 1 M solution of $ZnBr_2$ was cooled down to -20 °C and propargyl chloride **202** (335 µL, 2.12 mmol) was added dropwise. The reaction mixture was then cooled down to -78 °C and the freshly prepared solution of LDA was added dropwise over 45 min. The yellow reaction mixture was then stirred for 1 h at -78 °C before adding pivalaldehyde **205** (462 µL, 4.25 mmol) in one portion. The reaction mixture was then stirred for 1 h at -78 °C and 1 h at -20 °C before being poured onto a 0.5 M solution of NH_4Cl (20 mL). It was then diluted with Et_2O (50 mL). The reaction mixture was allowed to warm to room temperature before being filtered through celite. It was then extracted with Et_2O (x 3). Combined organic phases were washed with water (x 2) and brine, dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by flash column chromatography (0-5% Et_2O/PE) to afford an inseparable mixture of chlorohydrin **206** and epoxides **207** and **208** (1 : 1.7 : 0.1) as a pale yellow oil (324.8 mg, 1.55 mmol, 73% yield, 98% conversion). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 4.82 (1H, d, *J* = 2.0 Hz, C*H*Cl, **206**), 3.53 (1H, dd, *J* = 6.9, 2.0 Hz, C*H*OH, **206**), 3.35 (1H, d, *J* = 4.2 Hz, CH_{epo}, **208**), 3.19 (1H, d, *J* = 2.3 Hz, CH_{epo}, **207**), 2.92 (1H, d, *J* = 2.3 Hz, CH_{epo}, **207**), 2.79 (1H, d, *J* = 4.2 Hz, CH_{epo}, **208**), 2.33 (1H, d, *J* = 6.9 Hz, O*H*, **206**), 1.08 (9H, s, C(CH_3)$_3$, **208**), 1.02 (9H, s, C(CH_3)$_3$, **206**), 0.92 (9H, s, C(CH_3)$_3$, **207**), 0.18 (9H, s, Si(CH_3)$_3$, **206**), 0.17 (9H, s, Si(CH_3)$_3$, **207** & **208**); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 102.5 (*C*≡CTMS, **207**), 101.2 (*C*≡CTMS, **208**), 100.0 (*C*≡CTMS, **206**), 96.1 (C≡*C*TMS, **206**), 93.5 (C≡*C*TMS, **208**), 89.1 (C≡*C*TMS, **207**), 82.6 (*C*HOH, **206**), 68.4 (*C*H$_{epo}$C*t*-Bu, **207**), 66.3 (*C*H$_{epo}$C*t*-Bu, **208**), 51.8 (*C*HCl, **206**), 44.1 (*C*H$_{epo}$C≡C, **208**), 42.9 (*C*H$_{epo}$C≡C, **207**), 35.9

(*C*(CH_3)$_3$, **206**), 31.6 (*C*(CH_3)$_3$, **208**), 31.1 (*C*(CH_3)$_3$, **207**), 26.9 (C(*C*H_3)$_3$, **208**), 26.5 (C(*C*H_3)$_3$, **206**), 25.6 (C(*C*H_3)$_3$, **207**), -0.17 (Si(*C*H_3)$_3$, **206**), -0.38 (Si(*C*H_3)$_3$, **207 & 208**); **IR** (neat) 3546, 2959, 2904, 2180, 1480 cm^{-1}; **LRMS** (CI, **206**) 213 (26%), 197 (100%), 159 (20%), 141 (60%), 107 (23%); **LRMS** (CI, **207 & 208**) 213 (35%), 210 (22%), 197 (94%, $[M]^+$), 159 (71%), 141 (100%), 125 (49%), 121 (31%), 107 (91%); **HRMS** (CI, **206**) calcd for $C_{11}H_{22}OSiCl$ 233.1228; $[M]^+$ 233.1123 observed; **HRMS** (CI, **207 & 208**) calcd for $C_{11}H_{21}OSi$ 197.1362; $[M]^+$ 163.1357 observed.

General procedure for synthesis of chlorohydrins

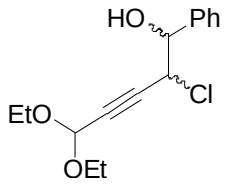
Zinc bromide (450 mg, 2.00 mmol) was melted under vacuum and after cooling to room temperature was dissolved in THF (2 mL) to make a 1 M solution of zinc bromide, which was then kept at -20 °C. A fresh solution of LDA was made by adding *n*-BuLi (1.5 M solution in hexane, 1.33 mL, 2.00 mmol) dropwise to a solution of diisopropylamine (280 μL, 2.00 mmol) in THF (390 μL) at -20 °C. The fresh LDA solution was kept at 0 °C. To the 1 M zinc bromide solution at -20 °C was added propargyl chloride **63** or **202** dropwise. The reaction mixture was then cooled down to -78 °C and the solution of LDA was added over 45 min in 0.5 mL aliquots. The reaction mixture was stirred for a further 2 h at -78 °C before adding commercially available benzaldehyde **87** or acetophenone **209** in one portion. The reaction mixture was then stirred for 2 h at -78 °C and then overnight at T, after having quickly reached temperature T. The reaction was quenched by pouring the reaction mixture onto a 0.5 M solution of NH_4Cl (20 mL), diluting it with Et_2O and allowing it to reach room temperature. It was extracted with Et_2O (x3). Combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated under vacuum to give crude chlorohydrin as an oil.

2-chloro-1-phenyl-4-trimethylsilanyl-but-3-yn-1-ol 210[136]



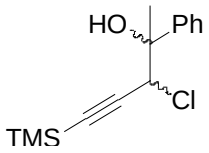
Chlorohydrin **210** was synthesised following the general procedure, using propargyl chloride **202** (160 μL, 1.00 mmol) and benzaldehyde **87** (101 μL, 1.00 mmol) and stirring the reaction mixture for 16 h at -20 °C. Crude chlorohydrin **210** was isolated (355 mg, 82% conversion, *anti* : *syn*: 1.8 : 1). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.34-7.39 (5H, m, CH_{Ar}, *anti* & *syn*), 4.92 (1H, d, *J* = 4.7 Hz, C*H*OH, *anti*), 4.83 (1H, d, *J* = 7.7 Hz, C*H*OH, *syn*), 4.69 (1H, d, *J* = 4.7 Hz, C*H*Cl, *anti*), 4.61 (1H, d, *J* = 7.7 Hz, C*H*Cl, *syn*), 0.17 (9H, s, Si(CH_3)$_3$, *anti*), 0.10 (9H, s, Si(CH_3)$_3$, *syn*).

