UNIVERSITY OF CAMBRIDGE

An Approach to Catalytic Asymmetric Electrocyclization

This Dissertation is submitted for the degree of Doctor of Philosophy

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Declaration

This dissertation describes the work carried out at the Department of Chemistry, University of Cambridge, between October 2006 and October 2008, and at the Chemistry Research Laboratory, University of Oxford, between November 2008 and December 2009. The dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text. This thesis does not exceed 60,000 words.

Abhishek Kothari

Signed Date:

Acknowledgements

It's indeed a great privilege to express my sincere gratitude to all who made my life enjoyable and fruitful at Cambridge and Oxford.

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Thanks to God.

Abhishek

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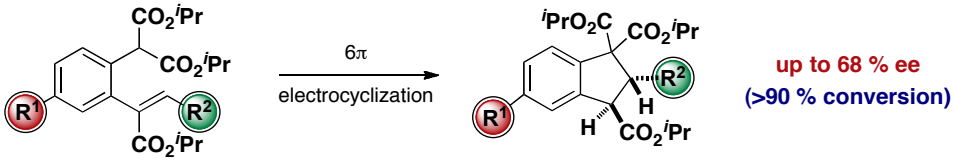
Abstract: An Approach to Catalytic Asymmetric Electrocyclization

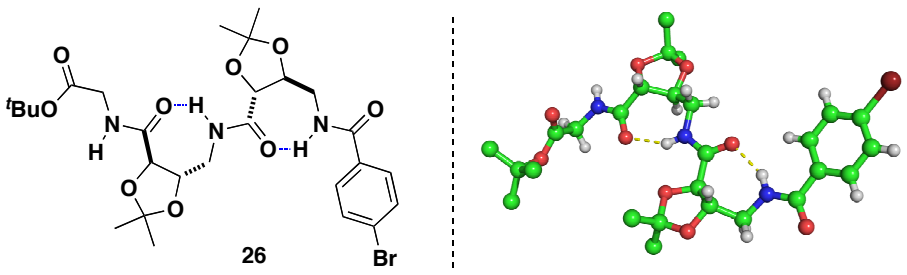
(by Abhishek Kothari)

Chapter 1 outlines the development of a catalytic electrocyclic process and its exploitation in asymmetric synthesis. Since Woodward and Hoffmann delineated a rationale for the mechanism and stereochemistry of these reactions they have become powerful synthetic tools. The aim of this project was to investigate catalytic asymmetric 6π electrocyclizations that will enable the rapid synthesis of highly functionalized molecules.

We have demonstrated that the transient hexatriene precursors for [1,6]-electrocyclization are difficult to synthesize. When possible the central *cis*-alkene prefers to exist in a *trans*-configured geometry, while the free ketone undergoes an essentially irreversible oxo-electrocyclization. However the precursors for [1,5]-electrocyclization could be assembled *via* the Suzuki or Stille reactions. We have established a methodology for [1,5]-electrocyclization using chiral phase-transfer catalysis. These reactions afford the electrocyclized products in excellent yield and diastereoselectivity with enantiomeric excess up to 68 %. These transformations offer a glimpse of the potential of electrocyclic reactions.



In chapter 2, the effects of cyclic backbones on the secondary structures of γ-peptides were evaluated. Two series of abiotic γ-peptides were synthesized with five and six-membered cyclic backbones. We have demonstrated that intra-residue nearest-neighbour hydrogen bonds may be favoured when the flexibility of the ring constraint can permit their formation. These cyclic backbone containing γ-peptides have been shown to populate a bend-ribbon conformation in the solution and solid phase by NMR and X-ray crystallography respectively.



Glossary of terms

The following abbreviations are used within the dissertation:

Ac	acyl
ax	axial
Ar	aryl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
Bz	benzoyl
c	concentration
cal	calorie
CCDC	Cambridge Crystallographic Database Centre
COSY	^{1}H-^{1}H correlation spectroscopy
CSA	camphor sulfonic acid
δ	chemical shift
d	doublet
DCC	dicyclohexylcarbodiimide
dr	diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEPT	distortionless enhancement by proton transfer
DIPEA	diisopropylethylamine
dm^3	cubic decimetre
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
eq	equatorial

Et	ethyl
ether	diethyl ether
FT	Fourier transform
g	gram
GABA	γ-aminobutyric acid
h	hour(s)
HMBC	heteronuclear multiple bond connectivity
HMQC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infra-red (spectroscopy)
J	coupling constant
KHMDS	potassium hexamethyldisilazane
L	milliliter
LCMS	liquid-chromatography tandem mass spectroscopy
LDA	lithium di-*iso*-propylamide
LiHMDS	lithium hexamethyldisilazane
LUMO	lowest occupied molecular orbital
$[M+H]^+$	parent ion bound to a proton
M	molar concentration ($mol.dm^{-3}$)
m	multiplet
m	meta
Me	methyl
mg	milligram
min	minute(s)
mol	mole(s)
m.p.	melting point
Nap	naphthyl

n	normal
NMM	*N*-methyl morpholine
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Nu	nucleophile
o	ortho
p	para
petrol	petroleum ether 40-60
Ph	phenyl
ppm	parts per million
Pr	propyl
q	quartet
R_f	retention factor
rt	room temperature
s	singlet
sept	septet
t	triplet
t	tertiary
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBTU	2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
tert	tertiary
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TOCSY	total correlation spectroscopy
Ts	*p*-toluenesulfonyl
ν	wavenumbers
Z	number of formula units per unit cell

CHAPTER 1: ASYMMETRIC ELECTROCYCLIZATION

1. Introduction

Electrocyclizations, a class of pericyclic reactions, are characterized by the formation of a ring from an open-chain conjugated system, with a σ-bond forming across the ends of a conjugated system (or *vice-versa*).[1]

Electrocyclization reactions can occur thermally or photochemically, *via* two possible modes known as *conrotatory* and *disrotatory*.[2] The simplest examples of thermal electrocyclization are illustrated in figure 1.1.

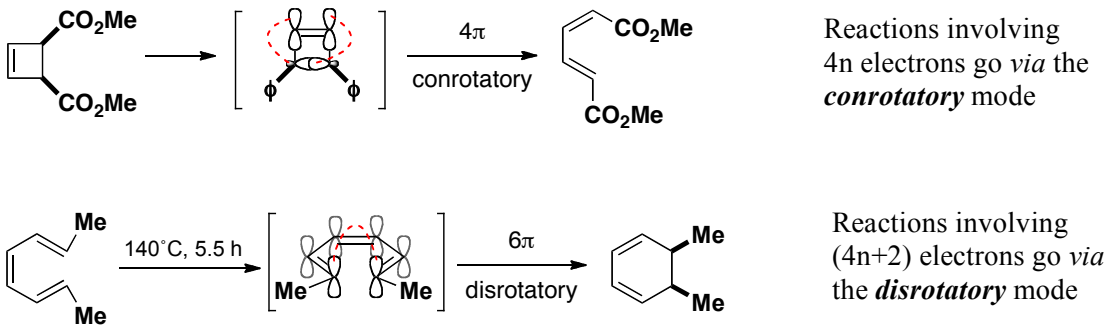


Figure 1.1: Thermal electrocyclization

1.1 Origin of orbital symmetry:

In his landmark synthesis of vitamin B_{12}, Woodward[3] planned to use an intramolecular Michael addition to close a six membered ring and introduce two new stereogenic centers, but no addition product was observed under basic conditions (figure 1.2).

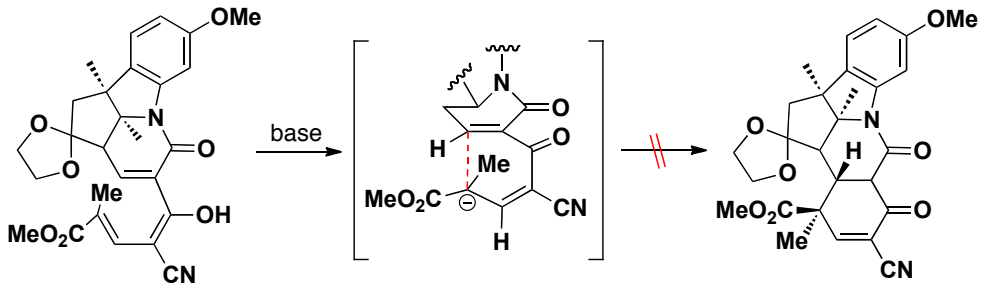


Figure 1.2: Intended Michael addition in vitamin B_{12} synthesis

However, the desired cyclization was found to take place when attempting a melting point of the crystalline enol (figure 1.3). This thermal reaction either on melting or when heated in inert solvent produces the opposite diastereoisomer to the one postulated on steric grounds.

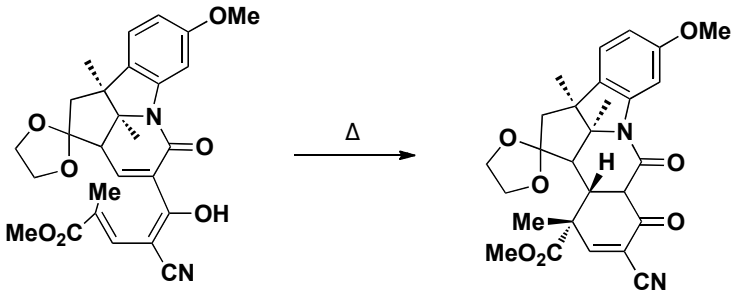


Figure 1.3: Cyclization on melting point determination

Careful examination of the reaction revealed that the olefin geometry of the starting material was isomerized under the reaction conditions, but each olefin isomer stereospecifically gives rise to a distinct diastereoisomer of the product (figure 1.4). However, irradiation of each product produced olefin geometry opposite to that from which it was formed.[3]

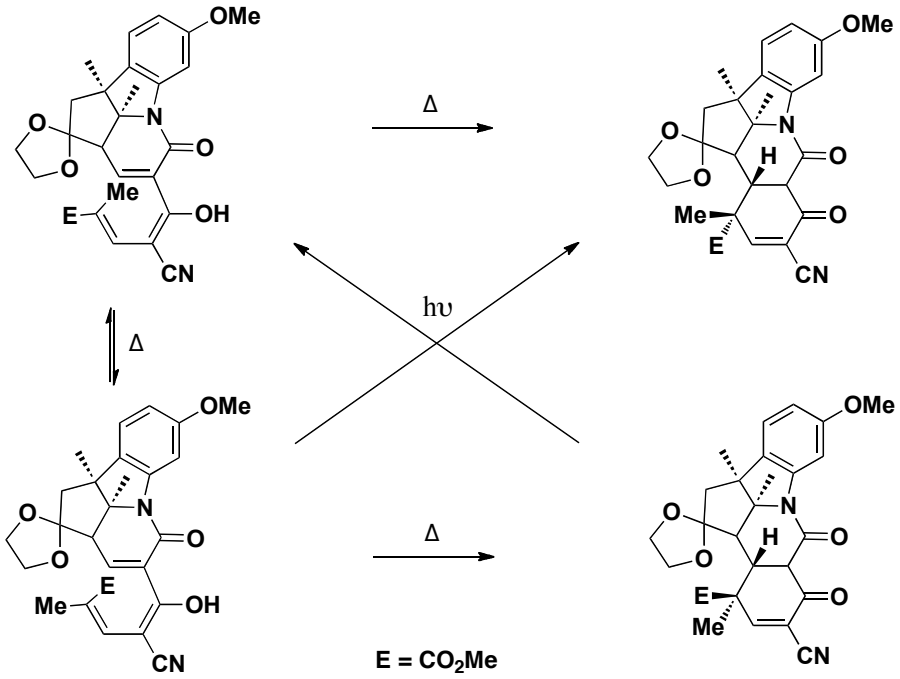


Figure 1.4: Observed electrocyclization in vitamin B_{12} synthesis

Further detailed investigations of these cyclization reactions lead to the development of the Woodward-Hoffmann rules for the conservation of orbital symmetry.[4] This type of

electrocyclization reaction has been proposed to be involved in biosynthesis of a range of natural products including the endiandric acids,[5] vitamin D,[6] (+)-occidentalol[7] and others.[8,9]

Other pericyclic reactions such as cycloadditions and sigmatropic rearrangements and their asymmetric variants have been extensively studied,[10-15] but in contrast, electrocyclizations have been given little attention by the synthetic community. Many electrocyclic reactions are not fully exploited due to the high temperatures often required to initiate these transformations and difficulties associated in assembling precursors.[16] Even more significantly, there are no general methods for the asymmetric catalysis of electrocyclization reaction, resulting in limited opportunities for exerting stereocontrol in these processes.

1.2 Asymmetric Nazarov (4π) cyclization:

The Nazarov cyclization, formation of cyclopentenones from divinyl ketones catalyzed by Lewis or Brønsted acid, is a 4π *conrotatory* electrocyclization.[17] Since the seminal work of Denmark[18-20] demonstrating the high chemoselectivity of this reaction (figure 1.5), the number of studies concerning Nazarov cyclization has grown significantly.[21-27] However, this reaction classically has limited synthetic utility due to the stoichiometric amounts of Lewis or Brønsted acid required for best results and poor regioselectivity of the elimination step to give mixtures of isomers. Recently, several research groups have taken significant steps towards overcoming these limitations.[28-33]

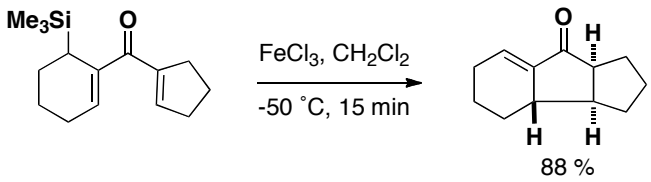


Figure 1.5: Silicon directed Nazarov cyclization

1.2.1 Lewis acid catalysis:

Trauner *et al.*[29,34] have demonstrated the use of scandium triflate pybox complexes as Lewis acid catalysts for an asymmetric Nazarov reaction that proceeds with high levels of enantioselectivity (figure 1.6 A). Concomitant to this report, Frontier *et al.*[35] disclosed exceptionally mild catalytic conditions for the cyclization of polarized enones (figure 1.6 B).

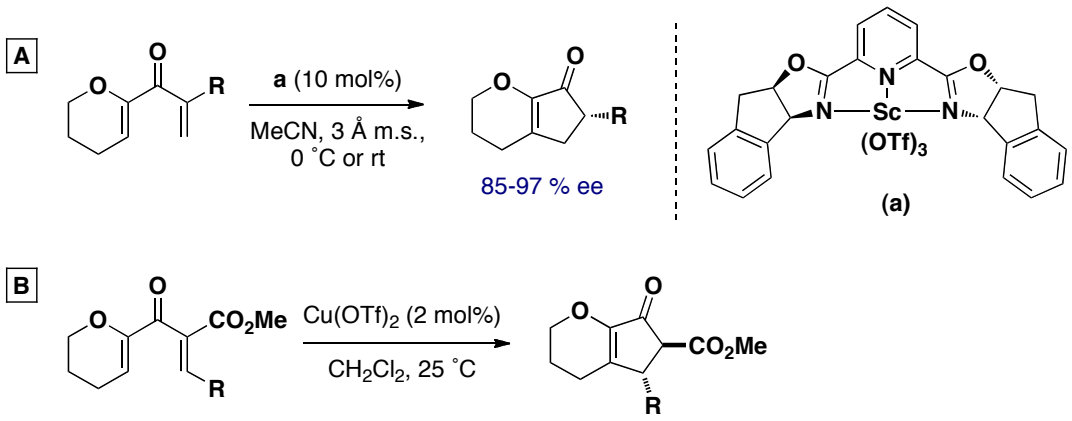


Figure 1.6: Catalytic asymmetric Nazarov cyclization

Similarly, Aggarwal and co-workers[28] have shown that stoichiometric amounts of copper-pybox complexes can be used for related asymmetric Nazarov cyclizations. In this case, the square-based pyramidal geometry of the catalyst-substrate complex pushes the alkene substituents away from the ^{i}Pr groups of the ligand. This steric interaction means that conrotatory cyclization can only occur *via* a clockwise rotation of the interacting π-orbitals (figure 1.7).[28]

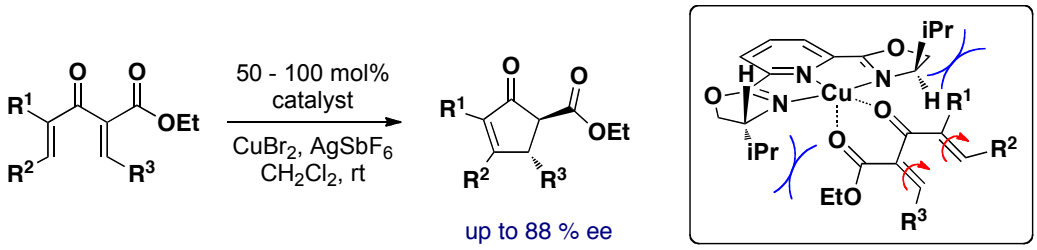


Figure 1.7: Stereochemical model for Nazarov cyclization

Jun-An Ma *et al.*[31] have further developed this reaction to a new catalytic tandem Nazarov cyclization-fluorination for the preparation of functionalized fluoroindanones (figure 1.8). Recently, the use of Ni(II)-complexes as catalysts to achieve asymmetry in these cyclizations has also been reported.[33]

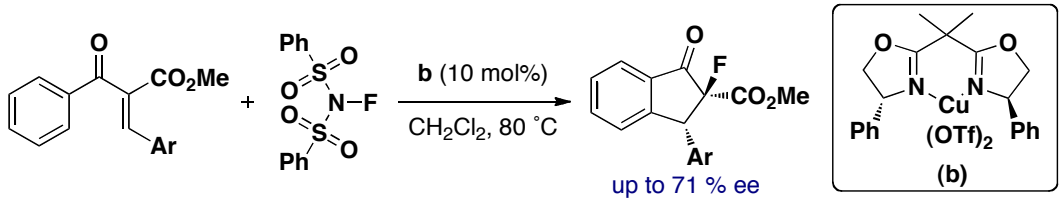


Figure 1.8: Tandem Nazarov cyclization-fluorination

1.2.2 Brønsted acid catalysis:

More recently, Rueping and co-workers[32,36] have developed the first enantioselective Brønsted-acid catalyzed Nazarov cyclization (figure 1.9). While metal-catalyzed reactions provide *trans*-cyclopentenones,[28-29,34-35] these reactions primarily generate *cis*- products. Compared to their metal-catalyzed counterpart these reactions require lower catalyst loadings (2 mol %) and give higher enantioselectivities (86-98 %).

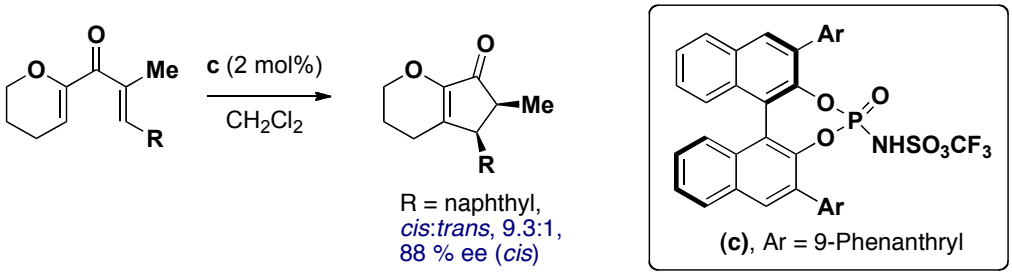


Figure 1.9: Brønsted acid catalyzed Nazarov cyclization

1.3 Asymmetric 6π electrocyclization:

1.3.1 [1,6]-Electrocyclic reactions:

The simplest example of a thermal disrotatory 6π electrocyclization is the interconversion of 1,3,5-hexatriene to 1,3-cyclohexadiene (see figure 1.1). A reaction temperature as high as 150-200 ˚C is often required to trigger these cyclizations, which disfavours the use of this elegant and efficient transformation in the synthesis of complex and delicate molecules. Thus, it is important to investigate systems with a lower energy barrier to hexatriene electrocyclization, as these could both be used under much milder conditions and be amenable to asymmetric catalysis. In this regard, an interesting finding by Magomedov[37,38] shows that the presence of electron-withdrawing groups at C-2 of 3-oxido hexatrienes significantly lowers the activation energy of 6π electrocyclization. This helps the reaction to proceed under mild conditions (figure 1.10).

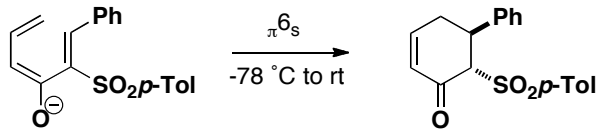


Figure 1.10: Low temperature 6π electrocyclization

Subsequently, Funk *et al.*[39] have reported novel indole annulations, which involved facile 6π electrocyclic ring closure of trienecarbamate (figure 1.11).

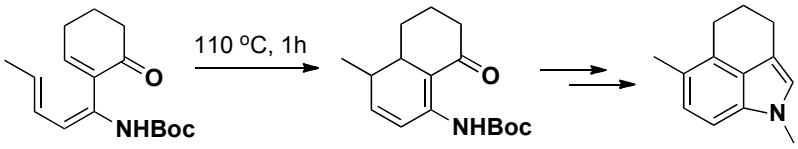


Figure 1.11: Novel indole annulation *via* 6π electrocyclization

A number of groups have conducted theoretical studies on electrocyclization of hexatrienes and shown that substitution at various positions of the 1,3,5-hexatriene can have profound effects on the rate of electrocyclization reactions.[40-43] Fu *et al.*[44] reported that synergistic combinations of electron-withdrawing and donating groups around the triene system significantly lowers the activation energies for the cyclization reaction by 10-12 kcal/mol compared to their unsubstituted counterpart (figure 1.12). This accelerates the rate of reaction up to 2 x 10^8 times, which may allow these reactions to proceed rapidly even at room temperature.

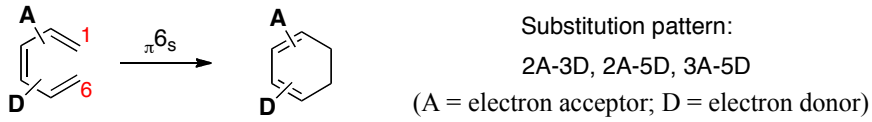


Figure 1.12: Hexatriene electrocyclization reaction with captodative substitution

More recently based on these observations, Bergman and Trauner[45] have reported the catalysis of the 6π electrocyclization of a 2-substituted system by transient binding with Lewis acids, thereby decreasing the energy barrier for electrocyclization. They have demonstrated that the rates of these electrocyclization reactions were increased up to 55-fold in the presence of Me_2AlCl as a Lewis acid (figure 1.13). The classical orbital symmetry effects and torquoselectivity* control the relative stereochemistry of the products in these transformations. These results provide proof-of-principle that catalysis of 6π electrocyclization can be achieved using a substituent-enhancing strategy.[45]

* As per the IUPAC definition, torquoselectivity is "the preference for 'inward' or 'outward' rotation of substituents in conrotatory or disrotatory electrocyclic ring opening reactions", however we apply the term to mean absolute direction of rotation of substituents during an electrocyclic ring-closing reaction.

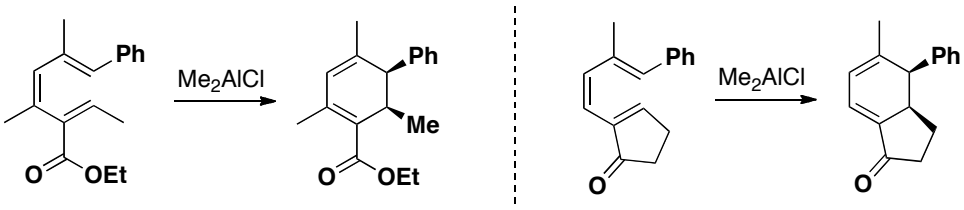


Figure 1.13: Lewis acid-catalyzed 6π electrocyclization

1.3.2 [1,5]-Electrocyclic reactions:

A typical [1,5]-electrocyclic reaction in which a pentadienyl anion undergoes a disrotatory six-electron cyclization to afford a functionalized cyclopentene with two stereocentres is shown below (figure 1.14 A).[46] This system also reacts *via* a suprafacial mode like the hexatriene electrocyclization. Similar to substituent effects in the hexatriene cyclization, the presence and positioning of heteroatoms within the [1,5]-π system is known to have profound effects on the propensity for cyclization.[47-49] Pentadienyl systems with nitrogen substituents cyclize at much lower temperatures compared to their all-carbon counterparts (figure 1.14 B).

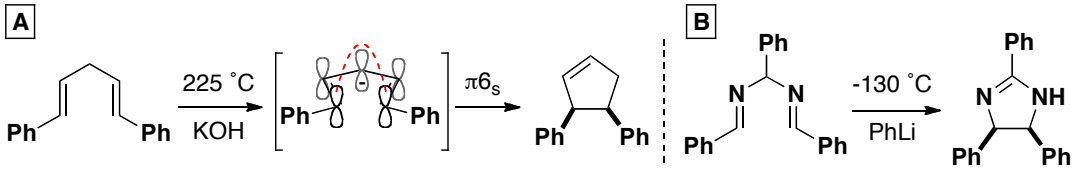


Figure 1.14: [1,5]-electrocyclization

A series of pioneering investigations by Speckamp[50-55] and others[56-59] have demonstrated that 2-aza-pentadienyl anions smoothly undergo an [1,5]-electrocyclic reaction. Speckamp *et al.*[60] have shown that these reactions can be rendered asymmetric with super-stoichiometric amounts of *N*-methylephedrine (figure 1.15). In a proposed model, it is assumed that the azomethine nitrogen hydrogen bonds to the hydroxy group and the tertiary amine coordinates with the enolate oxygen *via* $Li^{\oplus}$. This puts the azomethine and enolate oxygen in a helical conformation, giving rise to the *cis* product (figure 1.15 B). Although this is a powerful and efficient process, it is extremely substrate and catalyst specific.

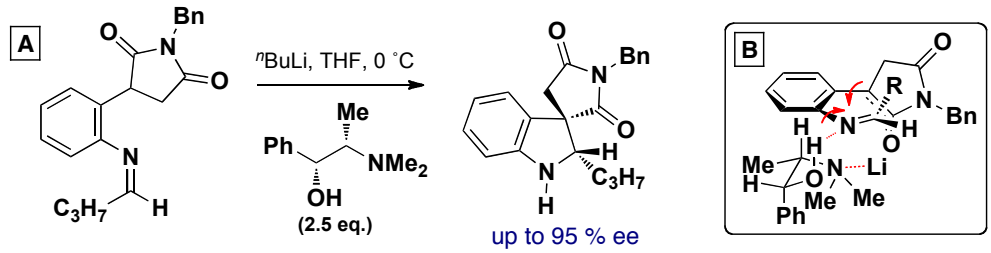


Figure 1.15: A. An asymmetric [1,5]-electrocyclization; B. Transition state

More recently, List *et al.*[61] have developed a catalytic asymmetric method for the synthesis of 2-pyrazolines using a chiral phosphoric acid as the catalyst (figure 1.16). The α,β-unsaturated hydrazones undergo a 6π electrocyclization to afford pyrazolines with good enantioselectivity.

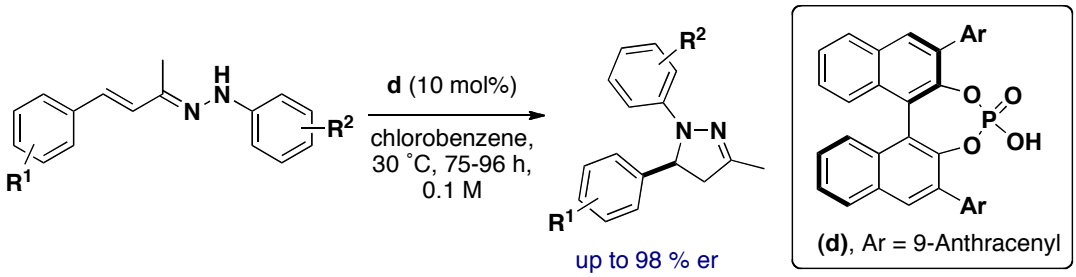


Figure 1.16: Pyrazoline synthesis *via* [1,5]-electrocyclization

All of these electrocyclic reactions described are extremely powerful, but these do not constitute general methods for the asymmetric catalysis of these transformations. There is need to establish a new paradigm for such processes, which will enable the rapid synthesis of sensitive and highly functionalized complex molecules, otherwise difficult by current methodologies.

2. Results and Discussion

2.1 [1,6]-Electrocyclization:

It has been postulated through theoretical studies that the rate of electrocyclization in a 6π system can be accelerated by a synergistic combination of electron-withdrawing and donating groups on a hexatriene (figure 2.1).[44]

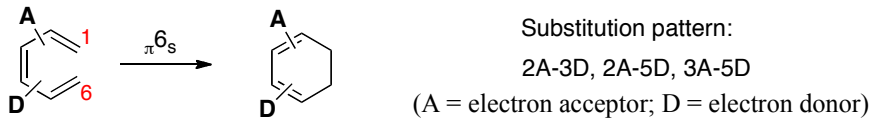


Figure 2.1: Hexatriene electrocyclization reaction with captodative substitution

This tenet has been confirmed through some experimental observations by Magomedov *et al.*[37,38] that demonstrated the presence of an electron-withdrawing group at C-2 and a donating group at C-3 of hexatriene (2A-3D system) significantly lowers the activation energy for 6π electrocyclization, allowing the reaction to proceed under mild conditions (figure 2.2).

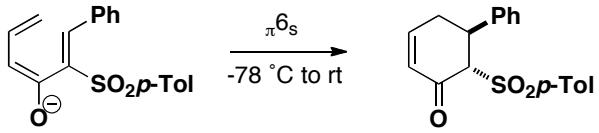


Figure 2.2: Low temperature 6π electrocyclization

With this in mind, we decided to synthesize substrates with suitable substituents, which will undergo accelerated 6π electrocyclization. As the hexatriene with system 2A-3D substituents had already been shown to undergo facile electrocyclization (see figure 2.2), we planned to synthesize the system with 2A-5D substituents (figure 2.3). An alkoxide is shown to function as an electron donor, but OH, OR and NR_2 will all work in the same manner. Similarly, an ester is depicted as an illustrative electron-withdrawing group, but groups such as NO_2, SO_2R and CN will also facilitate the process.

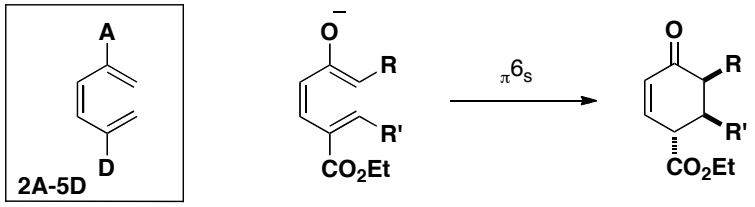


Figure 2.3: 2A-5D hexatriene electrocyclization

It was also anticipated that catalysis might render the process asymmetric. Variation of the nature of the R and R' groups and the double bond geometry of the alkene substituents will have a profound effect on the stereochemistry of the final product. In order to achieve an asymmetric transformation, we must control the facial selectivity of the process, and we envisaged that this could be achieved *via* secondary amine catalysis (figure 2.4).[62]

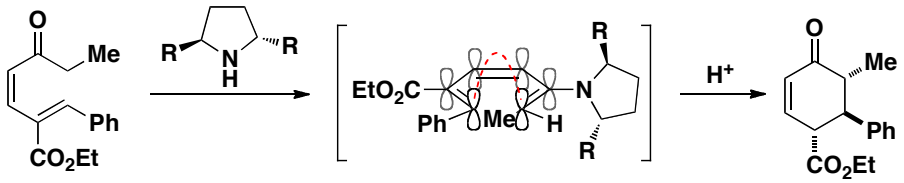
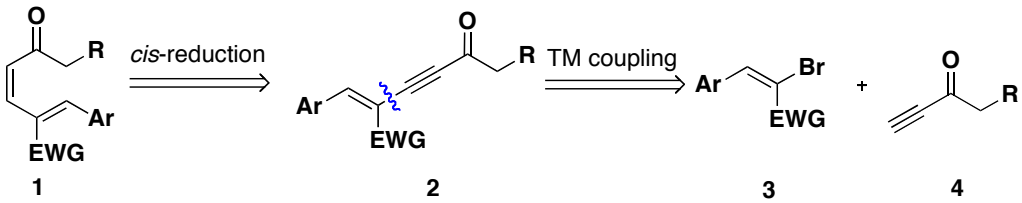


Figure 2.4: 6π electrocyclization using a secondary amine catalyst

In this case, the *in situ* generation of the reactive hexatriene in the presence of the catalyst initiates and accelerates the transformation. The use of a secondary amine catalysis generates an enamine of predictable geometry that also functions as an electron-donating group, allowing formation of the product.

2.1.1 Retrosynthesis of hexatriene precursor:

The plan was to synthesize the hexatriene substituted with an electron-withdrawing group at the 2-position and an electron-donating group at the 5-position. We envisaged that the electron-donating group could effectively be an enolate anion that can be derived from a ketone precursor. The general hexatriene skeleton would be assembled according to the key disconnections in figure 2.5. This route started with the transition metal coupling of halide **3** with alkyne **4** to generate the corresponding alkyne **2**. Subsequent selective *cis*-reduction of the alkyne followed by enolization would afford the desired hexatriene.

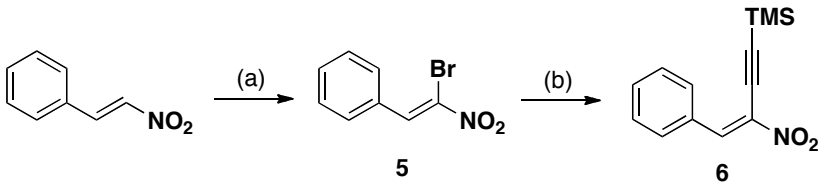


R = Alkyl, Aryl; EWG = NO_2, CO_2R, SO_2R

Figure 2.5: Retrosynthetic analysis for the preparation of 2A-5D hexatriene

2.1.2 Synthesis of hexatriene precursor:

Firstly, the decision was made to synthesize a hexatriene precursor an electron-withdrawing nitro group. Readily available nitrostyrene was subjected to bromination conditions, affording the bromonitrostyrene as needle-shaped crystals. A Sonogashira cross-coupling was then carried out to obtain the corresponding trimethyl silyl acetylene derivative **6** (scheme 2.1). It was found that Et_3N as a base and 1,4-dioxane as a solvent were the reagents of choice for this coupling reaction (table 2.1).



Reagents & conditions	Yield of **6**
$(C_6H_{11})_2NH$, MeCN, 80 ˚C, 3 h	29 %
Et_3N, 1,4-dioxane, rt, 1 h	86 %

Scheme 2.1 & Table 2.1: Reagents & conditions: (a) Br_2, AcOH, K_2CO_3, 0-120 ˚C, 1 h, 60 %; (b) TMS acetylene, $Pd(PPh_3)_2Cl_2$, CuI, base, solvent (see table 2.1)

The bromonitrostyrene **5** was obtained as single regioisomer, the geometry and structure of which was confirmed by X-ray crystallography (figure 2.6).

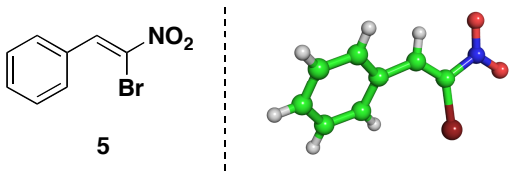
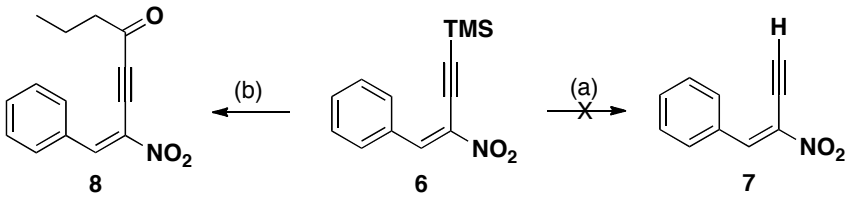


Figure 2.6: X-ray crystal structure of bromonitrostyrene **5**

The plan was then to carry out acylation on the terminal alkyne, but all attempts to desilylate the TMS acetylene **6** were unsuccessful (table 2.2). Based on a literature report,[63] it was found that **6** could be acylated directly in the presence of $AlCl_3$ to afford **8** (scheme 2.2).

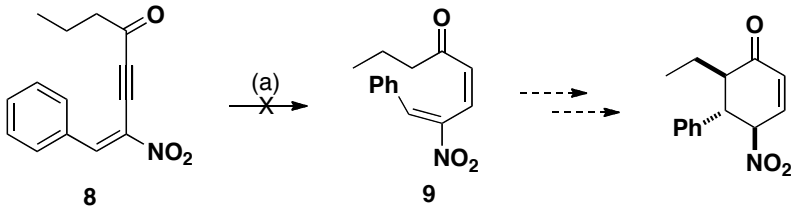


8 6 7

Reagents & conditions	Yield of **7**
TBAF, THF, rt, 1 h	none
NaF, TBAC, Et_2O:H_2O (1:1), rt	none
K_2CO_3, MeOH, 0 ˚C, 19 h	none

Scheme 2.2 & Table 2.2: Reagents & Conditions: (a) see table 2.2; (b) butyryl chloride, $AlCl_3$, 0 ˚C-rt, 1 h, 61 %

With the ynone **8** in hand, it was anticipated that the hexatriene precursor would be formed *via* a *cis*- selective reduction (scheme 2.3). A range of reduction conditions were attempted, but all failed to produce any desired alkene **9** (table 2.3). The susceptibility of the nitro group to undergo reduction under these reaction conditions made it a difficult reaction to perform with appropriate selectivity.

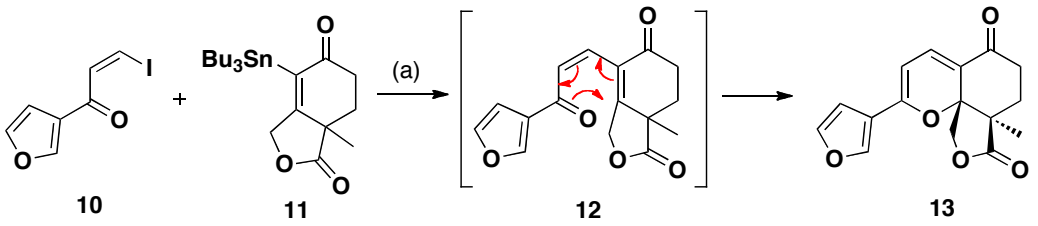


8 9

Reagents & conditions	Yield of **9**
H_2(g), Lindlar catalyst, quinoline, CH_2Cl_2, rt	none
$(KCO_2N)_2$, MeOH, AcOH, Δ	none
$Ni(OAc)_2$, $NaBH_4$, EDA, H_2 (g), EtOH, rt	none
$ZrCp_2(H)Cl$, THF, 0 ˚C	none

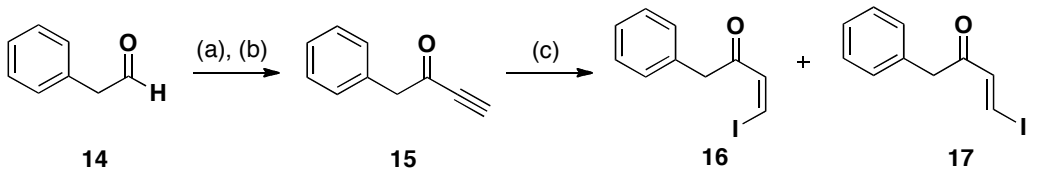
Scheme 2.3 & Table 2.3: Reagents & Conditions: (a) see table 2.3

Having realized the difficulty in reducing the alkyne in the presence of a nitro group, a change of strategy was required. Stoltz *et al.*[64,65] have developed a tandem Stille-oxa-electrocyclization reaction for the synthesis of Saudin (scheme 2.4).



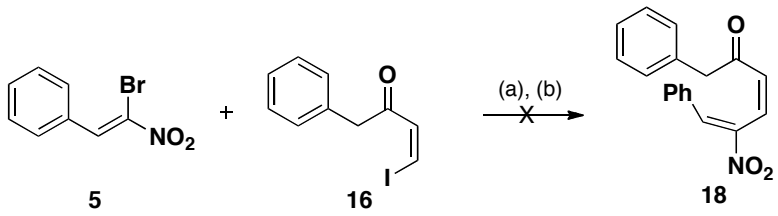
Scheme 2.4: Reagents & Conditions: (a) $Pd(PPh_3)_4$, CuI, DMF, dark, 60 %

In an analogous manner, the decision was made to install the alkene with the *cis* geometry already established through reaction of an alkyne. We envisaged that the production of a *Z*-configured vinyl iodide followed by a subsequent cross coupling could afford the desired hexatriene precursor. To this end, aldehyde **14** was subjected to a Grignard addition, followed by a Dess-Martin oxidation to afford the desired keto-alkyne **15**. The regiospecific hydrohalogenation of **15** was performed using LiI as shown by Lu *et al.*[66] to obtain the corresponding *cis*-iodoketone **16** as the major isomer (scheme 2.5).



Scheme 2.5: Reagents & Conditions: (a) Ethynylmagnesium bromide, THF, 0 ˚C, 30 mins, 92 %; (b) DMP, CH_2Cl_2, 0 ˚C, 1 h, 60 %; (c) LiI, AcOH, MeCN, rt, 2 h, 40 % (*cis*)

Halide **16** could be used as a partner for transition metal coupling. Bromonitrostyrene **5** was subjected to Negishi coupling with the halide **16** in an attempt to generate the hexatriene precursor. After repeated attempts, the cross-coupling failed to afford any desired product **18** (scheme 2.6).

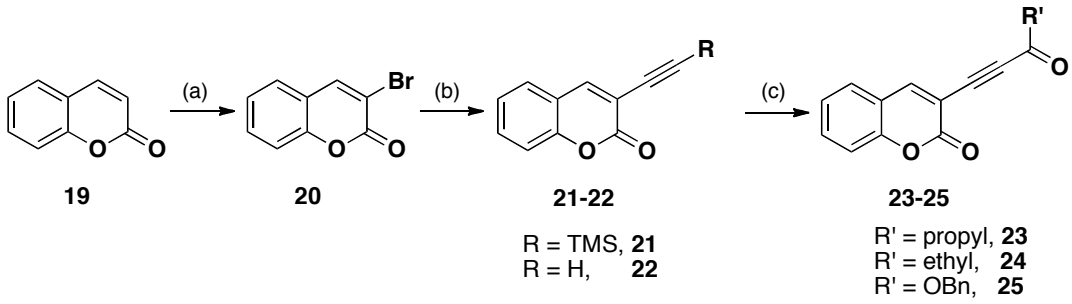


Scheme 2.6: Reagents & Conditions: (a) ^{t}BuLi, THF, -78 ˚C then $ZnBr_2$, THF, -78 - 0 ˚C; (b) **16**, $Pd(PPh_3)_2Cl_2$, DIBAL, THF, 0 ˚C

2.1.3 Using an ester as an electron-withdrawing group:

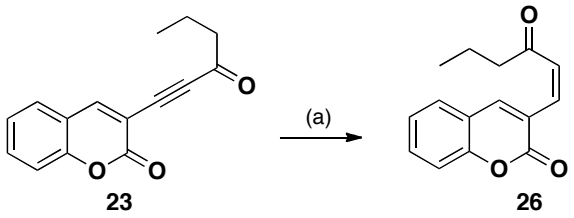
After the disappointing results obtained in generating a hexatriene system with nitro as an electron-withdrawing group, attention was switched to the use of an ester group in its place. A study within the group[67] has revealed that an acyclic enone could undergo an undesired isomerization reaction. With this in mind, our initial investigation focused on an alkene enveloped within a ring to prevent uncontrolled isomerization.

With this objective, the synthesis was started from coumarin in which the ester group is tethered within the ring as a lactone. According to a literature procedure,[68] bromocoumarin **20** was obtained by regioselective bromination of coumarin **19**, and subsequently subjected to Sonogashira coupling to afford alkyne **21**. The keto-alkynes **23-24** were obtained by acylation of **21** with acyl chlorides in acceptable yields (scheme 2.7). The alkyne **25** was not observed under the acylation conditions, instead a desilylated product **22** was obtained.



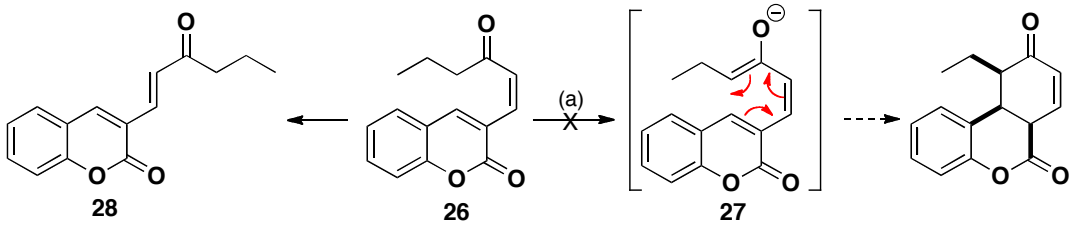
Scheme 2.7: Reagents & Conditions: (a) Oxone®, 2 M HBr, Et_3N, CH_2Cl_2 rt, 15 h, 93 %; (b) TMS acetylene, $Pd(PPh_3)_2Cl_2$, CuI, DMF, 60 ˚C, 3 h, 88 %; (c) alkyl chloride, $AlCl_3$, CH_2Cl_2, 0 ˚C, 1 h, 80-85 %

Once the ynone was in hand, the last step towards generating the hexatriene precursor was to selectively reduce the triple bond to obtain the *cis*-alkene. We were pleased to see that selective reduction of **23** in the presence of the Lindlar catalyst produced the desired alkene **26** in 79 % yield (scheme 2.8).

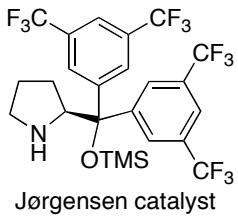


Scheme 2.8: Reagents & Conditions: (a) $H_2(g)$, Lindlar catalyst, CH_2Cl_2, rt, 7 h, 79 %

The ketone **26** was subjected to various conditions that it was anticipated could generate the reactive hexatriene, which would subsequently undergo 6π electrocyclization (table 2.4). However, no products of electrocyclization were observed, and the most common product was the *trans*-configured alkene **28** (scheme 2.9).



Entry	Reagents & conditions	Yield of **27**
1.	i. LDA, THF, -78 ˚C; ii. TBSOTf	none
2.	i. LDA, THF, -78 ˚C; ii. CD_3COOD	none
3.	KHMDS, THF, -78 ˚C	none
4.	Pyrrolidine, MeOH, 0 ˚C	none
5.	L-Proline, MeOH, 0 ˚C	none
6.	Jørgensen's catalyst, CH_2Cl_2, rt, dark	none
7.	DMSO-d_6, µwave	none
8.	DMF, µwave	none



Scheme 2.9 & Table 2.4: Reagents & Conditions: (a) see table 2.4

The alkene **26** was then subjected to iminium catalysis conditions, but failed to produce the desired electrocyclization product (table 2.4, entry 4-6). It was also heated under microwave conditions, however isomerization of *cis*-alkene **26** to *trans*-alkene **28** was the only observed reaction (table 2.4, entry 7-8). The geometry and structure of **28** was further confirmed by X-ray crystallography (figure 2.7).