2-chloro-5,5-diethoxy-1-phenyl-pent-3-yn-1-ol 211



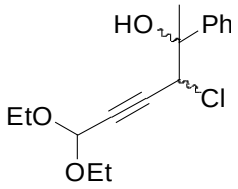
Chlorohydrin **211** was synthesised following the general procedure, using propargyl chloride **63** (140 μL, 1.00 mmol) and benzaldehyde **87** (101 μL, 1.00 mmol) and stirring the reaction mixture for 16 h at -20 °C. Crude chlorohydrin **211** was isolated (516 mg, 74% conversion, *anti* : *syn*: 3.2 : 1). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.42-7.44 (2H, m, CH_{Ar}, *anti* & *syn*), 7.32-7.38 (3H, m, CH_{Ar}, *anti* & *syn*), 4.95 (1H, d, *J* = 4.8 Hz, C*H*OH, *anti*), 4.86 (1H, d, *J* = 7.6 Hz, C*H*OH, *syn*), 4.76 (1H, dd, *J* = 4.8, 1.4 Hz, C*H*Cl, *anti*), 4.71 (1H, dd, *J* = 7.6, 1.3 Hz, C*H*Cl, *syn*), 3.61-3.68 (1H, m, C*H*(OEt)$_2$, *anti* & *syn*), 3.46-3.57 (2H, m, OCH_2CH$_3$, *anti* & *syn*), 1,20 (6H, t, *J* = 7.0 Hz, OCH$_2$CH_3, *anti*), 1.16 (6H, t, *J* = 7.1 Hz, OCH$_2$CH_3, *syn*).

3-chloro-2-phenyl-5-trimethylsilanyl-pentyl-4-yn-2-ol 212



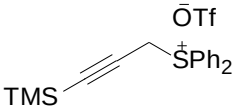
Chlorohydrin **212** was synthesised following the general procedure, using propargyl chloride **202** (160 μL, 1.00 mmol) and acetophenone **209** (117 μL, 1.00 mmol) and stirring the reaction mixture for 16 h at 0 °C. Crude chlorohydrin **212** was isolated (249 mg, 72% conversion, *anti* : *syn*: 2.1 : 1). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.32-7.43 (4H, m, C*H*$_{Ar}$, *anti* & *syn*), 7.29-7.30 (1H, m, C*H*$_{Ar}$, *anti* & *syn*), 3.51 (1H, s, C*H*Cl, *anti*), 3.30 (1H, s, C*H*Cl, *syn*), 1.82 (3H, s, C*H*$_3$, *syn*), 1.72 (3H, s, C*H*$_3$, *anti*), 0.21 (9H, s, Si(C*H*$_3$)$_3$, *syn*), -0.05 (9H, s, Si(C*H*$_3$)$_3$, *anti*).

3-chloro-6,6-diethoxy-2-phenyl-hex-4-yn-2-ol 213



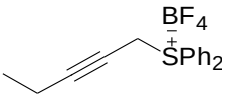
Chlorohydrin **213** was synthesised following the general procedure, using propargyl chloride **63** (140 μL, 1.00 mmol) and acetophenone **209** (117 μL, 1.00 mmol) and stirring the reaction mixture overnight at -20 °C and 5 h at room temperature. Crude chlorohydrin **213** was isolated (169 mg, 51% conversion, *anti* : *syn*: 3 : 1). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.41-7.42 (2H, m, C*H*$_{Ar}$, *anti* & *syn*), 7.32-7.35 (3H, m, C*H*$_{Ar}$, *anti* & *syn*), 5.34 (1H, d, *J* = 1.1 Hz, C*H*Cl, *syn*), 5.05 (1H, d, *J* = 1.0 Hz, C*H*Cl, *anti*), 3.59 (1H, d, *J* = 1.0 Hz, C*H*(OEt)$_2$, *anti*), 3.37 (1H, d, *J* = 1.1 Hz, C*H*(OEt)$_2$, *syn*), 3.30-3.36 (2H, m, OC*H*$_2$CH$_3$, *anti* & *syn*), 3.18-3.25 (2H, m, OC*H*$_2$CH$_3$, *anti* & *syn*), 1.83 (3H, s, C*H*$_3$, *syn*), 1.71 (3H, s, C*H*$_3$, *anti*), 1.08 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$, *anti* & *syn*), 1.04 (3H, t, *J* = 7.1 Hz, OCH$_2$C*H*$_3$, *anti* & *syn*).

Diphenyl (3-trimethylsilanyl-prop-2-yn-1-yl) sulfonium; trifluoromethanesulfonate 233



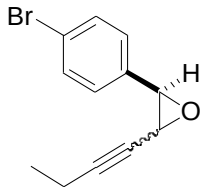
To a flask, equipped with a stirrer bar, having being flamed and cooled down to -25 °C under argon, was added trifluoromethanesulfonic anhydride (342 μL, 2.01 mmol). In a separate flask (flamed and cooled down to -25 °C under argon) was placed 3-(trimethylsilyl)-propargyl alcohol **231** (285 μL, 1.92 mmol), pyridine (166 μL, 2.05 mmol) and DCM (1.7 mL). This solution was added dropwise *via* canula to the stirred trifluoromethanesulfonic anhydride followed by DCM (0.65 mL) to ensure complete transfer. After 30 min strirring at -25 °C, hexane was added dropwise over 15 min. Reaction mixture was cooled down to -78 °C and stirred at this temperature for 30 min. While still at -78 °C, the 2-phase white slurry was filtered under argon to a flask cooled to -78 °C. It was rinsed with hexane (3 mL) and solvent was removed at -78 °C under vacuum (about 30 min in a -78 °C bath then lifted up in the air). Crude was dissolved in chloroform (4 mL) at -78 °C. Diphenyl sulphide **228** (482 μL, 2.88 mmol) was added and reaction mixture was stirred allowing reaction mixture to slowly reach room temperature. It was then evaporated and the residue was washed with hexane (2 x 4 mL) to remove excess sulphide. The residue was dissolved in THF and Et_2O was slowly added until the triflate crystallised. The reaction mixture was left in the freezer overnight and the resultant salt was filtered off and washed with cold Et_2O. The salt was purified by dissolving it in minimum of THF and slowly adding Et_2O, this resulted in the crystallisation of the salt. It was left in the freezer for another 6 h. The salt was then filtered off and washed with cold Et_2O to afford tetrafluoroborate sulfonium salt **233** as a white solid (188 mg, 0.42 mmol, 22%). **mp** = 98 °C; **^{1}H NMR** (600 MHz; $CDCl_3$) δ_H 7.93 (4H, d, *J* = 7.8 Hz, C*H*$_{Ar}$), 7.78 (2H, t, *J* = 7.5 Hz, C*H*$_{Ar}$), 7.70 (4H, t, *J* = 7.8 Hz, C*H*$_{Ar}$), 5.14 (2H, s, C*H*$_2$), 0.05 (9H, s, Si(C*H*$_3$)$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ_C 134.9 (*C*H), 131.3 (*C*H), 131.1 (*C*H), 123.3 (*C*), 100.5 (C), 90.6 (*C*), 39.2 (C*H*$_2$), -0.7 (C*H*$_3$); **IR** (neat) : 3099, 3068, 2964, 2919, 2184, 1585, 1484, 1447 cm^{-1}; **LRMS** (CI) 187 (100%), 186 (24%), 115 (23%), 112 (26%); **HRMS** (CI) calcd for $C_{18}H_{21}SSi$ 297.1133; $[M\text{-}BF_4^-]^+$ 297.1146 observed.

Diphenyl(Pent-2-yn-1-yl)sulfonium; tetrafluoroborate 239



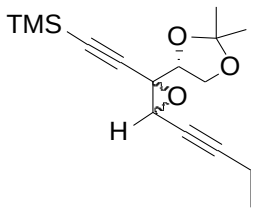
Under argon, silver tetrafluoroborate (3.6 g, 18.4 mmol) was dissolved in dry acetone (6 mL). Diphenyl sulphide **228** (20.0 mL, 119.5 mmol) was added to the reaction mixture. The flask was wrapped in aluminium foil and immersed in a 0 °C bath. 1-bromo-2-pentyne **240** (2.0 mL, 19.6 mmol) was added quickly and the reaction mixture was further stirred at 0 °C for 5 min and 2 h at room temperature (The solution began to turn light yellow : the yellow colour accompanied decomposition of the salt, the reaction was therefore terminated when the colour change was noted). The reaction mixture was filtered and the silver bromide was washed with DCM. The combined organic layers were combined and concentrated under vacuum to give a light yellow oil. Et_2O (*ca.* 80 mL) was added to the oil and the mixture was sonicated for 5 min to make the white solid precipitate. It was filtered off to give crude sulfonium salt. The crude was purified by a celite plug ($CHCl_3$ → MeOH(10%)/ $CHCl_3$). The mother liquor was concentrated under vacuum to give an oil. Et_2O was then added to the oil and mixture was sonicated for 5 min to make the white crystalline solid precipitate. It was filtered off and dried to afford tetrafluoroborate salt **239** as a white solid (5.46 g, 16.0 mmol, 88%). **mp** = 84 °C; **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.89-7.91 (4H, d, *J* = 7.8 Hz, C*H*$_{Ar}$), 7.76 (2H, d, *J* = 7.4 Hz, C*H*$_{Ar}$), 7.70 (4H, d, *J* = 7.8 Hz, C*H*$_{Ar}$), 4.98 (2H, t, *J* = 2.4 Hz, $^+$SC*H*$_2$), 2.11 (2H, qt, *J* = 7.5, 2.4 Hz, C*H*$_2$CH$_3$), 0.96 (3H, t, *J* = 7.5 Hz, C*H*$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 134.9 (*C*H), 131.4 (*C*H), 131.0 (*C*H), 123.3 (*C*), 96.1 (*C*), 66.0 (*C*), 38.7 (*C*H$_2$), 13.0 (*C*H$_3$), 12.6 (*C*H$_2$); **IR** (neat) 3099, 3064, 2976, 2933, 2315, 2243, 2014, 1985, 1903, 1820, 1686, 1583, 1481, 1448 cm^{-1}; **LRMS** (CI) 253 (21%, [M-BF_4^-]$^+$), 187 (100%), 186 (29%); **HMRS** (CI) calcd for $C_{17}H_{17}S$ 253.1051; [M-BF_4^-]$^+$ 253.1045 observed.

2-(4-bromophenyl)-3-(but-1-yn-1-yl)oxirane 242



A solution of 4-bromobenzaldehyde **241** (187 mg, 1.01 mmol) in (1 mL) was added in 0.3 mL aliquots over 15 min to a mixture of sulfonium salt **239** (516 mg, 1.52 mmol) and sodium hydride (65% volume, 59 mg, 1.60 mmol) in DCM (2 mL) that was stirring at -20 °C. The reaction mixture was stirred for a further 8 h at -20 °C before MeOH (81 μL, 2.00 mmol) was added. The reaction mixture was then allowed to reach room temperature before water was added. The aqueous phase was extracted with Et_2O (x 3). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. DMF (77 μL, 0.99 mmol) was added to the crude for NMR sample (100% conversion, 66% yield). The crude was purified by two flash chromatography (0-10% Et_2O/PE) and flash chromatography (0-30% DCM/PE) to afford epoxide **242** as an inseparable mixture of diastereoisomers (*cis* : *trans* : 1.6 : 1) for characterisation. **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.48 (2H, d, *J* = 8.5 Hz, C*H*$_{Ar}$, *cis*), 7.47 (2H, d, *J* = 8.5 Hz, C*H*$_{Ar}$, *trans*), 7.27 (2H, d, *J* = 8.5 Hz, C*H*$_{Ar}$, *cis*), 7.14 (2H, d, *J* = 8.5 Hz, C*H*$_{Ar}$, *trans*), 4.02 (1H, d, *J* = 4.0 Hz, ArC*H*$_{epo}$, *cis*), 3.93 (1H, d, *J* = 1.9 Hz, ArC*H*$_{epo}$, *trans*), 3.73-3.74 (1H, m, CCC*H*$_{epo}$, *cis*), 3.27-3.28 (1H, m, CCC*H*$_{epo}$, *trans*), 2.25 (2H, qt, *J* = 7.5, 1.6 Hz, $CH_3C\mathit{H}_2$, *trans*), 2.10 (2H, qd, *J* = 7.5, 1.9 Hz, $CH_3C\mathit{H}_2$, *cis*), 1.16 (3H, t, *J* = 7.5 Hz, $CH_2C\mathit{H}_3$, *trans*), 1.01 (3H, t, *J* = 7.5 Hz, $CH_2C\mathit{H}_3$, *cis*); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 135.2 (*C*$_{Ar}$, *trans*), 133.7 (*C*$_{Ar}$, *cis*), 131.8 (*C*H$_{Ar}$, *trans*), 130.8 (*C*H$_{Ar}$, *cis*), 128.9 (*C*H$_{Ar}$, *cis*), 127.3 (*C*H$_{Ar}$, *trans*), 122.3 (*C*Br, *cis*), 122.61 (*C*Br, *trans*), 89.4 ($CH_2\mathit{C}C$, *cis*), 87.0 ($CH_2\mathit{C}C$, *trans*), 75.5 (C*C*CH$_{epo}$, *trans*), 73.4 (C*C*CH$_{epo}$, *cis*), 59.6 (Ar*C*H$_{epo}$, *trans*), 58.4 (Ar*C*H$_{epo}$, *cis*), 50.0 (*C*H$_{epo}$CC, *trans*), 48.7 (*C*H$_{epo}$CC, *cis*), 13.6 (*C*H$_3$, *trans*), 13.5 (*C*H$_3$, *cis*), 12.6 (*C*H$_2$, *trans*), 12.5 (*C*H$_2$, *cis*); **IR** (neat) 2978, 2938, 2918, 2878, 2846, 2239, 1905, 1713, 1595, 1575, 1488, 1456 cm^{-1}; **LRMS** (EI) 252 (24%, [$C_{12}H_{11}O^{81}Br$]$^+$), 250 (25%, [$C_{12}H_{11}O^{79}Br$]$^+$), 223 (27%), 221 (29%), 185 (80%), 183 (68%), 171 (34%), 157 (39%), 155 (35%), 143 (55%), 142 (60%), 141 (34%), 128 (100%), 115 (24%), 89 (63%); **HRMS** (EI) calcd for $C_{12}H_{11}O^{79}Br$ 249.9988; [M]$^+$ 249.9994 observed.