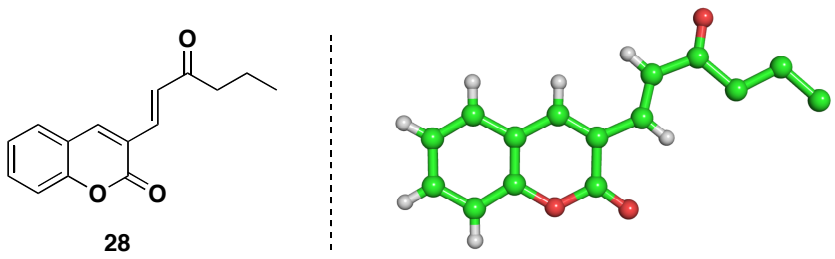
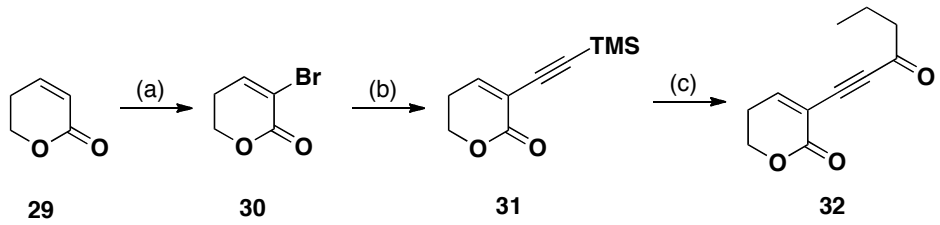


Figure 2.7: X-ray structure of **28**

We reasoned that the failure of **26** to undergo cyclization could be because of the aromatic ring in coumarin. The geometrical requirements of the ring-closing reaction could be preventing the substrate from undergoing 6π electrocyclization.

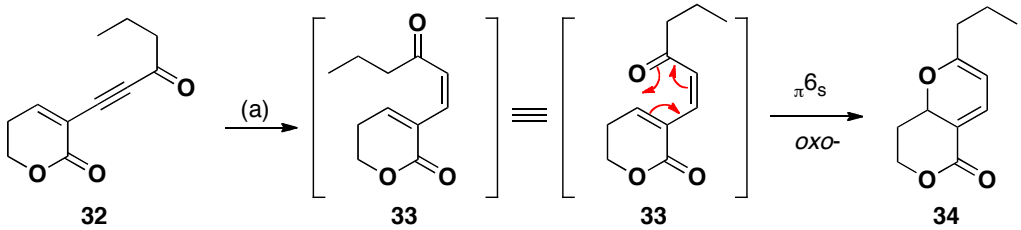
2.1.4 Dihydropyranone derivative:

As demonstrated earlier, we believed that presence of an aromatic ring in **26** could be preventing the cyclization. With this in mind, we decided to prepare a substrate similar to **26**, but without any aromatic ring. This could be achieved by synthesizing the corresponding dihydropyranone derivative **33**. According to a literature procedure,[69] commercially available dihydropyranone **29** was brominated at the 2-position to afford **30** in excellent yield. This subsequently underwent an efficient Sonogashira coupling followed by acylation to afford keto alkyne **32** (scheme 2.10).



Scheme 2.10: Reagents & Conditions: (a) Br_2, Et_3N, CH_2Cl_2, 0 ˚C-rt, 2 h, 94 %; (b) TMS acetylene, $Pd(PPh_3)_2Cl_2$, CuI, 1,4-dioxane, rt, 1 h, 78 %; (c) butyryl chloride, $AlCl_3$, CH_2Cl_2, 0 ˚C, 1 h, 53 %

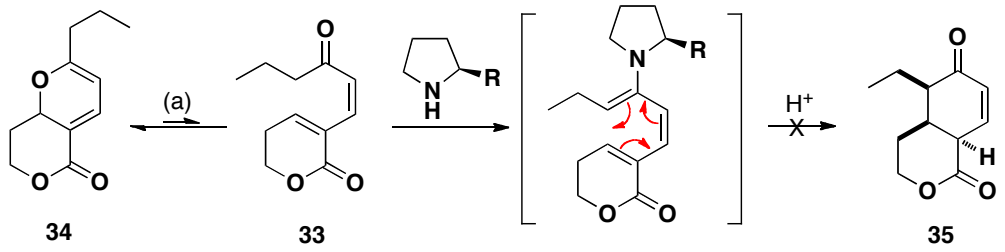
Similar to the coumarin derivative **26**, we envisaged that the stereospecific reduction of alkyne **32** would also furnish *cis*-alkene **33**. Alkyne **32** was subjected to hydrogenation in the presence of the Lindlar catalyst under similar conditions, however we did not observe any desired alkene **33**; instead isolated only the oxo-electrocyclized product **34**. We believe that the alkene **33** was formed *in situ* and underwent a rapid 6π electrocyclization involving the ketone to afford **34** (scheme 2.11).



Scheme 2.11: Reagents & Conditions: (a) H_2(g), Lindlar catalyst, CH_2Cl_2, rt, 1 h, 61 %

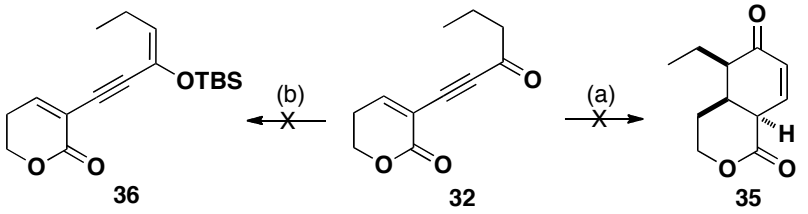
All electrocyclization reactions are reversible, and hence we anticipated that the *oxo*-electrocyclized product **34** could be in equilibrium with its open-chain form. Accordingly, we treated **34** with Jørgensen's catalyst, hoping that the open-chain product **33**, even if only

present in trace amounts of equilibrium, would undergo the desired hexatriene cyclization to afford **35**. However, we did not observe any formation of **35**, but recovered back all the SM **34** (scheme 2.12).



Scheme 2.12: Reagents & Conditions: (a) Jørgensen catalyst, CH_2Cl_2, 0 ˚C

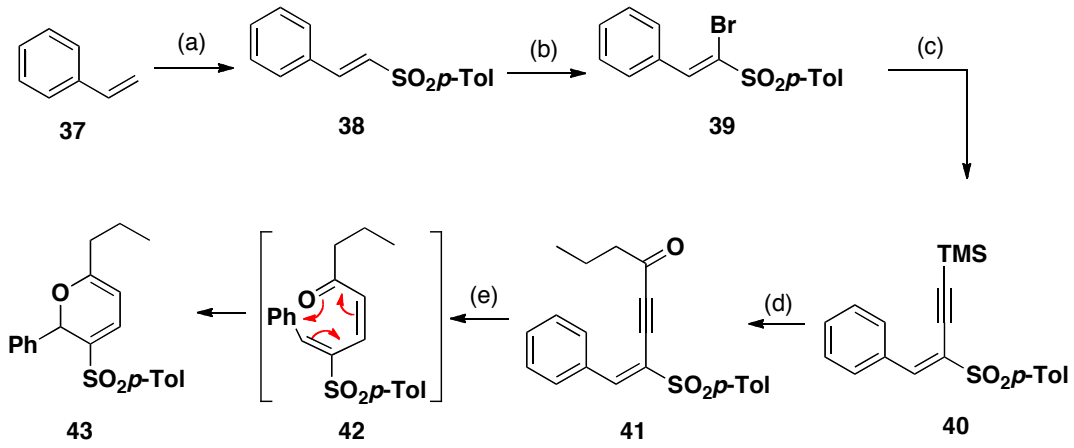
We also tried to generate silyl enol ether **36** from **32** and to subject **32** to reduction conditions in the presence of Jørgensen's catalyst, but without any success (scheme 2.13).



Scheme 2.13: Reagents & Conditions: (a) Jørgensen cat., Lindlar cat., $H_2(g)$, CH_2Cl_2, rt; (b) ^{n}BuLi, THF, -78 ˚C then TBSOTf, -78 ˚C

2.1.5 Sulfone derivative:

After failing to obtain any cyclohexene product with a nitro or an ester as an electron-withdrawing group, we decided to investigate the utility of a sulfone group. Similarly to coumarin **23** and dihydropyranone **32**, we synthesized alkyne **41** by a series of reliable steps. According to a literature procedure,[70] the vinyl sulfone **38** was prepared from commercially available styrene **37**, which then underwent bromination to furnish **39**. Sonogashira coupling of the halide **39** followed by acylation produced the ynone **41**. When **41** was subjected to reduction conditions in the presence of the Lindlar catalyst, we observed the pyran-derived product **43**; we rationalized this was formed through an electrocyclic 6π process (scheme 2.14).



Scheme 2.14: Reagents & Conditions: (a) NaI, CAN, MeCN, rt, 45 mins, 93 %; (b) Br_2, AcOH, K_2CO_3, Δ, 1 h, 95 %; (c) TMS acetylene, $Pd(PPh_3)_2Cl_2$, CuI, DMF, 50 ˚C, 5 h, 73 %; (d) butyryl chloride, $AlCl_3$, CH_2Cl_2, 0 ˚C, 1 h, 90 %; (e) Lindlar cat., quinoline, $H_2(g)$, CH_2Cl_2, 0 ˚C, 62 %

These findings confirmed that a ketone of this form could not be used as an intermediate en-route to a hexatriene, as it undergoes essentially an irreversible oxo-electrocylization. Moreover, the tendency of the *cis*-alkene to undergo isomerization to the unwanted *trans*-alkene also needed to be addressed.

2.1.6 Strategy revisited:

With the evident problems of alkene isomerization and oxo-electrocyclization, we decided to revisit our original strategy (figure 2.8). In an initial investigation our aims were to: (i) generate the alkene within a ring to prevent isomerization; (ii) avoid the use of a free ketone to preclude any oxo-electrocyclization.

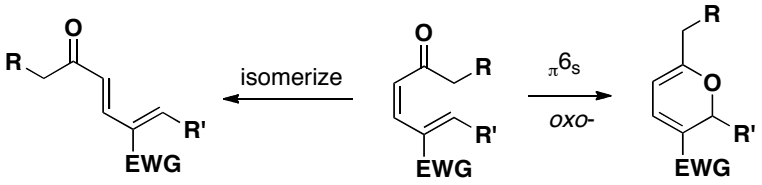


Figure 2.8: problems in hexatriene cyclization

Firstly, it was decided to place the alkene inside a ring and leave the ketone portion intact. A simple way to achieve this was to install the alkene component as an aryl ring. This was embodied in compound **44**, which could be assembled *via* a late stage Suzuki coupling of the

bromide **45** and the corresponding boronate **46** (figure 2.9). The bromide **45** could be prepared by Grignard addition to the aldehyde, followed by oxidation.

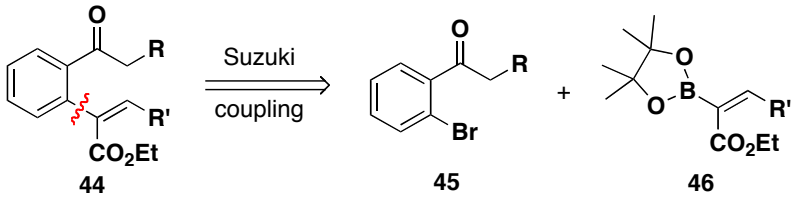
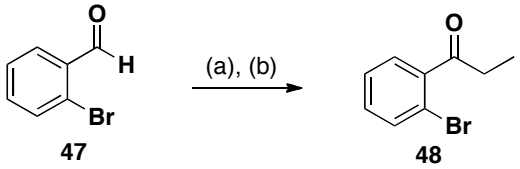


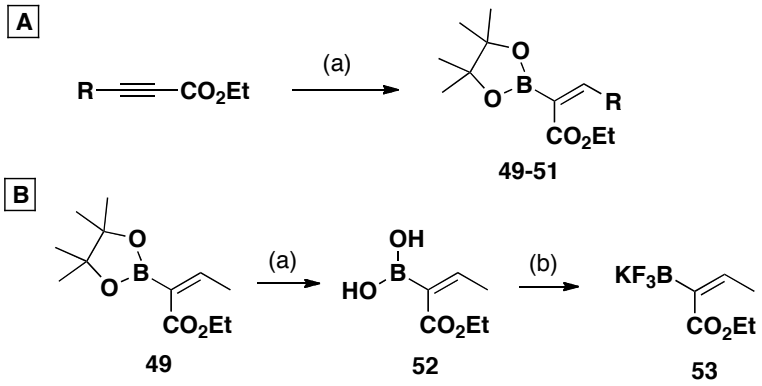
Figure 2.9: Retrosynthetic analysis

In a forward sense, the bromoketone **48** was synthesized according to a literature procedure[71] from the corresponding aldehyde **47**. Addition of ethylmagnesium bromide to the aldehyde **47**, followed by Swern oxidation produced the desired ketone **48** in 68 % over two steps (scheme 2.15).



Scheme 2.15: Reagents & Conditions: (a) EtMgBr, THF, 0 ˚C, 75 %; (b) DMSO, TFAA, Et_3N, CH_2Cl_2, -78 ˚C-rt, 1 h, 90 %

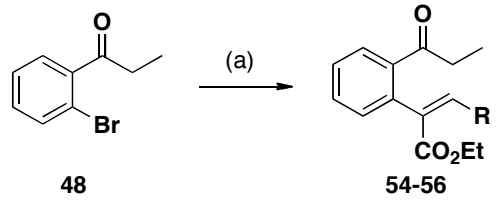
The boronate esters **49-51** were obtained by hydroboration of the alkyne using Stryker's reagent, a very reliable method demonstrated by Lipshutz and co-workers[72] (scheme 2.16 A). The alkyne underwent chemo- and stereoselective 1,2-addition of copper hydride followed by transmetallation with pinacolborane to generate the desired boronate with retention of stereochemistry. The boronate ester **49** could subsequently be converted into the boronic acid **52** and trifluoro borate salt **53**, which could also be used as coupling partners for the Suzuki reaction (scheme 2.16 B).



R	Product, yield
CH_3	**49**, 77 %
C_2H_5	**50**, 73 %
Ph	**51**, 96 %

Scheme 2.16 & Table 2.5: Reagents & Conditions: A. (a) $[(PPh_3)CuH]_6$, PPh_3, pinacolborane, THF, 0 ˚C, 10 min; B (a) $NaIO_4$, NH_4OAc, acetone:H_2O, rt, 15 mins, 91 %; (b) KHF_2, MeOH:H_2O, rt, 4 h, 55%

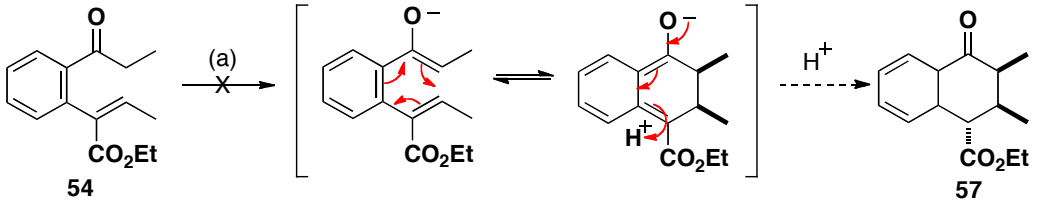
Consequently, bromoketone **48** was subjected to optimized Suzuki conditions with boronate esters or salts in aqueous solvent to obtain the desired coupling products **54-56**. The ethyl or methyl boronates readily underwent the desired coupling, but the phenyl boronate **51** failed to generate any product under the reaction conditions (scheme 2.17). With **54** and **55** in hand, we began to investigate their propensity to undergo in 6π electrocyclization.



Boronate	R	Product, yield
53	CH_3	**54**, 53 %
50	C_2H_5	**55**, 57 %
51	Ph	**56**, none

Scheme 2.17 & Table 2.6: Reagents & Conditions: (a) boronate, $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$, Et_3N, THF:H_2O, Δ

The hexatriene precursor **54** was subjected to a variety of conditions in an attempt to initiate the desired electrocyclization (scheme 2.18, table 2.7). In all the cases the SM was recovered and no electrocyclized product **57** was observed. The ketone **54** was subjected to heating at 100 ˚C and iminium catalysis using the Jørgensen catalyst, but without any success. We rationalized that in order to undergo electrocyclization the aromatic ring has to dearomatize, and this could be raising the kinetic barrier to electrocyclization significantly.

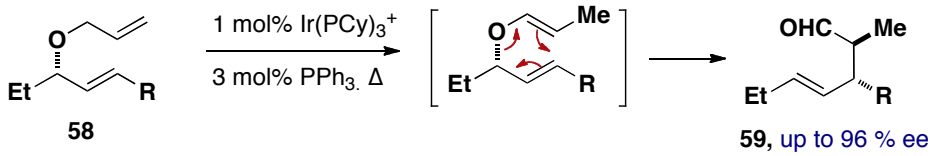


Reagents & Conditions	Yield of **57**
LDA, THF, -78 ˚C	none
Cs_2CO_3, toluene, rt, o/n	none
100 ˚C, o/n	none
Jørgensen cat., CH_2Cl_2, rt	none

Scheme 2.18 & Table 2.7: Reagents & Conditions: (a) see table 2.7

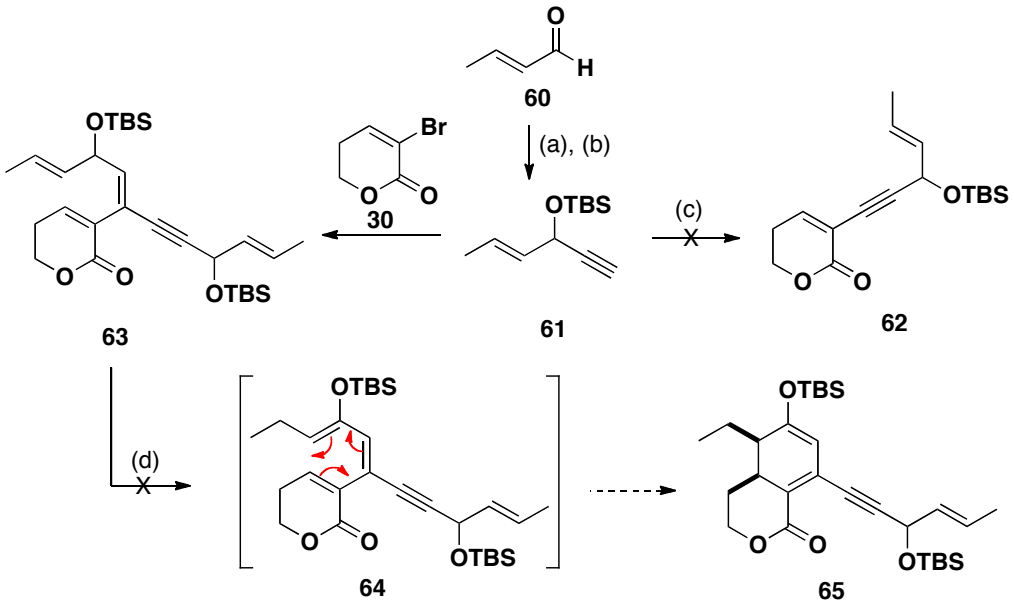
2.1.7 Isomerization approach:

After the failure of **54** to undergo any cyclization, we decided to pursue an approach shown by Nelson and co-workers.[73] In this work, he elegantly demonstrated an iridinium-catalyzed allyl isomerization for asymmetric Claisen rearrangements. When **58** was subjected to isomerization-Claisen rearrangement reaction conditions, it delivered the rearrangement product **59** in enantiomeric purity of up to 96 % (scheme 2.19).



Scheme 2.19: Isomerization-Claisen rearrangement

We envisioned that we could use a similar strategy to synthesize a hexatriene as a transient reactive intermediate. With this in mind, **61** was prepared in two steps from the commercially available aldehyde **60**.[74,75] When **61** was reacted with **30** under Sonogashira coupling conditions in an attempt to form **62**; we were surprised to see the formation of product **63** in 30 % yield (scheme 2.20). Nonetheless, the undesired product **63** was subjected to isomerization conditions similar to used by Nelson and co-workers,[73] but it failed to generate any desired transient hexatriene **64** that would subsequently undergo 6π electrocyclization (scheme 2.20).



Scheme 2.20: Reagents & Conditions: (a) ethynylmagnesium bromide, THF, -78 ˚C, 2 h, 95 %; (b) imidazole, TBSCl, CH_2Cl_2, rt, 2h, 76 %; (c) **30**, $Pd(PPh_3)_2Cl_2$, CuI, 1,4-dioxane, rt; (d) $Ir(PCy)_3^+$, $NaBPh_4$, PPh_3, CH_2Cl_2:acetone (25:1), Δ

We believe the formation of **63** could be due to a Sonogashira-hydropalladation-Sonogashira sequence of reactions. Initially the halide **30** undergoes coupling with alkyne **61** to afford the Sonogashira product **62**. The coupled product **62** subsequently undergoes oxygen-directed hydropalladation followed by another cycle of the Sonogashira coupling to produce **63** (figure 2.10).

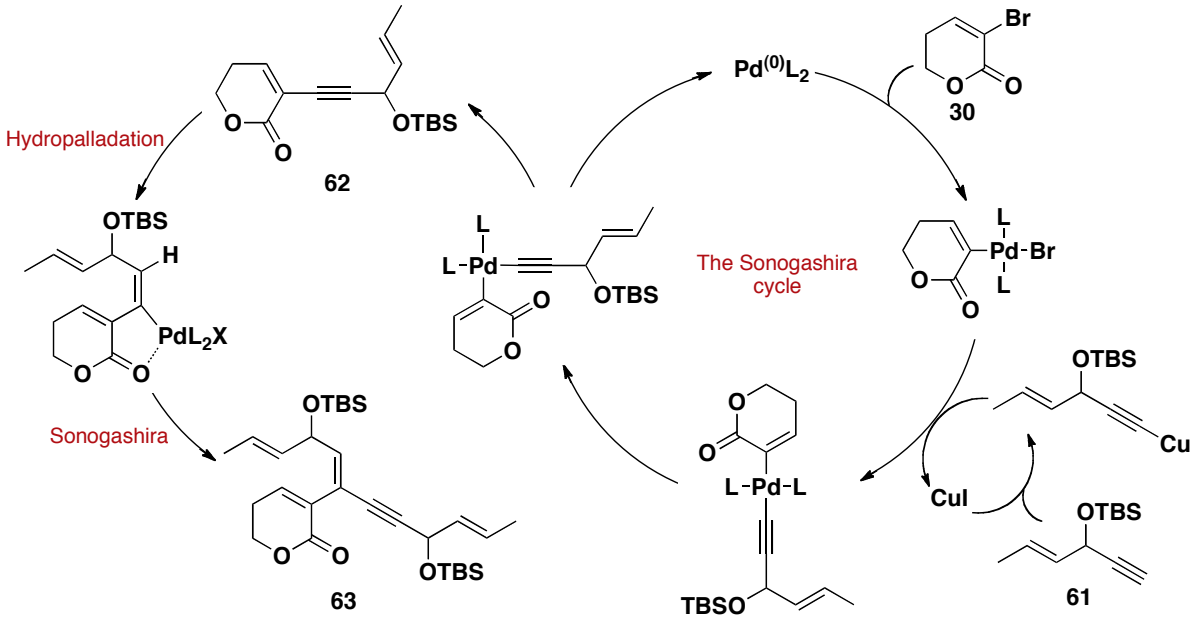


Figure 2.10: The Sonogashira-hydropalladation-Sonogashira cycle

At this stage it was clear that a viable system required: (i) a central double bond in a cyclohexene ring instead of an aromatic ring, and (ii) a transient enolate equivalent that was not derived from a free ketone. The approach was to use an isomerization strategy to generate the required evanescent hexatriene as demonstrated by Nelson *et al.* (see scheme 2.19).[73] With this in mind, we planned to synthesize a substrate similar to **66** that could undergo isomerization at the allylic position to generate the required hexatriene. We hoped to assemble **66** by Grignard addition to aldehyde **67**, which in turn could be generated *via* transition metal coupling from the corresponding aldehyde **68** and boronate **69** (figure 2.11).

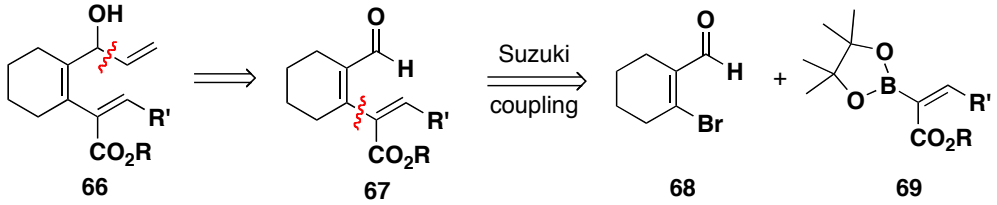
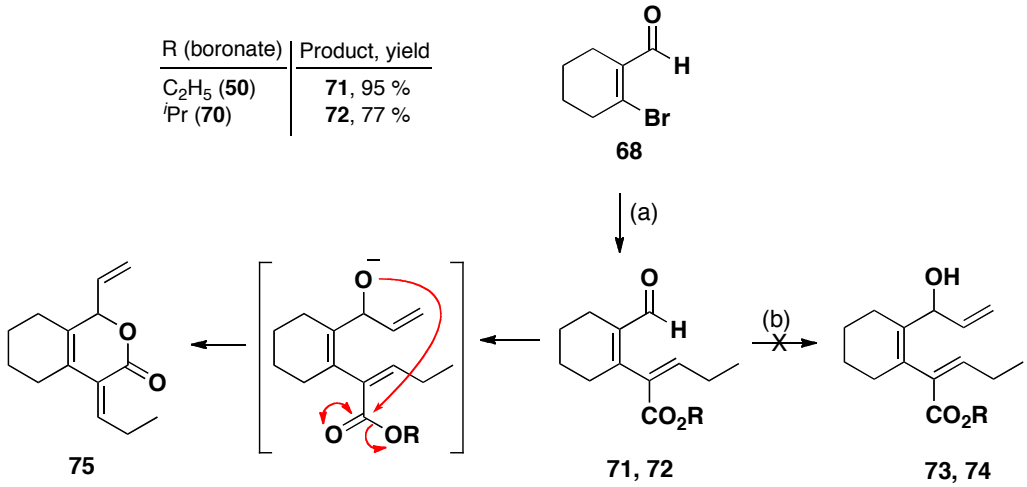


Figure 2.11: Retrosynthetic analysis

As described earlier, the alkynes undergo copper mediated *cis*-hydroboration to produce the boronate esters (see scheme 2.16). Subjecting these boronates **50** and **70** to the Suzuki reaction conditions with bromoaldehyde **68** generated the desired coupling products **71-72** in good yields (scheme 2.21).



Scheme 2.21 & Table 2.8: Reagents & Conditions: (a) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, SPhos, K_3PO_4, toluene:H_2O, 90 ˚C, 2 h; (b) Vinylmagnesium bromide, THF, -20 ˚C, 2 h, 83 %

We hoped to obtain the allyl alcohols **73-74** by vinyl magnesium bromide addition to the aldehydes **71-72**, which would subsequently be used to generate the transient hexatriene by the previously discussed isomerization approach. However, under the reaction conditions, the addition of the vinyl anion equivalent to the aldehyde generated an alkoxide functional group that intramolecularly trapped onto the ester to give lactone **75** (see scheme 2.21).

2.1.8 Conclusions:

The [1,6]- electrocyclization proved to be a challenging transformation to perform. The difficulty in synthesizing the hexatriene precursors makes it an intricate process. When possible (as in **28**) the central *cis*-alkene prefers to exist in *trans*-configured geometry, which makes it impossible to undergo any electrocyclization.

Equally, under the reaction conditions the free ketones (**34** and **43**) underwent an essentially irreversible oxo-electrocyclization, but failed to facilitate any carbon-cyclized product. From these observations, it was concluded that (i) the central alkene should always be inside a ring to prevent isomerization; (ii) the use of a free ketone must be avoided to preclude any oxo-electrocyclization.

The strategy was revised to transiently generate hexatriene as a reactive intermediate *via* an isomerization approach, elegantly demonstrated by Nelson.[73] In this case, we observed the formation of lactone **75** by vinyl nucleophile addition to the corresponding aldehydes **71** and **72**. We require a less basic source of vinyl anion, or a bulkier ester such as *tert*-butyl, to prevent any lactonization.

2.2 [1,5]-electrocyclization:

As mentioned earlier, in the archetypal [1,5]-electrocyclic reaction, a pentadienyl anion undergoes a disrotatory six-electron cyclization to afford a functionalized cyclopentene with two stereocentres (figure 2.12 A).[46] Like the hexatriene electrocyclization, this isoelectronic anionic system reacts suprafacially. It has been shown that the presence of a heteroatom inside this system has a profound effect on the rate of electrocyclization (figure 2.12 B).[47-49]

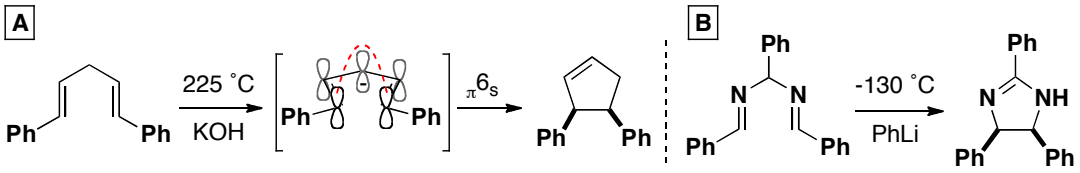


Figure 2.12: [1,5]-electrocyclization

A pioneering work by Speckamp and co-workers[60] has demonstrated a smooth asymmetric [1,5]-electrocyclization of a 2-aza-pentadienyl anion (figure 2.13). Although this is a powerful and efficient transformation, it requires super-stoichiometric amounts of *N*-methylephedrine as a catalyst and is extremely substrate and catalyst specific.

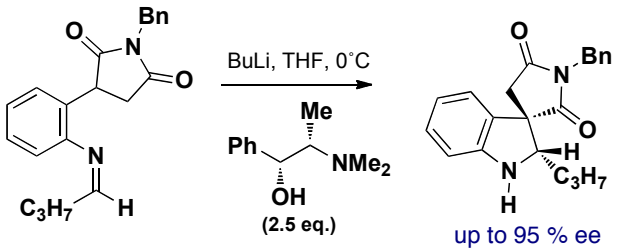


Figure 2.13: An asymmetric [1,5]-electrocyclization

With this in mind, we planned to synthesize substrates that would undergo [1,5]-electrocyclization. We knew that a substrate of the type **76** would be difficult to undergo electrocyclization. Similarly, as illustrated earlier for the hexatriene system, we envisaged that introduction of an electron-withdrawing group at the 2-position of **76** would enhance the rate of cyclization (see figure 2.2). To investigate this hypothesis we hoped to synthesize substrates similar to **77** and **78** (figure 2.14).

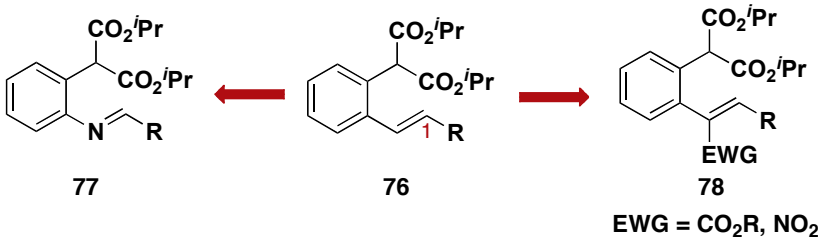


Figure 2.14: [1,5]-electrocyclic substrates

We rationalized that in order to control the absolute direction of rotation of the orbitals in the ring-closing process of these systems, we needed to block one π-face of the delocalized anion and rely on the stereospecificity of the electrocyclization to direct the stereochemical outcome (figure 2.15). One way to accomplish this would be to exploit tight-ion pairing in an organic solvent, using a chiral counterion to select one of the two faces of a pentadienyl anion or equivalent, and hence influence the enantioselectivity of the cyclization reaction.

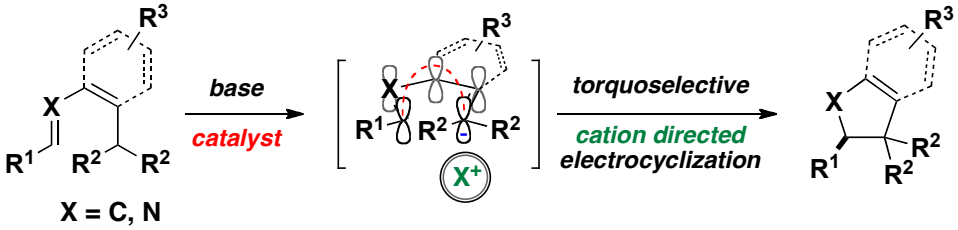


Figure 2.15: Strategy for asymmetric 6π electrocyclization

2.2.1 Retrosynthesis:

In order to test the feasibility of the electrocyclic process, we decided to synthesize substrate similar to **79**. We envisaged that **79** could be assembled *via* the Suzuki coupling of malonate **80** with boronate **69** as the other coupling partner (figure 2.16). The malonate **80** could be derived from the commercially available 2-iodophenylacetic acid.[76] As exemplified earlier, we hoped to obtain the boronate **69** by regiospecific hydroboration of the alkyne (see scheme 2.16).

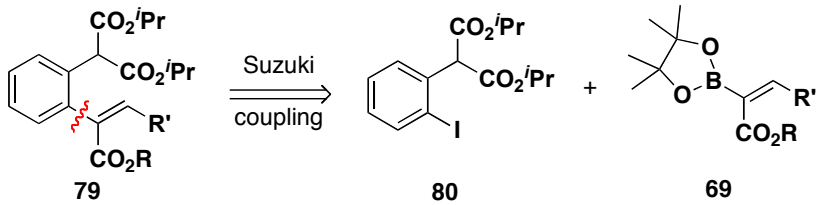
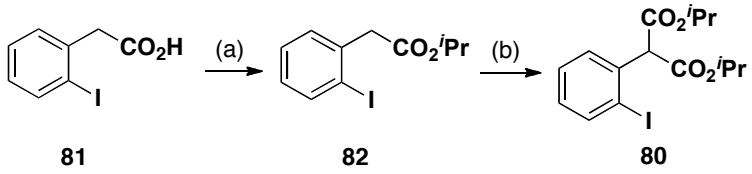


Figure 2.16: Retrosynthetic analysis

2.2.2 Synthesis of malonate:

The phenylmalonate **80** was formed from 2-iodophenyl acetic acid **81** in two high-yielding steps. The acid **81** underwent an esterification to generate the corresponding isopropyl ester **82** in good yield. This ester **82** was subsequently treated with a base and isopropyl chloroformate in order to obtain the malonate **80** (scheme 2.22). We found that NaH was a poor choice of base for this transformation, however switching to a stronger base LiHMDS gave complete conversion (table 2.9).

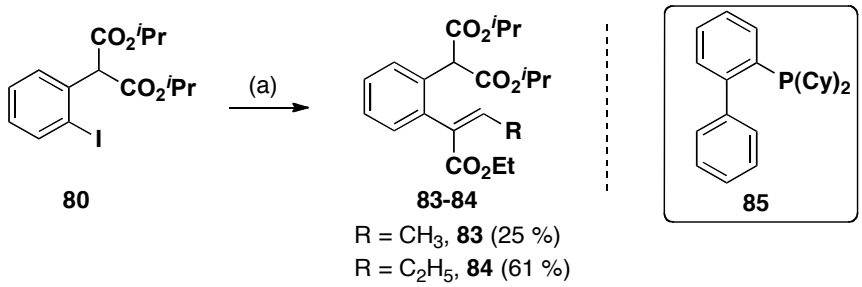


Base	Yield of **80**
NaH	none
KHMDS	50 %
LiHMDS	91 %

Scheme 2.22 and Table 2.9: Reagents & Conditions: (a) Conc. H_2SO_4, ^{i}PrOH, 90 ˚C, 3 h, 84 %; (b) base, THF, -78 ˚C then ^{i}PrOCOCl (see table 2.6)

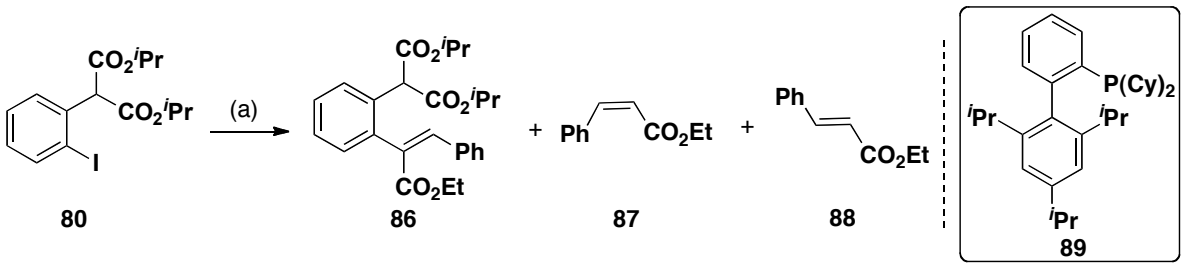
2.2.3 Suzuki coupling:

Once the malonate **80** was in hand, the next step was to subject it to the transition metal-catalyzed coupling reaction to afford the desired adducts. The ease of preparation of reactants, the mild reaction conditions and the non-toxic byproducts favored performing a Suzuki reaction on malonate **80** with boronates **49-51** as the coupling partners. The boronates **49-51** were obtained by hydroboration of the corresponding alkynes using the Stryker reagent (see scheme 2.16).[72] Some optimization of the cross-coupling reaction revealed that palladium(II) acetate and cyclohexyl JohnPhos **85** gave the best yields for alkyl boronates **49** and **50** (scheme 2.23).



Scheme 2.23: Reagents & Conditions: (a) $Pd(OAc)_2$, **85**, Et_3N, dioxane:H_2O, 60 ˚C,

Contrary to this, under similar reaction conditions phenyl boronate **51** failed to afford desired Suzuki adduct **86** (scheme 2.24); instead the deboronation products **87** and **88** were obtained. We reasoned that this could be due to the failure of the boronate to undergo transmetallation. The function of the base in the Suzuki cross-coupling reaction is to activate the boron by forming an 'ate' complex, thereby enhancing the polarization of the organic ligand, and accelerating the transmetallation.[77] We thought, in this particular case, the base triethylamine was incompatible with the functional groups present in the reactants. Literature reports[78,79] suggest that fluoride, due to its weak basicity and poor nucleophilicity, could be of particular value in these coupling reactions. The high affinity of fluoride ion for boron, and the considerable stability of the fluoroborate ion accelerate the transmetallation step. For this study we chose cesium fluoride and were pleased to observe the coupling adduct **86** (scheme 2.24) in moderate yield. The yield increased slightly to 50 % when phosphine ligand **85** was replaced by XPhos **89** (table 2.10). We performed a series of experiments and found that the palladium(II) acetate was the optimum source of 'Pd' for this reaction.

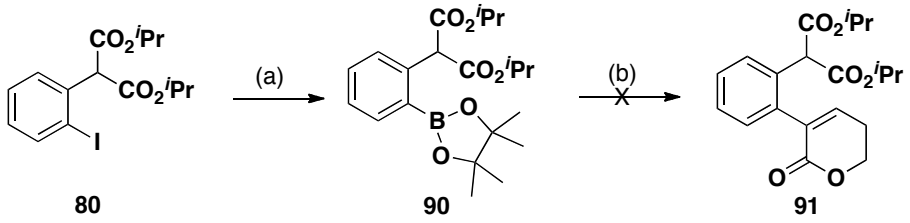


80 86 87 88 89

Entry	Reagents & Conditions	Yield of **86**
1.	$Pd(OAc)_2$, 85, Et_3N, dioxane:H_2O, Δ	none
2.	$Pd(OAc)_2$, 85, Et_3N, ^{n}PrOH:H_2O, Δ	20 %
3.	$Pd(OAc)_2$, 85, CsF, toluene, 50 ˚C	45 %
4.	$Pd(OAc)_2$, 89, CsF, toluene, rt	50 %

Scheme 2.24 & Table 2.10: Reagents & Conditions: (a) see table 2.10

Although we managed to get a decent yield of coupling product **86**, reproducibility was a problem. As a consequence we decided to reverse the coupling partners and carry the malonate component as a pinacolboronate and coupling it with the corresponding vinyl halides. The boronate **90** was prepared by pinacolborane addition to the malonate **80** in presence of palladium(II) acetate as a catalyst and cyclohexyl JohnPhos **85** as a phosphine ligand . Unfortunately, when boronate **90** was subjected to Suzuki conditions in the presence of halide **30**, we failed to observe any coupling product **91** (scheme 2.25).



80 90 91

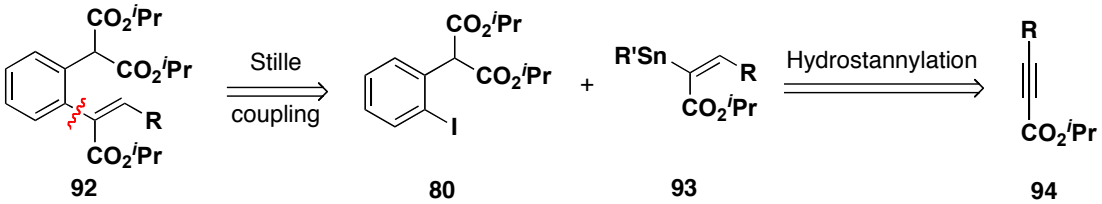
Scheme 2.25: Reagents & Conditions: (a) $Pd(OAc)_2$, **85**, Et_3N, pinacolborane, 1,4-dioxane, 3 h, 75 %; (b) **30**, $Pd(OAc)_2$, **85**, Et_3N, dioxane:H_2O, 80 ˚C

The difficulties associated the Suzuki reaction precluded its application in the generation of the desired pentadienyl anion precursor, and hence we decided to apply an alternative transition metal catalyzed process: the Stille reaction.

2.2.4 Stille coupling:

Since its first reported use in the late 1970's, the Stille reaction has been widely used for the coupling of both aromatic and vinylic systems.[80,81] Because of the problems experienced with the Suzuki reaction, the decision was made to apply the Stille coupling for the synthesis of the pentadienyl anion precursor, which has fewer limitations on the nature of the coupling partners.[81]

We envisaged that the precursor **92** could be assembled *via* the Stille coupling of the malonate **80** with the stannane **93** as the other coupling partner. The stannanes in turn could be generated by hydrostannylation of the corresponding alkynes (figure 2.17). At this point we also decided to employ a bulkier isopropyl ester as an electron-withdrawing group at the 2-position, to avoid any direct 1,2-addition to this functional group.



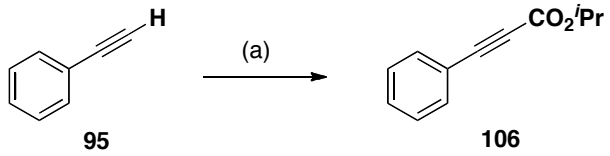
92 80 93 94

Figure 2.17: Retrosynthesis *via* the Stille reaction

2.2.4.1 Alkyne synthesis:

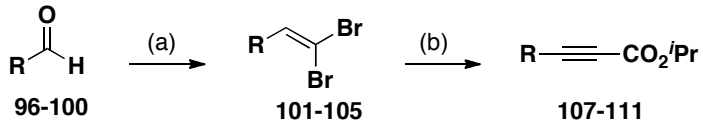
As illustrated earlier, the phenylmalonate **80** was obtained from 2-iodophenyl acetic acid **81** in two high-yielding steps (see scheme 2.22). An alkyne ester **94** could be synthesized (i) by

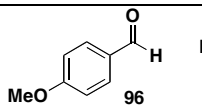
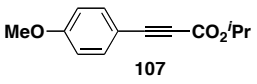
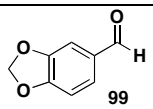
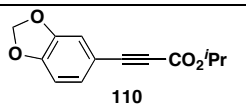
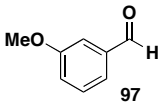
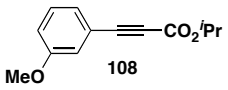
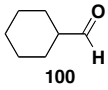
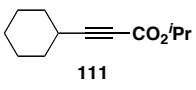
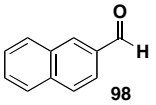
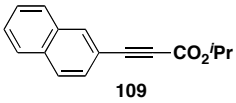
direct acylation of terminal alkyne, or (ii) *via* Corey-Fuchs reaction followed by trapping with chloroformate. When subjected to acylation conditions with isopropyl chloroformate, Phenylacetylene **95** afforded the desired isopropyl ester **106** in 70 % yield (scheme 2.26).



Scheme 2.26: Reagents & Conditions: (a) ^{n}BuLi, THF, -78 ˚C then ^{i}PrOCOCl, 76 %

Although some terminal alkynes are commercially available, they are expensive and hence we decided to employ the Corey-Fuchs reaction for the synthesis of alkyne esters **94**. In the first step, aldehydes were treated with carbon tetrabromide and triphenylphosphine, generating the dibromoalkenes **101-105** in excellent yields. Treatment of these dibromides with 2.2 equivalents of *n*-butyllithium followed by acylation with isopropyl chloroformate, afforded the corresponding alkyne esters (scheme 2.27). By this methodology a range of alkyne esters **107-111** were synthesized from the corresponding aldehydes (table 2.11).



Entry	Aldehyde	Alkyne ester	Entry	Aldehyde	Alkyne ester
1.	 96	 107	4.	 99	 110
2.	 97	 108	5.	 100	 111
3.	 98	 109			

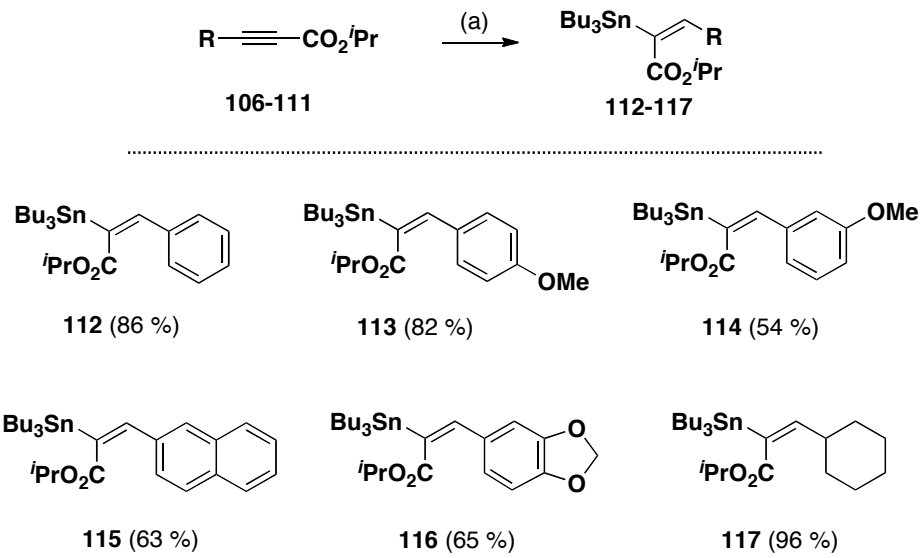
Scheme 2.27 & Table 2.11: Reagents & Conditions: (a) CBr_4, PPh_3, CH_2Cl_2, 0 ˚C, 90-99 %; (b) ^{n}BuLi, THF, -78 ˚C then ^{i}PrOCOCl; (c) $Pd(PPh_3)_4$, Bu_3SnH, THF, 0 ˚C, 44-95 %

2.2.4.2 Hydrostannylation:*

These alkyne esters were subsequently subjected to palladium-catalyzed hydrostannylation conditions. Treatment with palladium tetrakis(triphenylphosphine) and tributyltin hydride at

* This work was done in collaboration with Peter Knipe

0 ˚C generated the desired stannanes **112-117** in moderate to excellent yields (scheme 2.28). These would be then used as coupling partners for the Stille reaction.[82-84]



Scheme 2.28: Reagents & Conditions: $Pd(PPh_3)_4$, Bu_3SnH, THF, 0 ˚C

Palladium(0) catalyzed hydrostannylation of the alkyne esters proceeded to give a single regio- and geometric isomer in all cases (see scheme 2.28). In this catalytic cycle, palladium(0) undergoes oxidative addition to the tin-hydrogen bond to generate the palladium(II) complex **118**. This complex then coordinates with the alkyne and delivers the hydride preferentially to the aryl substituted terminus to afford **119**. This subsequently undergoes reductive elimination to generate the corresponding stannane (figure 2.18).[85,86]

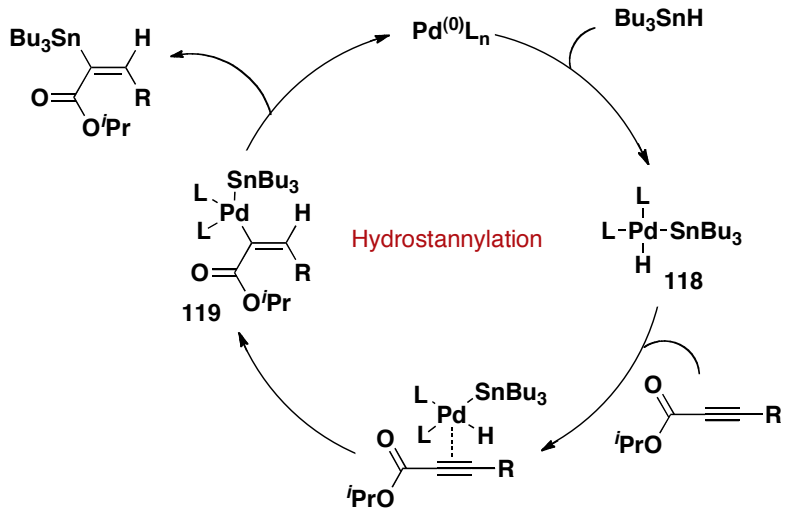


Figure 2.18: Palladium-catalyzed hydrostannylation

The stereochemistry of the stannanes obtained was further confirmed by NMR studies. The coupling constant between the vinyl proton and the Sn atom ($^3J_{Sn\text{-}H}$ = 28.5-29.6) was consistent with a literature report for (*E*)-vinyl stannane.[82] However, the coupling constant for (*Z*)-vinyl stannane synthesized by radical hydrostannylation was found to be > 50 (figure 2.19).