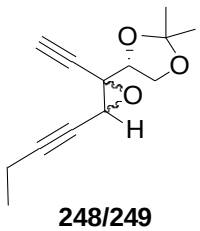
[3-But-1-ynyl-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-oxiranylethynyl]-trimethyl-silanes 246 or 247



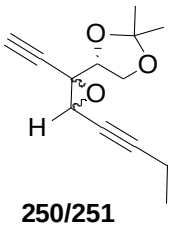
cis1

To a suspension of sulfonium salt **239** (243 mg, 0.71 mmol) in THF (0.8 mL) at -78 °C, LHMDS (1M solution in THF, 720 μL, 0.72 mmol) was added dropwise. The reaction mixture was stirred for 15 min at -78 °C before a solution of ketone **14** (109 mg, 0.48 mmol) in THF (0.6 mL) followed by THF (0.3 mL) to ensure complete transfer were added in 0.2 mL aliquots over 10 min. The reaction mixture was stirred for a further 30 min at -78 °C and then quickly warmed up to -10 °C. The reaction mixture was stirred for a further 3 h at -10 °C. The reaction was quenched with $NH_4Cl_{(sat)}$ at -10 °C and allowed to warm to room temperature. The aqueous phase was extracted with Et_2O (x 3). Combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. Crude epoxides *trans1*, *cis1*, *trans2* and *cis2* (226.8 mg, 100% conversion, 39% yield) were isolated as an inseparable mixture (23.2 : 6.5 : 4.7 : 1). Crude was purified by flash chromatography (50-100% $CHCl_3$/PE to 5-20% MeOH/PE) to allow partial separation of the epoxides and characterisation of the least polar epoxide *cis*1. **^{1}H NMR** (600 MHz; $CDCl_3$) δ 4.17-4.23 (2H, m, OCH_2), 4.05 (1H, app. t, *J* = 6.5 Hz, C*H*), 3.73 (1H, t, *J* = 1.6 Hz, CH_{epo}), 2.24 (2H, qd, *J* = 7.5, 1.5 Hz, CH_2CH$_3$), 1.52 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.14 (3H, t, *J* = 7.5 Hz, CH$_2$CH_3), 0.16 (9H, s, Si(CH_3)$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 110.8 (*C*(CH$_3$)$_2$), 99.6 (*C*≡CTMS), 91.6 (C≡*C*TMS), 90.1 (Et*C*≡C), 75.4 (*C*H), 72.2 (EtC≡*C*), 67.0 (*C*H$_2$), 56.0 (*C*$_{epo}$), 53.0 (*C*H$_{epo}$), 26.4 (*C*H$_3$), 25.8 (*C*H$_3$), 13.5 (CH$_2$*C*H$_3$), 12.7 (*C*H$_2$CH$_3$), -0.31 (Si(*C*H$_3$)$_3$); **IR** ($CHCl_3$ solution) 2927, 2239, 2177, 1741, 1560, 1456 cm^{-1}; **LRMS** (EI) 219 (24%), 195 (20%), 165 (33%), 153 (65%), 149 (28%), 137 (100%), 125 (20%), 118 (21%), 115 (22%), 107 (48%), 101 (38%), 97 (33%), 91 (25%); **HRMS** (EI) calcd for $C_{15}H_{21}O_3Si$ 277.1260; [M-Me]$^+$ 277.1263 observed.

4-(3-But-1-ynyl-2-ethynyl-oxiranyl)-2,2-dimethyl-[1,3]dioxolane 248, 249, 250 & 251



248/249



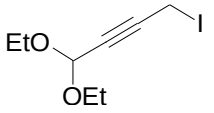
250/251

To a suspension of sulfonium salt **239** (272 mg, 0.80 mmol) in THF (0.9 mL) at -78 °C, LHMDS (1M solution in THF, 800 μL, 0.80 mmol) was added dropwise. The reaction mixture was stirred for 15 min at -78 °C before a solution of ketone **14** (119 mg, 0.53 mmol) in THF (0.8 mL) followed by THF (0.2 mL) to ensure complete transfer were added in 0.4 mL aliquots over 10 min. The reaction mixture was stirred for a further 30 min at -78 °C. MeOH (1.9 mL) was added and reaction mixture was then quickly warmed up to -10 °C. Potassium carbonate (155 mg, 1.12 mmol) was added and reaction mixture was stirred for a further 3 h at -10 °C. The reaction was quenched with $NH_4Cl_{(sat)}$ at -10 °C and was allowed to warm to room temperature. The aqueous phase was extracted with Et_2O (x 3). Combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated under vacuum. Crude epoxides *trans1, cis1, trans2* and *cis2* (202.9 mg, 100% conversion, 40% yield) were isolated as an inseparable mixture (11.0 : 3.3 : 1.2 : 1). The crude was purified by flash chromatography (0-5% Et_2O/PE) to allow partial separation of the epoxides and characterisation of major epoxide *trans1* and other epoxides *cis1, trans2* and *cis2* as an inseparable mixture (4.1 : 1.3 : 1.0).

Data for epoxide *trans1*: **^{1}H NMR** (600 MHz; $CDCl_3$) δ 4.21 (1H, dd, *J* = 8.6, 6.8 Hz, OCH_2), 4.10 (1H, dd, *J* = 8.6, 6.2 Hz, OCH_2), 4.05 (1H, app. t, *J* = 6.4 Hz, C*H*), 3.62 (1H, s, CH_{epo}), 2.50 (1H, s, CH_{alk}), 2.27 (2H, qd, *J* = 7.5, 1.4 Hz, CH_2CH$_3$), 1.47 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.16 (3H, t, *J* = 7.5 Hz, CH$_2$CH_3); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 111.0 (*C*(CH$_3$)$_2$), 89.6 (Et*C*≡C), 77.6 (HC≡*C*), 76.0 (*C*H), 75.5 (*C*H$_{alk}$), 73.1 (EtC≡*C*), 67.0 (*C*H$_2$), 57.8 (*C*$_{epo}$), 50.1 (*C*H$_{epo}$), 26.2 (*C*H$_3$), 25.3 (*C*H$_3$), 13.6 (CH$_2$*C*H$_3$), 12.7 (*C*H$_2$CH$_3$); **IR** ($CHCl_3$ solution) 3278, 2984, 2938, 2358, 2244, 2125, 1457 cm^{-1}; **LRMS** (EI) 205 (100%, [M-Me]$^+$), 161 (26%), 91 (22%), 81 (40%), 66 (21%), 65 (35%), 63 (27%), 59 (21%), 53 (71%), 52 (33%), 51 (47%); **HRMS** (EI) calcd for $C_{12}H_{13}O_3$ 205.0865; [M-Me]$^+$ 205.0870 observed;