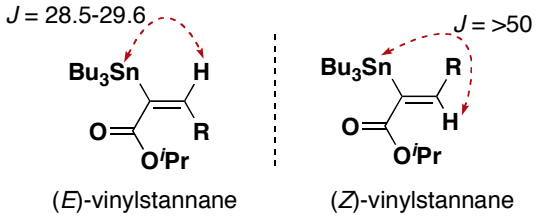
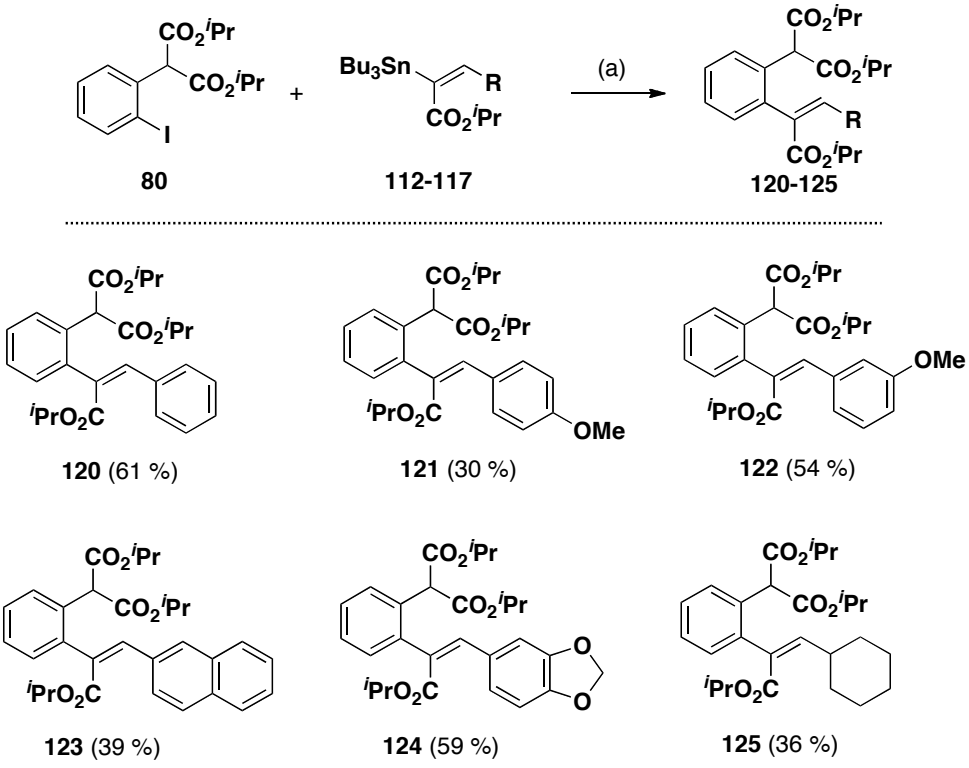


Figure 2.19: Coupling constants for vinyl stannanes

2.2.4.3 Transition metal coupling:

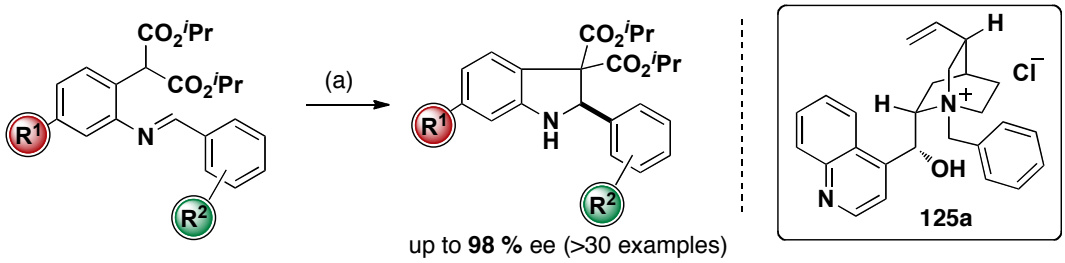
After obtaining the desired stannanes, they were subjected to the Stille coupling conditions. It was found that the phenylmalonate **80** underwent reaction with stannanes in the presence of palladium(II) acetate and cyclohexyl JohnPhos to generate the adducts **120-125** in moderate yields (scheme 2.29).



Scheme 2.29: Reagents & Conditions: (a) $Pd(OAc)_2$, cyclohexyl JohnPhos **85**, CuI, DMF, rt, 12-18 h

2.2.5 Asymmetric 6π electrocyclization:

After the success of Stille coupling in generating a series of precursors, we planned to investigate the electrocyclization of these substrates. A parallel work within the group by E. Macvier and S. Thompson had demonstrated that 2-aza-pentadienyl substrates can undergo 6π electrocyclization in the presence of base and a phase transfer catalyst.[87] Cinchonidinium derived catalyst **125a** was found to give the best enantioselectivity for this transformation (scheme 2.30). The reaction afforded the functionalized indolines in high yields and excellent enantioselectivity (up to 98 %).



Scheme 2.30: Reagents & Conditions: (a) catalyst **125a** (10 mol %), toluene, -15 ˚C, K_2CO_3 (aq.)

With these results in mind, we decided to probe the electrocyclization of an analogous all-carbon system. The substrate **84** was subjected to various basic conditions to establish the ease with which the electrocyclization occurs. As mentioned earlier, we envisaged that an asymmetric variant of this cyclization could be achieved by blocking one π-face of the delocalized anion, and relying on the stereospecificity of the electrocyclic process to direct the stereochemical outcome (figure 2.20). One way to achieve this would be to exploit tight-ion pairing in an organic solvent. Asymmetric phase-transfer catalysis[88,89] relies on the tight ion-pairing principle,[90-94] and has been demonstrated to be a powerful and practical approach to the generation of enantioenriched materials.

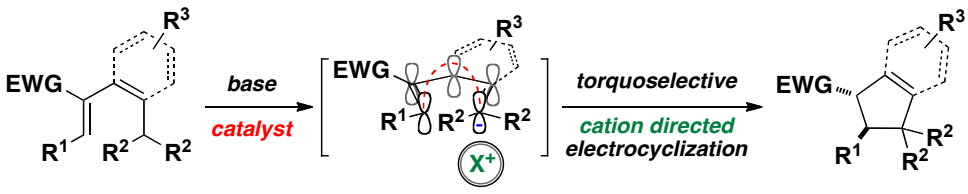
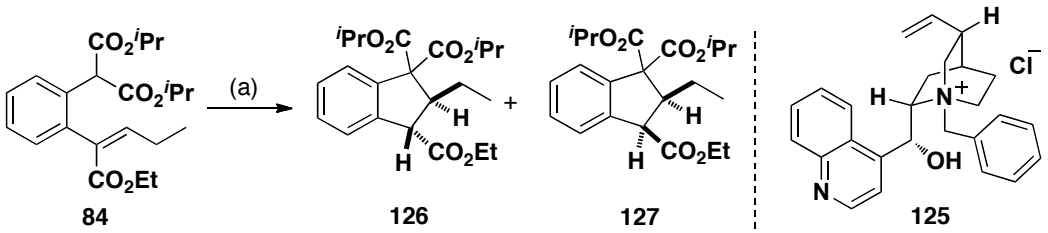


Figure 2.20: Strategy for asymmetric 6π electrocyclization

In a preliminary investigation, it was discovered that **84** underwent electrocyclization under racemic conditions, with Cs_2CO_3 as the base (scheme 2.31). This generated the cyclized product **126** and **127** with diastereoselectivity of 19:1 (entry 3, table 2.12). It was observed that 2.2 equivalents of Cs_2CO_3 at -20 ˚C for 3 days were the optimum conditions for full conversion with high dr. Under the same reaction conditions, using cinchonidinium derived **125a** as a phase-transfer catalyst, the diastereoselectivity increased to 33:1, but we did not observe any enantioselectivity (entry 4). When the temperature was further lowered to -55 ˚C, the reaction failed to give any electrocyclized product and all the starting material was recovered (entry 5 & 6). It was also found that the reaction did not proceed in the presence of aq. K_2CO_3 as the base (entry 7). The lack of any enantiomeric excess is consistent with cyclization of aza-pentadienyl anion with linear chain alkyl substitution.[87] However, higher enantioselectivities were obtained for branched and cyclized alkyl substitution in case of aza-pentadienyl substrates.[87]

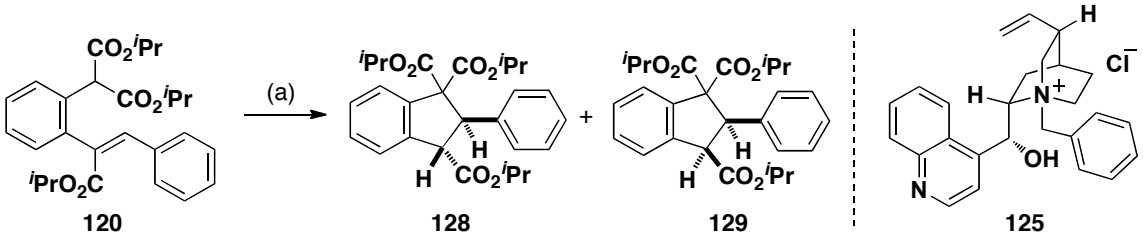


Entry	Reagents & Conditions	Product (dr)
1.	Cs_2CO_3, toluene, rt, 15 h	**126, 127** (9:1)
2.	Cs_2CO_3, **125a**, toluene, rt, 15 h	**126, 127** (9:1)
3.	Cs_2CO_3 (2.2 eq.), toluene, -20 ˚C, 3 days	**126, 127** (19:1)
4.	Cs_2CO_3 (2.2 eq.), **125a**, toluene, -20 ˚C, 3 days	**126, 127** (33:1)
5.	Cs_2CO_3 (2.2 eq.), toluene, -55 ˚C, 3 days	SM, **84**
6.	Cs_2CO_3 (2.2 eq.), **125a**, toluene, -55 ˚C, 3 days	SM, **84**
7.	33 % aq. K_2CO_3, **125a**, tol:$CHCl_3$ (5:1), -20 ˚C, 4 days	SM, **84**

Scheme 2.31 & Table 2.12: Reagents & Conditions: (a) see table 2.12

To establish whether changing the group at the β-position of the alkene could affect cyclization, we subjected phenyl substrate **120** to the same conditions. We observed that a stronger base such as $CsOH{\cdot}H_2O$ was necessary for the reaction to go to completion. We were delighted to see that in the presence of catalyst **125a**, the phenyl substrate **120** underwent 6π electrocyclization at -15 ˚C (scheme 2.32). This afforded the cyclized products **128** and **129** as a 5:1 mixture of diastereoisomers in 28 % ee (major) (entry 4, table 2.13). In the 2-aza-pentadienyl anion cyclization, an increase in enantioselectivity was observed at

lower temperature,[87] however in this case, lowering the temperature to -30 ˚C led to a reduction in enantioselectivity (entry 5).



Entry	Reagents & Conditions	Yield of **128**, (dr)	ee for **128**
1.	Cs_2CO_3, toluene, - 15 ˚C, o/n	none	-
2.	Cs_2CO_3, tol:CH_2Cl_2 (2:1), - 15 ˚C, o/n	none	-
3.	50 % aq. NaOH, **125a**, toluene, -15 ˚C	none	-
4.	CsOH·H_2O, **125a**, toluene, -15 ˚C, o/n	95 % (5:1)	28 %
5.	CsOH·H_2O, **125a**, toluene, -30 ˚C, 24 h	92 % (5:1)	9 %
6.	CsOH·H_2O, **125a**, toluene, -50 ˚C, 2 days	none	-

Scheme 2.32 & Table 2.13: Reagents & Conditions: (a) see table 2.13

2.2.6 Proposed mechanism:

There are two viable pathways for these cyclization reactions. An intramolecular Michael addition would formally constitute a 5-(*enolexo*)-*endo* trig reaction, which is stereoelectronically demanding as delineated by the Baldwin rules.[95,96] To enable any possibility of orbital overlap between the enolate HOMO and the alkene LUMO, the alkene and the malonate portion of the system must lie essentially perpendicular to the plane of the arene, but this places the reacting centers somewhat distant (figure 2.21). For the electrocyclic process to occur, deprotonation must lead to an essentially planar delocalized 6π anion, which in accord with the Woodward-Hoffmann rules[2,4] undergoes suprafacial cyclization to afford the desired product.

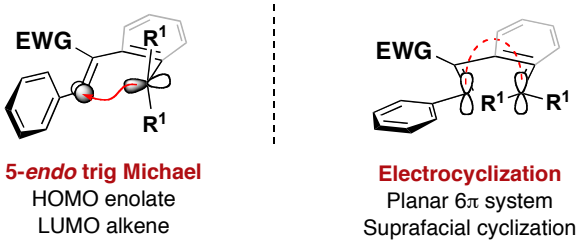


Figure 2.21: Mechanistic possibilities for cyclization ($R^1 = CO_2{}^iPr$)

2.2.7 Stereochemical model:

In asymmetric phase-transfer catalysis tight-ion pairing involving the ammonium cation is generally considered to be the dominant interaction.[90-94] The sense of stereoinduction in the electrocyclic mechanism may be tentatively rationalized using a modification of the tight-ion pair model for asymmetric phase transfer mediated alkylation proposed by Corey.[97] In this model, the enolate oxygen is closely associated with the bridgehead ammonium cation, of which only one face is accessible. Van der Waals interactions between the substrate, and both the quinoline and *N*-aryl units offer another binding surface. This effectively blocks one face of the substrate, with the torquoselectivity a consequence of rotation to place the pendant aryl substituent away from the steric bulk of the catalyst (figure 2.22).

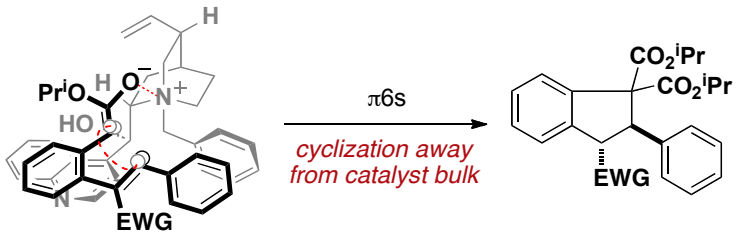
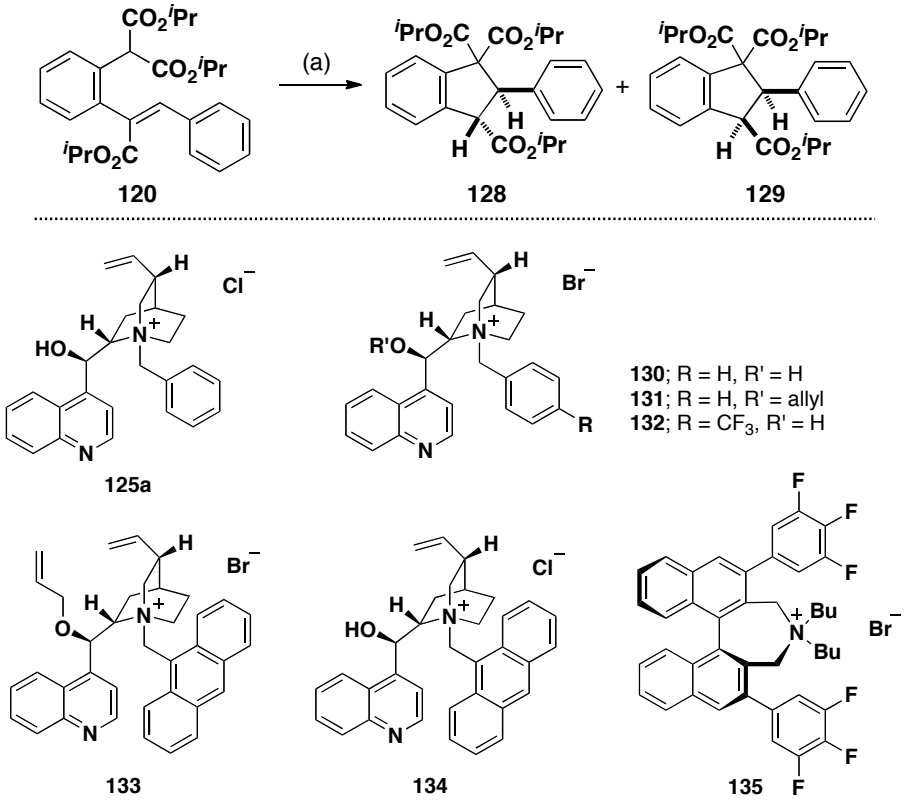


Figure 2.22: Stereochemical model for asymmetric electrocyclization

(Only one ester group is depicted for clarity)

2.2.8 Catalyst optimization:

With a practical procedure in hand, we examined the efficacy of a range of different cinchona alkaloid-derived ammonium salts in the cyclization process (scheme 2.33). It was discovered that treatment of the precursor **120** with 10 mol % (8*S*,9*R*)-*N*-benzyl cinchonidinium chloride **125a** and $CsOH{\cdot}H_2O$ afforded cyclized product **128** in an excellent yield (90 %) with promising ee of 28 %. With the corresponding bromide salt **130** a decrease in conversion of 80 % was observed. Changing the catalyst to trifluoromethyl derivative **132** led to a reduction in enantioselectivity (to 10 % ee). When we switched to catalyst **135**, synthesized by Maruoka,[98] we were delighted to find an increase in enantiomeric excess to 60 %. This generated the cyclized product as a 5:1 mixture of diastereoisomers, with opposite absolute configuration to that obtained with the cinchonidinium catalyst **128** as outlined above (table 2.14).

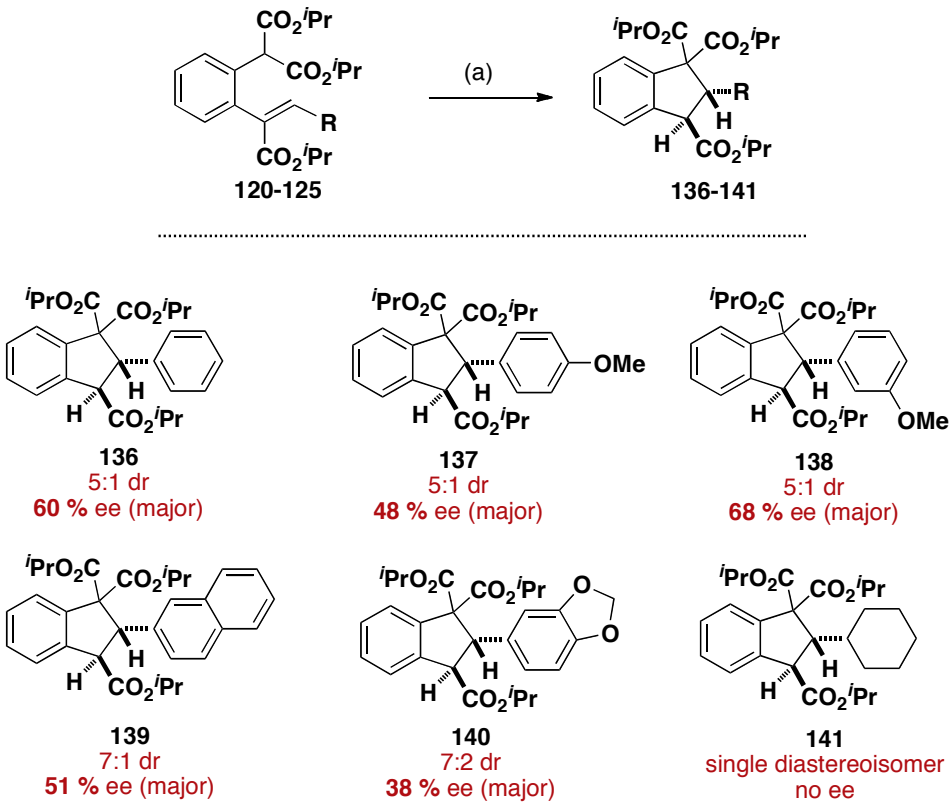


Catalyst	Yield of **128**	ee (dr)
125a	90 %	28 % (5:1)
130	~ 10-12 %	-
131	~ 10-12 %	-
132	92 %	10 % (7:2)
133	~ 10 %	-
134	90 %	No ee
135	95 %	(-) 60 %* (5:1)

Scheme 2.33 & Table 2.14: Reagents and conditions: (a) $CsOH{\cdot}H_2O$, toluene, -15 ˚C, 24 h (*opposite absolute configuration)

2.2.9 Substrate scope:

Once the conditions for electrocyclization were optimized, using catalyst **135** in toluene at -15 ˚C, we decided to determine the substrate scope for this reaction. We introduced different substituents on the pendant aryl ring and subjected them to similar electrocyclization conditions (scheme 2.34). In all instances the reactions generated the cyclized product in > 95 % yield. It was found that methoxy substitution at 4-position of the aryl ring slightly decreased the enantioselectivity to 48 %. An increase in enantioselectivity, however, was observed with the 3-methoxy substituent (to 68 %). Piperonyl substitution led to further reduction in ee to 38 %. In case of the cyclohexyl substituent we obtained a single diastereoisomer of the cyclized product, but did not observe any enantioselectivity.



Scheme 2.34: Reagents & Conditions: (a) $CsOH{\cdot}H_2O$, **135**, toluene, -15 ˚C, o/n

The relative configuration of **141** was established by nOe studies and by analogy extended to all other examples. For substrate **141**, H_6 showed strong nOes with H_7 and H_8 (in red), this implies the hydrogen atom at the 6-position and cyclohexyl ring are on the same face of the molecule. Similarly, H_5 shows a weak nOe to the isopropyl CH (in blue) (figure 2.23).

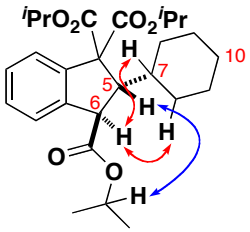


Figure 2.23: Key nOe's for **141**

2.2.10 Conclusions and future work:

In conclusion, we have developed an asymmetric synthesis of functionalized indanes that constitutes one of the few catalytic asymmetric electrocyclic processes described. The precursor for electrocyclization could be assembled *via* the Suzuki or Stille reactions, although the Stille coupling gave better results. It has been demonstrated that the alkynes underwent regioselective hydrostannylation to generate the corresponding stannanes as a partner for transition metal coupling.

We have established a methodology for [1,5]-electrocyclization using chiral phase-transfer catalysis. It was shown that in the presence of cinchonidinium-derived catalyst **125a**, the precursor **120** underwent 6π electrocyclization to generate cyclized products **128** and **129** as a 5:1 mixture of diastereoisomers in 28 % ee (major). However, with the catalyst **135**, synthesized by Maruoka,[98] the enantioselectivity increased to 60 % for the major diastereoisomer (see section 2.2.8).

We believe that these reactions proceed *via* an electrocyclic mechanism. Deprotonation leads to an essentially planar delocalized 6π anion, which in accord with the Woodward-Hoffmann rules[2,4] undergoes suprafacial cyclization. An intramolecular Michael addition, on the other hand, would formally constitute a 5-(*enolexo*)-*endo* trig cyclization, which is stereoelectronically demanding, as delineated by the Baldwin rules[95,96] (figure 2.21, see section 2.2.6).

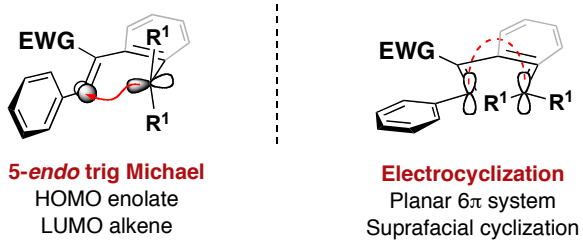


Figure 2.21: Mechanistic possibilities for cyclization ($R^1 = CO_2{}^iPr$)

This transformation offers a glimpse of the potential of electrocyclic reactions. However, it is evident that we require a catalyst that will afford higher enantioselectivities of the cyclized products. It is known that chiral dibenzazepinium halide **142**, developed and synthesized by Lygo,[99] is an effective phase-transfer catalyst for asymmetric catalysis.

With this in mind, the future work required on this project includes: (i) synthesis of chiral dibenzazepinium catalyst **142**, and (ii) investigation of its catalytic proficiency for an asymmetric 6π electrocyclic reaction (figure 2.24).

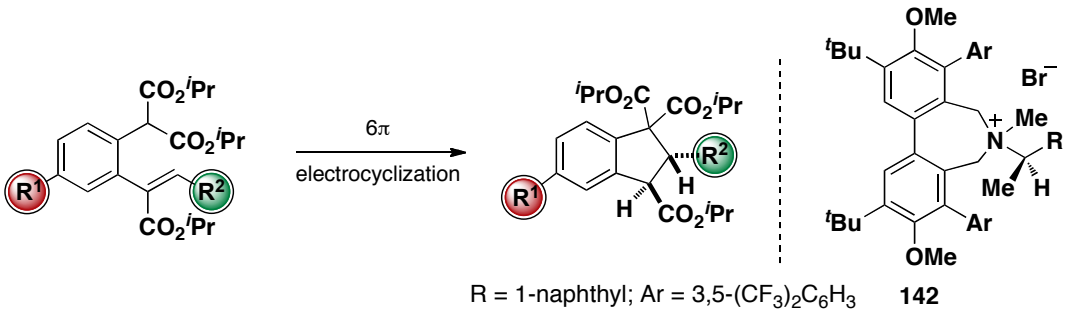


Figure 2.24: Future work: [1,5]-electrocyclization

CHAPTER 2: FOLDAMERS

1. Introduction

Nature's building blocks such as proteins, nucleic acids and polysaccharides can perform complex chemical operations such as highly selective catalysis and recognition.[100] These functions are linked to the folding of such biopolymers, which creates an active site by the juxtaposition of reactive groups. Synthetic oligomers or foldamers are intended to mimic the elegant features of structure and function observed in natural polymers and they display ordered structure in solution and solid states.

A foldamer, a term first coined by Gellman,[101] is defined as:
'Any oligomer that folds into a conformationally ordered state in solution, the structures of which are stabilized by noncovalent interactions between nonadjacent monomer units'.

Foldamers can adopt stable secondary structures with as few as four residues,[102] in contrast to natural oligomers that require a minimum of ten to twelve amino acids. This control over oligomer folding could lead to new types of molecules with useful properties and hence it is important to identify peptide backbones that will fold into stable secondary structures.

1.1 Ring constrained β-peptides:

Peptides constructed from naturally occurring α-amino acids must usually have a length of at least twelve to twenty units in order to populate a stable conformation in solution. In contrast, oligomers composed of β-amino acids populate stable secondary structures with five to eight units.[102] A wealth of research has been devoted to the fundamentals of β-peptide design[101-106] and they have been shown to adopt a range of helical,[107,108] turn,[109] and sheet conformations[110] in solution, all with remarkable stability. It has been demonstrated that substitution patterns and stereochemistry exert profound effects on the folding properties of β-peptides (see figure 1.1).

β-Peptides prepared from 1-(aminomethyl)cyclopropanecarboxylic acid form eight-membered H-bonded rings (figure 1.1a).[111] Fleet *et al.*[112] have reported that oligomers constructed from 2,3-*cis*-oxetane ring display an unprecedented 10-helical conformation (figure 1.1b), while peptides composed of 2,3-*trans*-cyclopentane[113] (figure 1.1c) and 2,3-

trans-cyclohexane[114,115] (figure 1.1d) β-amino acids adopt 12- and 14-helical conformations respectively. Fulop *et al.*[116] have demonstrated that strand (figure 1.1e) and alternating 10/12 helical conformations (figure 1.1f) may be accessed through homo- or heterochiral combinations of either 2,3-*cis*- or 2,3-*trans*-cyclopentane β-amino acids.[117] Oligomers based on 2,3-*trans*-oxanobornene adopt an 8-helical conformation (figure 1.1g),[118] while α/β-peptides containing *cis*-cyclopropane β-amino acids populate stable helical folds (figure 1.1h).[119]

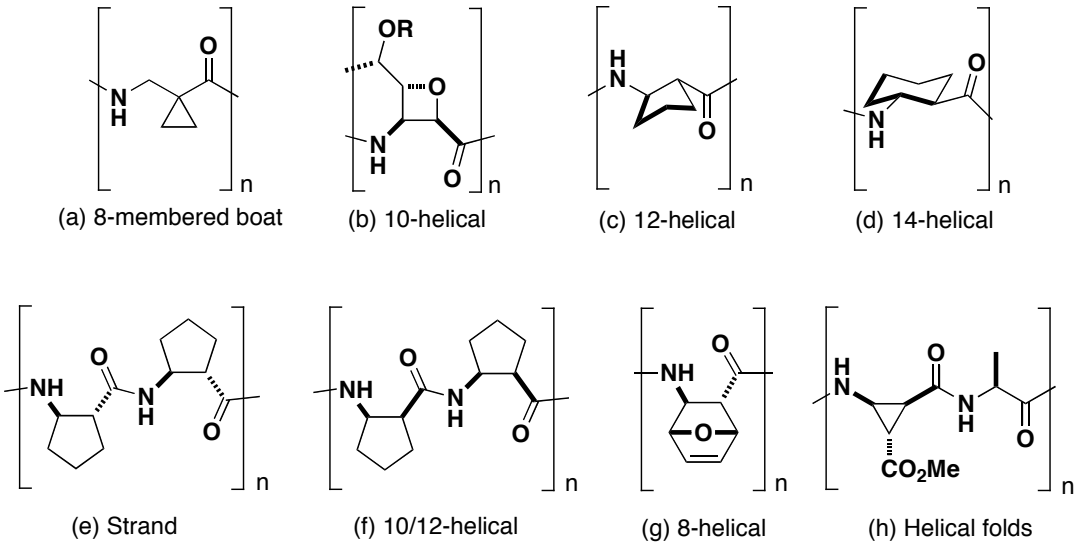


Figure 1.1: Ring-constrained β-peptides: (a) 1-(aminomethyl)cyclopropane; (b) 2,3-*cis*-oxetane; (c) 2,3-*trans*-cyclopentane; (d) 2,3-*trans*-cyclohexane; (e) alternating heterochiral 2,3-*trans* cyclopentane; (f) alternating heterochiral 2,3-*cis*-cyclopentane; (g) oxanobornene; (h) *cis*-cyclopropane

1.2 Ring constrained γ-peptides:

Although a vast amount of research has been dedicated to β-peptides and its conformations, relatively little attention has been paid to γ-peptides, despite the possibility of traversing larger conformational space. It was believed that the added torsional degrees of freedom in γ-amino acids could promote conformationally disordered chains and thus disfavor the formation of stable secondary structures.[102] Furthermore, in a model study, Dado and Gellman [100]have shown that γ-peptides have higher propensities than β-peptides to populate conformations stabilized by nearest-neighbour hydrogen-bonding by FT-IR and NMR spectroscopic studies (figure 1.2).

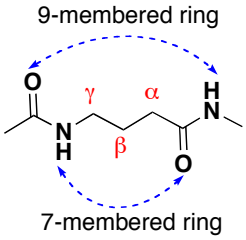


Figure 1.2: Possibilities of hydrogen-bonding in γ-peptide

1.2.1 Helical structure in γ-peptide:

Two independent research groups[120,121] have reported the presence of a stable secondary structure in γ-peptides at a much lower residue level than their α- and β-counterparts. Seebach *et al.*[108,121] demonstrated that γ-peptides containing residues bearing γ-substitution adopt 14-helical conformations stabilized by C=O(*i*) → N-H(*i*+3) hydrogen bonds (figure 1.3). The direction of the helix dipole has reversed (C→N to N→C) upon changing from a β-peptide to the corresponding γ-peptide. An increase in helix stability was also observed upon homologation from α- to β- to γ-peptides.[108]

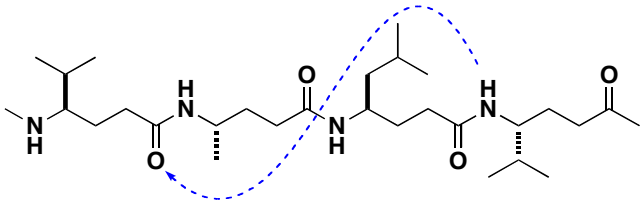


Figure 1.3: 14-helical conformation of γ-peptide

Seebach[122] has also shown unusual 9- and 14-membered ring hydrogen bond stabilized helical structures in the solid state for γ-dipeptide and tetrapeptide respectively (figure 1.4).

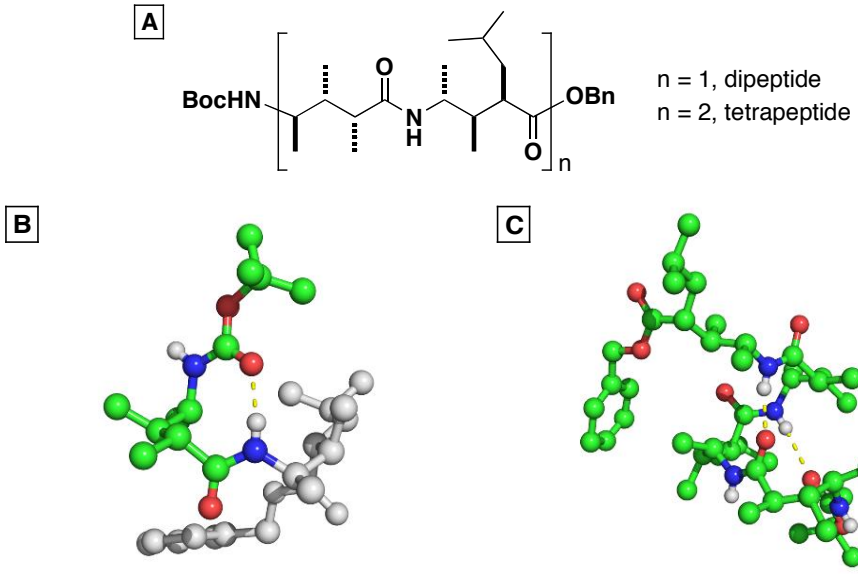


Figure 1.4: A. γ-peptides; B. 9-membered; C. 14-membered helix conformation in solid state

Recently, Balaram and co-workers[123] reported nine-membered hydrogen-bonded ring stabilized helices and ribbons in gabapentin oligomers (figure 1.5).

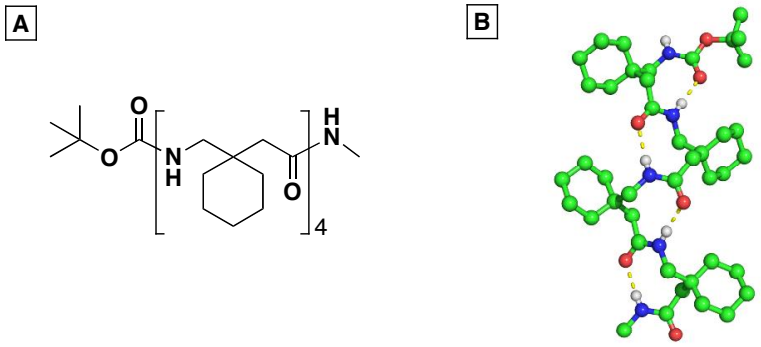


Figure 1.5: A. Gabapentin monomer unit; B. Intramolecular hydrogen bonds in BoC-$(Gpn)_4$-NHMe

Similarly, Kunwar *et al.*[124] reported a novel left-handed 9-helix in mixed γ-peptides derived from alternating γ-Caa and GABA residues (figure 1.6).

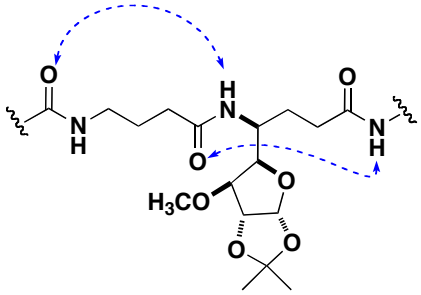


Figure 1.6: 9-Helix formation in mixed γ-peptide (hydrogen bonds shown in blue)

1.2.2 Secondary structure independent of ring size:

In an interesting study of 2,3-*trans*-β-aminoxy acid oligomers, Yang *et al.*[125] demonstrated that the formation of a nine-membered ring hydrogen bond was independent of ring size for five- or six-membered *trans*-configured constraints (figure 1.7). This is consistent with insightful theoretical studies by Hofmann and co-workers[126,127] that have predicted 9- and 14-membered ring hydrogen-bonded helices to be the most stable conformations for γ-peptides.

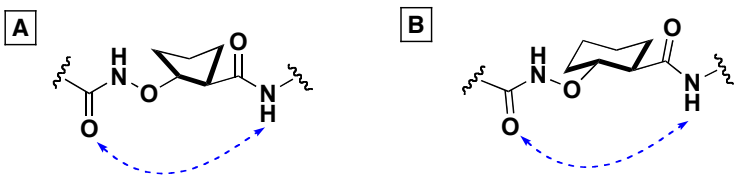


Figure 1.7: Hydrogen bonding independent of ring size
(A) 5-membered; (B) 6-membered ring constraint

1.2.3 Bend-ribbon conformation:

Farrera-Sinfreu *et al.*[128] reported the formation of β-sheets stabilized by nine-ring hydrogen bonds in γ-peptides comprised of cyclic γ-amino acids (figure 1.8). This peptide populates a bend-ribbon conformation in the solution phase.

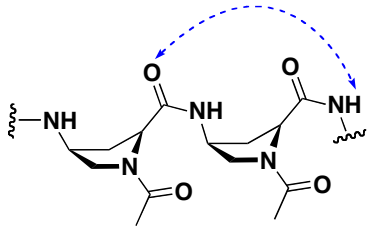


Figure 1.8: Nine-ring hydrogen bond to populate bend-ribbon conformation

1.2.4 Hybrid foldamers:

Recently, Sanjayan and co-workers[129] have designed a hybrid peptide, which displays periodic γ-turn conformations (figure 1.9). These γ-turns were stabilized by the presence of seven- and five-membered rings with bifurcated hydrogen bonds, both in the solution and solid phase. It was believed that conformational restriction, imposed by the individual amino acids, played an important role in pre-organization of the peptide backbone, thus allowing a periodic γ-turn conformation to be populated.

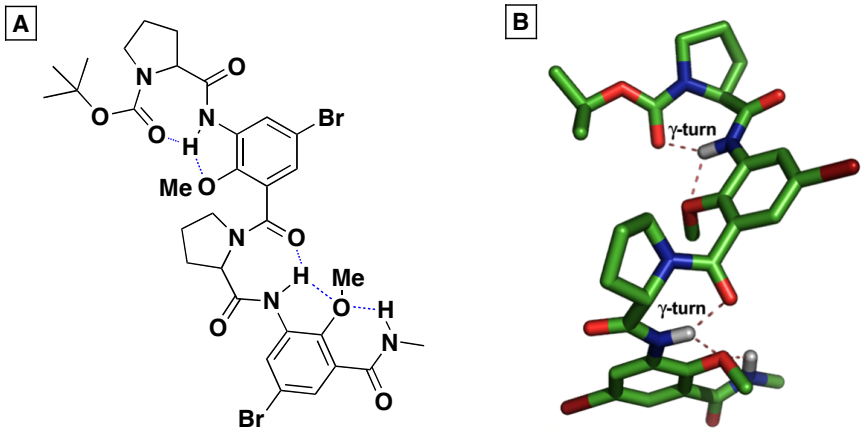


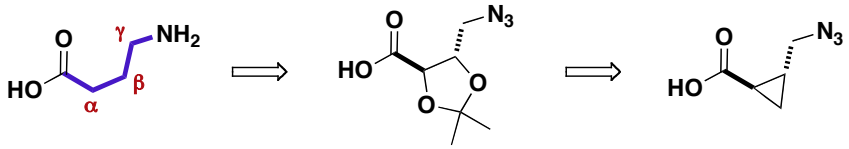
Figure 1.9: A. Hybrid foldamer showing γ-turn motif stabilized by bifurcated H-bond; B. X-ray structure

All of these examples demonstrate that γ-peptides are capable of forming more stable secondary structures compared to α- or β-peptides in the solid state as well as the solution phase.

2. Project Aims

The secondary structures of oligomeric organic molecules are known to possess fascinating architectures that can be responsible for their biological function. In this regard γ-peptides have been less explored than β-peptides congeners and recent literature (see section 1.2) indicates their potential to adopt secondary structures of even greater stability.

The project was designed to evaluate the effect of cyclic backbones on the secondary structures of γ-peptides. Two series of abiotic γ-peptides were synthesized with five and three-membered cyclic backbones (scheme 2.1). This study was aimed at improving the existing understanding of the design and architectural features of γ-peptides to control different possible secondary structures by varying backbone ring size and substitution pattern. It was planned to describe how the introduction of a five-membered ring constraint on the backbone of γ-amino acid units permits exploration of the intramolecular rather than intermolecular hydrogen bonding manifolds, and investigate the conformational effects of generating homo- and heterochiral systems.



γ-peptide unit | 5-ring constraint γ-peptide | 3-ring constraint γ-peptide

Figure 2.1: Model γ-peptide monomer units

3. Results And Discussion

γ-Peptides present the possibility of traversing a larger conformational space and adopt more stable secondary structures than β-peptides. The first step for the synthesis of a γ-peptide was to identify folding backbone. Once the backbone has been identified, the next step is to put ring constraint on it. The γ-peptides based on five-membered backbone were considered as a model system and it was planned to extend the findings from this study to other systems. The use of a dioxolane ring system rather than a cyclopentane as a five-ring constraint is envisaged to have little impact on the overall conformation whilst simplifying the synthetic approach and easing analysis of NMR spectra (figure 3.1).

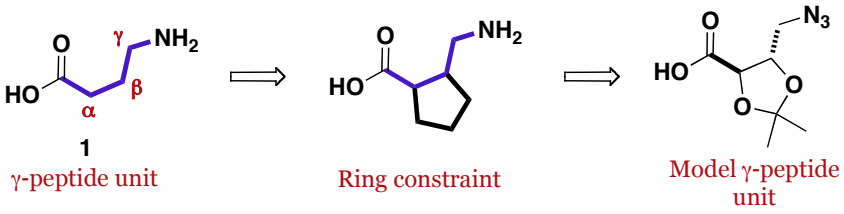


Figure 3.1: Identification of folding backbone

3.1 Preparation of monomer units:

Dimethyl tartrate was selected as the starting material for the synthesis of 2,3-*trans*-dioxolane-constrained monomer units as it is cheap and readily available in both enantiomeric forms. It was envisaged that the *N*-terminus would be protected as an azide, while the *C*-terminus could be masked as an isopropyl ester. The retrosynthetic analysis for the synthesis of a monomer unit is as follows:

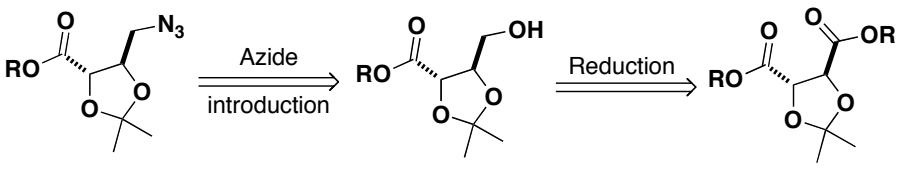


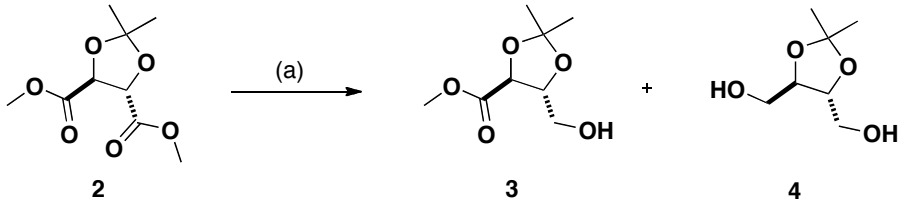
Figure 3.2: Retrosynthetic analysis for γ-peptide building block

Both D- and L-tartrate derived monomer units have been prepared, and the results for the D-series are presented here. Where a reference to a specific enantiomeric series is intended (for example in the preparation of heterochiral oligomers), the prefix D- or L- will used before the number of the compound.

3.1.1 Ester desymmetrization:

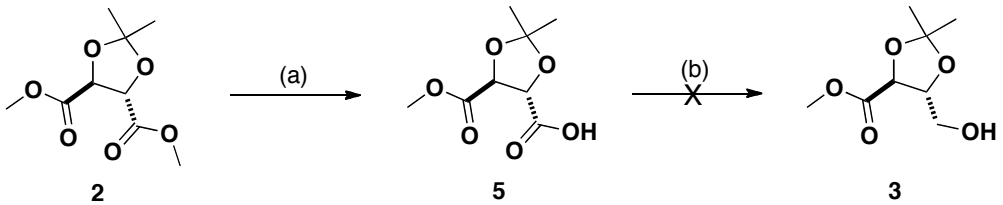
The first step in the synthesis involved the selective conversion of one of the methyl esters of isopropylidene protected dimethyl tartrate **2** into the corresponding alcohol. This presents a potential problem, as the C_2-symmetric diester has to be desymmetrised.

In an initial endeavor, sodium borohydride (0.6 eq.) was added portion-wise to a stirred solution of protected diester **2** in methanol at -10 ˚C (scheme 3.1).[130] TLC indicated the conversion of starting material into the desired mono alcohol **3** and over-reduced diol **4**. After flash column chromatography, the desired mono alcohol **3** was obtained in reasonable yield (31 %).



Scheme 3.1: Reagents & Conditions: (a) $NaBH_4$ (0.6 eq.), MeOH, -10 ˚C, 1 h, 31 %

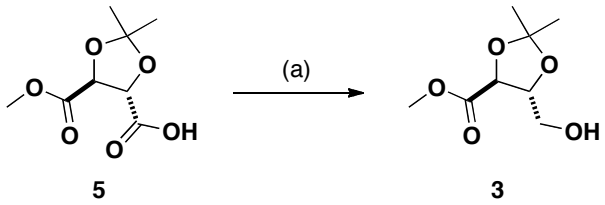
In an effort to improve the yield, selective conversion of diester **2** to monoacid and subsequent reduction to obtain the mono alcohol was considered. Following a literature procedure,[131] basic hydrolysis of **2** with methanolic potassium hydroxide afforded the mono acid **5** in quantitative yield (scheme 3.2). Selective reduction of monoacid **5** was attempted with NMM, ethylchloroformate and sodium borohydride at -10 ˚C. Unfortunately even after repeated attempts the method failed to produce the desired mono alcohol **3**, instead an unidentified product from NMM was obtained.



Scheme 3.2: Reagents & Conditions: (a) (i) KOH in MeOH, rt, 2 h then 3 N HCl, 99 %; (b) (i) NMM, EtOCOCl, THF, -10 ˚C, 10 min; (ii) $NaBH_4$, THF, -10 ˚C, 15 min

Following this unsuccessful attempt, it was planned to carry out selective reduction of acid **5** with borane. After optimization of reaction conditions, borane in THF solution was added

drop wise at -20 ˚C to afford the mono alcohol **3** as the sole product in 70 % yield (scheme 3.3).

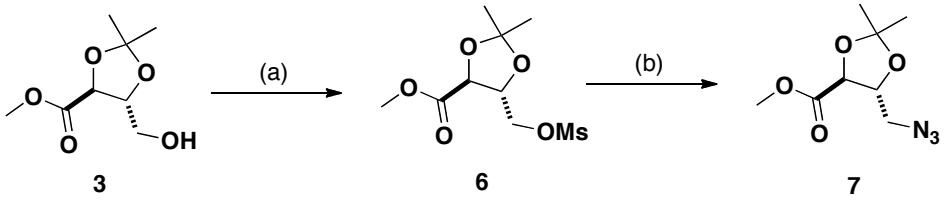


5 3

Scheme 3.3: Reagents & Conditions: (a) BH_3·THF, -20 ˚C to rt, 4 h, 70 %

3.1.2 Azide protection:

It was decided to introduce azide *via* the S_N2 displacement of an activated sulfonate ester **6** with azide anion. Methanesulfonyl chloride and Et_3N were added to a solution of alcohol **3** in dichloromethane at 0 ˚C to afford the mesylated product **6** in quantitative yield. Sodium azide was heated with crude mesylate **6** in DMF at 95 ˚C to afford azide **7** in 83 % yield over two steps after purification (scheme 3.4).

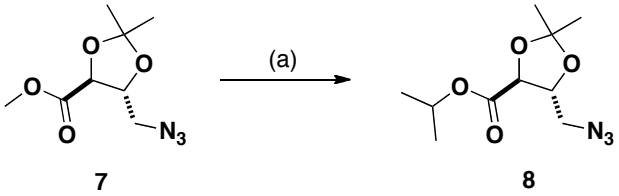


3 6 7

Scheme 3.4: Reagents & Conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 ˚C, 10 min;
(b) NaN_3, DMF, 95 ˚C, 3 h, 83 % (over two steps)

3.1.3 Transesterification:

The *C*-terminus would be protected as an isopropyl ester in order to prevent uncontrolled intermolecular polymerization once the *N*-terminus was unmasked. Transesterification was achieved by heating a solution of methyl ester **7** in isopropanol and potassium carbonate at 90 ˚C to afford **8** in 81 % yield (scheme 3.5).

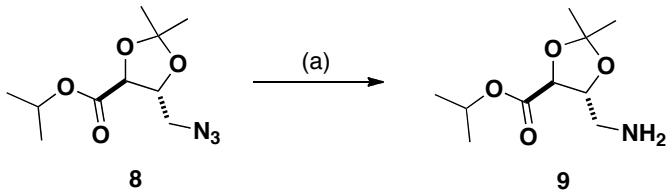


7 8

Scheme 3.5: Reagents & Conditions: (a) K_2CO_3, IPA, 90 ˚C, 3 h, 81 %

3.1.4 Reduction of azide:

The reduction of isopropyl-protected azide **8** was achieved using 10 % palladium on carbon under an atmosphere of hydrogen. Previous work within the group on similar substrates had demonstrated that azide hydrogenation using palladium on activated carbon resulted in the formation of unwanted reductive dimerization byproducts.[132] This could be avoided by pre-activating the palladium catalyst with hydrogen prior to addition of the azide. These conditions afforded free amine **9** that was used without further purification (scheme 3.6).

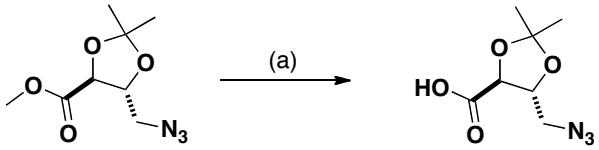


8 **9**

Scheme 3.6: Reagents & Conditions: (a) H_2, Pd/C, IPA, rt, 30 min, 99 %

3.1.5 Hydrolysis of ester:

Base catalyzed hydrolysis of methyl ester **7,** using aqueous sodium hydroxide followed by acidification with 3 N HCl, afforded the desired acid **10** in quantitative yield. This acid was used without further purification (scheme 3.7).



7 **10**

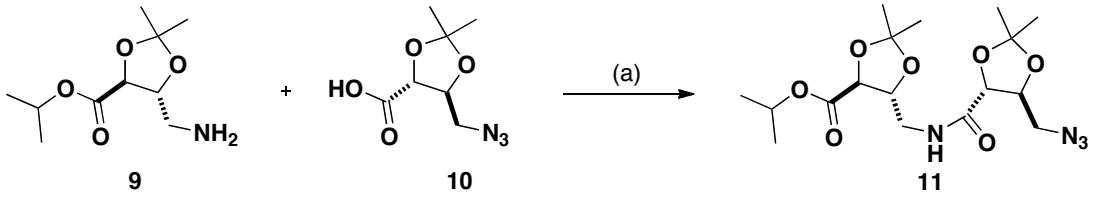
Scheme 3.7: Reagents & Conditions: (a) (i) 1 M aq. NaOH, EtOH, rt, 15 min then 3 N HCl, 99 %

3.2 Synthesis of γ-peptides:

A simple iterative procedure was devised for the synthesis of heterochiral oligomers from the monomer γ-peptide units.

3.2.1 Synthesis of heterochiral dimer (D-L):

The crude D-amine **9** was coupled with the crude L-acid **10** using TBTU as a suitable peptide coupling agent in the presence of DIPEA (scheme 3.8). The minimum amount of dichloromethane was used as solvent and the heterochiral dimer **11** was obtained in 83 % yield from monomer D-azido ester **8** after purification.

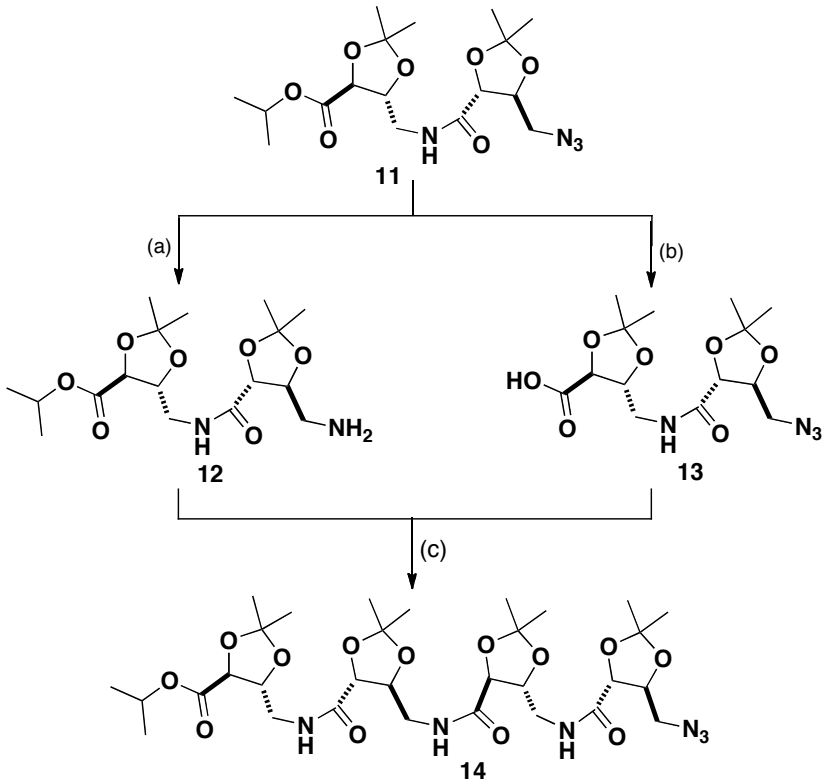


Scheme 3.8: Reagents & Conditions: (a) $^{i}Pr_2NEt$, TBTU, CH_2Cl_2, rt, 10 min, 83 %

3.2.2 Synthesis of heterochiral tetramer (D-L-D-L):

The dimer azide **11** was reduced using 10 % palladium on carbon under an atmosphere of hydrogen to afford free amine **12**. Subsequently, the dimer azide **11** was hydrolyzed with aqueous sodium hydroxide to afford free acid **13**, which was used without further purification.

Following the same coupling protocol, dimeric amine **12** was coupled with dimeric acid **13** using TBTU and DIPEA in a concentrated solution of dichloromethane (scheme 3.9). The heterochiral tetramer **14** was obtained in 59 % yield from dimer azido ester **11**. An intensive spectroscopic analysis was performed to assign and confirm the structure of tetramer (see section 3.3).



Scheme 3.9: Reagents & Conditions: (a) H_2, Pd/C, IPA, 1 h, 99 %; (b) (i) 1 M aq. NaOH, EtOH, rt, 15 min then 3 N HCl, 99 %; (c) $^{i}Pr_2NEt$, TBTU, CH_2Cl_2, rt, 15 min, 59 %

3.2.3 Synthesis of heterochiral oligomers:

It was decided to synthesize a homologous series of heterochiral oligomers up to the hexamer level. Following the same iterative coupling procedure, and using monomer and oligomer units as coupling partners, the heterochiral trimer **15**, pentamer **16** and hexamer **17** were generated (figure 3.3). Similar to the tetramer **14**, an intensive spectroscopic analysis was performed to assign and confirm the structure of these heterochiral oligomers.

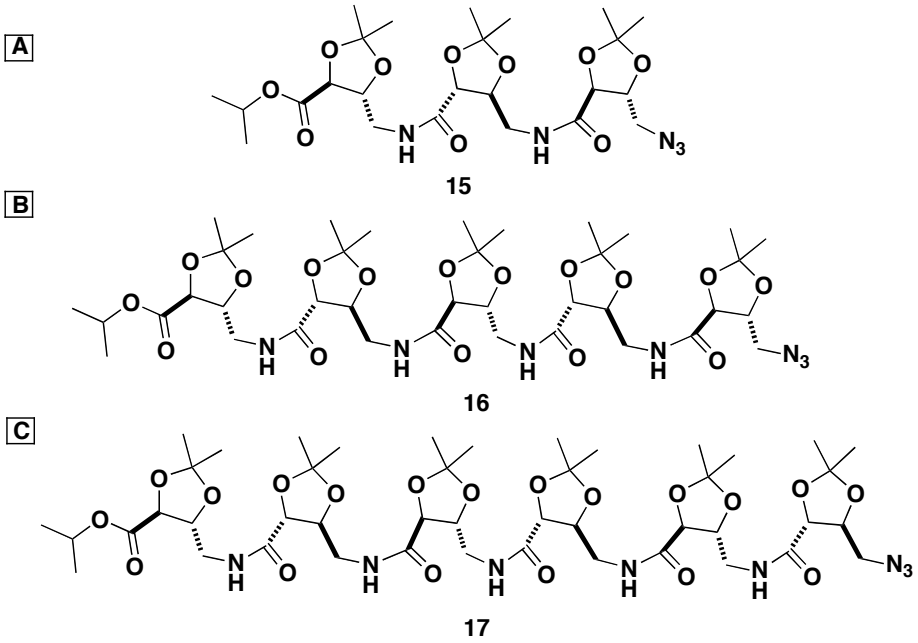


Figure 3.3: A. Trimer **15**; B. Pentamer **16**; C. Hexamer **17**

3.3 Structural assignments and investigation of conformations for oligomers:

An exhaustive spectroscopic analysis using 2D-NMR techniques was performed to assign and confirm the structure of the oligomers. As a representative example of the series, the assignment of tetramer (figure 3.4) and its preferred secondary structure is revealed here.

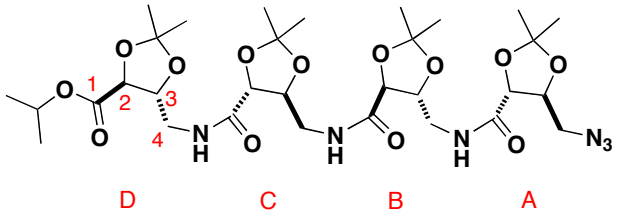


Figure 3.4: Heterochiral tetramer **14**

The solution conformation of the tetramer **(14)** was studied by NMR spectroscopy in organic solvents, and it was found that benzene-d_6 gave the best dispersion of resonances, particularly in the amide region (figure 3.5).

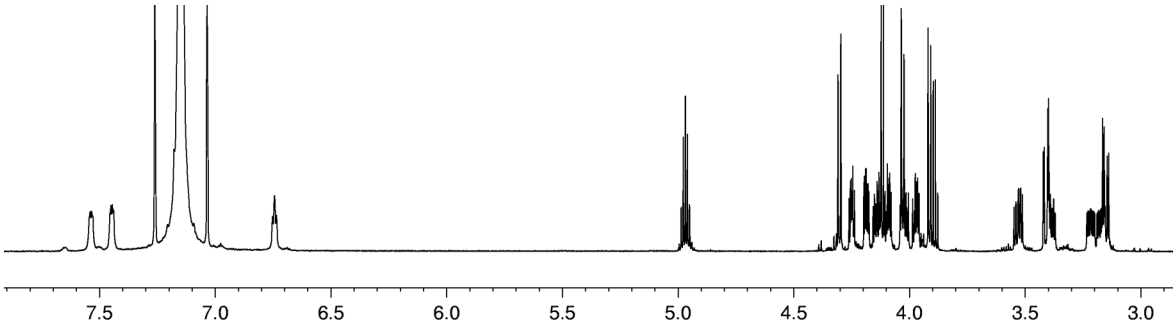


Figure 3.5: ^{1}H NMR of tetramer **14**

The resonance dispersion was excellent considering the repeating unit and was found to be independent of concentration below 10 mM, which is consistent with a highly populated solution conformation. All resonances could be unambiguously assigned through a combination of 2D experiments. COSY and TOCSY spectra allowed assignment within each residue, and semi-selective long-range heteronuclear correlations were used to establish unambiguous through-bond connectivity. Correlations between $H2^i$ and $C{=}O^i$ and also from NH^{i+1} and $H4^{i+1}$ to $C{=}O^i$ were observed, allowing all neighbouring residues to be identified. NOEs between the backbone protons (H2, H3, H4, H4') are only seen *within* each monomer unit, and all interresidue NOEs involve the amide protons (figure 3.6). No inter-residue ring-ring interactions were observed, suggesting the proposed intraresidue hydrogen bonds.

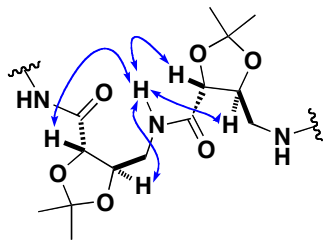


Figure 3.6: Representative NOEs for heterochiral tetramer **14** involving amide protons

Analysis of the amide regions of the ^{1}H NMR spectra of tetrameric oligomers indicated two distinct groups of amide proton resonances (see figure 3.5). The chemical shifts of amide protons are sensitive to the presence of hydrogen bonding; a decrease in diamagnetic

shielding due to involvement in a hydrogen bond should result in a downfield chemical shift. For the tetramer **14**, such a shift is observed for two of the three protons (NH^B, δ_H 7.55 and NH^C, δ_H 7.45) suggesting they are involved in hydrogen-bond formation. The remaining amide (NH^D) resonates at lower frequency (δ_H 6.78), similar to the chemical shift for dimeric amide **11** which is unable to form hydrogen bonds between the N-H and C=O groups. An equivalent pattern was observed for other oligomers.

To confirm the hypothesis for hydrogen bonding, titration experiments were performed, whereby aliquots (2 μL) of DMSO-d_6 were sequentially added to a solution of the tetramer **14** and ^{1}H NMR spectra taken. The protons that are shielded from the strongly hydrogen-bonding solvent (NH^B, NH^C) are less sensitive to perturbation on DMSO addition, whilst the solvent exposed amide proton (NH^D) shifts to higher frequency at a greater rate, consistent with its lower chemical shift (figure 3.7).

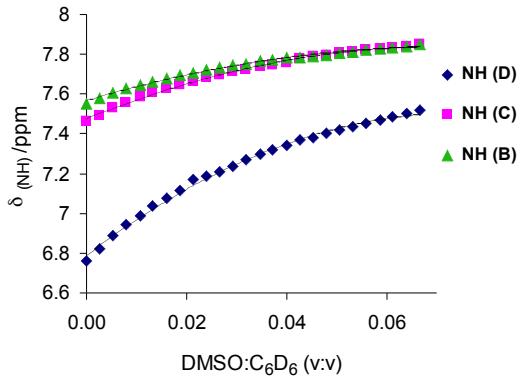


Figure 3.7: DMSO titration of heterochiral tetramer **14**

This pattern of shielded and deshielded amide protons is consistent with a repeating structural unit and suggests that tetramer **14** populates a bend-ribbon (or strand-type) conformation in benzene solution stabilized by intramolecular seven-membered-ring nearest-neighbour hydrogen bonds (figure 3.8). This conformation leaves the *C*-terminal amide (NH^D) solvent-exposed, which is consistent with an ester being a poorer hydrogen-bond acceptor than an amide.[133]

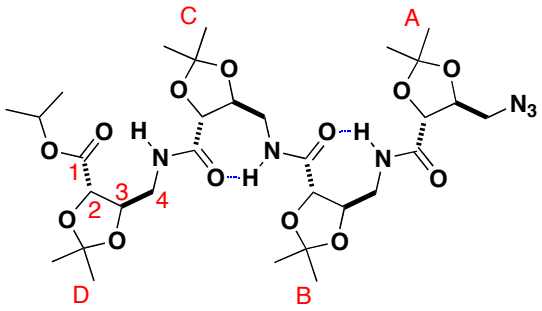


Figure 3.8: Observed bend-ribbon solution conformation of heterochiral tetramer **14** (hydrogen bonds shown in blue)

The isopropylidene groups present in all of these molecules project away from the peptidic backbone, which favours an intra-residue hydrogen bond despite the *trans*- configured ring constraint. These results are consistent with some elegant model studies on the folding of γ-amino butyric acid derivatives which demonstrated that both seven- and nine-membered nearest neighbour hydrogen bonds are favoured (figure 3.9).[100]

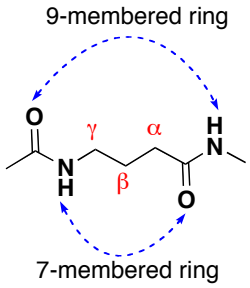


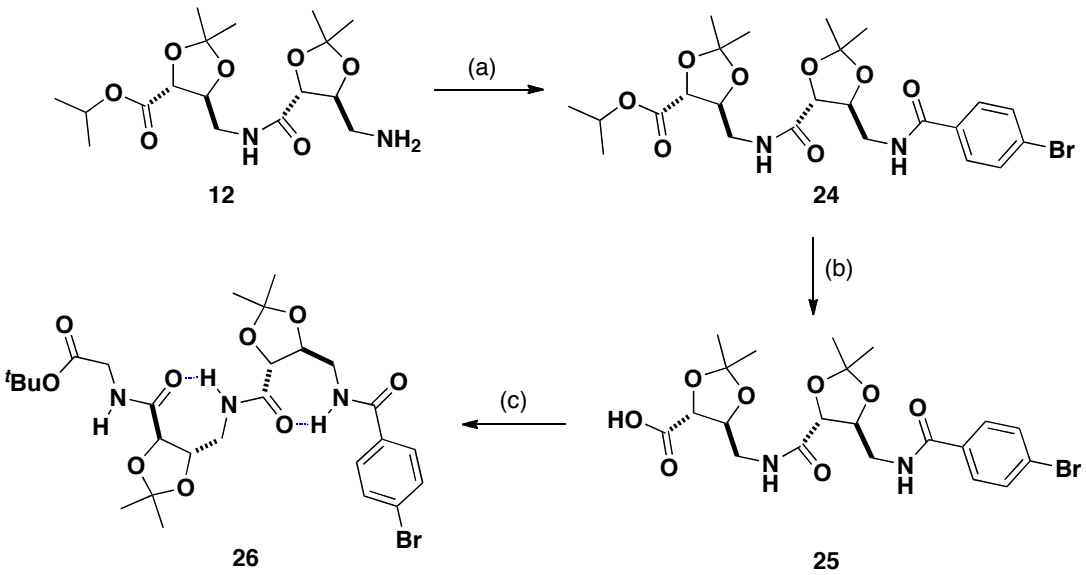
Figure 3.9: Hydrogen-bonding in γ-peptide

It is interesting to speculate why this *trans*-dioxolane constrained amino acid prefers to adopt an intra-residue hydrogen bond when the corresponding 2,3-*trans*-cyclopentane β-aminoxy acid oligomers, which effectively differ only by the substitution of the methylene group in monomers for an oxygen, form nine-membered inter-residue hydrogen bonds. The larger, nine-membered ring could be anticipated to be favoured as the geometry for the hydrogen bond can approach linearity.

A similar trend was observed in the solution conformation of the other oligomers **15**-**17**, which demonstrates that these oligomers populate bend-ribbon conformations in benzene solution stabilized by intramolecular seven-membered-ring nearest-neighbour hydrogen bonds.

3.4 Solid state conformation*:

It has been demonstrated that five-membered ring constraint γ-peptides populate a bend-ribbon conformation in solution. This could be further confirmed by the solid-state conformation of these oligomers, but unfortunately no crystals were obtained. To further investigate it was planned to synthesize a derivative of homochiral tetramer **14** (scheme 3.10).[134]



Scheme 3.10: Reagents & Conditions: (a) *p*-Bromobenzoylchloride, Et_3N, 2 h, 66 %; (b) (i) NaOH, 1,4-dioxane, 2 h; (ii) Amberlite IR-120 H^+ resin; (c) ^{t}butyl glycine ester, TBTU, Et_3N, DMF:CH_2Cl_2, 64 % (over two steps)

This derivatization provided a very similar chemical environment to the actual tetrameric γ-peptide **14** with respect to the central two units, as they were also shown to exhibit same secondary structure in the solution phase based on NMR spectroscopic data. Oligomer **26** preferred "bend ribbon" conformation in the X-ray crystal structure (figure 3.10). After correlating the results from both solution and solid phase studies it was concluded that bend ribbon shape was the most stable conformation for these γ- peptides.

* This work was done in collaboration with Dr. M. K. N. Qureshi.

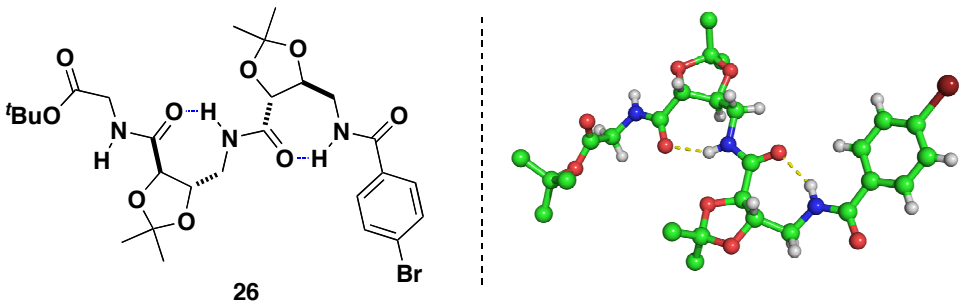


Figure 3.10: X-ray structure of **26** showing bend-ribbon conformation

3.5 Synthesis of mixed oligomers:

Concurrently, the synthesis of γ-peptide **18**, based on a six-membered ring constrained monomer unit (figure 3.11 A), was underway in the group.[135] Preliminary conformational investigations of the tetramer **18** obtained from this monomer unit demonstrated that it too populate a bend-ribbon type conformation stabilized by intra-residue seven-membered hydrogen bonded rings (figure 3.11 B).

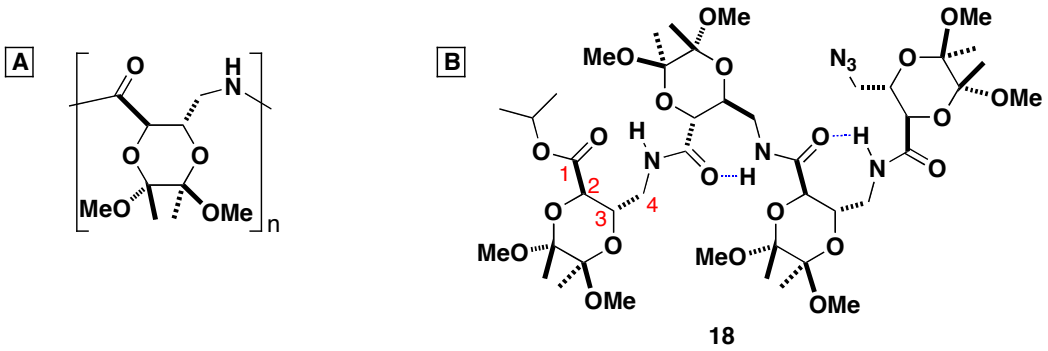


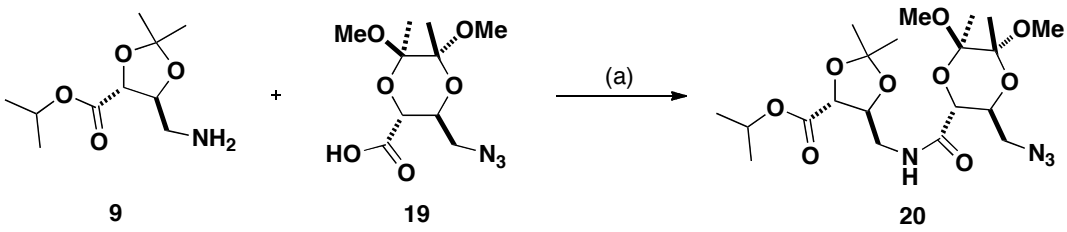
Figure 3.11: (A) Monomer unit; (B) Proposed bend-ribbon conformation of tetramer **18** (hydrogen bonds shown in blue)

Based on these observations, it was planned to synthesize oligomers with alternating five- and six-membered ring constrained monomer units utilizing the same iterative coupling strategy.

3.5.1 Synthesis of mixed dimer (5L-6L)*:

Monomer acid **19** (produced by a co-worker)[135] was used as one of the coupling partners in the synthesis of mixed dimer **20** (scheme 3.11).

* This Work was done in collaboration with Liz Jones

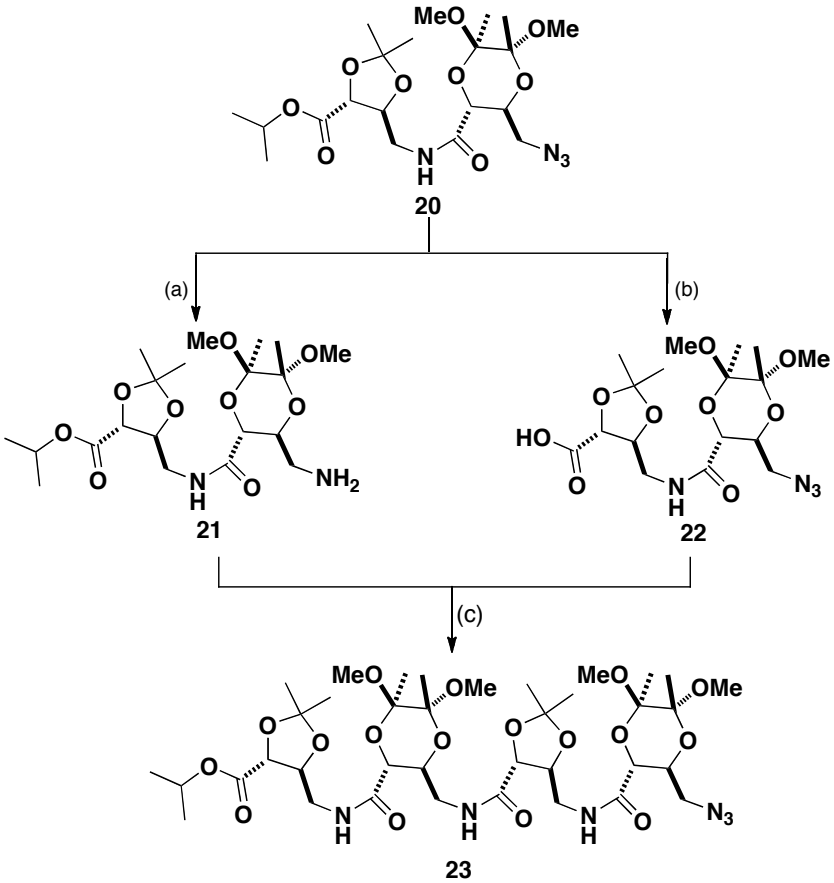


Scheme 3.11: Reagents & Conditions: (a) $^{i}Pr_2NEt$, TBTU, CH_2Cl_2, rt, 10 min, 58 %

The crude L-amine **9** was coupled with crude L-acid **19** using TBTU in the presence of DIPEA as a tertiary amine base. The minimum amount of dichloromethane was used as a solvent and the mixed dimer **20** was obtained in 58 % yield from monomer L-azido ester **8**.

3.5.2 Synthesis of mixed tetramer (5L-6L-5L-6L):

The dimeric azide **20** was reduced using 10 % palladium on carbon under an atmosphere of hydrogen to afford free amine **21**. Subsequently, the dimer azide **20** was hydrolyzed with aq. sodium hydroxide to afford free acid **22**, which was used without further purification (scheme 3.12).



Scheme 3.12: Reagents & Conditions: (a) H_2, Pd/C, IPA, 1 h, 99 %; (b) (i) 1 M aq. NaOH, EtOH, rt, 15 min then 3 N HCl, 99 %; (c) $^{i}Pr_2NEt$, TBTU, CH_2Cl_2, rt, 15 min, 59 %

Following the general coupling protocol, dimeric amine **21** was coupled with dimeric acid **22** using TBTU and DIPEA in a concentrated solution of dichloromethane. The mixed tetramer **23** was obtained in 59 % yield from dimeric azido ester **20**. An intensive spectroscopic analysis was performed to assign and confirm the structure of tetramer (see section 3.6).

3.6 Structural assignments and investigation of conformations for mixed tetramer:

A comprehensive spectrometric analysis using 2D-NMR spectroscopic techniques was performed for unambiguous assignment of the mixed tetramer structure (figure 3.12). The results are consistent with that of the heterochiral tetramer.

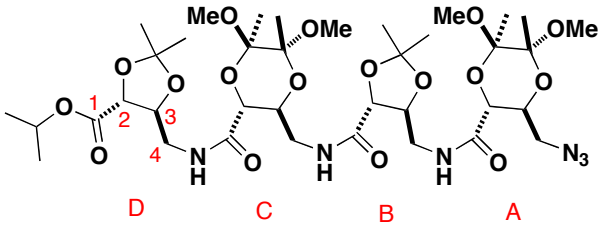


Figure 3.12: Mixed tetramer **23**

The ^{1}H NMR spectrum of mixed tetramer **23** demonstrates a similar pattern to that of heterochiral tetramer **14** in which two amide protons are shifted downfield (NH^{B}, δ_H 8.05 and NH^{C}, δ_H 7.42) (figure 3.13).

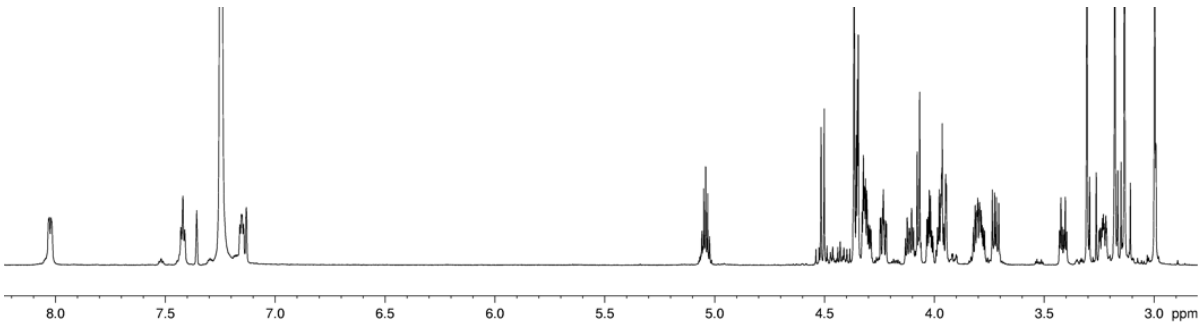


Figure 3.13: ^{1}H NMR of mixed tetramer **23**

Observations from 2D-NMR experiments and NOE data allowed unambiguous assignments of all the resonances. Correlations between $H2^{i}$ and $C{=}O^{i}$ and also from NH^{i+1} and $H4^{i+1}$ to $C{=}O^{i}$ were observed, allowing all neighbouring residues to be identified. NOEs between the backbone protons (H2, H3, H4, H4') are only seen *within* each monomer unit, and all interresidue NOEs involve the amide protons (figure 3.14).

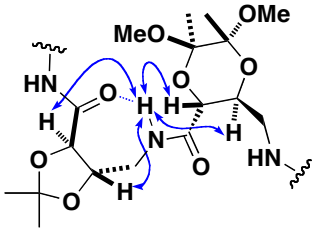


Figure 3.14: Representative NOEs for mixed tetramer **23** involving amide protons

^{1}H NMR and DMSO-d_6 titration data demonstrates that the protons shielded from the strongly hydrogen-bonding solvent are less sensitive to perturbation upon DMSO addition (NH^{B}, NH^{C}) whilst the solvent exposed amide proton (NH^{D}) shifts more rapidly to higher frequency (figure 3.15).

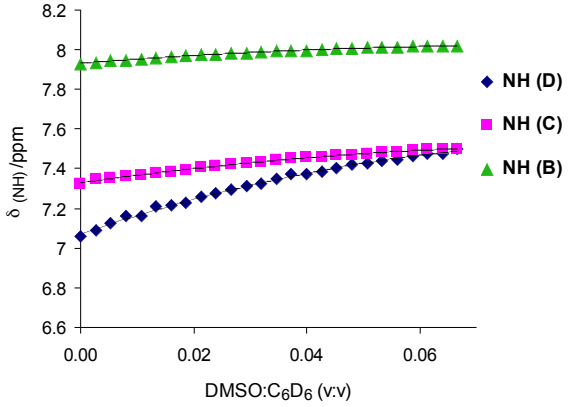


Figure 3.15: DMSO titration of mixed tetramer **23**

All of these results are consistent with those of the heterochiral tetramer and suggest that the mixed tetramer also populates a bend-ribbon conformation in solution stabilized by intramolecular seven-membered-ring nearest-neighbour hydrogen bonds (figure 3.16).

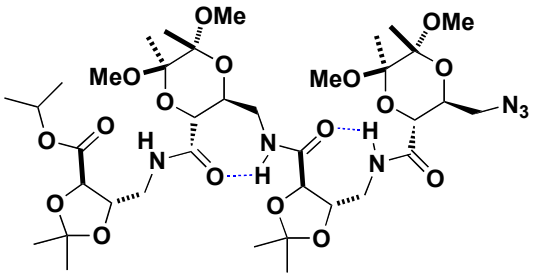


Figure 3.16: Observed bend-ribbon solution conformation of **23** (hydrogen bonds shown in blue)

3.7 Cyclopropane ring constrained γ-peptides:

Having established that five- and six-membered backbones are flexible enough to permit intramolecular hydrogen bonds, it was decided to test a more rigid three-membered cyclopropane backbone for any folding properties (figure 3.17).

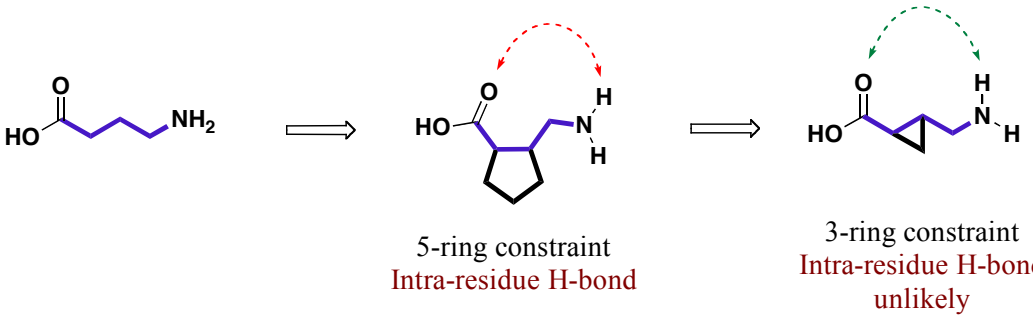


Figure 3.17: five- *vs* three-membered backbone

It was believed that intra-residue hydrogen-bonding would not be possible in these oligomers due to restricted rotation of three-membered ring constraint. Based on this hypothesis a co-worker within the group[136] synthesized oligomers from cyclopropane constrained γ-amino acids (figure 3.18 A). In contrast to five- and six-ring constrained, these oligomers form intermolecular rather than intramolecular hydrogen bonds in the solid state. Examination of the single crystal x-ray data demonstrates that the trimeric γ-peptide **27** adopts an extended conformation, and self-assembles into an infinite sheet structure through an intermolecular bifurcated hydrogen bond network in which the amide N-H and the C^{α}-H protons function as hydrogen bond donors (figure 3.18 B). [136]

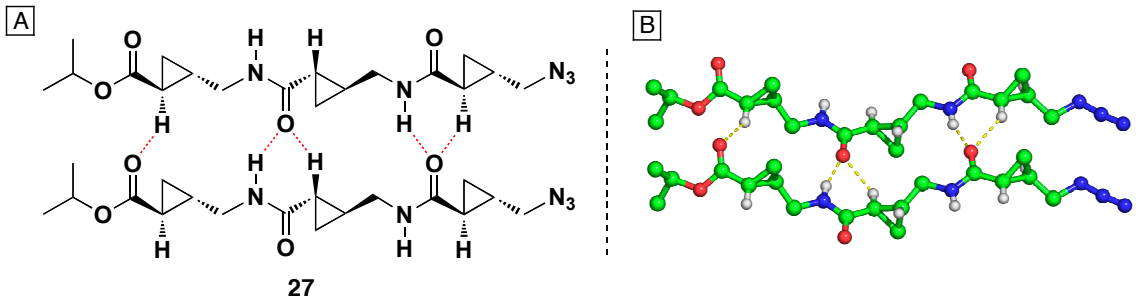


Figure 3.18: A. 3-membered ring constrained trimer **27**; B. X-ray structure of **27**

4. Conclusions

The synthesis of five-ring constrained γ-amino acid monomer units has been achieved successfully in five steps from readily available acetal-protected dimethyl tartrate. The heterochiral oligomers were synthesized in moderate yield using an iterative coupling procedure from the monomer units and the conformation of these oligomers was unambiguously assigned using 2D-NMR spectroscopic techniques.

NOE correlation data and DMSO-d_6 titration experiments suggest that these heterochiral oligomers populate a bend-ribbon (or strand-type) conformation in benzene-d_6 solution stabilized by intramolecular seven-membered-ring nearest-neighbour hydrogen bonds (figure 4.1 A). This pattern of hydrogen bonding is analogous to their homochiral counterpart. In this conformation, the isopropylidene groups project away from the peptidic backbone, thus favouring an intra-residue hydrogen bond despite the *trans*-configured ring constraint.

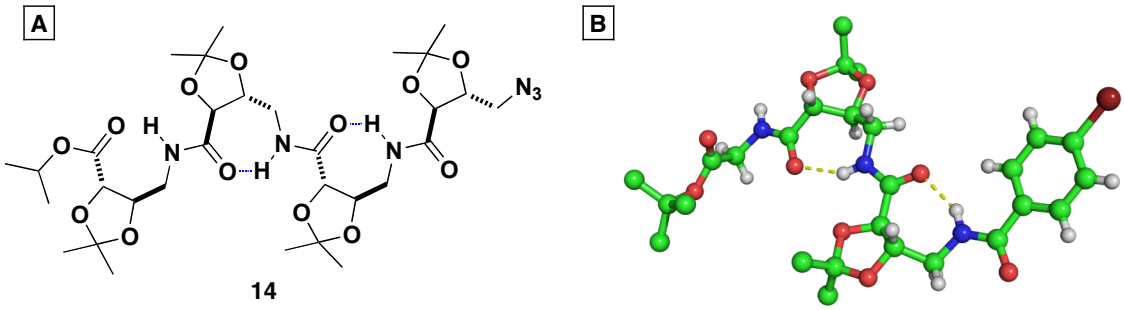


Figure 4.1: Observed bend-ribbon solution conformation of (A) Heterochiral tetramer **14**; (B) X-ray structure of **26**

Similarly, results for the mixed tetramer **23** and six-ring constrained tetramer **18** were consistent with that of the heterochiral tetramer **14** and suggest that they also populate bend-ribbon conformations in solution stabilized by intramolecular seven-membered-ring nearest-neighbour hydrogen bonds.

This study has confirmed that changing the size of the ring constraint may modulate the secondary conformation of ring-constrained γ-peptides. It has also demonstrated that intra-residue nearest-neighbour hydrogen bonds may be favoured when the flexibility of a ring constraint can permit their formation. In this scenario, the propensity for the formation of

such hydrogen bonds appears to override the influence of the absolute configuration of individual residues, as seen in the heterochiral derivatives **14**.

Three-membered cyclic backbone makes monomer units more rigid in terms of available conformations to γ-peptides and these peptides have been demonstrated to adopt an infinite parallel sheet structure in the solid state stabilized by intermolecular C–H···O hydrogen bonds (figure 4.2).[136]

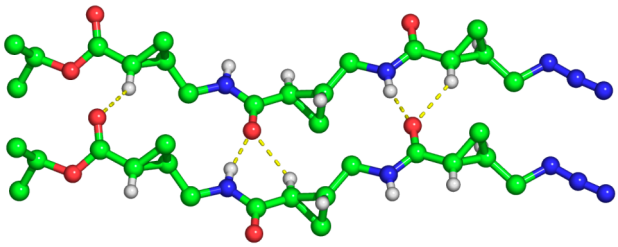


Figure 4.2: A parallel sheet structure in cyclopropane γ-peptides

This work has been extended to use these materials as scaffolds for catalysts and exploiting their scope for asymmetric catalysis of various reactions.[137,138]

CHAPTER 3: EXPERIMENTAL PROCEDURE

1. General experimental procedures.

1.1 Solvents and Reagents

THF was distilled under an atmosphere of dry nitrogen from lithium aluminium hydride and calcium hydride in the presence of triphenylmethane; dichloromethane was distilled from calcium hydride; triethylamine was distilled from calcium hydride and stored over potassium hydroxide. pH 7 Buffer was prepared by dissolving KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 mL). Petrol refers to the fraction of petroleum ether boiling between 40 and 60 ˚C. All other reagents and solvents were used as supplied, without prior purification.

1.2 Chromatography

Thin layer chromatography (TLC) was performed on glass or aluminium plates coated with Merck 60 F_{254} silica and visualization was achieved by UV light or by staining with ceric ammonium molybdate or potassium permanganate. Flash column chromatography was carried out using Merck Kieselgel (230-400 mesh).

1.3 Nuclear Magnetic Resonance Spectroscopy

NMR spectra were recorded on a Bruker Avance 700 (^{1}H: 700 MHz and ^{13}C: 175 MHz), Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100 MHz), a Bruker Avance Cryo 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz), or a Bruker DPX 200 (^{1}H: 200 MHz and ^{13}C: 50 MHz) spectrometer. Chemical shifts are quoted in ppm and are referenced to the residual non-deuterated solvent peak for proton NMR and deuterated solvent peak for carbon NMR, and are reported (based on appearance rather than interpretation) as follows: chemical shift δ/ppm (number of protons, multiplicity, coupling constant *J*/Hz, assignment) [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; sept, septet; m, multiplet]. ^{19}F spectra were run at 376 MHz on a Bruker Avance 400 with a QNP probe.

1.4 Infrared Spectroscopy

Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer fitted with an attenuated total reflectance attachment with internal referencing or a Bruker Tensor 27 FTIR with internal calibration.

1.5 Mass Spectrometry

Accurate mass measurements were performed on a Finnigan MAT 900 XLT (ES+) at the EPSRC National Mass Spectrometry Service Centre at Swansea, or on a Bruker microTOF (ES+) at the University of Oxford. LCMS were performed on an Agilent MSD LC-MS APCI 120-1000 full gradient machine or an Agilent LC-MS APCI 1100.

1.6 Polarimetry

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm.

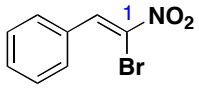
1.7 HPLC

Chiral HPLC was performed on an Agilent 1200 Series instrument or a Dionex 3000 system fitted with the appropriate Daicel Chiralpak column.

The numbering of the compounds is done solely for NMR predictions and do not corresponds to its IUPAC nomenclature.

2. For Catalytic Asymmetric Electrocyclization

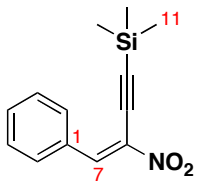
(*Z*)-(2-Bromo-2-nitrovinyl)benzene (5)



Bromine was added slowly *via* separating funnel to a solution of *trans*-β-nitrostyrene (6.0 g, 40.3 mmol) in acetic acid (21 mL) and followed by addition of K_2CO_3 (5.55 g, 40.3 mmol). When the evolution of gas had ceased, the mixture was heated to 120 °C. After 30 mins, the reaction mixture was cooled and poured into ice-cold water (40 mL) and shaken vigorously (a precipitate forms). The resultant solid was filtered off and recrystallized from ethanol to afford yellow coloured needles of **5** (5.5 g, 60 %).

m.p. 64-66 ˚C; **ν_{max}/cm^{-1} (film)**: 3061, 2966, 1620, 1528, 1246; **δ_H (400 MHz, $CDCl_3$)**: 8.65 (1H, s, *H2*), 7.89 (2H, dd, *J* 1.8, 7.5, *H4*, *H4'*), 7.50 (3H, m, *H5*, *H5'*, *H6*); **δ_C (100 MHz, $CDCl_3$)**: 135.2 (*C3*), 134.0 (*C2*), 128.5 (*C4*), 128.6 (*C5*), 127.9 (*C6*), 122.0 (*C1*); **m/z**: HRMS (ES+) found 249.9475; $C_8H_6BrNO_2$ $[M+Na]^+$ requires 249.9476.

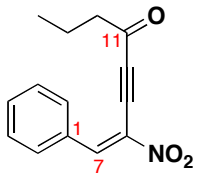
(*E*)-Trimethyl(3-nitro-4-phenylbut-3-en-1-yn-1-yl)silane (6)



$Pd(PPh_3)Cl_2$ (155 mg, 0.22 mmol) and CuI (42 mg, 0.22 mmol) were added to a solution of **5** (1.0 g, 4.4 mmol) in dioxane (40 mL) at RT, degassed and stirred for 15 mins. Et_3N (0.92 mL, 6.6 mmol) and trimethylsilylacetylene (0.93 mL, 6.6 mmol) were then added to the mixture. After 1 h, the solvent was evaporated and resulting mixture was filtered through Celite™ using diethyl ether. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford (*E*)-trimethyl(3-nitro-4-phenylbut-3-en-1-yn-1-yl)silane as a brown solid (930 mg, 86 %).

m.p. 58-60 ˚C; **ν_{max}/cm^{-1} (film)**: 3061, 2966, 2157, 1620, 1528, 1246; **δ_H (400 MHz, $CDCl_3$)**: 8.28 (1H, s, *H7*), 8.03 (2H, d, *J* 7.1, *H2* & *H6*), 7.53-7.46 (3H, m, *H3*, *H4* & *H5*), 0.33 (9H, s, *H11*); **δ_C (100 MHz, $CDCl_3$)**: 139.4 (*C7*), 132.7 (*C1*), 132.4 (Ar *C*H), 131.3 (Ar *C*H), 130.5 (*C8*), 128.9 (Ar *C*H), 111.7 (*C10*), 93.7 (*C9*), 0.6 (*C11*); **m/z**: HRMS (ES+) found 268.0776; $C_{13}H_{15}NO_2Si$ $[M+Na]^+$ requires 268.0770.

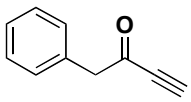
(*E*)-7-Nitro-8-phenyloct-7-en-5-yn-4-one (8)



Butyryl chloride (102 µL, 0.98 mmol) was added slowly to a mixture of **6** (200 mg, 0.82 mmol) and $AlCl_3$ (218 mg, 1.64 mmol) in CH_2Cl_2 (8 mL) at 0 ˚C and stirred for 30 mins. The reaction mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 10:1) to yield the desired product (120 mg, 61 %) as yellow oil.