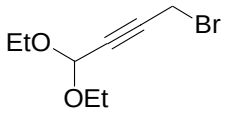
Data for *cis1*, *trans2* and *cis2*: **^{1}H NMR** (600 MHz; $CDCl_3$) δ 4.30 (1H, app. t, *J* = 6.3 Hz, OC*H*$_2$, *trans2*), 4.17-4.23 (4H, m, OC*H*$_2$, *cis1* (2H), *trans2* (1H), *cis2* (1H), 4.10-4.14 (2H, m, C*H* (*cis1*) & OC*H*$_2$ (*cis2*)), 4.07 (1H, dd, *J* = 8.6, 5.9 Hz, C*H*, *trans2*), 4.01 (1H, dd, *J* = 8.3, 7.3 Hz, C*H*, *cis2*), 3.74 (1H, t, *J* = 1.6 Hz, C*H*$_{epo}$, *cis1*), 3.68 (1H, t, *J* = 1.7 Hz, C*H*$_{epo}$, *cis2*), 3.65 (1H, t, *J* = 1.5 Hz, C*H*$_{epo}$, *trans2*), 2.49 (1H, s, C*H*$_{alk}$, *trans2*), 2.39 (1H, s, C*H*$_{alk}$, *cis2*), 2.38 (1H, s, C*H*$_{alk}$, *cis1*), 2.20-2.29 (6H, m, C*H*$_2$CH$_3$, *cis1*, *trans2* & *cis2*), 1.54 (6H, s, C*H*$_3$, *cis1* & *cis2*), 1.40 (3H, s, C*H*$_3$, *cis2*), 1.39 (3H, s, C*H*$_3$, *cis1*), 1.38 (3H, s, C*H*$_3$, *trans2*), 1.34 (3H, s, C*H*$_3$, *trans2*), 1.12-1.17 (9H, m, CH$_2$C*H*$_3$, *cis1*, *trans2* & *cis2*); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 110.97 (*C*(CH$_3$)$_2$, *trans2*), 110.88 (*C*(CH$_3$)$_2$, *cis2*), 110.87 (*C*(CH$_3$)$_2$, *cis1*), 90.4 (Et*C*≡C, *cis1*), 89.9 (Et*C*≡C, *trans2*), 89.2 (Et*C*≡C, *cis2*), 78.7 (HC≡*C*, *cis1*), 78.1 (HC≡*C*, *cis2*), 78.0 (HC≡*C*, *trans2*), 75.4 (*C*H, *cis2*), 75.20 (*C*H, *cis1*), 75.19 (*C*H, *trans2*), 73.8 (*C*H$_{alk}$, *trans2*), 73.6 (*C*H$_{alk}$, *cis1*), 73.3 (*C*H$_{alk}$, *cis2*), 72.1 (EtC≡*C*, *cis2*), 72.0 (EtC≡*C*, *cis1* & *trans2*), 66.8 (O*C*H$_2$, *cis1*), 66.4 (O*C*H$_2$, *trans2*), 66.1 (O*C*H$_2$, *cis2*), 57.1 (*C*$_{epo}$, *trans2*), 56.2 (*C*$_{epo}$, *cis2*), 55.8 (*C*$_{epo}$, *cis1*), 52.7 (*C*H$_{epo}$, *cis1*), 50.3 (*C*H$_{epo}$, *cis2*), 49.2 (*C*H$_{epo}$, *trans2*), 26.4 (*C*H$_3$, *cis2*), 26.3 (*C*H$_3$, *cis1*), 25.81 (*C*H$_3$, *trans2*), 25.80 (*C*H$_3$, *trans2*), 25.77 (*C*H$_3$, *cis2*), 25.5 (*C*H$_3$, *cis1*), 13.6 (CH$_2$*C*H$_3$, *trans2*), 13.4 (CH$_2$*C*H$_3$, *cis1* & *cis2*), 12.7 (*C*H$_2$CH$_3$, *cis1* & *trans2*), 12.6 (*C*H$_2$CH$_3$, *cis2*); **IR** ($CHCl_3$ solution) 3279, 2984, 2934, 2882, 2239, 2124, 1740, 1457 cm^{-1}; **LRMS** (EI) 205 (100%, [M-Me]$^+$), 133 (43%)**; HRMS** (EI) calcd for $C_{12}H_{13}O_3$ 205.0865; [M-Me]$^+$ 205.0869 observed.

4-iodo-1,1-diethoxybut-2-yne 262

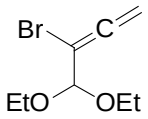


Propargyl chloride **63** (624 mg, 3.53 mmol) was placed in a sealed tube under argon. Acetone (21 mL) and potassium iodide (1.77 g, 10.7 mmol) were added. Tube was sealed and heated at 60 °C for 1 h. The reaction mixture was then cooled down to room temperature and further stirred until disappearance of propargyl chloride was seen by TLC. The reaction mixture was diluted with DCM, passed through a celite plug and thoroughly rinsed with DCM. Solvent was removed under vacuum and the crude was purified by flash chromatography (0-10% Et_2O/PE, on silica previously neutralised with NEt_3 (1% in PE)) to give propargyl iodide **262** as a transparent oil. **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.26 (1H, t, *J* = 1.5 Hz, C*H*$(OEt)_2$), 3.70-3.75 (2H, m, C*H*$_2$$CH_3$), 3.71 (2H, d, *J* = 1.5 Hz, C*H*$_2$I), 3.55-3.60 (2H, m, C*H*$_2$$CH_3$), 1.23 (3H, t, *J* = 7.1 Hz, C*H*$_3$); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 91.2 (*C*H), 82.2 (*C*), 80.3 (*C*), 61.0 (*C*H_2CH_3), 15.1 (CH_2*C*H_3), -20.1 (*C*H_2I); **IR** (neat) 2975, 2929, 2885, 2231, 1961, 1480 cm^{-1}; **LRMS** (EI) 224 (20%), 223 (74%), 195 (100%), 141 (24%), 96 (33%), 86 (43%), 84 (70%); **HRMS** (EI) calcd for $C_8H_{12}O_2I$ 266.9877; $[M-H]^+$ 266.9883 observed.

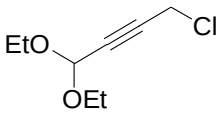
4-bromo-1,1-diethoxybut-2-yne 252[133], 3-bromo-4,4-diethoxy-buta-1,2-diene 253 and 4-chloro-1,1-diethoxybut-2-yne 63[66]



252



253



63

To a solution of 4-chloro-1,1-diethoxybut-2-yne **63** (242 mg, 1.37 mmol) in butanone (3 mL), sodium bromide (578 mg, 5.62 mmol) and tetrabutylammonium bromide (45 mg, 0.14 mmol) were added and the reaction mixture was refluxed for 6 and ½ days. The reaction mixture was then concentrated under vacuum before being diluted with DCM and water. The aqueous phase was extracted with DCM (x 2). The combined organic phases were washed with water (x 2) and brine, dried (MgSO4) and concentrated under vacuum to give an inseparable mixture of 4-bromo-1,1-diethoxybut-2-yne **252**, 3-bromo-4,4-diethoxy-buta-1,2-diene **253** and 4-chloro-1,1-diethoxybut-2-yne **63** (8.5 : 3.5 : 1) as brown oil (261 mg, 1.20 mmol, 87%). **^{1}H NMR** (600 MHz; $CDCl_3$) δ 5.30 (1H, t, *J* = 1.4 Hz, C*H*$(OEt)_2$, **252** & **63**), 5.05 (2H, d, *J* = 1.7 Hz, CCH_2, **253**), 4.89 (1H, t, *J* = 1.6 Hz, C*H*$(OEt)_2$, **63**), 4.17 (2H, d, *J* = 1.4 Hz, CH_2Cl, **63**), 3.93 (2H, d, *J* = 1.5 Hz, CH_2Br, **252**), 3.73 (2H, dq, *J* = 9.4, 7.1 Hz, CH_3CH_2O, **252** & **63**), 3.66 (2H, dq, *J* = 9.4, 7.1 Hz, CH_3CH_2O, **253**), 3.54-3.61 (2H, m, CH_3CH_2O, **252, 253** & **63**), 1.25 (6H, t, *J* = 7.0 Hz, CH_3CH_2O, **253**), 1.23 (6H, t, *J* = 7.0 Hz, CH_3CH_2O, **252** & **63**); **^{13}C NMR** (150 MHz; $CDCl_3$) δ 205.0 (C=*C*=C, **253**), 100.6 (*C*H, **253**), 91.26 (*C*H, **252**), 91.23 (*C*H, **63**), 90.2 (*C*, **253**), 83.7 (CH_2, **253**), 82.0 (*C*, **252**), 81.7 (*C*, **63**), 80.5 (*C*, **252**), 80.2 (*C*, **63**), 62.2 (CH_3CH_2O, **253**), 61.1 (CH_3CH_2O, **252** & **63**), 30.0 (CH_2Cl, **63**), 15.2 (CH_3, **252** & **63**), 15.1 (CH_3, **253**), 13.6 (CH_2Br, **252**); **IR** (neat) 2977, 2931, 2886, 1743, 1480 cm^{-1}; **LRMS** (CI, **252** & **253**) 175 (100%, $[M\text{-}OEt]^+$), 177 (99%); **HRMS** (CI) calcd for C_6H_8OBr 174.9759; $[M\text{-}OEt]^+$ 174.9763 observed.