ν_{max}/cm^{-1} (film): 3062, 2966, 2876, 2194, 1786, 1673, 1529, 1317; **δ_H (400 MHz, $CDCl_3$)**: 8.53 (1H, s, *H7*), 8.00 (2H, d, *J* 7.1, *H2* & *H6*), 7.58-7.54 (3H, m, *H3*, *H4* & *H5*), 2.71 (2H, t, *J* 7.3, *H12*), 1.82 (2H, td, *J* 7.3, *H13*), 1.01 (3H, t, *J* 7.4, *H14*); **δ_C (100 MHz, $CDCl_3$)**: 186.8 (*C11*), 144.5 (*C7*), 133.8 (*C1*), 131.8 (*C8*), 129.6 (Ar *C*H), 129.4 (Ar *C*H), 99.4 (*C10*), 78.2 (*C9*), 47.2 (*C12*), 17.4 (*C13*), 13.5 (*C14*); **m/z**: HRMS (ES+) found 266.0797; $C_{14}H_{13}NO_3$ $[M+Na]^+$ requires 266.0793.

1-Phenylbut-3-yn-2-one (15)[139]

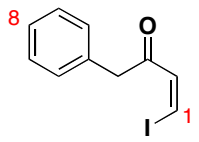


According to a literature procedure,[139] a solution of ethynylmagnesium bromide (0.5 M in THF, 55.0 mL, 27.5 mmol) was added slowly to a stirred solution of phenylacetaldehyde (3 g, 25.0 mmol) in THF (25 mL) at 0 ˚C. The solution was slowly warmed to RT. After 2 h, the reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc, 2:1) to afford the desired alcohol (2.9 g, 81 %) as a colourless oil.

A solution of alcohol (560 mg, 3.83 mmol) in CH_2Cl_2 (5 mL) was added to a solution of Dess-Martin Periodinane (1.80 g, 4.22 mmol) in CH_2Cl_2 (15 mL) at 0 ˚C. After 1 h, the reaction was quenched with 1:1 mixture of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $Na_2S_2O_3$ and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc, 5:1) to afford the desired product **15** (470 mg, 90 %) as oil.

ν_{max}/cm^{-1} (film): 3310, 3012, 2984, 2870, 2154, 1715, 1315; **δ_H (400 MHz, $CDCl_3$)**: 7.35-7.17 (5H, m, Ar C*H*), 3.71 (2H, s, CH_2), 2.84 (1H, s, C*H*); **δ_C (100 MHz, $CDCl_3$)**: 184.1 (CO), 130.7 (Ar *C*), 129.6 (Ar *C*H), 128.5 (Ar *C*H), 128.0 (Ar *C*H), 127.7 (Ar *C*H), 85.6 (*C*CH), 78.6 (C*C*H), 54.6 (*C*H$_2$); **m/z**: HRMS (ES+) found 167.0481; $C_{10}H_8O$ $[M+Na]^+$ requires 167.0473.

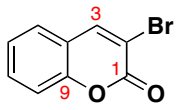
(*Z*)-4-iodo-1-phenylbut-3-en-2-one (16)[139]



According to a representative procedure,[139] acetic acid (0.22 mL, 3.80 mmol) was added to a solution of **15** (500 mg, 3.50 mmol) and LiI (501 mg, 3.80 mmol) in MeCN (4 mL) and stirred at RT. After 2 h, the resulting solution was added to ice-cold water (40 mL). Solid K_2CO_3 was added until bubbling ceased and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 15:1) to afford a mixture of *cis*-ketone (350 mg, 40 %) and *trans*-ketone (45 mg, 6 %).

ν_{max}/cm^{-1} (film): 3310, 3010, 2978, 1715; **δ_H (400 MHz, $CDCl_3$)**: 7.43-7.19 (7H, m, *H1*, *H2* & Ar C*H*), 3.85 (2H, s, *H4*); **δ_C (100 MHz, $CDCl_3$)**: 197.8 (*C3*), 145.4 (*C2*), 135.6 (q*C*), 129.6 (Ar *C*H), 129.4 (Ar *C*H), 128.7 (Ar *C*H), 91.6 (*C1*), 54.8 (*C4*); **m/z**: HRMS (ES+) found 294.9587; $C_{10}H_9IO$ $[M+Na]^+$ requires 294.9596.

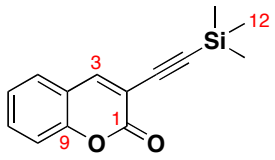
2-Bromocoumarin (20)[68]



According to a literature procedure,[68] 2 N HBr (15.1 mL, 30.1 mmol) was added in one portion to a mixture of coumarin (2.0 g, 13.7 mmol) and *OXONE*® (10.1 g, 16.5 mmol) in CH_2Cl_2 (50 mL) resulting a dark red solution. The mixture was stirred for 2 h at RT as the colour faded. Et_3N (9 mL, 64 mmol) was added slowly over 1 h and then stirred at RT for a further 12 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/petrol, 1:1) to afford 2-bromocoumarin as a white solid (2.85 g, 93 %).

m.p. 108-110 ˚C (Lit- 110-111 ˚C); **ν_{max}/cm^{-1} (film)**: 3053, 1728, 1605, 1245, 1121; **δ_H (400 MHz, $CDCl_3$)**: 8.11 (1H, s, *H3*), 7.62-7.53 (1H, m, *H7*), 7.47 (1H, dd, *J* 7.7, 1.5, *H5*), 7.35 (1H, dd, *J* 8.5, *H8*), 7.33-7.31 (1H, m, *H6*); **δ_C (100 MHz, $CDCl_3$)**: 157.5 (*C1*), 153.6 (*C9*), 144.8 (*C3*), 132.5 (*C7*), 127.5 (*C5*), 125.4 (*C6*), 119.8 (*C4*), 117.3 (*C8*), 112.3 (*C2*); **m/z**: HRMS (ES+) found 224.9545; $C_9H_5BrO_2$ $[M+H]^+$ requires 224.9546.

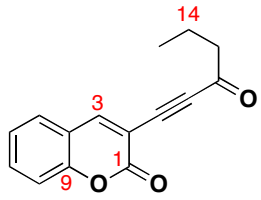
3-((Trimethylsilyl)ethynyl)-2*H*-chromen-2-one (21)



$Pd(PPh_3)Cl_2$ (0.316 g, 0.45 mmol) and CuI (0.086 g, 0.45 mmol) were added to a solution of **20** (2.0 g, 8.9 mmol) in DMF (20 mL) and degassed for 10 mins. The colour of the solution changed from yellow to light orange. Et_3N (2.5 mL, 17.8 mmol) and trimethylacetylene (1.9 mL, 13.35 mmol) were then added and the solution was heated to 60 ˚C. After 3 h, the reaction mixture was cooled to RT and then filtered through Celite™ and concentrated *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2/petrol, 1:1.5) to afford 3-((trimethylsilyl)ethynyl)-2*H*-chromen-2-one as a brown solid (1.9 g, 88 %).

m.p. 98-100 ˚C; **ν_{max}/cm^{-1} (film)**: 3068, 3035, 2960, 2154, 1726, 1605, 1250, 1058; **δ_H (400 MHz, $CDCl_3$)**: 7.88 (1H, s, *H3*), 7.50 (1H, ddd, *J* 8.6, 7.3, 1.6, *H7*), 7.43 (1H, dd, *J* 7.7, 1.5, *H5*), 7.30-7.23 (2H, m, *H6* & *H8*), 0.25 (9H, s, *H12*); **δ_C (100 MHz, $CDCl_3$)**: 159.1 (*C1*), 153.2 (*C9*), 145.9 (*C3*), 132.2 (*C7*), 127.7 (*C5*), 124.7 (*C6*), 118.5 (*C4*), 116.6 (*C8*), 112.6 (*C2*), 102.0 (*C11*), 98.0 (*C10*), 0.3 (*C12*); **m/z**: HRMS (ES+) found 243.0843; $C_{14}H_{14}O_2Si$ $[M+H]^+$ requires 243.0843.

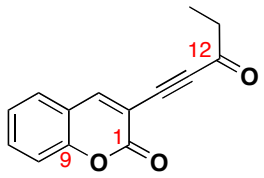
3-(3-Oxohex-1-yn-1-yl)-2*H*-chromen-2-one (23)



Butyryl chloride (0.47 mL, 4.5 mmol) was added to a solution of **21** (1.0 g, 4.1 mmol) in CH_2Cl_2 (40 mL) at 0 ˚C, followed by $AlCl_3$ (1.09 g, 8.2 mmol). After 30 mins, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under *vacuo*. The residue was purified by column chromatography (CH_2Cl_2/petrol, 4:1) to afford 3-(3-oxohex-1-yn-1-yl)-2*H*-chromen-2-one as white solid (840 mg, 85 %).

m.p. 92-95 ˚C; **ν_{max}/cm^{-1} (film)**: 3057, 2964, 2202, 1728, 1664, 1602, 1259, 1096; **δ_H (400 MHz, $CDCl_3$)**: 8.09 (1H, s, *H3*), 7.62 (1H, ddd, *J* 8.6, 7.3, 1.6, *H7*), 7.53 (1H, dd, *J* 7.8, 1.5, *H5*), 7.40-7.31 (2H, m, *H6* & *H8*), 2.68 (2H, t, *J* 7.3, *H13*), 1.78 (2H, sext., *J* 7.4, *H14*), 0.98 (3H, t, *J* 7.4, *H15*); **δ_C (100 MHz, $CDCl_3$)**: 187.5 (*C12*), 158.3 (*C1*), 154.0 (*C9*), 149.4 (*C3*), 133.8 (*C7*), 128.4 (*C5*), 125.2 (*C6*), 118.2 (*C4*), 117.0 (*C8*), 110.4 (*C2*), 92.2 (*C11*), 83.1 (*C10*), 47.3 (*C13*), 17.5 (*C14*), 13.5 (*C15*); **m/z**: HRMS (ES+) found 241.0860; $C_{15}H_{12}O_3$ $[M+H]^+$ requires 241.0859.

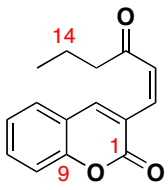
3-(3-Oxopent-1-yn-1-yl)-2*H*-chromen-2-one (24)



Propionyl chloride (79 μL, 0.91 mmol) was added to a solution of **21** (200 mg, 0.83 mmol) in CH_2Cl_2 (8 mL) at 0 ˚C, followed by $AlCl_3$ (221 mg, 1.67 mmol). After 30 mins, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/petrol, 4:1) to afford 3-(3-oxopent-1-yn-1-yl)-2*H*-chromen-2-one as a colourless oil (175 mg, 94 %).

ν_{max}/cm^{-1} (film): 3057, 2964, 2202, 1728, 1664, 1602, 1259, 1096; **δ_H (400 MHz, $CDCl_3$)**: 8.09 (1H, s, *H3*), 7.67-7.59 (1H, m, *H7*), 7.53 (1H, dd, *J* 7.7, 1.5, *H5*), 7.35 (2H, m, *H6* & *H8*), 2.74 (2H, q, *J* 7.4, *H13*), 1.22 (3H, t, *J* 7.4, *H14*); **δ_C (100 MHz, $CDCl_3$)**: 188.0 (*C12*), 158.3 (*C1*), 154.0 (*C9*), 149.3 (*C3*), 133.8 (*C7*), 128.5 (*C5*), 125.2 (*C6*), 118.3 (*C4*), 117.1 (*C8*), 110.5 (*C2*), 92.1 (*C11*), 83.3 (*C10*), 38.9 (*C13*), 8.0 (*C14*); **m/z**: HRMS (ES+) found 227.0700; $C_{14}H_{10}O_3$ $[M+H]^+$ requires 227.0703.

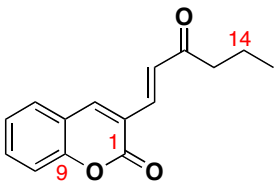
(*Z*)-3-(3-Oxopent-1-en-1-yl)-2*H*-chromen-2-one (26)



Quinoline (39 µL, 0.33 mmol) was added to a solution of **23** (800 mg, 3.33 mmol) in CH_2Cl_2 (30 mL). The mixture was degassed for 10 mins. Lindlar catalyst (160 mg, 20 % w/w) was added and the resulting mixture was stirred under a hydrogen atmosphere at RT. After 7 h, the reaction was filtered through Celite™ and concentrated under *vacuo*. The residue was purified by column chromatography (ether/petrol, 1:2) to afford (*Z*)-3-(3-oxopent-1-en-1-yl)-2*H*-chromen-2-one as a yellow crystalline solid (640 mg, 79 %).

m.p. 88-90 ˚C; **ν_{max}/cm^{-1} (film)**: 3057, 2962, 2869, 1691, 1605, 1457, 1285, 1185; **δ_H (400 MHz, $CDCl_3$)**: 8.76 (1H, s, *H3*), 7.62 (1H, d, *J* 7.7, *H5*), 7.60-7.55 (1H, m, *H7*), 7.37-7.30 (2H, m, *H6* & *H8*), 6.89 (1H, d, *J* 12.9, *H10*), 6.48 (1H, d, *J* 12.9, *H11*), 2.60 (2H, t, *J* 7.3, *H13*), 1.69 (2H, sext., *J* 7.4, 7.4, *H14*), 0.98 (3H, t, *J* 7.4, *H15*); **δ_C (100 MHz, $CDCl_3$)**: 201.4 (*C12*), 160.8 (*C1*), 153.9 (*C9*), 143.5 (*C3*), 133.0 (*C7*), 132.3 (*C10*), 130.4 (*C11*), 129.0 (*C5*), 124.6 (*C6*), 122.1 (*C4*), 119.0 (*C2*), 116.5(*C8*), 45.9 (*C13*), 17.4 (*C14*), 13.7 (*C15*); **m/z**: HRMS (ES+) found 265.0838; $C_{15}H_{14}O_3$ $[M+Na]^+$ requires 265.0835.

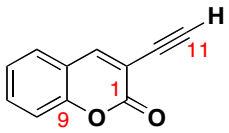
(*E*)-3-(3-Oxohex-1-en-1-yl)-2*H*-chromen-2-one (28)



^{n}BuLi (102 µL, 0.15 mmol, 1.47 M in hexane) was added to a cooled solution of diisopropylamine (22.5 µL, 0.16 mmol) in THF (1 mL) at 0 ˚C and stirred for 20 min. The reaction was cooled to -78 ˚C and **26** (32.5 mg, 0.14 mmol) in THF (1 mL) was added slowly and stirred for 30 mins. The resulting solution was warmed to RT over 1 h and stirred for 30 mins. The reaction was quenched with sat. NH_4Cl (5 mL) and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (ether/petrol, 1:2) to afford (*E*)-3-(3-oxohex-1-en-1-yl)-2*H*-chromen-2-one as a yellow solid (28 mg, 86 %).

m.p. 104-107 ˚C; **ν_{max}/cm^{-1} (film)**: 3068, 3035, 2962, 1724, 1595, 1250, 1058; **δ_H (400 MHz, $CDCl_3$)**: 7.91 (1H, s, *H3*), 7.58 (2H, m, *H5* & *H7*), 7.46 (1H, d, *J* 15.9, *H10*), 7.35 (1H, d, *J* 15.9, *H11*), 7.33 (2H, m, *H6* & *H8*), 2.65 (2H, t, *J* 7.3, *H13*), 1.71 (2H, m, *H14*), 0.97 (3H, t, *J* 7.4, *H15*); **δ_C (100 MHz, $CDCl_3$)**: 200.7 (*C12*), 159.3 (*C1*), 153.5 (*C9*), 143.7 (*C3*), 135.1 (*C10*), 133.0 (*C7*), 130.3 (*C11*), 128.5 (*C5*), 124.9 (*C6*), 122.6 (*C4*), 119.1 (*C2*), 116.7 (*C8*), 44.0 (*C13*), 17.6 (*C14*), 13.8 (*C15*); **m/z**: HRMS (ES+) found 265.0838; $C_{15}H_{14}O_3$ $[M+Na]^+$ requires 265.0835.

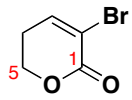
3-Ethynyl-2*H*-chromen-2-one (22)



2-(Benzyloxy)acetyl chloride (0.14 mL, 0.91 mmol) was added to a solution of **21** (200 mg, 0.83 mmol) in CH_2Cl_2 (8 mL) at 0 ˚C, followed by $AlCl_3$ (221.3 mg, 1.67 mmol). After 30 mins, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/petrol, 4:1) to afford 3-ethynyl-2*H*-chromen-2-one as a colourless oil (120 mg, 86 %).

ν_{max}/cm^{-1} (film): 3057, 2962, 2869, 2364, 1717, 1285, 1185; **δ_H (400 MHz, $CDCl_3$)**: 7.95 (1H, s, *H3*), 7.56 (1H, d, *J* 7.7, *H5*), 7.48 (dd, *J* 7.7, 1.5, *H7*), 7.32 (2H, m, *H6* & *H8*), 3.38 (1H, s, *H11*); **δ_C (100 MHz, $CDCl_3$)**: 159.4 (*C1*), 153.5 (*C9*), 146.6 (*C3*), 132.7 (*C7*), 127.9 (*C5*), 124.9 (*C6*), 118.5 (*C4*), 116.9 (*C8*), 112.0 (*C2*), 83.8 (*C10*), 81.6 (*C11*); **m/z**: HRMS (ES+) found 188.0705; $C_{11}H_6O_2$ $[M+NH_4]^+$ requires 188.0706.

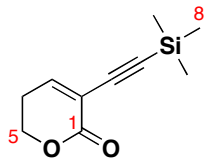
3-Bromo-5,6-dihydro-2*H*-pyran-2-one (30)[69]



According to a literature procedure,[69] a solution of bromine (2.7 mL, 52.7 mmol) in CH_2Cl_2 (50 mL) was added over 10 min to a stirred solution of dihydropyranone (4.70 g, 47.9 mmol) in CH_2Cl_2 (170 mL). The mixture was stirred at RT for 2 h, after which Et_3N (7.35 mL, 52.7 mmol) was added. After 3 h, the mixture was poured into water (200 mL) and the organic layer was separated. The aqueous fraction was extracted with CH_2Cl_2 (2 x 100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/petrol, 3:1) to yield the desired product **30** (7.9 g, 94 %) as a colourless crystalline solid.

m.p. 32-34 ˚C (Lit- 32-34 ˚C); **δ_H (400 MHz, $CDCl_3$)**: 7.28 (1H, t, *J* 4.6, *H3*), 4.48 (2H, t, *J* 6.2, *H5*), 2.56 (2H, dt, *J* 6.2, 4.6, *H4*); **δ_C (100 MHz, $CDCl_3$)**: 159.5 (*C1*), 146.1 (*C3*), 114.1 (*C2*), 67.0 (*C5*), 26.9 (*C4*); **m/z**: HRMS (ES+) found 198.9370; $C_5H_5BrO_2$ $[M+Na]^+$ requires 198.9371.

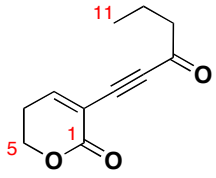
3-((Trimethylsilyl)ethynyl)-5,6-dihydro-2*H*-pyran-2-one (31)



Et_3N (9.5 mL, 68.2 mmol) and trimethylsilyl acetylene (7.23 mL, 51.2 mmol) were added to a mixture of **30** (6.0 g, 34.1 mmol), $Pd(PPh_3)_2Cl_2$ (1.2 g, 1.71 mmol) and CuI (325 mg, 1.71 mmol) in 1,4-dioxane (140 mL). The reaction mixture was stirred under argon at RT for 30 mins and then filtered through Celite™ with CH_2Cl_2. The filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (ether/petrol, 1.5:1) to yield the desired product (5.2 g, 78 %) as a brown solid.

m.p. 77-79 ˚C; **ν_{max}/cm^{-1} (film)**: 2966, 2159, 1714, 1677, 1252,1123; **δ_H (400 MHz, $CDCl_3$)**: 7.18 (1H, t, *J* 4.7, *H3*), 4.39 (2H, t, *J* 6.4, *H5*), 2.53 (2H, dt, *J* 6.4, 4.7, *H4*), 0.21 (9H, s, *H8*); **δ_C (100 MHz, $CDCl_3$)**: 161.8 (*C1*), 149.7 (*C3*), 118.4 (*C2*), 98.6 (*C7*), 78.9 (*C6*), 66.7 (*C5*), 25.1 (*C4*), 0.2 (*C8*); **m/z**: HRMS (ES+) found 217.0658; $C_{10}H_{14}O_2Si$ $[M+Na]^+$ requires 217.0661.

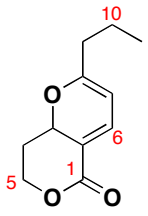
3-(3-Oxohex-1-yn-1-yl)-5,6-dihydro-2*H*-pyran-2-one (32)



Butyryl chloride (0.71 mL, 6.8 mmol) was slowly added to a mixture of **31** (1.1 g, 5.67 mmol) and $AlCl_3$ (1.5 g, 11.34 mmol) in CH_2Cl_2 (50 mL) at 0 ˚C and stirred for 15 mins. The reaction mixture was diluted with water (25 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/petrol, 1:1) to yield the desired product (580 mg, 53 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 2985, 2170, 1722, 1677, 1267, 1160; **δ_H (400 MHz, $CDCl_3$)**: 7.42 (1H, t, *J* 4.6, *H3*), 4.47 (2H, t, *J* 6.2, *H5*), 2.67-2.61 (2H, m, *H4*), 2.62 (2H, t, *J* 5.9, *H9*), 1.75 (2H, sext., *J* 7.4, *H10*), 0.96 (3H, t, *J* 7.4, *H11*); **δ_C (100 MHz, $CDCl_3$)**: 186.7 (*C8*), 165.1 (*C1*), 150.2 (*C3*), 119.4 (*C2*), 90.0 (*C7*), 86.7 (*C6*), 67.6 (*C5*), 46.5 (*C9*), 22.4 (*C4*), 17.1 (*C10*), 13.6 (*C11*); **m/z**: HRMS (ES+) found 193.0861; $C_{11}H_{12}O_3$ $[M+H]^+$ requires 193.0865.

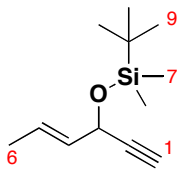
2-Propyl-8,8a-dihydropyrano[4,3-*b*]pyran-5(7*H*)-one (34)



A mixture of **32** (100 mg, 0.52 mmol) and Lindlar catalyst (20 mg, 20 wt%) in CH_2Cl_2 (5 mL) was stirred under a hydrogen atmosphere at RT. After 1 h, TLC indicated complete conversion of starting material. The reaction mixture was filtered through Celite™ with CH_2Cl_2 and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/petrol, 1:1) to yield the *oxo*-cyclized product (62 mg, 61 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2963, 2932, 1703, 1552, 1267, 1077; **δ_H (400 MHz, $CDCl_3$)**: 7.22 (1H, d, *J* 5.9, *H6*), 5.47 (1H, d, *J* 5.9, *H7*), 4.82-4.75 (1H, m, *H3*), 4.40 (1H, ddd, *J* 11.6, 5.3, 4.0, *H5*), 4.26-4.19 (1H, m, *H5*), 2.34 (2H, sext., *H4*), 2.20 (2H, t, *J* 7.5, *H9*), 1.57 (2H, dt, *J* 14.8, 7.0, *H10*), 0.94 (3H, t, *J* 7.4, *H11*); **δ_C (100 MHz, $CDCl_3$)**: 167.1 (*C8*), 165.1 (*C1*), 137.6 (*C6*), 109.6 (*C2*), 101.7 (*C7*), 71.7 (*C3*), 63.8 (*C5*), 35.6 (*C9*), 28.7 (*C4*), 20.3 (*C10*), 13.6 (*C11*); **m/z**: HRMS (ES+) found 217.0840; $C_{11}H_{14}O_3$ $[M+Na]^+$ requires 217.0841.

(*E*)-*tert*-Butyl(hex-4-en-1-yn-3-yloxy)dimethylsilane (61)[74]

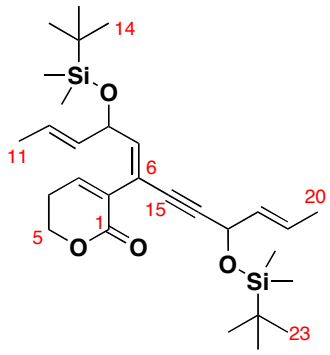


According to a literature procedure,[74] a solution of crotonaldehyde **60** (3.0 g, 42.8 mmol) in THF (25 mL) was added slowly to a solution of ethynylmagnesium bromide (0.5 M in THF, 94 mL, 47 mmol) at -78 ˚C. After 2 h, the reaction was quenched with sat. NH_4Cl and extracted with ether (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (CH_2Cl_2/petrol, 2:1) to afford (*E*)-hex-4-en-1-yn-3-ol (3.9 g, 95 %) as yellow oil.

According to a literature procedure,[75] imidazole (850 mg, 12.5 mmol) was added to a solution of alcohol (1.0 g, 10.4 mmol) in CH_2Cl_2 (5 mL). This was followed by addition of TBSCl (1.9 g, 12.5 mmol) at RT. After 2 h, the reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified over Et_3N doped silica by column chromatography (CH_2Cl_2/petrol, 1:10) to afford (*E*)-*tert*-butyl(hex-4-en-1-yn-3-yloxy)dimethylsilane **61** (2.2 g, 76 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 5.86-5.77 (1H, m, *H5*), 5.56 (1H, dd, *J* 5.6, *H4*), 4.83 (1H, d, *J* 5.6, *H3*), 2.47 (1H, s, *H1*), 1.71 (3H, d, *J* 6.6, *H6*), 0.90 (9H, s, *H9*), 0.12 (6H, d, *J* 5.0, *H7*); **δ_C (100 MHz, $CDCl_3$)**: 130.6 (*C4*), 127.0 (*C5*), 84.2 (*C2*), 73.0 (*C1*), 63.3 (*C3*), 25.6 (*C9*), 18.3 (*C8*), 17.4 (*C6*), -4.6 (*C7*); **m/z**: HRMS (ES+) found 210.1436; $C_{12}H_{22}OSi$ $[M]^+$ requires 210.1440.

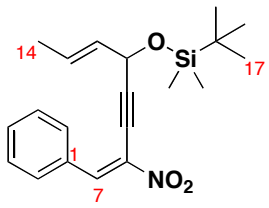
3-((*Z*)-2,2,3,3,12,12,13,13-Octamethyl-5,10-di((*E*)-prop-1-en-1-yl)-4,11-dioxa-3,12-disilatetradec-6-en-8-yn-7-yl)-5,6-dihydro-2*H*-pyran-2-one (63)



A solution of **30** (197 mg, 0.94 mmol), $Pd(PPh_3)Cl_2$ (29.8 mg, 0.043 mmol) and CuI (8.2 mg, 0.043 mmol) in 1,4-dioxane (6 mL) was degassed and stirred at RT for 15 mins. A solution of **61** (150 mg, 0.85 mmol) in dioxane (2 mL) was added, followed by Et_3N (0.18 mL, 1.28 mmol). After 1 h, the solvent was evaporated and residue was dissolved in CH_2Cl_2 and filtered through Celite™. The crude product was purified over Et_3N doped silica by column chromatography (petrol/EtOAc, 3:1) to afford the desired product (132 mg, 30 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2955, 2857, 1728, 1472, 1251, 1059; **δ_H (400 MHz, $CDCl_3$)**: 7.22 (1H, dd, *J* 8.2, 4.6 Hz, *H3*), 6.78 (1H, dd, *J* 8.5, 1.2, *H7*), 5.86-5.75 (1H, m, *H19*), 5.74-5.65 (1H, m, *H10*), 5.62-5.54 (1H, m, *H18*), 5.50-5.41 (1H, m, *H9*), 5.13 (1H, dd, *J* 6.4, 6.4, *H8*), 5.02 (1H, dd, *J* 5.1, *H17*), 4.31 (2H, t, *J* 6.2, *H5*), 2.53-2.50 (2H, m, *H4*), 1.72 (3H, d, *J* 6.4, *H20*), 1.66 (3H, d, *J* 6.5, *H11*), 0.91 (9H, s, *H23*), 0.87 (9H, s, *H14*), 0.12 (6H, s, *H21*), 0.05 (6H, s, *H12*); **δ_C (100 MHz, $CDCl_3$)**: 162.1 (*C1*), 144.6 (*C7*), 141.9 (*C3*), 131.7 (*C9*), 131.0 (*C18*), 129.2 (*C6*), 127.0 (*C10*), 125.6 (*C19*), 115.8 (*C2*), 96.7 (*C16*), 80.0 (*C15*), 72.9 (*C8*), 65.6 (*C5*), 64.0 (*C17*), 25.9 (*C14*), 25.8 (*C23*), 24.8 (*C4*), 18.3 (*C13*), 18.2 (*C22*), 17.7 (*C11*), 17.4 (*C20*), -4.4 (*C12*), -4.6 (*C21*); **m/z**: HRMS (ES+) found 539.2993; $C_{29}H_{48}O_4Si_2$ $[M+Na]^+$ requires 539.2989.

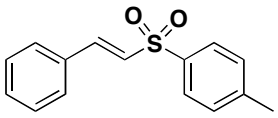
***tert*-Butyldimethyl(((2*E*,7*E*)-7-nitro-8-phenylocta-2,7-dien-5-yn-4-yl)oxy)silane**



A solution of **5** (200 mg, 0.88 mmol), $Pd(PPh_3)Cl_2$ (31.0 mg, 0.044 mmol) and CuI (8.4 mg, 0.044 mmol) in dioxane (6 mL) was degassed and stirred at RT for 15 mins. A solution of **61** (206 mg, 0.96 mmol) in dioxane (4 mL) was added to the above mixture, followed by Et_3N (0.18 mL, 1.32 mmol) and heated at 50 ˚C. After 3 h, the reaction was cooled to RT, the solvent was evaporated and the residue was dissolved in CH_2Cl_2 and filtered through Celite™. The crude product was purified over Et_3N doped silica by column chromatography (petrol/EtOAc, 20:1) to afford *tert*-butyldimethyl(((2*E*,7*E*)-7-nitro-8-phenylocta-2,7-dien-5-yn-4-yl)oxy)silane (255 mg, 81 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 3010, 2930, 2857,2337, 1624, 1532, 1324, 1251; **δ_H (400 MHz, $CDCl_3$)**: 8.27 (1H, s, *H7*), 7.99 (1H, d, *J* 7.4, *H2* & *H6*), 7.53-7.46 (1H, m, Ar C*H*), 7.46-7.42 (2H, m, Ar C*H*), 6.00-5.87 (1H, m, *H13*), 5.69-5.61 (1H, m, *H12*), 5.19 (1H, d, *J* 5.9, *H11*), 1.79-1.77 (3H, d, *J* 6.5, *H14*), 0.93 (9H, s, *H17*), 0.16 (6H, d, *J* 1.9, *H15*); **δ_C (100 MHz, $CDCl_3$)**: 138.8 (*C7*), 132.3 (Ar *C*H), 131.2 (Ar *C*H), 130.5 (*C1*), 129.6 (*C12*), 129.0 (Ar *C*H), 128.3 (*C13*), 104.2 (*C10*), 74.8 (*C9*), 64.2 (*C11*), 25.8 (*C17*), 18.3 (*C16*), 17.6 (*C14*), -4.6 (*C15*); **m/z**: HRMS (ES+) found 375.2102; $C_{20}H_{27}NO_3Si$ $[M+NH_4]^+$ requires 375.2098.

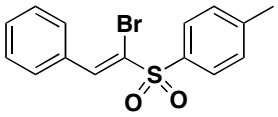
(*E*)-1-Methyl-4-(styrylsulfonyl)benzene (38)[70]



According to a literature procedure,[70] a solution of CAN (13.7 g, 25 mmol) in dry CH_3CN (80 mL) was added dropwise to a degassed mixture of styrene (1.04 g, 10 mmol), *p*-toluene sulfinate (2.10 g, 11.5 mmol) and NaI (1.73 g, 11.5 mmol) in dry acetonitrile (120 mL). The reaction mixture was stirred vigorously at RT under an argon atmosphere for 45 min. The solvent was removed *in vacuo*; the residue was diluted with water (300 mL) and extracted using dichloromethane (3 x 200 mL). The combined organic extracts were washed with water, saturated sodium thiosulfate and brine. The organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography on neutral alumina (EtOAc/petrol, 1:4) to afford the vinyl sulfone (2.4 g, 93 %) as a colourless crystalline solid.

m.p. 107-109 ˚C (lit: 119-121 ˚C); **δ_H (400 MHz, $CDCl_3$)**: 7.82 (2H, d, *J* 8.3, Ar C*H*), 7.65 (1H, d, *J* 15.4, C*H*), 7.54-7.42 (2H, m, Ar C*H*), 7.42-7.29 (5H, m, Ar C*H*), 6.83 (1H, d, *J* 15.4, SO_2CH), 2.43 (3H, s, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 144.2 (Ar *C*H), 141.7 (Ar *C*H), 137.9 (*C*H), 132.4 (Ar *C*H), 130.9 (Ar *C*H), 129.9 (Ar *C*H), 128.9 (Ar *C*H), 128.5 (Ar *C*H), 127.8 (Ar *C*H), 127.7 (SO_2CH), 21.5 (CH_3); **m/z**: HRMS (ES+) found 281.0613; $C_{15}H_{14}O_2S$ $[M+Na]^+$ requires 281.0612.

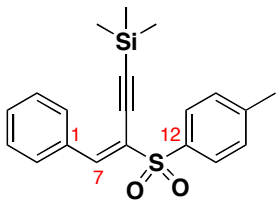
(*Z*)-1-((1-Bromo-2-phenylvinyl)sulfonyl)-4-methylbenzene (39)



Bromine (52 μL, 2.0 mmol) was added slowly to a solution of **38** (516 mg, 2.0 mmol) in acetic acid (10 mL) surrounded by a cold-water bath, followed by addition of anhydrous K_2CO_3 (145 mg, 1.0 mmol). When the evolution of gas had ceased, the mixture was refluxed for 30 mins, then cooled, poured into cold water and stirred vigorously. The mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified over alumina by column chromatography (petrol/EtOAc, 4:1) to afford (*Z*)-1-((1-bromo-2-phenylvinyl)sulfonyl)-4-methylbenzene (630 mg, 95 %) as a white crystalline solid.

m.p. 88-90 ˚C; **ν_{max}/cm^{-1} (film)**: 3045, 2915, 1615, 1597, 1491, 1324, 1153; **δ_H (400 MHz, $CDCl_3$)**: 8.34 (1H, s, C*H*), 7.88 (2H, d, *J* 8.3, Ar C*H*), 7.84-7.78 (2H, m, Ar C*H*), 7.46-7.40 (3H, m, Ar C*H*), 7.36 (2H, d, *J* 8.0, Ar C*H*), 2.46 (3H, s, C*H*$_3$); **δ_H (400 MHz, $CDCl_3$)**: 145.1 (Ar *C*H), 138.5 (Ar *C*H), 134.3 (*C*H), 131.9 (Ar *C*H), 130.9 (Ar *C*H), 130.1 (Ar *C*H), 129.8 (Ar *C*H), 129.2 (Ar *C*H), 128.7 (Ar *C*H), 121.1 (*C*Br), 21.7 (*C*H$_3$); **m/z**: HRMS (ES+) found 358.9714; $C_{15}H_{13}BrO_2S$ $[M+Na]^+$ requires 358.9712.

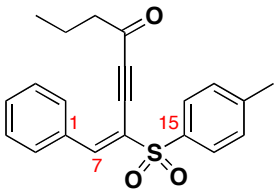
(*E*)-Trimethyl(4-phenyl-3-tosylbut-3-en-1-yn-1-yl)silane (40)



$Pd(PPh_3)Cl_2$ (21 mg, 0.03 mmol) and CuI (6 mg, 0.03 mmol) were added to a solution of **39** (202 mg, 0.6 mmol) in DMF (6 mL) at RT, degassed and stirred for 15 mins. Et_3N (126 µL, 0.9 mmol) and trimethylsilylacetylene (132 µL, 0.9 mmol) were added and the mixture was heated to 50 ˚C. After 5 h, the solvent was evaporated and resulting mixture was filtered through Celite™ using Et_2O. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (petrol/EtOAc, 6:1) to afford (*E*)-trimethyl(3-nitro-4-phenylbut-3-en-1-yn-1-yl)silane as a colourless oil (155 mg, 73 %).

ν_{max}/cm^{-1} (film): 3024, 2960, 2157, 1321, 1251, 1154, 1090, 846; **δ_H (400 MHz, $CDCl_3$)**: 7.96 (2H, dt, *J* 3.7, 2.2, Ar C*H*), 7.87 (1H, s, *H7*), 7.84 (2H, d, *J* 8.3, Ar C*H*), 7.43-7.34 (3H, m, Ar C*H*), 7.31 (2H, d, *J* 8.0, Ar C*H*), 2.42 (3H, s, CH_3), 0.19 (9H, s, *H11*); **δ_C (100 MHz, $CDCl_3$)**: 144.8 (*C8*), 142.2 (*C7*), 136.0 (q*C*), 133.0 (q*C*), 131.7 (Ar *C*H), 130.5 (Ar *C*H), 129.7 (Ar *C*H), 129.2 (Ar *C*H), 128.8 (Ar *C*H), 124.9 (q*C*), 110.4 (*C10*), 96.8 (*C9*), 21.9 (*C*H_3), -0.5 (*C11*); **m/z**: HRMS (ES+) found 377.1001; $C_{20}H_{22}O_2SSi$ $[M+Na]^+$ requires 377.1002.

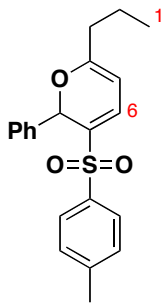
(*E*)-8-Phenyl-7-tosyloct-7-en-5-yn-4-one (41)



Butyryl chloride (18 µL, 0.17 mmol) was added slowly to a mixture of **40** (50 mg, 0.14 mmol) and $AlCl_3$ (37.3 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) at 0 ˚C and stirred for 30 mins. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 4:1) to yield the desired product (42 mg, 90 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 3010, 2966, 2876, 2194, 1786, 1673, 1529, 1321; **δ_H (400 MHz, $CDCl_3$)**: 8.12 (1H, s, *H7*), 7.93-7.88 (2H, m, Ar C*H*), 7.85 (2H, d, *J* 8.3, Ar C*H*), 7.51-7.41 (3H, m, Ar C*H*), 7.35 (2H, d, *J* 8.1, Ar C*H*), 2.55 (2H, t, *J* 7.3, *H12*), 2.43 (3H, s, C*H*$_3$), 1.69 (2H, m, *H13*), 0.94 (3H, t, *J* 7.4, *H14*); **δ_C (100 MHz, $CDCl_3$)**: 186.6 (*C11*), 147.2 (*C7*), 145.1 (*C8*), 135.5 (*C*CH_3), 132.6 (*C15*), 132.0 (q*C*), 130.7 (Ar *C*H), 129.9 (Ar *C*H), 129.0 (Ar *C*H), 128.7 (Ar *C*H), 122.4 (Ar *C*H), 98.2 (*C10*), 81.2 (*C9*), 47.2 (*C12*), 21.7 (*C*H_3), 17.4 (*C13*), 13.5 (*C14*); **m/z**: HRMS (ES+) found 375.1034; $C_{21}H_{20}O_3S$ $[M+Na]^+$ requires 375.1031.

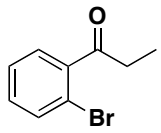
2-phenyl-6-propyl-3-tosyl-2*H*-pyran (43)



A mixture of **41** (20 mg, 0.06 mmol) and Lindlar catalyst (2 mg, 10 wt%) in CH_2Cl_2 (1 mL) was stirred under a hydrogen atmosphere at RT in the dark. After 1 h, the reaction mixture was filtered through Celite™ with CH_2Cl_2 and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/petrol, 1:6) to yield the *oxo*-cyclized product (14 mg, 70 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3010, 2980, 2874, 1780, 1673, 1530, 1308; **δ_H (400 MHz, $CDCl_3$)**: 7.55 (2H, d, *J* 8.3, Ar C*H*), 7.27-7.23 (3H, m, *H6* & Ar C*H*), 7.20-7.16 (3H, m, Ar C*H*), 7.12 (2H, d, *J* 8.1, Ar C*H*), 6.02 (1H, s, *H8*), 5.26 (1H, d, *J* 6.3, *H5*), 2.33 (3H, s, C*H*$_3$), 2.07-1.88 (2H, m, *H3*), 1.36-1.18 (2H, m, *H2*), 0.62 (3H, t, *J* 7.4, *H1*); **δ_C (100 MHz, $CDCl_3$)**: 167.0 (*C4*), 142.5 (*C7*), 141.2 (Ar *C*), 139.8 (Ar *C*CH_3), 137.2 (*C6*), 135.8 (Ar *C*SO_2), 129.6 (Ar *C*H), 129.4 (Ar *C*H), 128.8 (Ar *C*H), 127.9 (Ar *C*H), 127.0 (Ar *C*H), 102.1 (*C5*), 72.5 (*C8*), 35.4 (*C3*), 21.4 (*C*H_3), 20.2 (*C2*), 13.5 (*C1*); **m/z**: HRMS (ES+) found 377.1179; $C_{21}H_{22}O_3S$ $[M+Na]^+$ requires 377.1187.

1-(2-Bromophenyl)propan-1-one (48)[71]

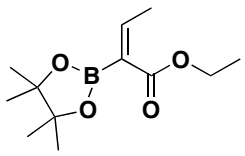


According to a literature procedure,[71] a solution of ethylmagnesium bromide (1.0 M in THF, 10 mL, 10 mmol) was added slowly to a stirred solution of 2-bromobenzaldehyde (1.1g, 6 mmol) in THF (10 mL) at 0 ˚C. The solution was slowly warmed to RT. After 2 h, the reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc, 2:1) to afford the desired alcohol (955 mg, 75 %) as a colourless oil.

A solution of trifluoroacetic anhydride (0.92 mL, 6.63 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of DMSO (0.63 mL, 8.84 mmol) in CH_2Cl_2 (8 mL) at -78 °C. After stirring for 10 min, a solution of the alcohol (950 mg, 4.42 mmol) in CH_2Cl_2 (8 mL) was added dropwise to the mixture. The reaction mixture was allowed warm to RT, and Et_3N (1.85 mL, 13.3 mmol) was added by syringe. After 1 h, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (petrol/EtOAc, 8:1) to afford the desired product **48** (850 mg, 90 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 7.60 (1H, dd, *J* 8.6, 0.8, Ar C*H*), 7.47-7.22 (3H, m, Ar C*H*), 2.77 (2H, q, *J* 7.4, CH_2), 1.26 (3H, t, *J* 7.4, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 205.1 (*C*O), 141.9 (q*C*), 133.6 (Ar *C*H), 131.3 (Ar *C*H), 128.1 (Ar *C*H), 127.4 (Ar *C*H), 118.5 (q*C*), 36.4 (*C*H_2), 8.1 (*C*H_3); **m/z**: HRMS (ES+) found 234.9728; C_9H_9BrO $[M+Na]^+$ requires 234.9729.

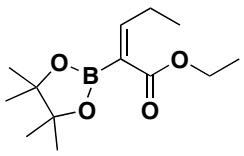
(*Z*)-Ethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (49)[72]



According to a literature procedure,[72] in a flame dried flask, Stryker's reagent $[(PPh_3)CuH]_6$ (35 mg, 0.10 mmol) and PPh_3 (52.5 mg, 0.20 mmol) were weighed under an argon atmosphere and dissolved in THF (3 mL). The resulting bright red solution was cooled in an ice bath and pinacolborane (0.8 mL, 5.5 mmol) was added and allowed to stir for 5 min. This caused the solution to turn to a darker colour. Ethyl but-2-ynoate (582 μL, 5.0 mmol) was then added dropwise over 5 min. The solvent was evaporated under reduced pressure and the residue was quickly purified over a short pad of silica (5% EtOAc/petrol) to afford the desired boronate (920 mg, 77 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2979, 2936, 1719, 1626, 1355, 1212, 1136, 1036; **δ_H (400 MHz, $CDCl_3$)**: 6.79 (1H, q, *J* 7.0, C*H*), 4.21 (2H, q, *J* 7.1, CH_2), 1.96 (3H, d, *J* 7.0, CH_3), 1.28 (3H, t, *J* 7.1, CH_3), 1.25 (12H, s, CCH_3); **δ_C (100 MHz, $CDCl_3$)**: 169.2 (*C*O), 151.6 (*C*H), 128.7 (*C*CH), 83.8 (O*C*CH_3), 60.2 (O*C*H_2), 24.6 (C*C*H_3), 17.2 (CH*C*H_3), 14.3 (CH_2*C*H_3); **m/z**: HRMS (ES+) found 263.1430; $C_{12}H_{21}BO_4$ $[M+Na]^+$ requires 263.1427.

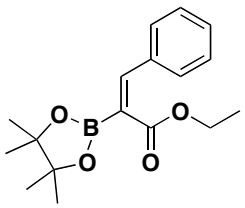
(*Z*)-Ethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate (50) [72]



According to a literature procedure,[72] in a flame dried flask, Stryker's reagent $[(PPh_3)CuH]_6$ (70 mg, 0.20 mmol) and triphenylphosphine (105 mg, 0.40 mmol) were weighed under an argon atmosphere and dissolved in THF (10 mL). The resulting bright red solution was cooled in an ice bath and pinacolborane (1.6 mL, 11 mmol) was added and allowed to stir for 5 min. This caused the solution to turn to a darker colour. Ethyl pent-2-ynoate (1.32 mL, 10 mmol) was then added dropwise over 5 min. The solvent was evaporated under reduced pressure and the residue was quickly purified over a short pad of silica (petrol/EtOAc, 10:1) to afford (*Z*)-ethyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate (1.84 g, 73 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 6.65 (1H, t, *J* 7.3, C*H*), 4.20 (2H, q, *J* 7.1, OCH_2), 2.36 (2H, dq, *J* 7.5, 7.1, CH_2CH_3), 1.28 (3H, t, *J* 7.1, ester CH_3), 1.25 (12H, s, CCH_3), 1.03 (3H, t, *J* 7.6, CH_2CH_3); **δ_C (100 MHz, $CDCl_3$)**: 169.3 (O*C*O), 157.9 (*C*H), 128.7 (*C*CH), 83.8 (O*C*CH_3), 60.2 (O*C*H_2), 24.6 (C*C*H_3), 24.5 (*C*H_2CH_3), 14.3 (ester *C*H_3), 13.2 (CH_2*C*H_3); **m/z**: HRMS (ES+) found 277.1599; $C_{13}H_{23}BO_4$ $[M+Na]^+$ requires 277.1587.

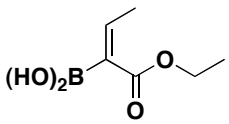
(*Z*)-Ethyl 3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (51) [72]



According to a literature procedure,[72] in a flame dried flask, Stryker's reagent $[(PPh_3)CuH]_6$ (7 mg, 0.02 mmol) and PPh_3 (10.5 mg, 0.04 mmol) were weighed under an argon atmosphere and dissolved in THF (1 mL). The resulting bright red solution was cooled in an ice bath and pinacolborane (160 μL, 1.1 mmol) was added and allowed to stir for 5 min. This caused the solution to turn to a darker colour. Ethyl 3-phenylpropiolate (166 μL, 1 mmol) was then added dropwise over 5 min. The solvent was evaporated under reduced pressure and the residue was quickly purified over a short pad of silica (5% EtOAc/petrol) to afford (*Z*)-ethyl 3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (290 mg, 96 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 7.45-7.37 (3H, m, C*H* & Ar C*H*), 7.37-7.29 (3H, m, Ar C*H*), 4.25 (2H, q, *J* 7.1, CH_2), 1.32 (12H, s, CCH_3), 1.20 (3H, t, *J* 7.1, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 170.8 (O*C*O), 146.9 (*C*H), 135.6 (Ar q*C*), 129.2 (Ar *C*H), 128.7 (Ar *C*H), 128.4 (Ar *C*H), 108.6 (*C*CH), 84.2 (O*C*CH_3), 60.7 (O*C*H_2), 24.8 (C*C*H_3), 13.9 (*C*H_3); **m/z**: HRMS (ES+) found 325.1584; $C_{17}H_{23}BO_4$ $[M+Na]^+$ requires 325.1587.