References

(1) Galm, U.; Hager, M. H.; Van Lanen, S. G.; Ju, J. H.; Thorson, J. S.; Shen, B. *Chem. Rev.* **2005**, *105*, 2, 739-758.
(2) Liang, Z. X. *Nat. Prod. Rep.* **2010**, *27*, 4, 499-528.
(3) Zhen, Y.; Ming, X.; Yu, B.; Otani, T.; Saito, H.; Yamada, Y. *J. Antibiot.* **1989**, *42*, 8, 1294-1298.
(4) http://replay.web.archive.org/20070403223644 /http://www.mayoclinic.com/health/drug-information/DR202209, **2012**
(5) La Ferla, B.; Airoldi, C.; Zona, C.; Orsato, A.; Cardona, F.; Merlo, S.; Sironi, E.; D'Orazio, G.; Nicotra, F. *Nat. Prod. Rep.* **2011**, *28*, 3, 630-648.
(6) Gredičak, M. J., I. *Acta Pharmaceut.* **2007**, *57*, 2, 133-150.
(7) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiot.* **1965**, *18*, 2, 68-76.
(8) Maeda, H.; Kumagai, K.; Ishida, N. *J. Antibiot.* **1966**, *19*, 6, 253-259.
(9) Meienhof.J; Glaser, C. B.; Czombos, J.; Maeda, H.; Kuromizu, K. *Science* **1972**, *178*, 4063, 875-876.
(10) Kuromizu, K.; Tsunasawa, S.; Maeda, H.; Abe, O.; Sakiyama, F. *Arch. Biochem. Biophys.* **1986**, *246*, 1, 199-205.
(11) Adjadj, E.; Mispelter, J.; Quiniou, E.; Dimicoli, J. L.; Favaudon, V.; Lhoste, J. M. *Eur. J. Biochem.* **1990**, *190*, 2, 263-271.
(12) Maeda, H. *Anticancer Res.* **1981**, *1*, 3, 175-185.
(13) Napier, M. A.; Holmquist, B.; Strydom, D. J.; Goldberg, I. H. *Biochem. Biophys. Res. Commun.* **1979**, *89*, 2, 635-642.
(14) Koide, Y.; Ishii, F.; Hasuda, K.; Koyama, Y.; Edo, K.; Katamine, S.; Kitame, F.; Ishida, N. *J. Antibiot.* **1980**, *33*, 3, 342-346.
(15) Edo, K.; Mizugaki, M.; Koide, Y.; Seto, H.; Furihata, K.; Otake, N.; Ishida, N. *Tetrahedron Lett.* **1985**, *26*, 3, 331-334.
(16) Myers, A. G.; Proteau, P. J.; Handel, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 21, 7212-7214.
(17) Teplyakov, A.; Obmolova, G.; Wilson, K.; Kuromizu, K. *Eur. J. Biochem.* **1993**, *213*, 2, 737-741.
(18) Kim, K. H.; Kwon, B. M.; Myers, A. G.; Rees, D. C. *Science* **1993**, *262*, 5136, 1042-1046.
(19) Povirk, L. F.; Goldberg, I. H. *Biochemistry* **1980**, *19*, 21, 4773-4780.
(20) Wang, B.; Merz, K. M. *PCCP* **2010**, *12*, 14, 3443-3449.
(21) Adjadj, E.; Quiniou, E.; Mispelter, J.; Favaudon, V.; Lhoste, J. M. *Eur. J. Biochem.* **1992**, *203*, 3, 505-511.
(22) Adjadj, E.; Quiniou, E.; Mispelter, J.; Favaudon, V.; Lhoste, J. M. *Biochimie* **1992**, *74*, 9-10, 853-858.
(23) Mohanty, S.; Sieker, L. C.; Drobny, G. P. *Biochemistry* **1994**, *33*, 35, 10579-10590.
(24) Caddick, S.; Muskett, F. W.; Stoneman, R. G.; Woolfson, D. N. *J. Am. Chem. Soc.* **2006**, *128*, 13, 4204-4205.
(25) Takahashi, K.; Tanaka, T.; Suzuki, T.; Hirama, M. *Tetrahedron* **1994**, *50*, 5, 1327-1340.

(26) Urbaniak, M. D.; Muskett, F. W.; Finucane, M. D.; Caddick, S.; Woolfson, D. N. *Biochemistry* **2002**, *41*, 39, 11731-11739.
(27) Urbaniak, M. D.; Bingham, J. P.; Hartley, J. A.; Woolfson, D. N.; Caddick, S. *J. Med. Chem.* **2004**, *47*, 19, 4710-4715.
(28) Heyd, B.; Pecorari, F.; Collinet, B.; Adjadj, E.; Desmadril, M.; Minard, P. *Biochemistry* **2003**, *42*, 19, 5674-5683.
(29) Tomioka, Y.; Kisara, S.; Yoshizawa, S.; Ozawa, M.; Suzuki, N.; Yamaguchi, H.; Hishinuma, T.; Mizugaki, M.; Goto, J. *Biol. Pharm. Bull.* **2006**, *29*, 5, 1010-1014.
(30) Nicaise, M.; Valerio-Lepiniec, M.; Minard, P.; Desmadril, M. *Protein Sci.* **2004**, *13*, 7, 1882-1891.
(31) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 11, 2103-2117.
(32) Gomibuchi, T.; Hirama, M. *J. Antibiot.* **1995**, *48*, 7, 738-740.
(33) Edo, K.; Akiyamamurai, Y.; Saito, K.; Mizugaki, M.; Koide, Y.; Ishida, N. *J. Antibiot.* **1988**, *41*, 9, 1272-1274.
(34) Stassinopoulos, A.; Ji, J.; Gao, X. L.; Goldberg, I. H. *Science* **1996**, *272*, 5270, 1943-1946.
(35) Myers, A. G. *Tetrahedron Lett.* **1987**, *28*, 39, 4493-4496.
(36) Goldberg, I. H. *Acc. Chem. Res.* **1991**, *24*, 7, 191-198.
(37) Myers, A. G.; Kort, M. E.; Hammond, M. *J. Am. Chem. Soc.* **1997**, *119*, 13, 2965-2972.
(38) Myers, A. G.; Harrington, P. M.; Kwon, B. M. *J. Am. Chem. Soc.* **1992**, *114*, 3, 1086-1087.
(39) Napier, M. A.; Goldberg, I. H.; Hensens, O. D.; Dewey, R. S.; Liesch, J. M.; Albersschonberg, G. *Biochem. Biophys. Res. Commun.* **1981**, *100*, 4, 1703-1712.
(40) Lazarus, H.; Raso, V.; Samy, T. S. A. *Cancer Res.* **1977**, *37*, 10, 3731-3736.
(41) Sakamoto, S.; Maeda, H.; Ogata, J. *Experientia* **1979**, *35*, 9, 1233-1235.
(42) Schaus, S. E.; Cavalieri, D.; Myers, A. G. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 20, 11075-11080.
(43) Izadi-Pruneyre, N.; Quiniou, E.; Blouquit, Y.; Perez, J.; Minard, P.; Desmadril, M.; Mispelter, J.; Adjadj, E. *Protein Sci.* **2001**, *10*, 11, 2228-2240.
(44) Takashima, H.; Yoshida, T.; Ishino, T.; Hasuda, K.; Ohkubo, T.; Kobayashi, Y. *J. Biol. Chem.* **2005**, *280*, 12, 11340-11346.
(45) Myers, A. G.; Arvedson, S. P.; Lee, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 19, 4725-4726.
(46) Kappen, L. S.; Goldberg, I. H. *Science* **1993**, *261*, 5126, 1319-1321.
(47) Maeda, H. *Adv. Drug Del. Rev.* **2001**, *46*, 1-3, 169-185.
(48) Caddick, S.; Shanmugathasan, S.; Smith, N. J. In *The Chemical Synthesis of Natural Products*; ERC, Ed. **2000**, p 229-263.
(49) Basak, A.; Roy, S. K.; Roy, B.; Basak, A. *Curr. Top. Med. Chem.* **2008**, *8*, 6, 487-504.
(50) Myers, A. G.; Hammond, M.; Wu, Y. S.; Xiang, J. N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 41, 10006-10007.
(51) Myers, A. G.; Liang, J.; Hammond, M.; Harrington, P. M.; Wu, Y. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1998**, *120*, 21, 5319-5320.