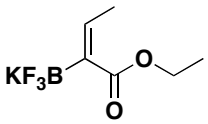
(*Z*)-(1-ethoxy-1-oxobut-2-en-2-yl)boronic acid (52)



$NaIO_4$ (3.2 g, 14.7 mmol) and NH_4OAc (1.05 g, 13.6 mmol) were dissolved in an acetone/water mixture (37.5 mL + 15 mL) at RT. The boronate **49** (500 mg, 2.1 mmol) was added and the mixture stirred for 15 min. Acetone was evaporated *in vacuo* and the mixture extracted with EtOAc. The solvent was evaporated to afford (*Z*)-(1-ethoxy-1-oxobut-2-en-2-yl)boronic acid (300 mg, 91 %) as white crystals. ^1H and ^{13}C NMR were consistent with previously reported data.*

m.p. 54-56 ˚C; **ν_{max}/cm^{-1} (film)**: 3230, 2978, 2936, 1719, 1626, 1355, 1212, 1136, 1036; **δ_H (400 MHz, $CDCl_3$)**: 7.33 (1H, q, *J* 7.2, C*H*), 5.95 (2H, s, O*H*), 4.27 (2H, q, *J* 7.1, CH_2), 2.14 (3H, d, *J* 7.2, CHCH_3), 1.34 (3H, t, *J* 7.1, CH_2CH_3); **δ_C (100 MHz, $CDCl_3$)**: 158.1 (*C*O), 131.7 (*C*H), 111.1 (q*C*), 60.8 (O*C*H_2), 18.9 (CH*C*H_3), 14.4 (CH_2CH_3); **m/z**: HRMS (ES+) found 181.0644; $C_6H_{11}BO_4$ $[M+Na]^+$ requires 181.0648.

Potassium (*Z*)-1-ethoxy-1-oxobut-2-en-2-yltrifluoroborate (53)

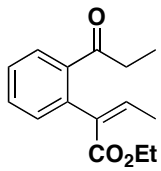


Boronic acid **52** (330 mg, 2.1 mmol) and KHF_2 (447 mg, 5.7 mmol) were suspended in a water/MeOH mixture (2:1, 6 mL) and stirred at RT for 4 h under argon. The reaction mixture was cooled in an ice bath for 30 mins and filtered to afford white crystals (250 mg, 55 %).

m.p. 161-165 ˚C; **ν_{max}/cm^{-1} (film)**: 2978, 2930, 1722, 1620, 1355, 1210, 1136, 1036; **δ_H (400 MHz, *d_6*-DMSO)**: 5.55 (1H, q, *J* 6.4, C*H*), 3.97 (2H, q, *J* 7.1, CH_2), 1.51 (3H, d, *J* 6.7, CH_3), 1.14 (3H, t, *J* 7.1, CH_2CH_3); **δ_C (100 MHz, *d_6*-DMSO)**: 159.8 (*C*O), 145.4 (*C*H), 129.3 (q*C*), 58.7 (O*C*H_2), 17.2 (CH*C*H_3), 15.2 (CH_2CH_3); **δ_F (376 MHz, *d_6*-DMSO)**: -139.1; **m/z**: HRMS (ES+) found 243.086; $C_6H_9BF_3KO_2$ $[M+Na]^+$ requires 243.0182.

* Gravel M. *et al. Org. Prep. Proced. Int.* **2004**, *36*, 573.

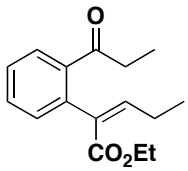
(*Z*)-Ethyl 2-(2-propionylphenyl)but-2-enoate (54)



$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (9 mg, 0.01 mmol) was added to a solution of **48** (105 mg, 0.50 mmol) in THF (3 mL) and stirred at RT for 15 mins. **53** (143 mg, 0.65 mmol), Et_3N (210 μL, 1.50 mmol) and water (150 μL, 8.3 mmol) were added and the mixture was heated to 50 ˚C. After 3 h, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 10:1) to afford (*Z*)-ethyl 2-(2-propionylphenyl)but-2-enoate (25 mg, 53 %) as a colourless oil and SM **48** (65 mg, 0.31 mmol).

ν_{max}/cm^{-1} (film): 3030, 2970, 2940, 1735, 1715, 1645, 1370; **δ_H (400 MHz, $CDCl_3$)**: 7.74 (1H, dd, *J* 7.7, 1.2, Ar C*H*), 7.50-7.43 (1H, m, Ar C*H*), 7.43-7.35 (1H, m, Ar C*H*), 7.14 (1H, dd, *J* 7.5, 1.2, Ar C*H*), 7.08 (1H, q, *J* 7.2, C*H*), 4.14 (2H, q, *J* 7.1, OCH_2), 2.87 (2H, q, *J* 7.2, C$H_2$$CH_3$), 1.63 (3H, d, *J* 7.2, CHCH_3), 1.20 (3H, t, *J* 7.1, ester CH_3), 1.10 (3H, t, *J* 7.2, CH_2CH_3); **δ_C (100 MHz, $CDCl_3$)**: 203.3 (*C*O), 166.3 (O*C*O), 144.6 (*C*CH), 138.4 (Ar *C*H), 137.9 (Ar *C*H), 135.4 (Ar *C*H), 131.8 (*C*H), 131.2 (Ar *C*H), 128.4 (Ar *C*H), 127.7 (Ar *C*H), 60.7 (O*C*H_2), 33.7 (*C*$H_2$$CH_3$), 15.4 (ester *C*$H_3$), 14.2 (CH*C*$H_3$), 8.3 ($CH_2$$CH_3$); **m/z**: HRMS (ES+) found 269.1148; $C_{15}H_{18}O_3$ $[M+Na]^+$ requires 269.1148.

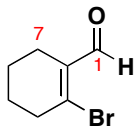
(*Z*)-Ethyl 2-(2-propionylphenyl)pent-2-enoate (55)



$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (9 mg, 0.01 mmol) was added to a solution of **48** (100 mg, 0.47 mmol) in THF (3 mL) and stirred at RT for 15 mins. **50** (144 mg, 0.57 mmol), Et_3N (197 µL, 1.41 mmol) and water (140 µL, 7.8 mmol) were added and the mixture was heated to 70 ˚C. After 15 h, the reaction was quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 10:1) to afford (*Z*)-ethyl 2-(2-propionylphenyl)pent-2-enoate (70 mg, 57 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3032, 2970, 2948, 1732, 1712, 1635, 1372; **δ_H (400 MHz, $CDCl_3$)**: 7.73 (1H, dd, *J* 7.5, 1.6, Ar C*H*), 7.53-7.32 (2H, m, Ar C*H*), 7.13 (1H, dd, *J* 7.0, 1.8, Ar C*H*), 6.96 (1H, t, *J* 7.7, C*H*), 4.14 (2H, q, *J* 7.1, OCH_2), 2.87 (2H, q, *J* 7.2, COCH_2), 1.96 (2H, m, CHCH_2), 1.20 (3H, t, *J* 7.1, CH_3), 1.10 (3H, t, *J* 7.2, OCH_2CH_3), 0.97 (3H, t, *J* 7.5, $CHCH_2CH_3$); **δ_C (100 MHz, $CDCl_3$)**: 203.3 (*C*O), 166.3 (O*C*O), 144.6 (*C*H), 138.4 (q*C*), 137.9 (q*C*), 135.4 (Ar *C*H), 131.8 (q*C*), 131.2 (Ar *C*H), 128.4 (Ar *C*H), 127.7 (Ar *C*H), 60.7 (OCH_2), 33.7 ($COCH_2$), 22.6 ($CHCH_2$), 14.2 (OCH_2CH_3), 13.1 (CH_3), 8.3 ($CHCH_2CH_3$); **m/z**: HRMS (ES+) found 283.1303; $C_{13}H_{20}O_3$ $[M+Na]^+$ requires 283.1305.

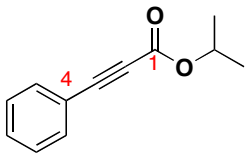
2-Bromocyclohex-1-enecarbaldehyde (68)[140]



According to the literature procedure,[140] PBr_3 (13.0 mL, 0.14 mol) was slowly added to a solution of DMF (12.0 mL, 0.15 mol) in $CHCl_3$ (100 mL) at 0 ˚C. After 30 mins the reaction was warmed to RT and a solution of cyclohexanone (5.0 g, 0.05 mol) in $CHCl_3$ (50 mL) was added. The reaction mixture was refluxed for 3 h, cooled to RT and poured onto ice water. Solid sodium bicarbonate was slowly added to neutralize the aqueous phase, which was then separated and extracted with ether. The combined organic layers were washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (2% ether/petrol) to afford 2-bromocyclohex-1-enecarbaldehyde (6.2 g, 65 %) as yellow oil.

δ_H (400 MHz, $CDCl_3$): 10.01 (1H, s, *H1*), 2.76-2.73 (2H, m, *H7*), 2.26 (2H, ddd, *J* 8.3, 5.9, 2.3, *H4*), 1.77-1.75 (2H, m, *H6*), 1.68-1.66 (2H, m, *H5*); **δ_C (100 MHz, $CDCl_3$)**: 193.9 (*C1*), 143.7 (*C2*), 135.5 (*C3*), 39.0 (*C4*), 25.2 (*C5*), 24.4 (*C6*), 21.3 (*C6*); **m/z**: HRMS (ES+) found 210.9730; C_7H_9BrO $[M+Na]^+$ requires 210.9734.

Isopropyl 3-phenylpropiolate isopropyl 3-phenylpropiolate (106)

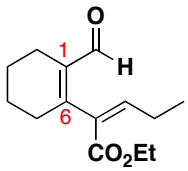


^{n}BuLi (1.47 M in THF, 6.6 mL, 9.8 mmol) was slowly added to a solution of phenylacetylene **95** (1.0 g, 9.8 mmol) in THF (20 mL) at -78 ˚C and stirred for 20 mins at this temperature. Isopropyl chloroformate (1.0 M in toluene, 9.8 mL, 9.8 mmol) was slowly added and allowed to warm to RT. The reaction was quenched with sat. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 8:1) to afford isopropyl 3-phenylpropiolate (1.4 g, 76 %) as a colourless oil. ^{1}H and ^{13}C NMR were consistent with previously reported data.[*]

ν_{max}/cm^{-1} (film): 3010, 2983, 2216, 1705, 1285, 1195, 1104; **δ_H (400 MHz, $CDCl_3$)**: 7.61-7.53 (2H, m, Ar C*H*), 7.45-7.39 (1H, m, Ar C*H*), 7.34 (2H, ddd, *J* 6.5, 5.6, 2.5, Ar C*H*), 5.14 (1H, sept., *J* 6.3, C*H*(CH_3)$_2$), 1.32 (6H, d, *J* 6.3, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 153.6 (O*C*O), 133.0 (Ar *C*H), 130.5 (Ar *C*H), 128.5 (Ar *C*H), 119.4 (*C4*), 85.5 (*C3*), 81.1 (*C2*), 70.0 (O*C*H), 21.7 (CH(*C*H_3)$_2$); **m/z**: HRMS (ES+) found 211.0727; $C_{12}H_{12}O_2$ [M+Na]$^+$ requires 211.0730.

[*] Wadsworth D. H. *et al. J. Org Chem.* **1987**, *52*, 3662.

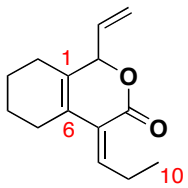
(*Z*)-Ethyl 2-(2-formylcyclohex-1-en-1-yl)pent-2-enoate (71)



$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (65 mg, 0.08 mmol) and SPhos (66 mg, 0.16 mmol) were added to a solution of **68** (150 mg, 0.80 mmol) in toluene (2 mL) and stirred at RT for 15 mins. K_3PO_4 (340 mg, 1.6 mmol), **50** (270 mg, 1.06 mmol) in toluene (1 mL) and water (300 µL, 16 mmol) were added to this mixture and heated to 90 ˚C. After 2 h, the reaction was cooled and quenched with water and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 12:1) to afford (*Z*)-ethyl 2-(2-formylcyclohex-1-en-1-yl)pent-2-enoate (180 mg, 95 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2970, 2936, 1745, 1735, 1640, 1350; **δ_H (400 MHz, $CDCl_3$)**: 9.62 (1H, s, C*H*O), 6.94 (1H, t, *J* 7.7, C*H*), 4.44-3.87 (2H, q, *J* 7.1 OC*H*$_2$), 2.58-2.11 (4H, m, *H2* & *H5*), 2.11-1.93 (2H, m, CHC*H*$_2$), 1.82-1.50 (4H, m, *H3* & *H4*), 1.25 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$), 1.00 (3H, t, *J* 7.5, C*H*$_3$), **δ_C (100 MHz, $CDCl_3$)**: 192.6 (C*H*O), 165.7 (O*C*O), 154.1 (*C6*), 146.9 (*C*H), 136.8 (*C1*), 130.8 (*C*CH), 61.0 (O*C*H$_2$), 32.4 (*C*H$_2$), 23.0 (*C5*), 22.0 (*C2*), 21.7 (*C3*), 21.4 (*C4*), 14.2 (OCH$_2$*C*H$_3$), 12.9 (CH$_2$*C*H$_3$); **m/z**: HRMS (ES-) found 235.1330; $C_{14}H_{20}O_3$ $[M-H]^+$ requires 235.1334.

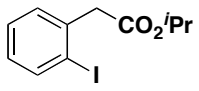
(*Z*)-4-Propylidene-1-vinyl-5,6,7,8-tetrahydro-1*H*-isochromen-3(4*H*)-one (75)



Vinylmagnesium bromide (1.0 M in THF, 0.15 mL, 0.15 mmol) was added dropwise to a solution of **71** (30 mg, 0.13 mmol) in THF (0.5 mL) at -20 ˚C. After 2 h, the reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 10:1) to afford (*Z*)-4-propylidene-1-vinyl-5,6,7,8-tetrahydro-1*H*-isochromen-3(4*H*)-one (23 mg, 83 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 2934, 1724, 1613, 1367, 1228, 1193, 1049; **δ_H (400 MHz, $CDCl_3$)**: 6.72 (1H, t, *J* 7.7, *H8*), 5.75 (1H, ddd, *J* 17.0, 10.1, 6.9, OCHC*H*), 5.20 (2H, dd, *J* 16.7, 10.1, CHCH_2), 4.85 (1H, d, *J* 6.9, OC*H*), 2.54-2.30 (2H, m, *H9*), 2.29-2.16 (2H, m, *H5*), 2.07 (2H, m, *H2*), 1.86-1.75 (2H, m, *H3*), 1.60-1.37 (2H, m, *H4*), 1.07 (3H, t, *J* 7.5, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 167.8 (O*C*O), 142.7(*C7*), 134.4 (q*C*), 132.1 (OCH*C*H), 128.2 (q*C*), 125.3 (q*C*), 117.7 (CH*C*H_2), 81.4 (O*C*H), 28.2 (*C9*), 26.5 (*C5*), 23.0 (*C2*), 22.5 (*C3*), 21.8 (*C4*), 13.9 (*C10*); **m/z**: HRMS (ES+) found 241.1208; $C_{14}H_{18}O_2$ $[M+Na]^+$ requires 241.1204.

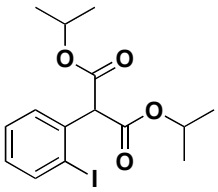
Isopropyl 2-(2-iodophenyl)acetate (82)[76]



According to a representative procedure,[76] Conc. H_2SO_4 (0.6 mL) was added to a solution of (2-iodophenyl)acetic acid **81** (2.0 g, 7.63 mmol) in ^{i}PrOH (6 mL) and refluxed for 3 h. The solution was cooled to RT and poured into water (15 mL) and extracted with ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified column chromatography (petrol/EtOAc, 5:1) to afford isopropyl 2-(2-iodophenyl)acetate (1.95 g, 84 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3035, 2979, 2935, 1732, 1467, 1255, 1107; **δ_H (400 MHz, $CDCl_3$)**: 7.85 (1H, dd, *J* 7.9, 0.9, Ar C*H*), 7.38-7.19 (2H, m, Ar C*H*), 7.01-6.88 (1H, m, Ar C*H*), 5.07 (1H, sept., *J* 6.3, OC*H*), 3.76 (2H, s, CH_2), 1.27 (6H, d, *J* 6.3, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 170.1 (O*C*O), 139.5 (Ar *C*H), 138.0 (*C*CH_2), 130.6 (Ar *C*H), 128.8 (Ar *C*H), 128.4 (Ar *C*H), 101.0 (*C*I), 68.5 (O*C*H), 46.6 (*C*H_2), 21.8 (*C*H_3); **m/z**: HRMS (ES+) found 326.9853; $C_{11}H_{13}IO_2$ $[M+Na]^+$ requires 326.9852.

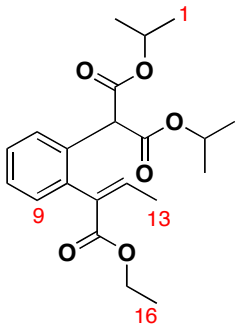
Diisopropyl 2-(2-iodophenyl)malonate (80)



A solution of LiHMDS in toluene (12 mL, 1.0 M, 12 mmol) was slowly added *via* syringe pump to a solution of **82** (1.65 g, 5.4 mmol) in THF (6 mL) at -78 ˚C over 30 mins. The reaction mixture was stirred at this temperature for 1 h and a solution of isopropyl chloroformate (10.8 mL, 1.0 M, 10.8 mmol) was added slowly. The reaction was allowed to warm to RT and stirred for 3 h. The reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford the desired product as a light yellow oil (1.90 g, 91 %).

ν_{max}/cm^{-1} (film): 3063, 2982, 2936, 1731, 1468, 1375, 1261, 1163, 1101, 1012; **δ_H (400 MHz, $CDCl_3$)**: 7.84 (1H, dd, *J* 8.0, 1.1, Ar C*H*), 7.47-7.39 (1H, m, Ar C*H*), 7.34 (1H, td, *J* 7.7, 1.2, Ar C*H*), 6.99 (1H, ddd, *J* 9.1, 7.7, 1.7, Ar C*H*), 5.08 (2H, sept., *J* 6.3, OC*H*), 5.02 (1H, s, CH_2), 1.26 (6H, d, *J* 6.3, CH_3), 1.23 (6H, d, *J* 6.3, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 167.3 (O*C*O), 139.5 (Ar *C*H), 136.7 (q*C*), 129.6 (Ar *C*H), 128.4 (Ar *C*H), 101.8 (q*C*), 69.7 (O*C*H), 62.6 (*C*H), 21.6 (*C*H_3); **m/z**: HRMS (ES+) found 413.0213; $C_{15}H_{19}IO_4$ $[M+Na]^+$ requires 413.0220.

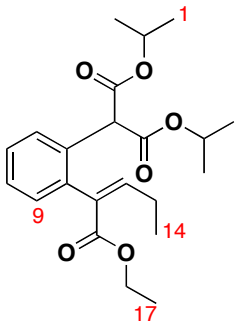
(*Z*)-Diisopropyl 2-(2-(1-ethoxy-1-oxobut-2-en-2-yl)phenyl)malonate (83)



$Pd(OAc)_2$ (3.4 mg, 0.015 mmol) and cyclohexyl JohnPhos **85** (21 mg, 0.06 mmol) was added to a solution of **80** (120 mg, 0.3 mmol) in dioxane:H_2O (9:1, 1.2 mL) at RT and stirred for 10 mins. Et_3N (126 µL, 0.9 mmol) and **49** (86.4 mg, 0.36 mmol) in dioxane:H_2O (0.6 mL) were added and the mixture was heated to 60 ˚C o/n. The flask was cooled and the mixture was filtered through Celite™ using ether. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/ether, 10:1) to afford (*Z*)-diisopropyl 2-(2-(1-ethoxy-1-oxobut-2-en-2-yl)phenyl)malonate (23 mg, 25 %) as a yellow oil and SM **80** (25 mg).

ν_{max}/cm^{-1} (film): 3035, 2982, 2940, 1725, 1642, 1375, 1174. 1101; **δ_H (400 MHz, C_6D_6)**: 8.04 (1H, dd, *J* 7.9, 0.8, *H9*), 7.19 (1H, td, *J* 7.7, 1.4, *H8*), 7.05 (1H, td, *J* 7.6, 1.2, *H7*), 6.94 (1H, dd, *J* 7.7, 1.0, *H6*), 5.97 (1H, q, *J* 7.3, *H12*), 5.18 (1H, s, *H4*), 5.14-5.00 (2H, m, *H2*), 4.08 (2H, q, *J* 7.2, *H15*), 2.09 (3H, d, *J* 7.2, *H13*), 1.08 (6H, d, *J* 6.3, *H1*), 1.04 (3H, t, *J* 7.1, *H16*), 1.00 (6H, d, *J* 6.3, *H1'*); **δ_C (100 MHz, C_6D_6)**: 167.9 (*C3*), 166.2 (*C14*), 144.7 (*C10*), 139.3 (*C12*), 134.5 (*C5*), 130.2 (Ar *C*H), 128.1 (Ar *C*H), 127.4 (Ar *C*H), 121.4 (Ar *C*H), 69.2 (*C2*), 60.1 (*C15*), 55.1 (*C4*), 21.4 (*C1*), 15.8 (*C13*), 14.2 (*C16*); **m/z**: HRMS (ES+) found 399.1780; $C_{21}H_{28}O_6$ $[M+Na]^+$ requires 399.1778.

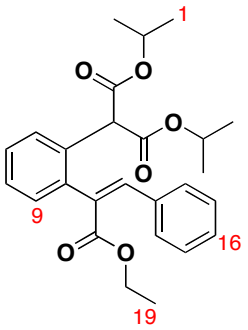
(Z)-Diisopropyl 2-(2-(1-ethoxy-1-oxopent-2-en-2-yl)phenyl)malonate (84)



$Pd(OAc)_2$ (17 mg, 0.075 mmol) and cyclohexyl JohnPhos **85** (105 mg, 0.3 mmol) were added to a solution of **80** (600 mg, 1.5 mmol) in dioxane:H_2O (9:1, 3 mL) and degassed. Et_3N (0.64 mL, 4.5 mmol) was then added and stirred for 10 min. Boronate **50** (460 mg, 1.8 mmol) in dioxane:H_2O was added to this solution and heated to 60 ˚C o/n. The flask was cooled and the mixture was filtered through Celite™ using ether. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (10 % ether in petrol) to afford the desired product as a yellow oil (365 mg, 61 %).

ν_{max}/cm^{-1} (film): 3084, 2982, 2940, 1735, 1731, 1466, 1374, 1202, 1102, 1033; **δ_H (400 MHz, $CDCl_3$)**: 7.52 (1H, dd, *J* 7.8, 1.2, Ar C*H*), 7.35-7.20 (2H, m, Ar C*H*), 7.14 (1H, dd, *J* 7.5, 1.5, Ar C*H*), 5.98 (1H, t, *J* 7.5, *H12*), 5.02 (2H, sept., *J* 6.3, *H2*), 4.74 (1H, s, *H4*), 4.11 (2H, q, *J* 7.1, *H16*), 2.62 (2H, m, *H13*), 1.22 (6H, d, *J* 6.3, *H1*), 1.18 (6H, d, *J* 6.2, *H1'*), 1.18-1.14 (3H, t, *J* 7.1, *H14*), 1.09 (3H, t, *J* 7.5, *H17*); **δ_C (100 MHz, $CDCl_3$)**: 167.9 (*C3*), 166.6 (*C15*), 149.5 (*C12*), 139.5 (*C10*), 131.8 (*C5*), 131.5 (*C11*), 129.9 (Ar *C*H), 129.0 (Ar *C*H), 127.7 (Ar *C*H), 127.6 (Ar *C*H), 69.2 (*C2*), 60.6 (*C16*), 54.8 (*C4*), 23.2 (*C13*), 21.6 (*C1*), 14.1 (*C14*), 13.7 (*C17*); **m/z**: HRMS (ES+) found 413.1928; $C_{22}H_{30}O_6$ $[M+Na]^+$ requires 413.1935.

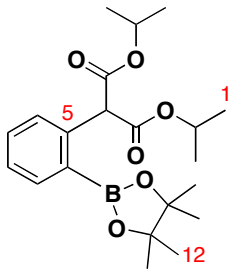
(*Z*)-diisopropyl 2-(2-(3-ethoxy-3-oxo-1-phenylprop-1-en-2-yl)phenyl)malonate (86)



$Pd(OAc)_2$ (1.2 mg, 0.005 mmol) and XPhos **89** (2.4 mg, 0.005 mmol) were added to a solution of **80** (600 mg, 1.5 mmol) in toluene (0.5 mL) and degassed. CsF (30.4 mg, 0.20 mmol) was then added and stirred for 10 min. Boronate **51** (31 mg, 0.10 mmol) in toluene (0.3 mL) was added to this solution and stirred at RT for 24 h. The flask was cooled and the mixture was filtered through Celite™ using ether. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by preparative TLC (petrol/EtOAc, 10:1) to afford the desired product as a yellow oil (12 mg, 54 %).

ν_{max}/cm^{-1} (film): 3070, 2980, 2954, 1733, 1440, 1374, 1105, 1030; **δ_H (400 MHz, $CDCl_3$)**: 7.66-7.57 (1H, m, Ar C*H*), 7.47-7.30 (8H, m, Ar C*H*), 6.72 (1H, s, *H12*), 5.10 (1H, s, *H4*), 5.06 (2H, sept., *J* 6.3, *H2*), 4.15 (2H, q, *J* 7.1, *H18*), 1.26 (6H, d, *J* 6.3, *H1*), 1.19 (6H, d, *J* 6.3, *H1'*), 1.13 (3H, t, *J* 7.1, *H19*); **δ_C (100 MHz, $CDCl_3$)**: 168.2 (*C3*), 167.9 (*C17*), 138.7 (*C12*), 137.7 (*C10*), 135.2 (*C5*), 133.2 (*C11*), 131.9 (*C13*), 129.5 (Ar *C*H), 128.6 (Ar *C*H), 128.5 (Ar *C*H), 128.4 (Ar *C*H), 127.8 (Ar *C*H), 69.3 (*C2*), 61.2 (*C18*), 54.8 (*C4*), 21.6 (*C1*), 13.8 (*C19*); **m/z**: HRMS (ES+) found 461.1937; $C_{26}H_{30}O_6$ $[M+Na]^+$ requires 461.1935.

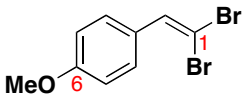
Diisopropyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)malonate (90)



$Pd(OAc)_2$ (8.5 mg, 0.038 mmol) and cyclohexyl JohnPhos **85** (52.5 mg, 0.15 mmol) were added to a solution of **80** (300 mg, 0.75 mmol) in dioxane (3 mL) and degassed. Et_3N (0.32 mL, 2.25 mmol) was then added and stirred for 10 min. Pinacolborane (0.22 mL, 1.5 mmol) was added to this solution and heated to 60 ˚C. After 3 h, the flask was cooled and the mixture was filtered through Celite™ using ether. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/ether, 10:1) to afford the desired product as an orange solid (225 mg, 75 %).

m.p. 70-72 ˚C; **ν_{max}/cm^{-1} (film)**: 3036, 2980, 2937, 1730, 1601, 1493, 1350, 1146, 1069; **δ_H (400 MHz, $CDCl_3$)**: 7.82 (1H, dd, *J* 7.5, 0.9, Ar C*H*), 7.47-7.35 (2H, m, Ar C*H*), 7.28 (1H, td, *J* 7.3, 1.5, Ar C*H*), 5.60 (1H, s, *H4*), 5.06 (2H, sept., *J* 6.3, *H2*), 1.31 (12H, s, *H12*), 1.25 (6H, d, *J* 6.2, *H1*), 1.22 (6H, d, *J* 6.3, *H1'*); **δ_C (100 MHz, $CDCl_3$)**: 168.8 (*C3*), 139.5 (q*C*), 136.2 (Ar *C*H), 131.1 (Ar *C*H), 128.4 (q*C*), 127.0 (Ar *C*H), 83.8 (*C11*), 68.9 (*C2*), 56.6 (*C4*), 24.8 (*C12*), 21.6 (*C1*); **m/z**: HRMS (ES+) found 413.2213; $C_{21}H_{31}BO_6$ $[M+Na]^+$ requires 413.2210.

1-(2,2-Dibromovinyl)-4-methoxybenzene (101) [*]



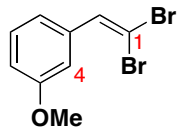
According to a literature procedure,[*] PPh_3 (4.8 g, 18 mmol) was added in portions to a solution of CBr_4 (3.0 g, 9 mmol) in CH_2Cl_2 (16 mL) at 0 ˚C. After 30 mins, 4-methoxybenzaldehyde **96** (1.0 g, 7.4 mmol) was added and the mixture was stirred at 0 ˚C for 1 h. A mixture of 1:1 mixture of H_2O:brine was added and layers were separated. The aqueous layer was extracted with a 1:1 mixture of petrol:CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 15:1) to afford 1-(2,2-dibromovinyl)-4-methoxybenzene (2.04 g, 95 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 2994, 2928, 2897, 1592, 1417, 1254, 1223, 1146, 1017; **δ_H (400 MHz, $CDCl_3$)**: 7.51 (2H, d, *J* 8.5, *H4*), 7.41 (1H, s, *H2*), 6.90 (2H, d, *J* 8.6, *H5*), 3.83 (3H, s, OC*H*$_3$), **δ_C (100 MHz, $CDCl_3$)**: 136.3 (*C6*), 133.7 (*C2*), 129.9 (Ar *C*H), 128.6 (Ar *C*H), 113.8 (*C5*), 88.7 (*C1*), 55.3 (O*C*H$_3$); **m/z**: HRMS (ES-): 290.8.

[*] Zheng W. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4932.

[*] Zheng W. et al. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4932.

1-(2,2-Dibromovinyl)-3-methoxybenzene (102)[*]

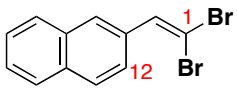


According to a literature procedure,[*] PPh_3 (4.8 g, 18 mmol) was added in portions to a solution of CBr_4 (3.0 g, 9 mmol) in CH_2Cl_2 (16 mL) at 0 ˚C. After 30 mins, 3-methoxybenzaldehyde **97** (1.0 g, 7.4 mmol) was added and mixture was stirred at 0 ˚C for 1 h. A mixture of 1:1 mixture of H_2O:brine was added and the layers were separated. The aqueous layer was extracted with a 1:1 mixture of petrol:CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 15:1) to afford 1-(2,2-dibromovinyl)-3-methoxybenzene (2.0 g, 93 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 2990, 2930, 2897, 1592, 1410, 1250, 1223, 1146, 1017; **δ_H (400 MHz, $CDCl_3$)**: 7.47 (1H, s, *H2*), 7.30-7.23 (1H, m, Ar C*H*), 7.14-7.06 (2H, m, Ar C*H*), 6.90 (1H, dd, *J* 8.3, 2.5, Ar C*H*), 3.83 (3H, s, OC*H*$_3$); **δ_C (00 MHz, $CDCl_3$)**: 136.7 (*C2*), 133.8 (q*C*), 129.4 (Ar *C*H), 128.8 (q*C*), 128.5 (Ar *C*H), 121.0 (Ar *C*H), 113.6 (Ar *C*H), 89.8 (*C1*), 55.3 (O*C*H$_3$); **m/z**: HRMS (ES-): 290.8.

[*] Khan Z.; Wirth T. *Org. Lett.* **2009**, *11*, 229.
[*] Khan Z.; Wirth T. *Org. Lett.* **2009**, *11*, 229.

2-(2,2-Dibromovinyl)naphthalene (103)[*]

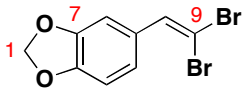


According to a literature procedure,[*] PPh_3 (4.1 g, 15.4 mmol) was added in portions to a solution of CBr_4 (2.6 g, 7.7 mmol) in CH_2Cl_2 (13 mL) at 0 ˚C. After 30 mins, 2-naphthaldehyde **98** (1.0 g, 6.4 mmol) was added and mixture was stirred at 0 ˚C for 1 h. A mixture of 1:1 mixture of H_2O:brine was added and the layers were separated. The aqueous layer was extracted with a 1:1 mixture of petrol:CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 15:1) to afford 2-(2,2-dibromovinyl)naphthalene (1.9 g, 95 %) as a yellow solid.

m.p. 84-86 ˚C, **ν_{max}/cm^{-1} (film)**: 2994, 2928, 2897, 1592, 1417, 1254, 1223, 1146, 1017; **δ_H (400 MHz, $CDCl_3$)**: 8.02 (1H, s, *H2*), 7.84 (3H, m, Ar C*H*), 7.64 (2H, dd, *J* 5.7, 2.6, Ar C*H*), 7.55-7.45 (2H, m, Ar C*H*); **δ_C (100 MHz, $CDCl_3$)**: 136.9 (*C2*), 133.0 (q*C*), 132.9 (q*C*), 132.7 (q*C*), 128.3 (Ar *C*H), 128.1 (Ar *C*H), 127.9 (Ar *C*H), 127.7 (Ar *C*H), 126.7 (Ar *C*H), 126.5 (Ar *C*H), 125.6 (Ar *C*H), 89.8 (q*C*); **m/z**: (ES-): 333.8.

[*] Khan Z.; Wirth T. *Org. Lett.* **2009**, *11*, 229.
[*] Khan Z.; Wirth T. *Org. Lett.* **2009**, *11*, 229.

5-(2,2-Bibromovinyl)benzo[*d*][1,3]dioxole (104)[*]

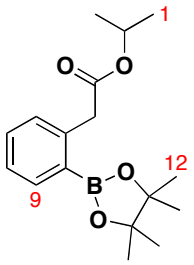


According to a literature procedure,[*] PPh_3 (3.84 g, 14.7 mmol) was added in portions to a solution of CBr_4 (2.21 g, 7.3 mmol) in CH_2Cl_2 (12 mL) at 0 ˚C. After 30 mins, piperonal **99** (1.0 g, 6.7 mmol) was added and mixture was stirred at 0 ˚C for 3 h. A mixture of 1:1 mixture of H_2O:brine was added and layers were separated. The aqueous layer was extracted with a 1:1 mixture of petrol:CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/ether, 20:1) to afford 5-(2,2-dibromovinyl)benzo[d][1,3]dioxole (2.03 g, 99 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2990, 2928, 2897, 1590, 1417, 1254, 1223, 1146, 1017; **δ_H (400 MHz, $CDCl_3$)**: 7.37 (1H, s, *H8*), 7.19 (1H, d, *J* 1.5, *H6*), 6.95 (1H, dd, *J* 8.1, 1.6, *H4*), 6.80 (1H, d, *J* 8.1, *H3*), 5.99 (2H, s, *H1*); **δ_C (100 MHz, $CDCl_3$)**: 147.8 (*C2*), 147.6 (*C7*), 136.3 (*C8*), 129.2 (*C5*), 123.4 (*C4*), 108.3 (*C3*), 108.1 (*C6*), 101.4 (*C1*), 87.8 (*C9*); **m/z**: (ES-) 304.8

[*] Khan Z.; Wirth T. *Org. Lett.* **2009**, *11*, 229.
[*] Sai H. *et al. Synthesis* **1995**, *5*, 582.

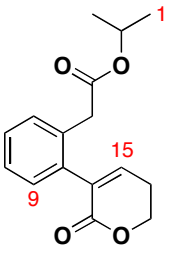
Isopropyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (90a)



$Pd(OAc)_2$ (11 mg, 0.05 mmol) and cyclohexyl JohnPhos **85** (64 mg, 0.18 mmol) were added to a solution of **82** (270 mg, 0.9 mmol) in dioxane (3.6 mL) and stirred at RT for 15 mins. This was followed by addition of Et_3N (377 µL, 2.7 mmol) and pinacolborane (262 µL, 1.8 mmol) and the reaction mixture was heated to 80 ˚C. After 3 h, the reaction was cooled to RT, quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (3 x 30 mL). The crude product was purified by column chromatography (petrol/EtOAc, 7:1) to afford isopropyl 2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (240 mg, 89 %) as an orange oil.

ν_{max}/cm^{-1} (film): 3055, 2883, 2938, 1728, 1444, 1351, 1266, 1145, 1070; **δ_H (400 MHz, $CDCl_3$)**: 7.80 (1H, dd, *J* 7.4, 1.2, Ar C*H*), 7.35 (1H, m, Ar C*H*), 7.31-7.19 (1H, m, Ar C*H*), 7.17 (1H, d, *J* 7.6, Ar C*H*), 4.97 (1H, sept., *J* 6.2, *H2*), 3.91 (2H, s, *H4*), 1.30 (12H, s, *H12*), 1.20 (6H, d, *J* 6.3, *H1*); **δ_C (100 MHz, $CDCl_3$)**: 173.4 (O*C*O), 136.0 (*C10*), 131.0 (*C5*), 130.0 (Ar *C*H), 129.2 (Ar *C*H), 126.2 (Ar *C*H), 83.7 (*C11*), 67.7 (*C2*), 41.2 (*C4*), 24.8 (*C12*), 21.9 (*C1*); **m/z**: HRMS (ES+) found 327.1747; $C_{17}H_{25}BO_4$ $[M+Na]^+$ requires 327.1741.

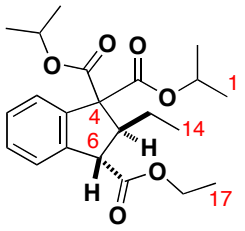
Isopropyl 2-(2-(2-oxo-5,6-dihydro-2*H*-pyran-3-yl)phenyl)acetate (91a)



$Pd(dppf)Cl_2$ (8.2 mg, 0.01 mmol), cyclohexyl JohnPhos **85** (14 mg, 0.04 mmol), Et_3N (84 µL, 0.6 mmol) and boronate **90a** (67 mg, 0.22 mmol) were added to a solution of **30** (35.4 mg, 0.2 mmol) in dioxane:H_2O (9:1, 0.8 mL) and heated to 80 ˚C. After 1 h, the reaction was cooled to RT and filtered through Celite™. The solvent was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 2:1) to afford isopropyl 2-(2-(2-oxo-5,6-dihydro-2*H*-pyran-3-yl)phenyl)acetate (15 mg, 27 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 3429, 2982, 1722, 1685, 1339, 1258, 1213, 1155; **δ_H (400 MHz, $CDCl_3$)**: 7.34-7.25 (3H, m, Ar C*H*), 7.15 (1H, d, *J* 7.3, *H9*), 6.86 (1H, t, *J* 4.3, *H15*), 4.94 (1H, sept., *J* 6.3, *H2*), 4.52 (2H, t, *J* 6.2, *H13*), 3.53 (2H, s, *H4*), 2.60 (2H, td, *J* 6.2, 4.3, *H14*), 1.18 (6H, d, *J* 6.3, *H1*); **δ_C (100 MHz, $CDCl_3$)**: 167.9 (*C3*), 166.6 (*C12*), 149.5 (*C15*), 139.5 (*C10*), 131.8 (*C5*), 131.5 (*C11*), 129.9 (Ar *C*H), 129.0 (Ar *C*H), 127.7 (Ar *C*H), 127.6 (Ar *C*H), 69.2 (*C2*), 60.6 (*C13*), 54.8 (*C4*), 23.2 (*C14*), 21.6 (*C1*); **m/z**: HRMS (ES+) found 297.1098; $C_{16}H_{18}O_4$ $[M+Na]^+$ requires 297.1097.

(2*S*,3*S*)-3-Ethyl 1,1-diisopropyl 2-ethyl-2,3-dihydro-1*H*-indene-1,1,3-tricarboxylate (126)



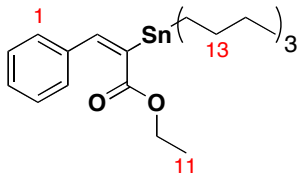
Racemic: Cs_2CO_3 (27.6 mg, 0.085 mmol) was added to a solution of **84** (30 mg, 0.077 mmol) in toluene (0.5 mL) and stirred at RT. After 15 h, the reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/ether, 5:1) to afford the desired product (19:1 dr) as a yellow oil (23 mg, 80 %).

Asymmetric: A solution of **84** (30 mg, 0.08 mmol) and catalyst (8*S*,9*R*)-(–)-*N*-benzylcinchonidinium chloride **125a** (3.4 mg, 0.008 mmol) in toluene (0.4 mL) was stirred at 0 ˚C for 30 mins. $CsCO_3$ (27 mg, 0.9 mmol) was added and the solution was stirred for 15 h. The reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (2 x 20 mL). The crude product was purified by column chromatography (petrol/ether, 5:1). The desired product was obtained as a mixture of two diastereoisomers **126** & **127** (33:1) as a yellow oil (20 mg, 67 %, 0 % ee)

ν_{max}/cm^{-1} (film): 3035, 2980, 2940, 1728, 1726, 1466, 1374, 1260; **Major diastereoisomer**: **δ_H (700 MHz, C_6D_6)**: 7.95-7.91 (1H, m, Ar C*H*), 7.39 (1H, d, *J* 7.5, Ar C*H*), 7.15-7.09 (2H, m, Ar C*H*), 5.06 (1H, sept., *J* 6.2, *H2*), 4.92 (1H, sept., *J* 6.2, *H2'*), 4.17 (1H, d, *J* 9.2, *H6*), 4.09-3.99 (3H, m, *H5* & *H16*), 2.26-2.18 (1H, m, *H13*), 1.73 (1H, m, *H13'*), 1.15 (3H, t, *J* 7.5, *H14*), 1.08 (3H, d, *J* 6.3, *H1*), 0.99 (3H, d, *J* 6.3, *H1*), 0.96 (3H, t, *J* 7.1, *H17*), 0.92 (3H, d, *J* 6.3, *H1'*), 0.88 (3H, d, *J* 6.3, *H1'*); **m/z**: HRMS (ES+) found 413.1938; $C_{22}H_{30}O_6$ $[M+Na]^+$ requires 413.1935; **Minor diastereoisomer**: **δ_H (700 MHz, C_6D_6)**: 7.85 (1H, d, *J* 7.7, Ar C*H*), 7.38 (1H, d, *J* 7.3, Ar C*H*), 7.15-7.08 (2H, m, Ar C*H*), 5.14 (1H, sept., *J* 6.3, *H2*), 5.05-5.00 (1H, m, *H2'*), 4.22 (1H, d, *J* 7.5, *H6*), 3.92-3.84 (2H, m, *H16*), 3.69 (1H, ddd, *J* 9.5, 7.6, 5.0, *H5*), 2.29-2.25 (1H, m, *H13*), 2.14-2.10 (1H, m, *H13'*), 1.13 (3H, d, *J* 6.3, *H1*), 1.08 (3H, d, *J* 6.3, *H1*), 1.06 (3H, d, *J* 6.2, *H1'*), 0.99 (3H, d, *J* 6.3, *H1'*), 0.96 (3H, t, *J*

7.1, *H14*), 0.90 (3H, t, *J* 7.1, *H17*); **δ_C (175 MHz, C_6D_6)**: 173.2 (*C3*), 169.5 (*C15*), 143.0 (q*C*), 141.6 (q*C*), 129.3 (Ar *C*H), 126.9 (Ar *C*H), 124.7 (Ar *C*H), 69.5 (*C2*), 69.3 (*C2'*), 61.3 (*C16*), 55.5 (*C6*), 52.1 (*C5*), 25.2 (*C13*), 21.8 (*C1*), 14.6 (*C14*), 13.5 (*C14*); **m/z**: HRMS (ES+) found 413.1936; $C_{22}H_{30}O_6$ $[M+Na]^+$ requires 413.1935.

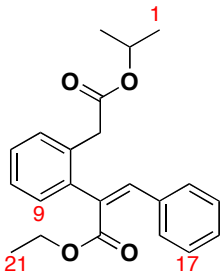
(*E*)-Ethyl 3-phenyl-2-(tributylstannyl)acrylate (112a)



According to a modified literature procedure,[84] $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) and tributyltin hydride (715 µL, 2.65 mmol) were added to a solution of ethyl 3-phenylpropiolate (415 µL, 2.5 mmol) in THF (10 mL) at 0 ˚C. After 1 h, the solvent was evaporated and the residue was filtered through Celite™ using ether. The crude product was chromatographed (petrol/ether, 20:1) to afford (*E*)-ethyl 3-phenyl-2-(tributylstannyl)acrylate (1.1 g, 94 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$): 7.37-7.28 (5H, m, Ar C*H*), 6.71 (1H, t, $^3J_{Sn\text{-}H}$ 28.5, *H7*), 4.18 (2H, q, *J* 7.1, *H10*), 1.57-1.52 (6H, m, *H12*), 1.47-1.28 (6H, m, *H13*), 1.23 (3H, t, *J* 7.1, *H11*), 1.14-1.01 (6H, m, *H14*), 0.90 (9H, t, *J* 7.2, *H15*); **δ_C (100 MHz, $CDCl_3$)**: 173.2 (*C9*), 142.1 (*C7*), 139.8 (*C6*), 137.0 (Ar *C*H), 128.3 (Ar *C*H), 128.1 (Ar *C*H), 128.0 (*C8*), 60.3 (*C10*), 28.9 (*C13*), 27.3 (*C14*), 14.2 (*C11*), 13.7 (*C15*), 10.6 (*C12*); **m/z** HRMS (ES+) found 489.1785; $C_{23}H_{38}O_2Sn$ $[M+Na]^+$ requires 489.1791.

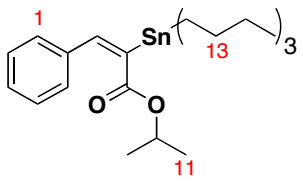
(*Z*)-Ethyl 2-(2-(2-isopropoxy-2-oxoethyl)phenyl)-3-phenylacrylate (86a)



$Pd(OAc)_2$ (15.2 mg, 0.07 mmol) and PPh_3 (53.6 mg, 0.21 mmol) were added to a solution of **82** (200 mg, 0.68 mmol) in DMF (4 mL) at RT and stirred for 15 mins. CuI (28 mg, 0.14 mmol) and **112a** (368 mg, 0.80 mmol) in DMF (4 mL) were added and the mixture was heated to 80 ˚C. After 6 h, the reaction was cooled to RT, the solvent was evaporated under reduced pressure and the residue was filtered through Celite™ using ether. The crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford (*Z*)-ethyl 2-(2-(2-isopropoxy-2-oxoethyl)phenyl)-3-phenylacrylate (214 mg, 92 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 3034, 2980, 2940, 1722, 1642, 1375, 1174, 1101; **δ_H (400 MHz, $CDCl_3$)**: 7.42-7.28 (9H, m, Ar C*H*), 6.82 (1H, s, *H12*), 5.15-4.88 (1H, sept., *J* 7.3, *H2*), 4.20 (2H, q, *J* 6.7, *H20*), 3.75 (2H, s, *H4*), 1.19 (6H, d, *J* 6.3, *H1*), 1.13 (3H, t, *J* 6.7, *H21*); **δ_C (100 MHz, $CDCl_3$)**: 171.2 (*C3*), 168.2 (*C19*), 140.9 (*C12*), 135.3 (q*C*), 133.5 (q*C*), 132.7 (Ar *C*H), 128.6 (Ar *C*H), 127.1 (Ar *C*H), 68.3 (*C2*), 61.1 (*C20*), 39.5 (*C4*), 21.5 (*C1*), 14.7 (*C21*); **m/z**: HRMS (ES+) found 375.1572; $C_{22}H_{24}O_4$ $[M+Na]^+$ requires 375.1570.