(52) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y. S.; Xiang, J. N. *J. Am. Chem. Soc.* **2002**, *124*, 19, 5380-5401.
(53) Myers, A. G.; Subramanian, V.; Hammond, M. *Tetrahedron Lett.* **1996**, *37*, 5, 587-590.
(54) Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 19, 1809-1812.
(55) Myers, A. G.; Hammond, M.; Wu, Y. S. *Tetrahedron Lett.* **1996**, *37*, 18, 3083-3086.
(56) Kobayashi, S.; Hori, M.; Wang, G. X.; Hirama, M. *J. Org. Chem.* **2006**, *71*, 2, 636-644.
(57) Koyama, Y.; Lear, M. J.; Yoshimura, F.; Ohashi, I.; Mashimo, T.; Hirama, M. *Org. Lett.* **2005**, *7*, 2, 267-270.
(58) Kobayashi, S.; Das, P.; Wang, G. X.; Mita, T.; Lear, M. J.; Hirama, M. *Chem. Lett.* **2002**, 3, 300-301.
(59) Magnus, P.; Carter, R.; Davies, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 18, 6283-6306.
(60) Caddick, S.; Khan, S. *J. Chem. Soc., Chem. Commun.* **1995**, 19, 1971-1972.
(61) Caddick, S.; Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 13, 2355-2358.
(62) Caddick, S.; Khan, S.; Smith, N. J.; Barr, D. M.; Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 28, 5035-5036.
(63) Caddick, S.; Delisser, V. M.; Doyle, V. E.; Khan, S.; Avent, A. G.; Vile, S. *Tetrahedron* **1999**, *55*, 9, 2737-2754.
(64) Caddick, S.; Khan, S.; Frost, L. M.; Smith, N. J.; Cheung, S.; Pairaudeau, G. *Tetrahedron* **2000**, *56*, 45, 8953-8958.
(65) Caddick, S.; Cheung, S.; Doyle, V. E.; Frost, L. M.; Soscia, M. G.; Delisser, V. M.; Williams, M. R. V.; Etheridge, Z. C.; Khan, S.; Hitchcock, P. B.; Pairaudeau, G.; Vile, S. *Tetrahedron* **2001**, *57*, 29, 6295-6303.
(66) Baker, J. R.; Thominet, O.; Britton, H.; Caddick, S. *Org. Lett.* **2007**, *9*, 1, 45-48.
(67) Thominet, O.; Baker, J. R.; Britton, H.; Etheridge, Z. C.; Sosciab, M. G.; Caddick, S. *Org. Biomol. Chem.* **2007**, *5*, 22, 3703-3712.
(68) Toyama, K.; Iguchi, S.; Sakazaki, H.; Oishi, T.; Hirama, M. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 6, 997-1008.
(69) Thominet, O. PhD thesis, University College London, **2007**.
(70) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 15, 3053-3061.
(71) Kim, S. G.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 52, 7627-7630.
(72) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 1, 182-187.
(73) Ando, T.; Ishii, M.; Kajiura, T.; Kameyama, T.; Miwa, K.; Sugiura, Y. *Tetrahedron Lett.* **1998**, *39*, 36, 6495-6498.
(74) Kobayashi, S.; Ashizawa, S.; Takahashi, Y.; Sugiura, Y.; Nagaoka, M.; Lear, M. J.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 45, 11294-11295.
(75) Ji, N.; O'Dowd, H.; Rosen, B. M.; Myers, A. G. *J. Am. Chem. Soc.* **2006**, *128*, 46, 14825-14827.

(76) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 10, 1668-1698.
(77) Furstner, A. *Topics in Catalysis* **1997**, *4*, 3-4, 285-299.
(78) Bunz, U. H. F.; Kloppenburg, L. *Angew. Chem. Int. Ed.* **1999**, *38*, 4, 478-481.
(79) Denmark, S. E. In *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Volumes 1-9* Pergamon, Ed.; Trost, B. M. Fleming, I.: **1991**; Vol. 5, p 751-784.
(80) Davis, D. R.; Garratt, P. J. In *Comprehensive Organic Synthesis - Selectivity, Strategy and Efficiency in Modern Organic Chemistry, Volumes 1-9*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: **1991**; Vol. 2, p 795.
(81) Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 11, 752-757.
(82) Kharasch, M. S.; Mayo, F. R. *J. Am. Chem. Soc.* **1933**, *55*, 6, 2521-2530.
(83) Fossey, J.; Lefort, D.; Sorba, J. *Topics in Current Chemistry* **1993**, *164*99-113.
(84) Parsons, A. F. *Free radical chemistry*; Blackwell Science, **2000**.
(85) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis, Volume 1*, **2001**.
(86) Curran, D. P. *Synthesis-Stuttgart* **1988**, 6, 417-439.
(87) Francisco, C. G.; Gonzalez, C. C.; Herrera, A. J.; Paz, N. R.; Suarez, E. *Tetrahedron Lett.* **2006**, *47*, 51, 9057-9060.
(88) Chatgilialoglu, C. *Chem. Rev.* **1995**, *95*, 5, 1229-1251.
(89) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 8, 1991-2069.
(90) Petragnani, N.; Stefani, H. A. *Tetrahedron* **2005**, *61*, 7, 1613-1679.
(91) Yokoe, H.; Mitsuhashi, C.; Matsuoka, Y.; Yoshimura, T.; Yoshida, M.; Shishido, K. *J. Am. Chem. Soc.*, *133*, 23, 8854-8857.
(92) Bennasar, M. L.; Roca, T.; Garcia-Diaz, D. *J. Org. Chem.* **2007**, *72*, 12, 4562-4565.
(93) Fitzmaurice, R. J.; Ahern, J. M.; Caddick, S. *Org. Biomol. Chem.* **2009**, *7*, 2, 235-237.
(94) Chudasama, V.; Fitzmaurice, R. J.; Ahern, J. M.; Caddick, S. *Chem. Commun.* **2010**, *46*, 1, 133-135.
(95) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat Chem* **2010**, *2*, 7, 592-6.
(96) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 7, 1513-1524.
(97) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 14, 4708-4709.
(98) Duan, X. F.; Shen, G.; Zhang, Z. B. *Synthesis-Stuttgart* **2010**, 15, 2547-2552.
(99) McMurry, J. E.; Krepski, L. R. *J. Org. Chem.* **1976**, *41*, 24, 3929-3930.
(100) Furstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed.* **1996**, *35*, 21, 2442-2469.
(101) Williams, D. R.; Heidebrecht, R. W. *J. Am. Chem. Soc.* **2003**, *125*, 7, 1843-1850.
(102) Nazare, M.; Waldmann, H. *Chem. Eur. J.* **2001**, *7*, 15, 3363-3376.

(103) Lake, K.; Dorrell, M.; Blackman, N.; Khan, M. A.; Nicholas, K. M. *Organometallics* **2003**, *22*, 21, 4260-4264.
(104) Klein, M.; Zabel, M.; Bernhardt, G.; Konig, B. *J. Org. Chem.* **2003**, *68*, 24, 9379-9383.
(105) Kato, N.; Wu, X.; Nishikawa, H.; Nakanishi, K.; Takeshita, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 8, 1047-1053.
(106) Merner, B. L.; Dawe, L. N.; Bodwell, G. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 30, 5487-5491.
(107) Paquette, L. A.; Dressel, J.; Pansegrau, P. D. *Tetrahedron Lett.* **1987**, *28*, 42, 4965-4968.
(108) Nowitzki, O.; Munnich, I.; Stucke, H.; Hoffmann, H. M. R. *Tetrahedron* **1996**, *52*, 36, 11799-11810.
(109) Swindell, C. S.; Fan, W. M. *J. Org. Chem.* **1996**, *61*, 3, 1109-1118.
(110) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 2, 624-633.
(111) Yamato, T.; Hironaka, T.; Saisyo, T.; Manabe, T.; Okuyama, K. *J. Chem. Res.-S* **2003**, 2, 63-65.
(112) Eckhardt, M.; Bruckner, R. *Angew. Chem. Int. Ed.* **1996**, *35*, 10, 1093-1096.
(113) Yet, L. *Chem. Rev.* **2000**, *100*, 8, 2963-3007.
(114) Okuyama, K.; Momoi, Y.; Sugimoto, K.; Okano, K.; Tokuyama, H. *Synlett* **2011**, *1*73-76.
(115) Speicher, A.; Backes, T.; Hesidens, K.; Kolz, J. *Beilstein J. Org. Chem.* **2009**, *5*, 71.
(116) Honda, T.; Namiki, H.; Nagase, H.; Mizutani, H. *Arkivoc* **2003**188-198.
(117) Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 23, 7990-7995.
(118) Eguchi, T.; Arakawa, K.; Terachi, T.; Kakinuma, K. *J. Org. Chem.* **1997**, *62*, 7, 1924-1933.
(119) Eguchi, T.; Ibaragi, K.; Kakinuma, K. *J. Org. Chem.* **1998**, *63*, 8, 2689-2698.
(120) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 5, 354-356.
(121) Su, Z.; Tamm, C. *Helv. Chim. Acta* **1995**, *78*, 5, 1278-1290.
(122) Sheldon, R. A. *Green Chem.* **2008**, *10*, 4, 359-360.
(123) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 3, 154-162.
(124) Hartwig, J. F. *Nature* **2008**, *455*, 7211, 314-322.
(125) Herrerias, C. I.; Yao, X. Q.; Li, Z. P.; Li, C. J. *Chem. Rev.* **2007**, *107*, 6, 2546-2562.
(126) Barton, D. H.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 19, 4076-4083.
(127) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 17, 5900-5902.
(128) Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, B.; Uguen, D.; Groeger, F. A. *Tetrahedron* **1975**, *31*, 15, 1737-1744.
(129) Ahern, J. M., University College London, **2010**.
(130) Chudasama, V. PhD, University College London, **2011**.

(131) Burton, G. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 21, 6472-6477.
(132) Hammerschmidt, F.; Schmidt, S. *Eur. J. Org. Chem.* **2000**, 12, 2239-2245.
(133) Le Strat, F.; Maddaluno, J. *Org. Lett.* **2002**, *4*, 16, 2791-2793.
(134) Etheridge, Z. C. D. Phil, University of Sussex, **2003**.
(135) Hoffmann, H. M. R.; Herden, U.; Breithor, M.; Rhode, O. *Tetrahedron* **1997**, *53*, 25, 8383-8400.
(136) Chemla, F.; Bernard, N.; Ferreira, F.; Normant, J. F. *Eur. J. Org. Chem.* **2001**, 17, 3295-3300.
(137) Devoss, J. J.; Sui, Z. H.; Decamp, D. L.; Salto, R.; Babe, L. M.; Craik, C. S.; Demontellano, P. R. O. *J. Med. Chem.* **1994**, *37*, 5, 665-673.
(138) Wang, H., CN 101225029, **2008**
(139) Crandall, J. K.; Magaha, H. S.; Henderson, M. A.; Widener, R. K.; Tharp, G. A. *J. Org. Chem.* **1982**, *47*, 27, 5372-5380.
(140) Akiyama, H.; Ohshima, K.; Fujimoto, T.; Yamamoto, I.; Iriye, R. *Heteroat. Chem* **2002**, *13*, 3, 216-222.
(141) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J. L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 36, 10926-10940.
(142) Nishimura, Y.; Shiraishi, T.; Yamaguchi, M. *Tetrahedron Lett.* **2008**, *49*, 21, 3492-3495.
(143) Terada, A.; Kishida, Y. *Chem. Pharm. Bull.* **1970**, *18*, 5, 991-996.
(144) Larochel.Rw; Trost, B. M.; Krepski, L. *J. Org. Chem.* **1971**, *36*, 8, 1126-1136
(145) SolladieCavallo, A.; DiepVohuule, A.; Sunjic, V.; Vinkovic, V. *Tetrahedron-Asymmetry* **1996**, *7*, 6, 1783-1788.
(146) Ciaccio, J. A.; Drahus, A. L.; Meis, R. M.; Tingle, C. T.; Smrtka, M.; Geneste, R. *Synthetic Commun.* **2003**, *33*, 12, 2135-2143.
(147) Edwards, D. R.; Du, J.; Crudden, C. M. *Org. Lett.* **2007**, *9*, 12, 2397-2400.
(148) Aliev, A., *unpublished work*, University College London, **2012**
(149) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 23, 5331-5334.
(150) Yarovaya, O. I.; Salomatina, O. V.; Korchagina, D. V.; Polovinka, M. P.; Barkhash, V. A. *Russ. J. Org. Chem.* **2002**, *38*, 11, 1594-1605.
(151) Lee, D. S.; Otte, R. D. *J. Org. Chem.* **2004**, *69*, 10, 3569-3571.