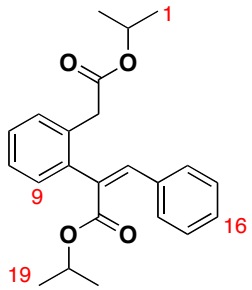
(*E*)-Isopropyl 3-phenyl-2-(tributylstannyl)acrylate (112)



$Pd(PPh_3)_4$ (296 mg, 0.26 mmol) and Bu_3SnH (3.6 mL, 13.5 mmol) were added to a solution of isopropyl 3-phenylpropiolate **106** (2.4 g, 12.8 mmol) in THF (50 mL) at 0 ˚C. After 1 h, the solvent was evaporated and residue was filtered through Celite™ using ether. The crude product was chromatographed (petrol/ether, 20:1) to afford (*E*)-isopropyl 3-phenyl-2-(tributylstannyl)acrylate (5.3 g, 86 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2957, 2948, 1695, 1605, 1510, 1464, 1253, 1106; **δ_H (400 MHz, $CDCl_3$)**: 7.37-7.28 (5H, m, Ar C*H*), 6.71 (1H, t, $^3J_{Sn-H}$ 28.5, *H7*), 5.15 (1H, sept., *J* 7.2, *H10*), 1.58-1.52 (6H, m, *H12*), 1.47-1.28 (6H, m, *H13*), 1.22 (6H, d, *J* 6.3, *H11*), 1.14-1.01 (6H, m, *H14*), 0.90 (9H, t, *J* 7.2, *H15*); **δ_C (100 MHz, $CDCl_3$)**: 185.0 (*C9*), 141.7 (*C7*), 140.2 (*C6*), 137.1 (Ar *C*H), 128.2 (Ar *C*H), 127.9 (*C8*), 67.6 (*C10*), 28.9 (*C13*), 27.3 (*C14*), 21.8 (*C11*), 13.7 (*C15*), 10.5 (*C12*);); **m/z**: HRMS (ES+) found 503.1957; $C_{24}H_{40}O_2Sn$ $[M+Na]^+$ requires 503.1947.

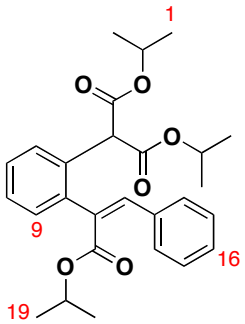
(*Z*)-Isopropyl 2-(2-(2-isopropoxy-2-oxoethyl)phenyl)-3-phenylacrylate (86b)



$Pd(OAc)_2$ (3.8 mg, 0.017 mmol) and PPh_3 (13.4 mg, 0.051 mmol) were added to a solution of **82** (50 mg, 0.17 mmol) in DMF (1 mL) at RT and stirred for 15 mins. CuI (7 mg, 0.034 mmol) and **112** (87 mg, 0.18 mmol) in DMF (1 mL) were added and the mixture was heated to 80 ˚C. After 15 h, the reaction was cooled to RT, the solvent was evaporated under reduced pressure and the residue was filtered through Celite™ using ether. The crude product was purified by column chromatography (petrol/EtOAc, 10:1) to afford (*Z*)-isopropyl 2-(2-(2-isopropoxy-2-oxoethyl)phenyl)-3-phenylacrylate (52 mg, 86 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 3010, 2982, 1728, 1466, 1375, 1216, 1105; **δ_H (400 MHz, $CDCl_3$)**: 7.42-7.28 (9H, m, Ar C*H*), 6.78 (1H, s, *H12*), 5.09-4.93 (2H, m, *H2* & *H18*), 3.75 (2H, s, *H4*), 1.18 (6H, d, *J* 6.3, *H1*), 1.11 (6H, d, *J* 6.3, *H19*); **δ_C (100 MHz, $CDCl_3$)**: 176.2 (*C3*), 174.1 (*C17*), 136.8 (*C12*), 130.5 (q*C*), 129.7 (Ar *C*H), 128.6 (Ar *C*H), 128.4 (Ar *C*H), 128.3 (Ar *C*H), 128.2 (Ar *C*H), 127.1 (Ar *C*H), 68.8 (*C2*), 68.2 (*C18*), 39.2 (*C4*), 21.8 (*C1*), 21.4 (*C19*); **m/z**: HRMS (ES+) found 389.1727; $C_{23}H_{26}O_4$ $[M+Na]^+$ requires 389.1723

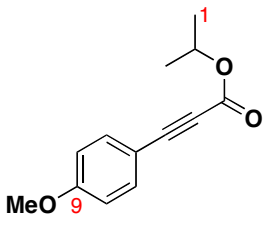
(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-3-oxo-1-phenylprop-1-en-2-yl)phenyl)malonate (120)



$Pd(OAc)_2$ (90 mg, 0.4 mmol) and cyclohexyl JohnPhos **85** (211 mg, 0.6 mmol) were added to a solution of **80** (780 mg, 2 mmol) in DMF (6 mL) at RT and stirred for 15 min under argon. CuI (77 mg, 0.4 mmol) and **112** (1.15 g, 2.4 mmol) in DMF (4 mL) were added and the mixture was heated to 80 ˚C. After 15 h, the solvent was evaporated under reduced pressure. The residue was filtered through Celite ™ using ether. The solvent was evaporated and the crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford (*Z*)-diisopropyl 2-(2-(3-isopropoxy-3-oxo-1-phenylprop-1-en-2-yl)phenyl)malonate (546 mg, 61 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3010, 2982, 1728, 1466, 1375, 1216, 1104; **δ_H (400 MHz, $CDCl_3$)**: 7.60 (1H, d, *J* 7.4, Ar C*H*), 7.45-7.29 (8H, m, Ar C*H*), 6.66 (1H, s, *H12*), 5.13 (1H, s, *H4*), 5.11-4.98 (3H, m, *H2* & *H18*), 1.26 (6H, d, *J* 6.2, *H1*), 1.19 (6H, d, *J* 6.3, *H1'*), 1.12 (6H, d, *J* 6.2, *H19*). **δ_C (100 MHz, $CDCl_3$)**: 168.1 (*C3*), 168.0 (*C17*), 138.7 (q*C*), 136.9 (*C12*), 135.3 (q*C*), 133.6 (q*C*), 131.8 (q*C*), 129.5 (Ar *C*H), 129.3 (Ar *C*H), 128.5 (Ar *C*H), 128.4 (Ar *C*H), 128.2 (Ar *C*H), 127.8 (Ar *C*H), 69.2 (*C2*), 68.9 (*C18*), 54.8 (*C4*), 21.6 (*C1*), 21.5 (*C1'*), 21.4 (*C19*); **m/z**: HRMS (ES+) found 475.2083; $C_{27}H_{32}O_6$ $[M+Na]^+$ requires 475.2091.

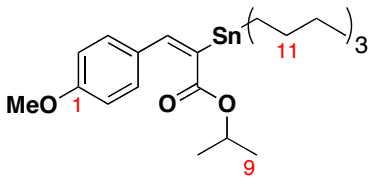
Isopropyl 3-(4-methoxyphenyl)propiolate (107)



^{n}BuLi (1.6 M in THF, 9.1 mL, 14.5 mmol) was added slowly *via* syringe pump to a solution of dibromide **101** (2.0 g, 6.9 mmol) in THF (20 mL) at -78 ˚C. The reaction was stirred at -78 ˚C for 45 mins and then at 0 ˚C for 45 mins. The flask was re-cooled to -78 ˚C and isopropyl chloroformate (1.0 M in toluene, 8.3 mL, 8.3 mmol) was added. The mixture was allowed to warm to 0 ˚C and stirred for 1 h. The reaction was quenched with sat. NH_4Cl and extracted with ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford isopropyl 3-(4-methoxyphenyl)propiolate (650 mg, 44 %) as a white solid.

m.p. 45-48 ˚C; **ν_{max}/cm^{-1} (film)**: 3010, 2983, 2216, 1705, 1285, 1195, 1104; **δ_H (400 MHz, $CDCl_3$)**: 7.54 (2H, d, *J* 8.2, *H7*), 6.88 (2H, d, *J* 8.2, *H8*), 5.15 (1H, sept., *J* 6.2, *H2*), 3.83 (3H, s, OCH_3), 1.33 (6H, d, *J* 6.3, *H1*); **δ_C (100 MHz, $CDCl_3$)**: 161.4 (*C3*), 153.9 (*C9*), 134.9 (*C7*), 114.2 (*C8*), 111.5 (*C6*), 86.5 (*C5*), 80.2 (*C4*), 69.8 (*C2*), 55.4 (OCH_3), 21.7 (*C1*); **m/z**: HRMS (ES+) found 241.0834; $C_{13}H_{14}O_3$ $[M+Na]^+$ requires 241.0830.

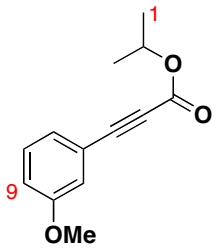
(*E*)-Isopropyl 3-(4-methoxyphenyl)-2-(tributylstannyl)acrylate (113)



$Pd(PPh_3)_4$ (60 mg, 0.05 mmol) and Bu_3SnH (0.73 mL, 2.75 mmol) were added to a solution of alkyne **107** (545 mg, 2.50 mmol) in THF (10 mL) at 0 ˚C. After 1 h, the solvent was evaporated and the residue was filtered through Celite™ using ether. The crude product was purified by column chromatography (petrol/ether, 20:1) to afford (*E*)-isopropyl 3-(4-methoxyphenyl)-2-(tributylstannyl)acrylate (1.04 g, 82 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2957, 2950, 1696, 1606, 1510, 1464, 1374, 1107, 1036; **δ_H (400 MHz, $CDCl_3$)**: 7.30 (2H, d, *J* 8.3, *H3*), 6.82 (2H, d, *J* 8.1, *H2*), 6.61 (1H, t, $^3J_{Sn\text{-}H}$ 29.7, *H5*), 5.15-5.03 (1H, sept., *J* 6.2, *H8*), 3.80 (3H, s, OC*H*$_3$), 1.59-1.52 (6H, m, *H11*), 1.33 (6H, m, *H12*), 1.23 (6H, d, *J* 6.3, *H9*), 1.05 (6H, dd, *J* 15.3, 6.9, *H10*), 0.94-0.87 (9H, m, *H13*); **δ_C (100 MHz, $CDCl_3$)**: 172.3 (*C7*), 159.6 (*C1*), 141.5 (*C5*), 129.7 (*C3*), 113.5 (*C2*) 112.9 (*C6*), 67.6 (*C8*), 55.3 (O*C*H$_3$), 28.8 (*C11*), 27.3 (*C12*), 21.9 (*C9*), 13.7 (*C10*), 10.5 (*C13*); **m/z**: HRMS (ES+) found 533.2054; $C_{25}H_{42}O_3Sn$ $[M+Na]^+$ requires 533.2053.

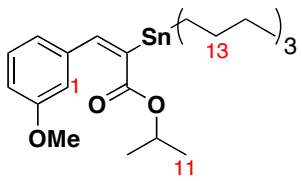
Isopropyl 3-(3-methoxyphenyl)propiolate (108)



^{n}BuLi (1.6 M in THF, 9.1 mL, 14.5 mmol) was added slowly *via* syringe pump to a solution of dibromide **102** (2.0 g, 6.9 mmol) in THF (20 mL) at -78 ˚C. The reaction was stirred at -78 ˚C for 45 mins and then at 0 ˚C for 45 mins. The flask was re-cooled to -78 ˚C and isopropyl chloroformate (1.0 M in toluene, 8.3 mL, 8.3 mmol) was added. The mixture was allowed to warm to 0 ˚C and stirred for 1 h. The reaction was quenched with sat. NH_4Cl and extracted with ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford isopropyl 3-(3-methoxyphenyl)propiolate (720 mg, 48 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3010, 2983, 2216, 1705, 1285, 1195, 1104; **δ_H (400 MHz, $CDCl_3$)**: 7.32-7.25 (1H, m, Ar C*H*), 7.19 (1H, dd, *J* 7.6, 1.1, Ar C*H*), 7.13-7.09 (1H, m, Ar C*H*), 7.02-6.97 (1H, m, Ar C*H*), 5.17 (1H, sept., *J* 6.2, *H2*), 3.81 (3H, s, OC*H*$_3$), 1.35 (6H, d, *J* 6.2, *H1*); **δ_C (100 MHz, $CDCl_3$)**: 159.3 (*C3*), 153.6 (*C8*), 129.6 (Ar *C*H), 125.5 (Ar *C*H), 120.6 (*C6*), 117.4 (Ar *C*H), 117.3 (Ar *C*H), 85.6 (*C5*), 80.7 (*C4*), 70.1 (*C2*), 55.4 (O*C*H$_3$), 21.7 (*C1*); **m/z**: HRMS (ES+) found 241.0837; $C_{13}H_{14}O_3$ $[M+Na]^+$ requires 241.0835.

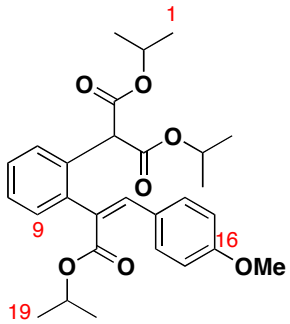
(*E*)-Isopropyl 3-(3-methoxyphenyl)-2-(tributylstannyl)acrylate (114)



$Pd(PPh_3)_4$ (70 mg, 0.06 mmol) and Bu_3SnH (0.89 mL, 3.3 mmol) were added to a solution of alkyne **108** (654 mg, 3.0 mmol) in THF (12 mL) at 0 ˚C. After 1 h, the solvent was evaporated and the residue was filtered through Celite™ using ether. The crude product was purified by column chromatography (petrol/ether, 20:1) to afford (*E*)-isopropyl 3-(3-methoxyphenyl)-2-(tributylstannyl)acrylate (820 mg, 54 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2957, 2950, 1696, 1606, 1510, 1464, 1374, 1107, 1036; **δ_H (400 MHz, $CDCl_3$)**: 7.20 (1H, t, *J* 7.9, Ar C*H*), 6.92 (1H, d, *J* 7.6, Ar C*H*), 6.88 (1H, s, *H1*), 6.82-6.77 (1H, m, Ar C*H*), 6.65 (1H, t, $^3J_{Sn\text{-}H}$ 29.6, *H7*), 5.10 (1H, sept., *J* 6.2, *H10*), 3.79 (3H, s, OCH_3), 1.61-1.50 (6H, m, *H13*), 1.40-1.28 (6H, m, *H14*), 1.20 (6H, d, *J* 6.3, *H11*), 1.09-1.00 (6H, m, *H12*), 0.90 (9H, t, *J* 7.3, *H15*); **δ_C (100 MHz, $CDCl_3$)**: 170.3 (*C9*), 159.6 (*C2*), 141.5 (*C7*), 129.7 (Ar *C*H), 128.5, (Ar *C*H), 128.3 (Ar *C*H), 113.5 (*C1*) 112.9 (*C8*), 67.6 (*C10*), 55.3 (O*C*H$_3$), 28.8 (*C13*), 27.3 (*C14*), 21.9 (*C11*), 13.7 (*C12*), 10.5 (*C15*); **m/z**: HRMS (ES+) found 533.2054; $C_{25}H_{42}O_3Sn$ $[M+Na]^+$ requires 533.2053.

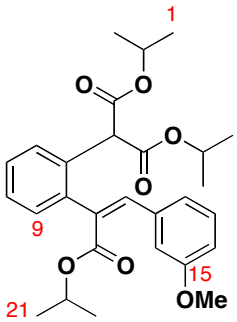
(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl)malonate (121)



$Pd(OAc)_2$ (13.5 mg, 0.06 mmol) and cyclohexyl JohnPhos **85** (63 mg, 0.18 mmol) were added to a solution of **80** (240 mg, 0.6 mmol) in DMF (2 mL) at RT and stirred for 15 min under argon. CuI (22.8 mg, 0.12 mmol) and **113** (381 mg, 0.75 mmol) in DMF (1 mL) were added and the mixture was heated to 80 ˚C. After 15 h, the solvent was evaporated under reduced pressure. The residue was filtered through Celite™ using ether. The solvent was evaporated and the crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford (*Z*)-diisopropyl 2-(2-(3-isopropoxy-1-(4-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl) malonate (85 mg, 30 %) as a colourless oil and SM **80** (122 mg).

ν_{max}/cm^{-1} (film): 3010, 2982, 1728, 1466, 1375, 1216, 1104; **δ_H (400 MHz, $CDCl_3$)**: 7.63-7.56 (1H, m, Ar C*H*), 7.43-7.30 (5H, m, Ar C*H*), 6.89 (2H, d, *J* 8.6, Ar C*H*), 6.58 (1H, s, *H12*), 5.13 (1H, s, *J* 6.6, *H4*), 5.12-5.01 (3H, m, *H2* & *H18*), 3.84 (3H, s, OCH_3), 1.26 (6H, d, *J* 6.3, *H19*), 1.19 (6H, d, *J* 6.3, *H1*), 1.16 (6H, d, *J* 6.3, *H1'*); **δ_C (100 MHz, $CDCl_3$)**: 168.1 (*C3* & *C17*), 159.9 (*C16*), 139.2 (*C12*), 136.8 (*C10*), 131.9 (*C5*), 131.2 (*C11*), 130.2 (Ar C*H*), 129.4 (Ar C*H*), 128.0 (Ar C*H*), 127.7 (Ar C*H*), 113.7 (*C15*), 69.2 (*C18*), 68.8 (*C2*), 55.3 (OCH_3), 54.8 (*C4*), 21.6 (*C19*), 21.5 (*C1*), 21.4 (*C1'*); **m/z**: HRMS (ES+) found 505.2193; $C_{28}H_{34}O_7$ $[M+Na]^+$ requires 505.2197.

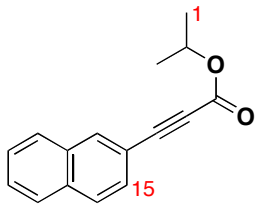
(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(3-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl)malonate (122)



$Pd(OAc)_2$ (28 mg, 0.13 mmol) and cyclohexyl JohnPhos **85** (63 mg, 0.18 mmol) were added to a solution of **80** (240 mg, 0.6 mmol) in DMF (2 mL) at RT and stirred for 15 min under argon. CuI (23 mg, 0.12 mmol) and **114** (381 mg, 0.75 mmol) in DMF (1 mL) were added and the mixture was heated to 80 ˚C. After 15 h, the solvent was evaporated under reduced pressure. The residue was filtered through Celite™ using ether. The solvent was evaporated and the crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford (*Z*)-diisopropyl 2-(2-(3-isopropoxy-1-(3-methoxyphenyl)-3-oxoprop-1-en-2-yl)phenyl) malonate (160 mg, 54 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3012, 2985, 1725, 1470, 1375, 1216, 1105; **δ_H (400 MHz, $CDCl_3$)**: 7.63-7.58 (1H, m, Ar C*H*), 7.42-7.31 (3H, m, Ar C*H*), 7.31-7.24 (1H, m, Ar C*H*), 7.01 (1H, d, *J* 7.6, Ar C*H*), 6.97 (1H, s, *H14*), 6.91-6.84 (1H, m, Ar C*H*), 6.63 (1H, s, *H12*), 5.14 (1H, s, *H4*), 5.12-4.99 (3H, m, *H2* & *H20*), 3.82 (3H, s, OCH_3), 1.27 (6H, d, *J* 6.3, *H21*), 1.20 (6H, d, *J* 6.3, *H1*), 1.13 (6H, d, *J* 6.3, *H1'*); **δ_C (100 MHz, $CDCl_3$)**: 168.1 (*C2*), 167.8 (*C20*), 159.5 (*C15*), 136.6 (q*C*), 132.2 (q*C*), 129.5 (Ar *C*H), 129.3 (Ar *C*H), 128.2 (Ar *C*H), 127.8 (Ar *C*H), 121.0 (Ar *C*H), 114.1 (Ar *C*H). 113.8 (Ar *C*H), 69.3 (*C20*), 68.9 (*C2*), 55.2 (OCH_3), 54.8 (*C4*), 21.6 (*C21*), 21.5 (*C1*), 21.4 (*C1'*); **m/z**: HRMS (ES+) found 505.2193; $C_{28}H_{34}O_7$ $[M+Na]^+$ requires 505.2197.

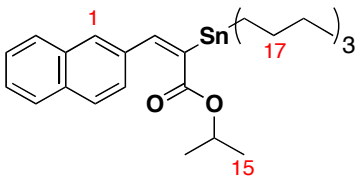
Isopropyl 3-(naphthalen-2-yl)propiolate (109)



^{n}BuLi (1.3 M in THF, 10.8 mL, 14.1 mmol) was added slowly *via* the syringe pump to a solution of dibromide **103** (2.0 g, 6.4 mmol) in THF (20 mL) at -78 ˚C. The reaction was stirred at -78 ˚C for 45 mins and then at 0 ˚C for 45 mins. The flask was re-cooled to -78 ˚C and isopropyl chloroformate (1.0 M in toluene, 7.7 mL, 7.7 mmol) was added. The mixture was allowed to warm to 0 ˚C and stirred for 1 h. The reaction was quenched with sat. NH_4Cl and extracted with ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford isopropyl 3-(naphthalen-2-yl)propiolate (1.45 g, 95 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3010, 2983, 2216, 1705, 1285, 1195, 1104; **δ_H (400 MHz, $CDCl_3$)**: 8.16 (1H, s, *H7*), 7.86-7.82 (3H, m, Ar C*H*), 7.60-7.50 (3H, m, Ar C*H*), 5.19 (1H, sept., *J* 6.2, *H2*), 1.36 (6H, d, *J* 6.3, *H1*); **δ_C (100 MHz, $CDCl_3$)**: 153.7 (*C3*), 134.2 (q*C*), 133.8 (q*C*), 132.6 (Ar *C*H), 128.4 (Ar *C*H), 128.3 (Ar *C*H), 128.1 (Ar *C*H), 127.9 (Ar *C*H), 126.9 (Ar *C*H), 116.9 (q*C*), 86.1 (*C5*), 81.2 (*C4*), 70.1 (*C2*), 21.7 (*C1*); **m/z**: HRMS (ES+) found 261.0886; $C_{16}H_{14}O_2$ $[M+Na]^+$ requires 261.0886.

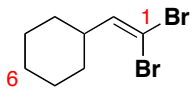
(*E*)-Isopropyl 3-(naphthalen-2-yl)-2-(tributylstannyl)acrylate (115)



$Pd(PPh_3)_4$ (146 mg, 0.13 mmol) and Bu_3SnH (1.9 mL, 7.0 mmol) were added to a solution of alkyne **109** (1.5 g, 6.3 mmol) in THF (25 mL) at 0 ˚C. After 1 h, the solvent was evaporated and residue was filtered through Celite™ using ether. The crude product was purified by column chromatography (petrol/ether, 20:1) to afford (*E*)-isopropyl 3-(naphthalen-2-yl)-2-(tributylstannyl)acrylate (2.1 g, 63 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2957, 2950, 1696, 1606, 1510, 1464, 1374, 1107, 1036; **δ_H (400 MHz, $CDCl_3$)**: 7.86-7.75 (4H, m, Ar C*H*), 7.57-7.41 (3H, m, Ar C*H*), 6.90 (1H, s, $^3J_{Sn\text{-}H}$ 29.6, *H11*), 5.16 (1H, sept., *J* 6.3, *H14*), 1.70-1.59 (6H, m, *H17*), 1.42 (6H, m, *H18*), 1.25 (6H, d, *J* 6.3, *H15*), 1.19-1.12 (6H, m, *H16*), 0.97 (9H, t, *J* 7.3, *H19*); **δ_H (400 MHz, $CDCl_3$)**: 172.9 (*C13*), 141.7 (*C11*), 140.8 (q*C*), 134.6 (q*C*), 133.3 (q*C*), 133.0 (q*C*), 128.2 (Ar *C*H), 127.7 (Ar *C*H), 127.6 (Ar *C*H), 127.5 (Ar *C*H), 126.2 (Ar *C*H), 126.1 (Ar *C*H), 125.8 (Ar *C*H), 67.8 (*C14*), 28.9 (*C17*), 27.4 (*C18*), 21.9 (*C15*), 13.7 (*C16*), 10.6 (*C19*); **m/z**: HRMS (ES+) found 553.2087; $C_{28}H_{42}O_2Sn$ $[M+Na]^+$ requires 553.2104.

(2,2-Dibromovinyl)cyclohexane (105)[*]

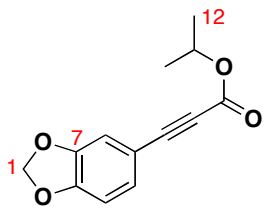


According to a literature procedure,[*] PPh_3 (5.12 g, 19.5 mmol) was added in portions to a solution of CBr_4 (3.23 g, 9.76 mmol) in CH_2Cl_2 (12 mL) at 0 ˚C. After 30 mins, cyclohexanecarbaldehyde (1.08 mL, 8.87 mmol) was added and mixture was stirred at 0 ˚C for 3 h. A mixture of 1:1 mixture of H_2O:brine was added and layers were separated. The aqueous layer was extracted with a 1:1 mixture of petrol:CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/ether, 50:1) to afford (2,2-dibromovinyl)cyclohexane (2.29 g, 97 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2990, 2928, 2897, 1590, 1417, 1254, 1223, 1146, 1017; **δ_H (400 MHz, $CDCl_3$)**: 6.23 (1H, d, *J* 9.1, *H2*), 2.35-2.19 (1H, m, *H3*), 1.81-1.56 (5H, m, CH_2), 1.40-1.02 (5H, m, CH_2); **δ_C (100 MHz, $CDCl_3$)**: 143.7 (*C2*), 86.9 (*C1*), 42.4 (*C3*), 31.2 (*C4*), 25.7 (*C5*), 25.5 (*C6*); **m/z**: HRMS (ES+) found 290.9175; $C_8H_{12}Br_2$ $[M+Na]^+$ requires 290.9183.

[*] Khan Z.; Wirth T. *Org. Lett.* **2009**, *11*, 229.
[*] Trost B. M.; Livingston R. C. *J. Am. Chem. Soc.* **2008**, *130*, 11970.

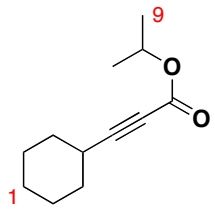
Isopropyl 3-(benzo[d][1,3]dioxol-5-yl)propiolate (110)



^{n}BuLi (1.48 M in THF, 14.4 mL, 21.3 mmol) was added slowly *via* the syringe pump to a solution of dibromide **104** (3.11 g, 10.2 mmol) in THF (20 mL) at -78 ˚C. The reaction was stirred at -78 ˚C for 45 mins and then at 0 ˚C for 45 mins. The flask was recooled to -78 ˚C and isopropyl chloroformate (1.0 M in toluene, 12.2 mL, 12.2 mmol) was added. The mixture was allowed to warm to 0 ˚C and stirred for 1 h. The reaction was quenched with sat. NH_4Cl and extracted with ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/ether, 9:1) to afford isopropyl 3-(benzo[*d*][1,3]dioxol-5-yl)propiolate (1.67 g, 71 %) as a yellow crystalline solid.

m.p. 68-72 ˚C; **ν_{max}/cm^{-1} (film)**: 3010, 2983, 2216, 1705, 1285, 1195, 1104; **δ_H (400 MHz, $CDCl_3$)**: 7.14 (1H, dd, *J* 8.1, 1.6, *H4*), 7.00 (1H, d, *J* 1.6, *H6*), 6.78 (1H, d, *J* 8.1, *H3*), 6.00 (2H, s, *H1*), 5.14 (1H, sept., *J* 6.2, *H11*), 1.32 (6H, d, *J* 6.3, *H12*); **δ_C (100 MHz, $CDCl_3$)**: 153.7 (*C10*), 149.9 (*C2*), 147.6 (*C7*), 128.9 (*C4*), 112.7 (*C5*), 112.6 (*C6*), 108.9 (*C3*), 101.6 (*C1*), 86.1 (*C8*), 80.0 (*C9*), 69.9 (*C11*), 21.7 (*C12*); **m/z**: HRMS (ES+) found 255.0630; $C_{13}H_{12}O_4$ $[M+Na]^+$ requires 255.0630.

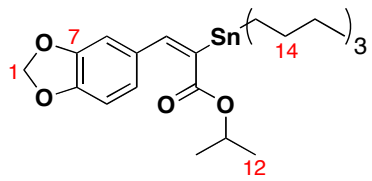
Isopropyl 3-cyclohexylpropiolate (111)



^{n}BuLi (1.3 M in THF, 9.04 mL, 11.8 mmol) was added slowly *via* syringe pump to a solution of dibromide **105** (1.50 g, 5.60 mmol) in THF (10 mL) at -78 ˚C. The reaction was stirred at -78 ˚C for 45 mins and then at 0 ˚C for 45 mins. The flask was recooled to -78 ˚C and isopropyl chloroformate (1.0 M in toluene, 6.7 mL, 6.7 mmol) was added. The mixture was allowed to warm to 0 ˚C and stirred for 1 h. The reaction was quenched with sat. NH_4Cl and extracted with ether (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/ether, 9:1) to afford isopropyl 3-cyclohexylpropiolate (761 mg, 70 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3010, 2980, 2218, 1710, 1286, 1195, 1110; **δ_H (500 MHz, $CDCl_3$)**: 5.07 (1H, hept., *J* 6.3, *H8*), 2.49 (1H, m, *H4*), 1.89-1.78 (2H, m, CH_2), 1.69 (2H, m, CH_2), 1.59-1.42 (2H, m, CH_2), 1.34-1.26 (4H, m, CH_2), 1.28 (6H, d, *J* 6.3, *H9*); **δ_C (125 MHz, $CDCl_3$)**: 153.7 (*C7*), 92.4 (*C5*), 73.4 (*C6*), 69.5 (*C8*), 31.5 (*C3*), 28.9 (*C4*), 25.6 (*C2*), 24.7 (*C1*), 21.7 (*C9*); **m/z**: HRMS (ES+) found 217.1209; $C_{12}H_{18}O_2$ $[M+Na]^+$ requires 217.1204.

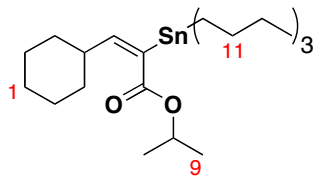
(*E*)-Isopropyl 3-(benzo[d][1,3]dioxol-5-yl)-2-(tributylstannyl)acrylate (116)



$Pd(PPh_3)_4$ (146 mg, 0.13 mmol) and Bu_3SnH (1.91 mL, 7.09 mmol) were added to a solution of alkyne **110** (1.5 g, 6.46 mmol) in THF (40 mL) at 0 ˚C. After 1 h, the solvent was evaporated and residue was filtered through Celite™ using ether. The crude product was purified by column chromatography (petrol/ether, 50:1) to afford (*E*)-isopropyl 3-(benzo[d][1,3]dioxol-5-yl)-2-(tributylstannyl)acrylate (2.19 g, 65 %) as a yellow oil.

ν_{max}/cm^{-1} (film): 2960, 2950, 1696, 1606, 1510, 1464, 1374, 1107, 1036; **δ_H (500 MHz, $CDCl_3$)**: 6.89 (1H, d, *J* 1.3, *H6*), 6.82 (1H, dd, *J* 8.1, 1.2, *H4*), 6.74 (1H, d, *J* 8.0, *H3*), 6.56 (1H, t, $^3J_{Sn\text{-}H}$ 29.6, *H8*), 5.94 (2H, s, *H1*), 5.09 (1H, sept., *J* 6.2, *H11*), 1.60-1.51 (6H, m, *H14*), 1.39-1.29 (6H, m, *H15*), 1.24 (6H, d, *J* 6.3, *H12*), 1.08-1.02 (6H, m, *H13*), 0.90 (9H, t, *J* 7.3, *H16*); **δ_C (125 MHz, $CDCl_3$)**: 172.7 (*C10*), 147.6 (*C2*), 147.4 (*C7*), 141.1 (*C8*), 138.1 (*C5*), 131.6 (*C4*), 122.9 (*C9*), 108.1 (*C6*), 107.9 (*C3*), 101.1 (*C1*), 67.6 (*C11*), 29.7 (*C14*), 27.3 (*C15*), 21.8 (*C12*), 13.7 (*C16*), 10.2 (*C13*); **m/z**: HRMS (ES+) found 547.1840; $C_{25}H_{40}O_4Sn$ $[M+Na]^+$ requires 547.1846.

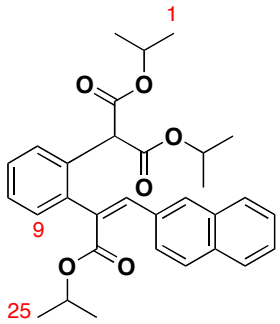
(*E*)-Isopropyl 3-cyclohexyl-2-(tributylstannyl)acrylate (117)



$Pd(PPh_3)_4$ (60 mg, 0.052 mmol) and Bu_3SnH (0.76 mL, 2.82 mmol) were added to a solution of alkyne **111** (500 mg, 2.57 mmol) in THF (15 mL) at 0 ˚C. After 1 h, the solvent was evaporated and residue was filtered through Celite™ using ether. The crude product was purified by column chromatography (petrol/ether, 50:1) to afford (*E*)-isopropyl 3-cyclohexyl-2-(tributylstannyl)acrylate (1.20 g, 96 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 2957, 2952, 1692, 1610, 1512, 1464, 1380, 1110, 1036; **δ_H (500 MHz, $CDCl_3$)**: 5.89-5.70 (1H, d, $^3J_{Sn\text{-}H}$ 29.6, *H5*), 5.02 (1H, sept., *J* 6.2, *H8*), 2.82-2.69 (1H, m, *H4*), 1.76-1.55 (6H, m, CH_2), 1.54-1.43 (6H, m, *H11*), 1.35-1.27 (6H, m, *H12*), 1.25 (6H, d, *J* 6.3, *H9*), 1.21-0.96 (4H, m, CH_2), 0.97-0.90 (6H, m, *H10*), 0.88 (9H, t, *J* 7.3, *H13*); **δ_C (125 MHz, $CDCl_3$)**: 170.8 (*C7*), 158.2 (*C5*), 133.5 (*C6*), 67.1 (*C8*), 40.6 (*C4*), 33.4 (*C3*), 28.9 (*C12*), 27.1 (*C11*), 25.9 (*C1*), 25.6 (*C2*), 22.0 (*C9*), 13.7 (*C13*), 10.1 (*C10*); **m/z**: HRMS (ES+) found 509.2421; $C_{24}H_{46}O_2Sn$ $[M+Na]^+$ requires 509.2417.

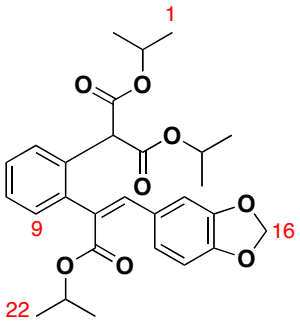
(*Z*)-Diisopropyl 2-(2-(3-isopropoxy-1-(naphthalen-2-yl)-3-oxoprop-1-en-2-yl)phenyl)malonate (123)



$Pd(OAc)_2$ (28 mg, 0.13 mmol) and cyclohexyl JohnPhos **85** (63 mg, 0.18 mmol) were added to a solution of **80** (240 mg, 0.6 mmol) in DMF (2 mL) at RT and stirred for 15 min under argon. CuI (23 mg, 0.12 mmol) and **115** (424 mg, 0.8 mmol) in DMF (1 mL) were added to this mixture and heated to 80 ˚C. After 15 h, the solvent was evaporated under reduced pressure. The residue was filtered through Celite™ using ether. The solvent was evaporated and the crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford (*Z*)-diisopropyl 2-(2-(3-isopropoxy-1-(naphthalen-2-yl)-3-oxoprop-1-en-2-yl)phenyl) malonate (120 mg, 39 %) as oil.

ν_{max}/cm^{-1} (film): 3020, 2980, 1730, 1470, 1375, 1216, 1105; **δ_H (500 MHz, $CDCl_3$)**: 7.87 (1H, s, *H14*), 7.82 (3H, m, Ar C*H*), 7.56-7.34 (7H, m, Ar C*H*), 6.81 (1H, s, *H12*), 5.19 (1H, s, *H4*), 5.12-5.03 (3H, m, *H2* & *H24*), 1.26 (6H, d, *J* 6.2, *H25*), 1.20 (6H, d, *J* 6.3, *H1*), 1.11 (6H, d, *J* 6.3, *H1'*); **δ_C (125 MHz, $CDCl_3$)**: 168.1 (*C3*), 167.9 (*C23*), 138.8 (q*C*), 136.9 (*C12*), 133.8 (q*C*), 133.1 (q*C*), 132.8 (q*C*), 131.9 (q*C*), 129.5 (Ar *C*H), 129.4 (Ar *C*H), 128.3 (Ar *C*H), 128.2 (Ar *C*H), 128.1 (Ar *C*H), 127.8 (Ar *C*H), 127.6 (Ar *C*H), 126.5 (Ar *C*H), 126.4 (Ar *C*H), 126.0 (Ar *C*H), 69.3 (*C24*), 69.0 (*C2*), 54.8 (*C4*), 21.6 (*C25*), 21.5 (*C1*), 21.4 (*C1'*); **m/z**: HRMS (ES+) found 525.2245; $C_{31}H_{34}O_6$ $[M+Na]^+$ requires 525.2248.

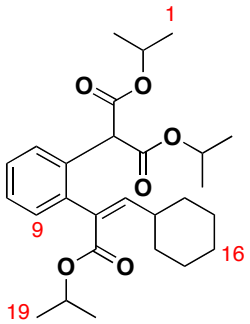
(*Z*)-Diisopropyl 2-(2-(1-(benzo[*d*][1,3]dioxol-5-yl)-3-isopropoxy-3-oxoprop-1-en-2-yl)phenyl)malonate (124)



$Pd(OAc)_2$ (12 mg, 0.052 mmol) and cyclohexyl JohnPhos **85** (30 mg, 0.084 mmol) were added to a solution of **80** (100 mg, 0.26 mmol) in DMF (2 mL) at RT and stirred for 15 min under argon. CuI (10 mg, 0.052 mmol) and **116** (161 mg, 0.31 mmol) in DMF (1 mL) were added to this mixture and heated to 80 ˚C. After 15 h, the solvent was evaporated under reduced pressure. The residue was filtered through Celite™ using ether. The solvent was evaporated and crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford (*Z*)-diisopropyl 2-(2-(1-(benzo[*d*][1,3]dioxol-5-yl)-3-isopropoxy-3-oxoprop-1-en-2-yl)phenyl)malonate (74 mg, 59 %) as a solid.

m.p. 76-79 ˚C; **ν_{max}/cm^{-1} (film)**: 3012, 2985, 1720, 1472, 1375, 1216, 1105; **δ_H (500 MHz, $CDCl_3$)**: 7.58 (1H, d, *J* 7.9, Ar C*H*), 7.40-7.28 (3H, m, Ar C*H*), 6.98 (1H, d, *J* 1.4, Ar C*H*), 6.89 (1H, dd, *J* 8.1, 1.3, Ar C*H*), 6.79 (1H, d, *J* 8.0, Ar C*H*), 6.52 (1H, s, *H12*), 5.98 (2H, s, *H16*), 5.10 (1H, s, *H4*), 5.09-5.00 (3H, m, *H2* & *H21*), 1.25 (6H, d, *J* 6.2, *H22*), 1.19 (6H, d, *J* 6.3, *H1*), 1.16 (6H, d, *J* 6.3, *H1'*); **δ_C (125 MHz, $CDCl_3$)**: 168.1 (*C20*), 167.8 (*C3*), 147.9 (*C15*), 147.7 (*C17*), 138.9 (q*C*), 136.6 (*C12*), 131.9 (q*C*), 129.5 (Ar *C*H), 129.3 (Ar *C*H), 129.2 (Ar *C*H), 128.1 (Ar *C*H), 127.7 (Ar *C*H), 123.5 (Ar *C*H), 108.4 (*C14*), 108.1 (*C18*), 101.2 (*C16*), 69.2 (*C21*), 68.9 (*C2*), 54.8 (*C4*), 21.6 (*C22*), 21.5 (*C1*), 21.4 (*C1'*); **m/z**: HRMS (ES+) found 519.1984; $C_{28}H_{32}O_8$ $[M+Na]^+$ requires 519.1989.

(*Z*)-Diisopropyl 2-(2-(1-cyclohexyl-3-isopropoxy-3-oxoprop-1-en-2-yl)phenyl)malonate (125)



$Pd(OAc)_2$ (24 mg, 0.11 mmol) and cyclohexyl JohnPhos **85** (60 mg, 0.16 mmol) were added to a solution of **80** (200 mg, 0.52 mmol) in DMF (3 mL) at RT and stirred for 15 min under argon. CuI (20 mg, 0.104 mmol) and **117** (301 mg, 0.62 mmol) in DMF (2 mL) were added to this mixture and heated to 80 ˚C. After 15 h, the solvent was evaporated under reduced pressure. The residue was filtered through Celite™ using ether. The solvent was evaporated and crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford (*Z*)-diisopropyl 2-(2-(1-cyclohexyl-3-isopropoxy-3-oxoprop-1-en-2-yl)phenyl)malonate (85 mg, 36 %) as a colourless oil.

ν_{max}/cm^{-1} (film): 3010, 2982, 2940, 1725, 1470, 1375, 1220, 1108; **δ_H (500 MHz, $CDCl_3$)**: 7.52 (1H, d, *J* 6.9, Ar C*H*), 7.31 (1H, td, *J* 7.6, 1.3, Ar C*H*), 7.28-7.22 (1H, m, Ar C*H*), 7.16 (1H, dd, *J* 7.6, 1.2, Ar C*H*), 5.75 (1H, d, *J* 9.8 Hz, *H12*), 5.10-5.02 (3H, sept., *J* 6.2, *H2*, *H2'* & *H18*), 4.80 (1H, s, *H4*), 2.99 (1H, m, *H13*), 1.84 (2H, d, *J* 12.6, CH_2), 1.73 (4H, m, CH_2), 1.41-1.29 (2H, m, CH_2), 1.24 (6H, d, *J* 6.2, *H19*), 1.20 (6H, d, *J* 6.2, *H1*), 1.19 (6H, d, *J* 6.2, *H1'*), 1.12 (2H, m, CH_2); **δ_C (125 MHz, $CDCl_3$)**: 168.0 (*C17*), 166.4 (*C3*), 151.4 (*C12*), 139.5 (q*C*), 131.7 (q*C*), 130.5 (q*C*), 129.8 (Ar *C*H), 129.0 (Ar *C*H), 127.6 (Ar *C*H), 127.5 (Ar *C*H), 69.1 (*C18*), 68.1 (*C2*), 54.7 (*C4*), 38.5 (*C13*), 32.6 (*C*H_2), 25.9 (*C*H_2), 25.5 (*C*H_2), 21.7 (*C19*), 21.6 (*C1*), 21.5 (*C1'*); **m/z**: HRMS (ES+) found 481.2563; $C_{27}H_{38}O_6$ $[M+Na]^+$ requires 481.2561.

2.1 General procedure for 6π-electrocyclization:

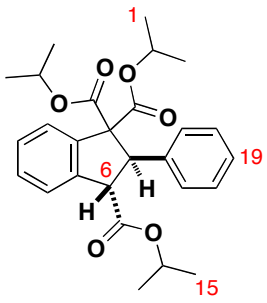
Racemic:

$CsOH \cdot H_2O$ was added to a stirred solution of electrocyclic precursor in toluene at -15 ˚C and stirred for 18 h. The reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford the desired electrocyclic product.

Asymmetric:

$CsOH \cdot H_2O$ was added to a stirred solution of electrocyclic precursor and phase-transfer catalyst in toluene at -15 ˚C and stirred for 18 h. The reaction was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (petrol/EtOAc, 20:1) to afford the desired electrocyclic product.

(2*R*,3*S*)-Triisopropyl 2-phenyl-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (128)

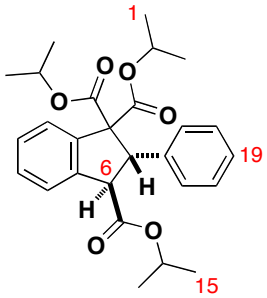


Racemic: The reaction was performed according to the general procedure using $CsOH \cdot H_2O$ (8 mg, 0.048 mmol) and **120** (20 mg, 0.044 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product as a colourless oil in quantitative yield (5:1 dr).

Asymmetric: The asymmetric reaction was performed according to the general procedure using $CsOH \cdot H_2O$ (8 mg, 0.048 mmol) and **120** (20 mg, 0.044) and (8*S*,9*R*)-(−)-*N*-benzylcinchonidinium chloride **125a** in toluene (0.2 mL) at -15 ˚C to afford the desired product as a colourless oil (18 mg, 90 %) as a mixture of two diastereoisomers (5:1 dr), 28 % ee (major diastereoisomer).

Major diastereoisomer: $[\alpha]_D^{22}$: +22.5° (c 0.041, $CHCl_3$), ν_{max}/cm^{-1} **(film)**: 2985, 2940, 1729, 1470, 1252, 1104; δ_H **(500 MHz, $CDCl_3$)**: 7.66-7.62 (1H, m, Ar C*H*), 7.42 (1H, t, *J* 7.4, Ar C*H*), 7.40-7.31 (4H, m, Ar C*H*), 7.25-7.18 (3H, m, Ar C*H*), 5.16-5.07 (1H, sept., *J* 6.2, *H2*), 5.08-5.00 (1H, hept., *J* 6.2, *H14*), 4.93 (1H, d, *J* 8.0, *H5*), 4.61-4.51 (1H, m, *H2'*), 4.41 (1H, d, *J* 8.0, *H6*), 1.28 (3H, d, *J* 6.3, *H1*), 1.26 (3H, d, *J* 6.3, *H1*), 1.22 (3H, d, *J* 6.3, *H15*), 1.21 (3H, d, *J* 6.3, *H15*), 1.05 (3H, d, *J* 6.3, *H1'*), 0.55 (3H, d, *J* 6.3, *H1'*); δ_C **(125 MHz, $CDCl_3$)**: 171.2 (*C3*), 168.7 (*C3*), 168.6 (*C13*), 141.0 (q*C*), 139.3 (q*C*), 139.1 (q*C*), 128.9 (Ar *C*H), 128.1 (Ar *C*H), 127.9 (Ar *C*H), 127.3 (Ar *C*H), 126.4 (Ar *C*H), 124.8 (Ar *C*H), 70.1 (*C4*), 69.5 (*C2*), 69.2 (*C2'*), 68.6 (*C14*), 55.3 (*C6*), 53.7 (*C5*), 21.8 (*C1*), 21.7 (*C1*), 21.6 (*C15*), 21.5 (*C15*), 21.4 (*C1'*), 20.7 (*C1'*); **m/z**: HRMS (ES+) found 475.2091; $C_{27}H_{32}O_6$ $[M+Na]^+$ requires 475.2091.

(2*S*,3*R*)-Triisopropyl 2-phenyl-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (136)

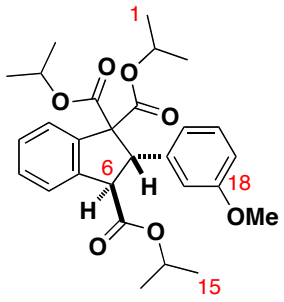


Asymmetric: The asymmetric reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (18 mg, 0.12 mmol) and **120** (27 mg, 0.06) and catalyst **135** (5 mg, 0.006 mmol) in toluene (0.2 mL) at -15 °C to afford the desired product (25 mg, 93 %) as a mixture of two diastereoisomers (5:1 dr), 60 % ee (major diastereoisomer).

Major diastereoisomer: $[\alpha]_D^{22}$: -18.6° (c 0.107, $CHCl_3$), ν_{max}/cm^{-1} **(film)**: 2984, 2940, 1729, 1470, 1252, 1104; δ_H **(500 MHz, $CDCl_3$)**: 7.65-7.62 (1H, m, Ar C*H*), 7.42 (1H, t, *J* 7.4, Ar C*H*), 7.40-7.31 (4H, m, Ar C*H*), 7.25-7.18 (3H, m, Ar C*H*), 5.16-5.07 (1H, sept., *J* 6.2, *H2*), 5.08-5.00 (1H, hept., *J* 6.2, *H14*), 4.93 (1H, d, *J* 8.0, *H5*), 4.61-4.51 (1H, m, *H2'*), 4.41 (1H, d, *J* 8.0, *H6*), 1.28 (3H, d, *J* 6.3, *H1*), 1.26 (3H, d, *J* 6.3, *H1*), 1.22 (3H, d, *J* 6.3, *H15*), 1.21 (3H, d, *J* 6.3, *H15*), 1.05 (3H, d, *J* 6.3, *H1'*), 0.55 (3H, d, *J* 6.3, *H1'*); δ_C **(125 MHz, $CDCl_3$)**: 171.2 (*C3*), 168.7 (*C3*), 168.6 (*C13*), 141.0 (q*C*), 139.3 (q*C*), 139.1 (q*C*),

128.9 (Ar *C*H), 128.1 (Ar *C*H), 127.9 (Ar *C*H), 127.3 (Ar *C*H), 126.4 (Ar *C*H), 124.8 (Ar *C*H), 70.1 (*C4*), 69.5 (*C2*), 69.2 (*C2'*), 68.6 (*C14*), 55.3 (*C6*), 53.7 (*C5*), 21.8 (*C1*), 21.7 (*C1*), 21.6 (*C15*), 21.5 (*C15*), 21.4 (*C1'*), 20.7 (*C1'*); **m/z**: HRMS (ES+) found 475.2091; $C_{27}H_{32}O_6$ $[M+Na]^+$ requires 475.2091.

(2*S*,3*R*)-Triisopropyl 2-(3-methoxyphenyl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (138)



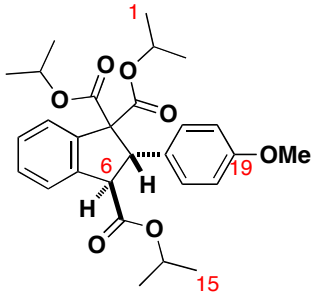
Racemic: The reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (13 mg, 0.084 mmol) and **122** (20 mg, 0.042 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product as a colourless oil in quantitative yield (5:1 dr).

Asymmetric: The asymmetric reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (13 mg, 0.084 mmol) and **122** (20 mg, 0.042) and catalyst **135** (3 mg, 0.004 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product (18 mg, 90 %) as oil as a mixture of two diastereoisomers (5:1 dr), 68 % ee (major diastereoisomer).

Major diastereoisomer: $[\alpha]_D^{22}$: -16.1˚ (c 0.190, $CHCl_3$); ν_{max}**/cm^{-1} (film)**: 3010, 2985, 2940, 1729, 1470, 1252, 1104; δ_H **(500 MHz, $CDCl_3$)**: 7.65-7.62 (1H, m, Ar C*H*), 7.42 (1H, d, *J* 7.2, Ar C*H*), 7.35 (2H, m, Ar C*H*), 7.15 (1H, m, Ar C*H*), 6.94-6.88 (2H, m, Ar C*H*), 6.78-6.73 (1H, m, Ar C*H*), 5.12 (1H, sept., *J* 12.4, 6.2, *H2*), 5.04 (1H, sept., *J* 12.7, 6.4, *H14*), 4.92 (1H, d, *J* 8.0, *H5*), 4.59 (1H, sept., *J* 12.5, 6.2, *H2'*), 4.39 (1H, d, *J* 8.0, *H6*), 3.75 (3H, s, OC*H*$_3$), 1.29 (3H, d, *J* 6.3, *H1*), 1.26 (3H, d, *J* 6.3, *H1*), 1.23 (6H, d, *J* 6.3, *H15*), 1.06 (3H, d, *J* 6.3, *H2'*), 0.60 (3H, d, *J* 6.3, *H2'*); δ_C **(125 MHz, $CDCl_3$)**: 171.2 (*C13*), 168.6 (*C3*), 168.5 (*C3'*), 159.3 (*C18*), 140.9 (q*C*), 140.7 (q*C*), 139.3 (q*C*), 129.1 (Ar *C*H), 128.9 (Ar *C*H), 128.1 (Ar *C*H), 126.3 (Ar *C*H), 124.8 (Ar *C*H), 121.1 (Ar *C*H), 114.7 (*C17*), 112.9

(*C19*), 70.1 (*C4*), 69.5 (*C2*), 69.1 (*C2*), 68.6 (*C14*), 55.3 (*C5*), 55.2 (O*C*H$_3$), 53.6 (*C6*), 21.8 (*C1*), 21.7 (*C1*), 21.6 (*C15*), 21.5 (*C15'*), 21.4 (*C1'*), 20.7 (*C1'*); **m/z** HRMS (ES+) found 505.2192; $C_{28}H_{34}O_7$ $[M+Na]^+$ requires 505.2197; **Minor diastereoisomer**: $[\alpha]_D^{22}$: +29.5° (c 0.043, $CHCl_3$); ν_{max}**/cm^{-1} (film)**: 3015, 2980, 2942, 1725, 1480, 1250, 1104;δ_H **(500 MHz, CDCl$_3$)**: 7.71 (1H, d, *J* 7.3, Ar C*H*), 7.62 (1H, d, *J* 7.3, Ar C*H*), 7.42-7.33 (2H, m, Ar C*H*), 6.93 (1H, t, *J* 8.0, Ar C*H*), 6.64 (1H, dd, *J* 8.2, 2.4, Ar C*H*), 6.52 (1H, s, Ar C*H*), 6.46 (1H, d, *J* 7.7, Ar C*H*), 4.94 (1H, sept., *J* 12.2, 6.1, *H2*), 4.79 (1H, d, *J* 7.9, *H5*), 4.71 (1H, d, *J* 7.4, *H6*), 4.73-4.61 (2H, m, *H2* & *H14*), 3.61 (3H, s, OC*H*$_3$), 1.24 (3H, d, *J* 6.3, *H1*), 1.10 (3H, d, *J* 6.3, *H1*), 1.07 (6H, d, *J* 6.3, *H15*), 0.74 (3H, d, *J* 6.3, *H1'*), 0.69 (3H, d, *J* 6.3, *H1'*); δ_C **(125 MHz, CDCl$_3$)**: 170.0 (*C3*), 168.7 (*C13*), 167.2 (*C3'*), 158.6 (*C18*), 140.7 (q*C*), 139.0 (q*C*), 138.9 (q*C*), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 127.7 (Ar *C*H), 127.4 (Ar *C*H), 126.4 (Ar *C*H), 121.3 (Ar *C*H), 115.5 (*C19*), 113.2 (*C17*), 69.5 (*C4*), 69.4 (*C2*), 68.7 (*C14*), 67.8 (*C2'*), 54.9 (O*C*H$_3$), 54.8 (*C6*), 53.3 (*C5*), 21.6 (*C1*), 21.5 (*C1*), 21.4 (*C15*), 21.3 (*C15*), 20.9 (*C1'*), 20.8 (*C1'*); **m/z** HRMS (ES+) found 505.2196; $C_{28}H_{34}O_7$ $[M+Na]^+$ requires 505.2197.

(2*S*,3*R*)-Triisopropyl 2-(4-methoxyphenyl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (137)



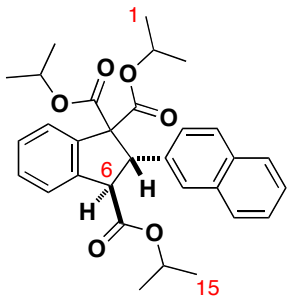
Racemic: The reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (13 mg, 0.084 mmol) and **121** (20 mg, 0.042 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product as a colourless oil in quantitative yield (5:1 dr).

Asymmetric: The asymmetric reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (13 mg, 0.084 mmol) and **121** (20 mg, 0.042) and catalyst **135** (3 mg, 0.004 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product (19 mg, 95 %) as oil as a mixture of two diastereoisomers (5:1 dr), 48 % ee (major diastereoisomer).

Major diastereoisomer: $[\alpha]_D^{22}$: -13.2˚ (c 0.125, $CHCl_3$); ν_{max}/cm^{-1} **(film)**: 3010, 2985, 2940, 1729, 1470, 1252, 1104; δ_H **(500 MHz, $CDCl_3$)**: 7.65-7.62 (1H, m, Ar C*H*), 7.41 (1H, d, *J* 7.2, Ar C*H*), 7.35 (2H, m, Ar C*H*), 7.26 (2H, d, *J* 8.7, Ar C*H*), 6.78 (2H, d, *J* 8.7, Ar C*H*), 5.16-5.07 (1H, sept., *J* 6.1, *H2*), 5.08-4.99 (1H, sept., *J* 6.2, *H14*), 4.87 (1H, d, *J* 8.3, *H5*), 4.64-4.55 (1H, sept., *J* 6.2, *H2'*), 4.38 (1H, d, *J* 8.3, *H6*), 3.76 (3H, s, OC*H*$_3$), 1.29 (3H, d, *J* 6.3, *H1*), 1.26 (3H, d, *J* 6.3, *H1*), 1.23 (3H, d, *J* 6.3, *H15*), 1.21 (3H, d, *J* 6.3, *H15*), 1.07 (3H, d, *J* 6.3, *H1'*), 0.63 (3H, d, *J* 6.3, *H1'*); δ_C **(125 MHz, $CDCl_3$)**: 171.3 (*C3*), 168.7 (*C13*), 168.6 (*C3'*), 158.9 (*C19*), 141.1 (q*C*), 139.4 (q*C*), 130.0 (q*C*), 128.8 (Ar *C*H), 128.0 (Ar *C*H), 126.3 (Ar *C*H), 124.7 (Ar *C*H), 113.5 (*C18*), 112.9 (*C20*), 70.0 (*C4*), 69.4 (*C2*), 69.1 (*C14*), 68.5 (*C2'*), 55.3 (O*C*H$_3$), 55.2 (*C6*), 53.1 (*C5*), 21.8 (*C1*), 21.7 (*C1*), 21.6 (*C15*), 21.5 (*C15*), 21.4 (*C1'*), 20.9 (*C1'*); **m/z**: HRMS (ES+) found 505.2193; $C_{28}H_{34}O_7$ $[M+Na]^+$ requires 505.2197; **Minor diastereoisomer**: $[\alpha]_D^{22}$: +16.8˚ (c 0.115, $CHCl_3$); ν_{max}/cm^{-1} **(film)**: 2996, 2978, 2930 1730, 1470, 1250, 1104; δ_H **(500 MHz, $CDCl_3$)**: 7.70 (1H, d, *J* 7.2, Ar C*H*), 7.60 (1H, d, *J* 7.3, Ar C*H*), 7.42-7.33 (2H, m, Ar C*H*), 6.83 (2H, d, *J* 8.4, Ar C*H*),

6.58 (2H, d, *J* 8.8, Ar C*H*), 4.94 (1H, sept., *J* 6.1, *H2*), 4.77 (1H, d, *J* 7.8, *H5*), 4.69 (1H, d, *J* 7.9, *H6*), 4.72-4.58 (2H, m, *H2* & *H14*), 3.66 (3H, s, OCH_3), 1.24 (3H, d, *J* 6.3, *H1*), 1.12 (3H, d, *J* 6.3, *H1*), 1.08 (6H, dd, *J* 6.3, *H15*), 0.75 (3H, d, *J* 6.3, *H1'*), 0.71 (3H, d, *J* 6.3, *H1'*); **δ_C (125 MHz, $CDCl_3$)**: 170.1 (*C3*), 168.8 (*C13*), 167.3 (*C3'*), 159.0 (*C19*), 140.7 (q*C*), 138.9 (q*C*), 130.4 (q*C*), 129.5 (Ar *C*H), 128.7 (Ar *C*H), 127.8 (Ar *C*H), 127.4 (Ar *C*H), 126.4 (Ar *C*H), 114.3 (*C18*), 112.9 (*C20*), 69.5 (*C4*), 69.4 (*C2*), 68.7 (*C14*), 65.8 (*C2*), 55.1 (O*C*H_3), 54.0 (*C6*), 53.4 (*C5*), 21.7 (*C1*), 21.5 (*C1*), 21.4 (*C15*), 21.3 (*C15*), 21.0 (*C1'*), 20.9 (*C1'*); **m/z**: HRMS (ES+) found 505.2179; $C_{28}H_{34}O_7$ $[M+Na]^+$ requires 505.2197.*

(2*S*,3*R*)-Triisopropyl 2-(naphthalen-2-yl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (139)



Racemic: The reaction was performed according to the general procedure using CsOH·H_2O (12 mg, 0.08 mmol) and **123** (20 mg, 0.04 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product as a colourless oil in quantitative yield (5:1 dr).

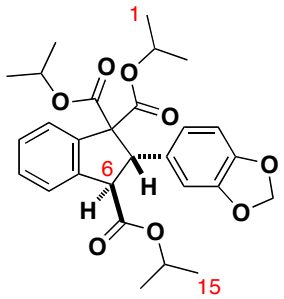
Asymmetric: The asymmetric reaction was performed according to the general procedure using CsOH·H_2O (12 mg, 0.08 mmol), **123** (20 mg, 0.04 mmol) and catalyst **135** (3 mg, 0.004 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product (19 mg, 94 %) as a mixture of two diastereoisomers (7:1 dr), 51 % ee (major diastereoisomer).

Major diastereoisomer: **$[\alpha]_D^{22}$**: -13.8˚ (c 0.590, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3010, 2985, 2940, 1729, 1470, 1252, 1104; **δ_H (500 MHz, $CDCl_3$)**: 7.84-7.71 (5H, m, Ar C*H*), 7.66 (1H, dd, *J* 6.6, 5.2, Ar C*H*), 7.49-7.34 (5H, m, Ar C*H*), 5.18-5.09 (1H, m, *H2*), 5.12 (1H, d, *J* 8.3, *H5*), 5.07-5.00 (1H, m, *H14*), 4.55 (1H, d, *J* 8.2, *H6*), 4.52-4.43 (1H, m, *H2'*), 1.28 (6H, d, *J*

* ppm error 3.40

6.3, *H1*), 1.22 (3H, d, *J* 6.3, *H15*), 1.20 (3H, d, *J* 6.3, *H15*), 0.99 (3H, d, *J* 6.3, *H1'*), 0.27 (3H, d, *J* 6.3, *H1'*); **δ_C (125 MHz, $CDCl_3$)**: 171.2 (*C3*), 168.7 (*C13*), 168.6 (*C3'*), 141.0 (q*C*), 139.4 (q*C*), 136.6 (q*C*), 133.2 (q*C*), 132.8 (q*C*), 129.0 (Ar *C*H), 128.1 (Ar *C*H), 127.9 (Ar *C*H), 127.8 (Ar *C*H), 127.7 (Ar *C*H), 127.4 (Ar *C*H), 127.1 (Ar *C*H), 126.4 (Ar *C*H), 125.9 (Ar *C*H), 125.7 (Ar *C*H), 124.8 (Ar *C*H), 120.1 (Ar *C*H), 70.2 (*C4*), 69.5 (*C2*), 69.2 (*C14*), 68.7 (*C2*), 55.3 (*C6*), 53.7 (*C5*), 21.8 (*C1*), 21.7 (*C1*), 21.6 (*C15*), 21.5 (*C15*), 21.3 (*C1'*), 20.5 (*C1'*); **m/z**: HRMS (ES+) found 525.2249; $C_{31}H_{34}O_6$ $[M+Na]^+$ requires 525.2253; **Minor diastereoisomer**: **$[\alpha]_D^{25}$**: +17.9° (c 0.145, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3010, 2985, 2940, 1725, 1472, 1250, 1110; **δ_H (500 MHz, $CDCl_3$)**: 7.77-7.73 (1H, m, Ar C*H*), 7.64 (3H, m, Ar C*H*), 7.52-7.48 (2H, m, Ar C*H*), 7.47-7.39 (2H, m, Ar C*H*), 7.38-7.34 (2H, m, Ar C*H*), 6.94 (1H, d, *J* 9.4, Ar C*H*), 4.98 (1H, sept., *J* 6.3, *H2*), 4.93 (1H, d, *J* 7.9, *H5*), 4.87 (1H, d, *J* 7.9, *H6*), 4.56 (1H, sept., *J* 6.2, *H14*), 4.50 (1H, sept., *J* 6.2, *H2'*), 1.25 (3H, d, *J* 6.3, *H1*), 1.11 (3H, d, *J* 6.3, *H1*), 0.99 (3H, d, *J* 6.3, *H15*), 0.96 (3H, d, *J* 6.3, *H15*), 0.51 (3H, d, *J* 6.3, *H2'*), 0.45 (3H, d, *J* 6.3, *H2'*); **δ_C (125 MHz, $CDCl_3$)**: 170.0 (*C3*), 168.8 (*C13*), 167.3 (*C3'*), 140.7 (q*C*), 139.0 (q*C*), 135.1 (q*C*), 132.8 (q*C*), 132.7 (q*C*), 128.8 (Ar *C*H), 127.8 (Ar *C*H), 127.7 (Ar *C*H), 127.6 (Ar *C*H), 127.4 (Ar *C*H), 127.1 (Ar *C*H), 126.5 (Ar *C*H), 125.7 (Ar *C*H), 125.5 (Ar *C*H), 69.6 (*C4*), 69.5 (*C2*), 68.6 (*C14*), 67.8 (*C2'*), 54.9 (*C6*), 53.5 (*C5*), 21.6 (*C1*), 21.5 (*C1*), 21.4 (*C15*), 21.3 (*C1'*), 20.8 (*C1'*); **m/z**: HRMS (ES+) found 525.2251; $C_{31}H_{34}O_6$ $[M+Na]^+$ requires 525.2253.

(2*S*,3*R*)-Triisopropyl 2-(benzo[d][1,3]dioxol-5-yl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (140)



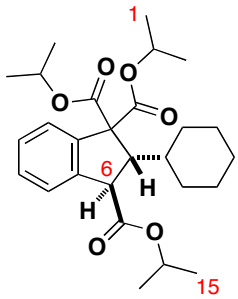
Racemic: The reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (12 mg, 0.08 mmol) and **124** (20 mg, 0.04 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product as a colourless oil in quantitative yield (7:2 dr).

Asymmetric: The asymmetric reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (12 mg, 0.08 mmol), **124** (20 mg, 0.04 mmol) and catalyst **135** (3 mg, 0.004 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product (19 mg, 94 %) as a colourless oil as a mixture of two diastereoisomers (7:2 dr), 38 % ee (major diastereoisomer).

Major diastereoisomer: $[\alpha]_D^{22}$: -9.6˚ (c 0.380, $CHCl_3$); ν_{max}/cm^{-1} **(film)**: 3010, 2985, 2940, 1729, 1470, 1252, 1104; δ_H **(500 MHz, $CDCl_3$)**: 7.64-7.60 (1H, m, Ar C*H*), 7.41 (1H, d, *J* 7.2, Ar C*H*), 7.38-7.31 (2H, m, Ar C*H*), 6.86-6.81 (2H, m, Ar C*H*), 6.70 (1H, d, *J* 8.6, Ar C*H*), 5.89 (2H, 2 x s, OCH_2), 5.12 (1H, sept., *J* 6.2, *H2*), 5.09-5.01 (1H, sept., *J* 6.3, *H14*), 4.85 (1H, d, *J* 8.4, *H5*), 4.70-4.62 (1H, m, *H2'*), 4.34 (1H, d, *J* 8.3, *H6*), 1.29 (3H, d, *J* 6.3, *H1*), 1.26 (3H, d, *J* 6.3, *H1*), 1.24 (3H, d, *J* 6.3, *H15*), 1.23 (3H, d, *J* 6.3, *H15*), 1.10 (3H, d, *J* 6.2, *H1'*), 0.72 (3H, d, *J* 6.3, *H1'*); δ_C **(125 MHz, $CDCl_3$)**: 171.1 (*C3*), 168.6 (*C13*), 168.5 (*C3'*), 147.3 (q*C*), 146.7 (q*C*), 140.9 (q*C*). 139.3 (q*C*), 132.7 (q*C*), 128.9 (Ar *C*H), 128.0 (Ar *C*H), 126.3 (Ar *C*H), 124.7 (Ar *C*H), 122.3 (Ar *C*H), 109.5 (*C18*), 107.9 (*C22*), 100.8 (OCH_2), 70.0 (*C4*), 69.5 (*C2*), 69.1 (*C14*), 68.6 (*C2'*), 55.3 (*C6*), 53.5 (*C5*), 21.8 (*C1*), 21.7 (*C1*), 21.6 (*C15*), 21.5 (*C15*), 21.4 (*C1'*), 20.9 (*C1'*); **m/z**: HRMS (ES+) found 519.1972; $C_{28}H_{32}O_8$ $[M+Na]^+$ requires 519.1989.*

* ppm error 2.1

(2*R*,3*R*)-Triisopropyl 2-cyclohexyl-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (141)



Racemic: The reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (13 mg, 0.088 mmol) and **125** (20 mg, 0.044 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product as a colourless oil in quantitative yield as a single diastereoisomer.

Asymmetric: The asymmetric reaction was performed according to the general procedure using $CsOH{\cdot}H_2O$ (13 mg, 0.088 mmol), **125** (20 mg, 0.04 mmol) and catalyst **135** (3.3 mg, 0.0044 mmol) in toluene (0.2 mL) at -15 ˚C to afford the desired product (19 mg, 95 %) as a single diastereoisomer; no ee obtained.

ν_{max}/cm^{-1} (film): 3010, 2980, 2940, 1728, 1470, 1251, 1105; **δ_H (500 MHz, $CDCl_3$)**: 7.51 (1H, d, *J* 7.0, Ar C*H*), 7.30-7.19 (3H, m, Ar C*H*), 5.17-5.09 (2H, m, *H2* & *H2'*), 5.08-4.97 (1H, sept., *J* 6.3, *H14*), 3.93 (1H, d, *J* 8.7, *H6*), 3.60 (1H, dd, *J* 8.6, 7.2, *H5*), 1.91 (1H, m, *H16*), 1.71 (2H, m, CH_2), 1.66-1.59 (2H, m, CH_2), 1.54 (1H, m, CH_2), 1.31 (6H, dd, *J* 6.3, *H1*), 1.28 (6H, d, *J* 6.3, *H15*), 1.24 (3H, d, *J* 6.3, *H1'*), 1.20 (3H, d, *J* 6.3, *H1'*), 1.17-1.09 (3H, m, CH_2), 1.05-0.94 (2H, m, CH_2); **δ_C (125 MHz, $CDCl_3$)**: 172.9 (*C3*), 169.3 (*C13*), 169.1 (*C3'*), 141.8 (q*C*), 140.7 (q*C*), 128.6 (Ar *C*H), 127.6 (Ar *C*H), 125.2 (Ar *C*H), 123.7 (Ar *C*H), 69.3 (*C4*), 69.2 (*C2*), 68.3 (*C14*), 68.0 (*C2'*), 54.7 (*C5*), 52.4 (*C6*), 39.4 (*C16*), 33.2 (*C*H_2), 30.4 (*C*H_2), 26.7 (*C*H_2), 26.6 (*C*H_2), 26.2 (*C*H_2), 21.9 (*C1*), 21.7 (*C15*), 21.6 (*C15*), 21.5 (*C1'*); **m/z**: HRMS (ES+) found 481.2543; $C_{27}H_{38}O_6$ $[M+Na]^+$ requires 481.2561.*

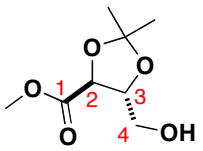
* ppm error 3.51

3. For Ring Constrained γ-peptides

3.1 Experimental procedures and data for monomer units

Both D- and L-tartrate derived monomer units have been prepared, and the data for the D-series is presented here. Where a reference to a specific enantiomeric series is intended (eg in the preparation of heterochiral oligomers), the prefix D- or L- will be used before the number of the compound.

(4*S*,5*R*)-Methyl 5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (3)



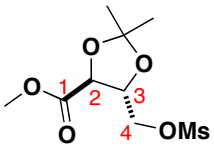
According to a literature procedure,[131] a solution of 1 M methanolic KOH (8.77 mL) was added dropwise to a solution of diester **2** (2.0 g, 9.17 mmol) in methanol (9 mL) over 1 h. The reaction mixture was stirred at RT. After 1.5 h, the mixture was dissolved in water and acidified to pH 1 with 3 N HCl solution and extracted with $CHCl_3$ (4 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude acid **5** in quantitative yield as a viscous, colourless oil, which was used without further purification.

Borane (1 M solution in THF, 1 mL, 0.98 mmol) was added dropwise to a solution of **5** (200 mg, 0.98 mmol) in THF at -20 ^oC over 1 h. The reaction mixture was stirred at RT. After 4 h, water (10 mL) was cautiously added dropwise until no more gas evolved. Subsequently, sodium bicarbonate solution (10 mL) was added slowly with stirring. The resulting mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/petrol, 1:2 to 1:1) to yield the desired alcohol D-**3** (130 mg, 70 %) as a pale yellow oil.

$[\alpha]_D^{25}$: +8.3° (c 0.53, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3485 , 2991, 2940, 1737, 1206, 1100; **δ_H (400 MHz, $CDCl_3$)**: 4.47 (1H, d, *J* 7.7, *H2*), 4.24 (1H, td, *J* 6.9, 3.4, *H3*), 3.95 (1H, dd, *J*

12.2, 3.1, *H4*), 3.80 (3H, s, CO_2CH_3), 3.75 (1H, dd, *J* 12.2, 3.8, *H4'*), 1.89 (1H, brs, O*H*), 1.49 (3H, s, CH_3), 1.45 (3H, s, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 171.6 (*C1*), 111.8 (q*C*), 79.6 (*C*H), 75.3 (*C*H), 62.2 (CH_2), 52.9 (CO_2CH_3), 27.2 (CH_3), 26.0 (CH_3); **m/z**: HRMS (ES+) found 191.0913; $C_8H_{14}O_5$ $[M+H]^+$ requires 191.0913.

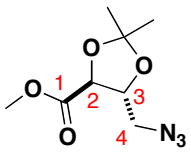
(4*S*,5*R*)-Methyl 2,2-dimethyl-5-((methylsulfonyloxy)methyl)-1,3-dioxolane-4-carboxylate (6)



Methanesulfonyl chloride (1.18 mL, 15.2 mmol) and triethylamine (2.64 mL, 18.9 mmol) were added to a stirred solution of alcohol D-**3** (2.4 g, 12.6 mmol) in CH_2Cl_2 (25 mL) at 0 ˚C. After 10 mins the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with sat. NH_4Cl (30 mL) and water (30 mL). The aqueous washes were extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the desired product D-**6** (3.3 g, 97 %) as a pale yellow coloured oil. A small quantity was purified by column chromatography (EtOAc/petrol, 1:2 to 1:1) for analytical purposes.

$[\alpha]_D^{25}$: +20.4˚ (c 0.41, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 2992, 2942, 1759, 1733, 1296, 1168; **δ_H (400 MHz, $CDCl_3$)**: 4.54 (1H, d, *J* 10.2, *H2*), 4.45-4.40 (1H, m, *H3*), 4.38 (1H, dd, *J* 3.8, 1.7, *H4*), 4.36 (1H, dd, *J* 2.9, 1.8, *H4'*), 3.82 (3H, s, CO_2CH_3), 3.08 (3H, s, SO_2CH_3), 1.49 (3H, s, CH_3), 1.45 (3H, s, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 170.2 (*C1*), 112.3 (q*C*), 76.5 (*C*H), 75.0 (*C*H), 68.1 (CH_2), 52.7 (CO_2CH_3), 37.8 (SO_2CH_3), 26.7 (CH_3), 25.7 (CH_3); **m/z**: HRMS (ES+) found 286.0955; $C_9H_{16}O_7S$ $[M+NH_4]^+$ requires 286.0955.

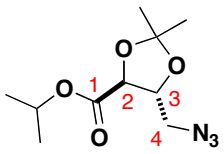
(4*S*,5*R*)-Methyl 5-(azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (7)



Sodium azide (800 mg, 12.3 mmol) was added to a stirred solution of D-**6** (3.3 g, 12.3 mmol) in DMF (25 mL). The reaction mixture was heated to 95 °C. After 3 h, the reaction mixture was diluted with ethyl acetate (50 mL) and washed with 10 % $MgSO_4$ solution (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/petrol, 1:2 to 1:1) to yield D-**7** (2.35 g, 87 %) over two steps as a yellow oil.

$[\alpha]_D^{25}$: +84.9° (c 0.69, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 2991, 2956, 2100, 1762, 1733, 1205 1097; **δ_H (400 MHz, $CDCl_3$)**: 4.43 (1H, d, *J* 7.5, *H2*), 4.32 (1H, ddd, *J* 7.5, 4.5, 3.1, *H3*), 3.79 (3H, s, CO_2CH_3), 3.70 (1H, dd, *J* 13.3, 3.1, *H4*), 3.36 (1H, dd, *J* 13.3, 4.5, *H4'*), 1.52 (3H, s, CH_3), 1.44 (3H, s, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 170.6 (*C1*), 111.9 (q*C*), 77.9 (*C*H), 75.6 (*C*H), 52.5 (CO_2CH_3), 51.6 (CH_2), 26.6 (CH_3), 25.7 (CH_3); **m/z**: HRMS (ES+) found 233.1244; $C_8H_{13}N_3O_4$ $[M+NH_4]^+$ requires 233.1244.

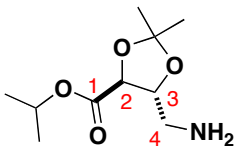
(4*S*,5*R*)-Isopropyl 5-(azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (8)



Potassium carbonate (1.42 g, 10.3 mmol) was added to a stirred solution of methyl ester D-**7** (2.0 g, 9.30 mmol) in isopropanol (83 mL). The reaction mixture was heated to 90 ˚C. After 3 h, the reaction mixture was filtered, diluted with chloroform (100 mL) and washed with pH 7 buffer (2 x 30 mL). The aqueous washes were extracted with chloroform (2 x 50 mL) and the combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/petrol, 1:1) to give isopropyl ester D-**8** as a colourless liquid (1.73 g, 77 %).

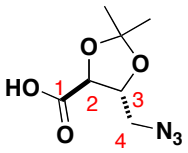
$[\alpha]_D^{25}$: +72.6˚ (c 0.43, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 2986, 2938, 2099, 1754, 1724, 1201, 1092; **δ_H (400 MHz, $CDCl_3$)**: 5.12 (1H, sept, *J* 6.3, ^{i}Pr C*H*), 4.38 (1H, d, *J* 7.4, *H2*), 4.30 (1H, ddd, *J* 7.5, 4.6, 3.2, *H3*), 3.69 (1H, dd, *J* 13.3, 3.1, *H4*), 3.36 (1H, dd, *J* 13.3, 4.6, *H4'*), 1.53 (3H, s, C*H*$_3$), 1.45 (3H, s, C*H*$_3$), 1.29 (3H, d, *J* 2.3, ^{i}Pr C*H*$_3$), 1.27 (3H, d, *J* 2.3, ^{i}Pr C*H*$_3$); **δ_C (100 MHz, $CDCl_3$)**: 170.6 (*C1*), 112.2 (q*C*), 78.4 (*C*H), 76.3 (*C*H), 69.8 (^{i}Pr *C*H), 52.2 (*C*H$_2$), 27.1 (*C*H$_3$), 26.1 (*C*H$_3$), 22.1 & 22.0 (^{i}Pr *C*H$_3$); **m/z**: HRMS (ES+) found 261.1557; $C_{10}H_{17}N_3O_4$ $[M+NH_4]^+$ requires 261.1557.

(4*S*,5*R*)-Isopropyl 5-(aminomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (9)



Palladium on activated carbon 10 wt% (10 % w/w, 35 mg) was added to isopropanol and stirred under a hydrogen atmosphere for 30 mins. The isopropyl ester D-**8** (350 mg, 1.44 mmol) was dissolved in isopropanol and added slowly to the reaction mixture (still under a hydrogen atmosphere) *via* syringe. After 30 min, the reaction mixture was filtered through Celite™ using isopropanol. The solvent was evaporated *in vacuo* to afford D-**9** in quantitative yield, which was used without further purification.

(4*S*,5*R*)-5-(Azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (10)

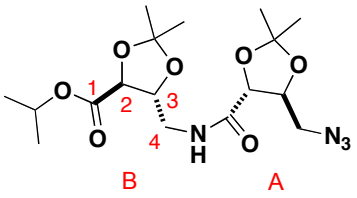


1 M Aqueous NaOH (21 mL, 20.9 mmol) was added to a stirred solution of azido ester D-**7** (1.5 g, 6.97 mmol) in ethanol (35 mL) at RT. After 15 mins, the solvent was removed under reduced pressure and the resulting residue was dissolved in water (25 mL) and acidified to pH 2-3 with 3 N aqueous HCl. The resulting mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the azido acid D-**10** (1.34 g, 96 %) as a yellow solid.

$[\alpha]_D^{25}$: +77.4° (c 0.795, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3112, 2991, 2937, 1733, 1210, 1095; **δ_H (400 MHz, $CDCl_3$)**: 5.76 (1H, brs, CO_2H), 4.48 (1H, d, *J* 7.7, *H2*), 4.36 (1H, ddd, *J* 7.5, 4.4, 2.9, *H3*), 3.74 (1H, dd, *J* 4.9, 2.1, *H4*), 3.40 (1H, dd, *J* 13.4, 4.4, *H4'*), 1.54 (3H, s, CH_3), 1.47 (3H, s, CH_3); **δ_C (100 MHz, $CDCl_3$)**: 173.4 (*C1*), 112.3 (q*C*), 78.0 (*C*H), 75.1 (*C*H), 51.4 (CH_2), 26.7 (CH_3), 25.7 (CH_3); **m/z**: (ES+) $[M+H]^+$ 201.1.

3.2 Experimental procedures and data for heterochiral oligomers

(4*S*,5*R*)-Isopropyl 5-(((4*R*,5*S*)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (11)



DIPEA (0.16 mL, 0.92 mmol) and TBTU (224 mg, 0.69 mmol) were added to a stirred solution of crude amino ester D-**9** (100 mg, 0.46 mmol) and crude azido acid L-**10** (93 mg, 0.46 mmol) in CH_2Cl_2 (1 mL). After 10 mins the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 x 15 mL). The aqueous washes were extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc/petrol, 1:1) to yield the desired dimer **11** (152 mg, 83 % from D-**8**).

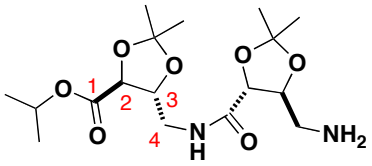
$[\alpha]_D^{25}$: -35.2° (c 0.165, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3424, 2987, 2938, 2101, 1752, 1726, 1676, 1526, 1209, 1094; **m/z**: HRMS (ES+) found 401.2030; $C_{17}H_{28}N_4O_7$ $[M+H]^+$ requires 401.2031.

^{1}H (500 MHz, 5.6 mM in benzene-d_6 @ 7.15 ppm) & ^{13}C (125 MHz, benzene-d_6 @ 128.0 ppm)

Residue	Position		δ_H (ppm)	Multiplicity	*J* (Hz)	δ_C (ppm)
A	C-1		-	-	-	169.9
	C-2		4.19	d	8.22	76.3
	C-3		4.02	ddd	8.2, 4.4, 2.6	79.2
	C-4	4	3.30	dd	13.5, 2.6	51.8
		4’	3.08	dd	13.5, 4.4	
B	C-1		-	-	-	170.1
	C-2		4.15	d	7.2	77.1
	C-3		4.25	ddd	7.1, 5.1, 4.1	78.1
	C-4	4	3.53	ddd	14.0, 6.9, 5.1	40.5
		4’	3.41	ddd	13.8, 5.0, 4.2	
	NH		6.65	s	-	-

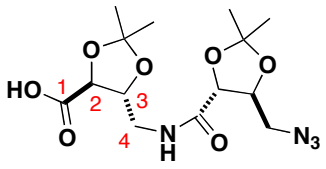
Residue	Position	δ_H (ppm)	Multiplicity	*J* (Hz)	δ_C (ppm)
Others	C*H*$(CH_3)_2$	4.95	sept	6.3	69.0
	^{i}Pr Me	1.00 (3H)	d	6.3	21.5
	^{i}Pr Me	0.99 (3H)	d	6.3	21.5
	Isopropylidene q*C*$(CH_3)_2$	-	-	-	111.4, 111.0
	Isopropylidene CH_3 groups	1.35, 1.35 1.30, 1.18	s	-	27.0, 26.7, 26.0, 25.6

(4*S*,5*R*)-Isopropyl 5-(((4*R*,5*S*)-5-(aminomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (12)



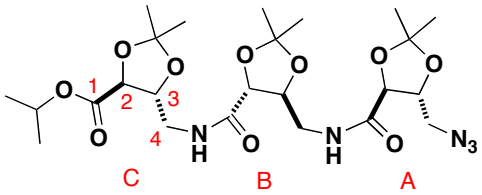
Palladium on activated carbon, 10 wt% (10 % w/w, 20 mg) was added to isopropanol and stirred under a hydrogen atmosphere for 30 mins. The isopropyl ester **11** (200 mg, 0.50 mmol) was dissolved in isopropanol and added to the reaction mixture (still under a hydrogen atmosphere) *via* syringe. After 1 h, the mixture was filtered through Celite™ using isopropanol. The solvent was evaporated *in vacuo* to afford desired product **12** in quantitative yield, which was used without further purification.

(4*S*,5*R*)-5-(((4*R*,5*S*)-5-(Azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido) methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (13)



1 M Aqueous NaOH (1.5 mL, 1.5 mmol) was added to a stirred solution of azido ester **11** (200 mg, 0.50 mmol) in ethanol (2.5 mL) at RT. After 15 mins, the solvent was removed under reduced pressure and the resulting residue was dissolved in water (30 mL) and acidified to pH 2-3 with 3 N aqueous HCl. The resulting mixture was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude azido acid **13** which was used without further purification.

(4*S*,5*R*)-Isopropyl 5-(((4*R*,5*S*)-5-(((4*S*,5*R*)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (15)



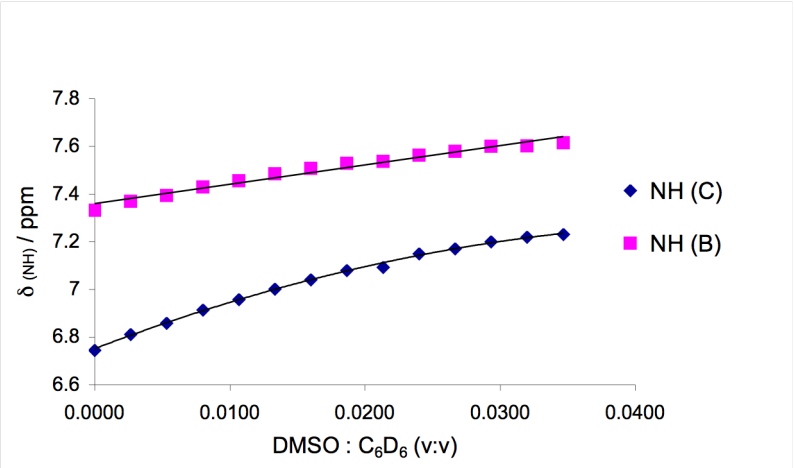
DIPEA (90 μL, 0.53 mmol) and TBTU (129 mg, 0.40 mmol) were added to a stirred solution of crude amino ester **12** (100 mg, 0.27 mmol) and crude azido acid D-**10** (53 mg, 0.27 mmol) in CH_2Cl_2 (0.5 mL). After 10 mins, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 x 15 mL). The aqueous washes were extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield the desired trimer **15** (105 mg, 70 % from **11**).

$[\alpha]_D^{25}$: +37.4° (c 0.265, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3425, 2987, 2938, 2102, 1752, 1726, 1670, 1526, 1210, 1087; **m/z**: HRMS (ES+) found 558.2771; $C_{24}H_{40}N_5O_{10}$ $[M+H]^+$ requires 558.2770.

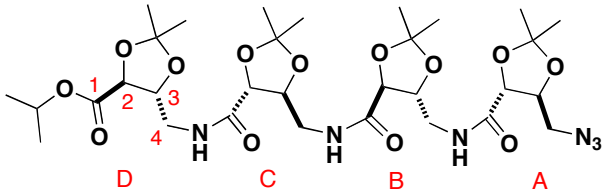
^{1}H (500 MHz, 5.6 mM in benzene-d_6 @ 7.15 ppm) and ^{13}C (125 MHz, benzene-d_6 @ 128.0 ppm)

Residue	Position		δ_H (ppm)	Multiplicity	*J* (Hz)	δ_C (ppm)
A	C-1		-	-	-	170.0
	C-2		4.29	d	8.2	76.7
	C-3		4.13-4.16	m	-	79.3
	C-4	4	3.37	dd	13.4, 2.6	52.0
		4’	3.12	dd	13.4, 4.7	
B	C-1		-	-	-	170.3
	C-2		3.93	d	7.7	79.0
	C-3		3.97-4.00	m	-	77.9
	C-4	4	4.01-4.05	m	-	41.4
		4’	3.18-3.23	m	-	
	NH		7.33	dd	9.9, 6.1	-
C	C-1		-	-	-	170.1
	C-2		4.12	d	7.1	77.1
	C-3		4.23-4.26	m	-	77.9
	C-4	4	3.52	ddd	14.0, 6.9, 5.1	40.6
		4’	3.40	td	8.3, 5.1	
	NH		6.74	t	5.8	-
Others	C*H*$(CH_3)_2$		4.96	sept	6.3	69.0
	^{i}Pr Me		1.02 (3H)	d	6.3	21.6
	^{i}Pr Me		0.99 (3H)	d	6.3	21.5
	Isopropylidene q*C*$(CH_3)_2$		-	-	-	111.4, 111.1, 110.5
	Isopropylidene CH_3 groups		1.39, 1.37, 1.35, 1.34, 1.21, 1.17	s	-	27.0, 26.9, 26.8, 26.1, 25.8, 25.5

DMSO titration for (**15**) (addition of 2 μL aliquots of DMSO-d_6 to a 5.6 mM solution of trimer **15** in benzene-d_6, 400 MHz, referenced to TMS @ 0 ppm)



(4*S*,5*R*)-Isopropyl 5-(((4*R*,5*S*)-5-(((4*S*,5*R*)-5-(((4*R*,5*S*)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (14)



DIPEA (85 μL, 0.50 mmol) and TBTU (120 mg, 0.374 mmol) were added to a stirred solution of crude amino ester **12** (94 mg 0.25 mmol) and crude azido acid **13** (90 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL). After 10 mins, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 x 15 mL). The aqueous washes were extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield the desired tetramer **14** (105 mg, 59 % from **11**).

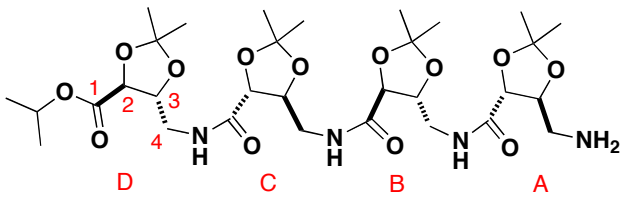
$[\alpha]_D^{25}$: -19.0° (c 0.105, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3426, 2987, 2937, 2102, 1751, 1726, 1667, 1525, 1210, 1087; **m/z**: HRMS (ES+) found 715.3506; $C_{31}H_{50}N_6O_{13}$ $[M+H]^+$ requires 715.3509.

^{1}H (700 MHz, 5.6 mM in benzene-d_6 @ 7.15 ppm) & ^{13}C (175 MHz, benzene-d_6 @ 128.0 ppm)

Residue	**Position**		**δ_H (ppm)**	**Multiplicity**	***J* (Hz)**	**δ_C (ppm)**
A	C-1		-	-	-	170.1
	C-2		4.30	d	8.2	76.8
	C-3		4.18-4.20	m	-	79.3
	C-4	4	3.41	dd	13.4, 2.6	52.1
		4’	3.15	dd	13.4, 4.8	
B	C-1		-	-	-	170.4
	C-2		4.03	d	7.9	79.6
	C-3		4.08-4.11	m	-	77.9
	C-4	4	4.13-4.16	m	-	41.6
		4’	3.22	ddd	13.4, 7.1, 3.6	
	NH		7.55	dd	7.3, 3.0	-
C	C-1		-	-	-	170.3
	C-2		3.90	dd	14.7, 7.5	79.1
	C-3		3.96-3.99	m	-	77.7
	C-4	4	4.00-4.04	m	-	41.5
		4’	3.17-3.19	m	-	
	NH		7.45	dd	7.2, 3.2	-
D	C-1		-	-	-	170.1
	C-2		4.12	d	7.1	77.1
	C-3		4.25	ddd	7.1, 5.0, 4.3	77.9
	C-4	4	3.53	ddd	7.1, 6.9, 5.1	40.7
		4’	3.38	dd	9.4, 4.6	
	NH		6.74	t	6.0	-
Others	C*H*$(CH_3)_2$		4.97	sept	6.3	69.1
	^{i}Pr Me		1.03 (3H)	d	6.3	21.6
	^{i}Pr Me		1.00 (3H)	d	6.3	21.5
	Isopropylidene q*C*$(CH_3)_2$		-	-	-	111.5, 111.3, 110.7, 110.6
	Isopropylidene CH_3 groups		1.42, 1.40, 1.36, 1.35, 1.34, 1.30, 1.23, 1.18	s	-	27.1, 27.0, 27.0, 26.8, 26.1, 25.9, 25.8, 25.5

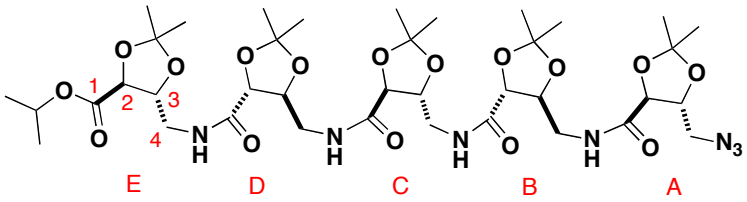
Residue	Position	NOEs to
A	H-2	3A, 4A, 4'A, $C(CH_3)_2$
	H-3	2A, 4A, 4'A, $C(CH_3)_2$
	H-4	2A, 3A, 4'A
	H-4'	2A, 3A, 4A
B	H-2	3B, 4B, 4'B, $C(CH_3)_2$
	H-3	2B, 4B, 4'B, $C(CH_3)_2$
	H-4	2B, 3B, 4'B
	H-4'	2B, 3B, 4B
	NH^B	H_2^B, H_3^B, H_4^B, $H_{4'}^B$
C	H-2	3C, 4C, 4'C, $C(CH_3)_2$
	H-3	2C, 4C, 4'C, $C(CH_3)_2$
	H-4	2C, 3C, 4'C
	H-4'	2C, 3C, 4C
	NH^C	H_2^C, H_3^C, H_4^C, $H_{4'}^C$
D	H-2	3D, 4D, 4'D, $C(CH_3)_2$
	H-3	2D, 4D, 4'D, $C(CH_3)_2$
	H-4	2D, 3D, 4'D
	H-4'	2D, 3D, 4D
	NH^D	H_2^C (w), H_2^D, H_3^D, H_4^D, $H_{4'}^D$

(4*S*,5*R*)-Isopropyl 5-(((4*R*,5*S*)-5-(((4*S*,5*R*)-5-(((4*R*,5*S*)-5-(aminomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido) methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (14a)



Palladium on activated carbon, 10 wt% (10 % w/w, 20 mg) was added to ^{i}PrOH and stirred under a hydrogen atmosphere for 30 mins. The isopropyl ester **14** (200 mg, 0.28 mmol) was dissolved in ^{i}PrOH and added to the reaction mixture (still under a hydrogen atmosphere) *via* syringe. After 1 h, the mixture was filtered through Celite™ using ^{i}PrOH. The solvent was evaporated *in vacuo* to afford desired product **14a** in quantitative yield, which was used without further purification.

(4*S*,5*R*)-Isopropyl 5-(((4*R*,5*S*)-5-(((4*S*,5*R*)-5-(((4*R*,5*S*)-5-(((4*S*,5*R*)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (16)



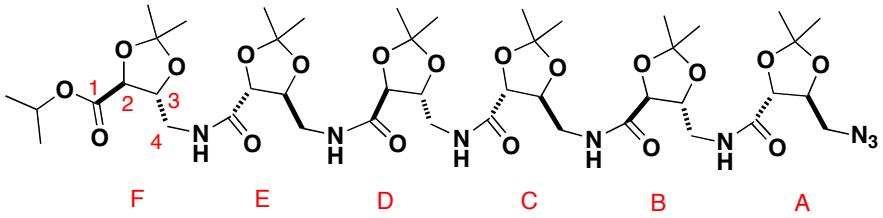
DIPEA (85 μL, 0.50 mmol) and TBTU (120.4 mg, 0.374 mmol) were added to a stirred solution of crude amino ester **14a** (172 mg 0.25 mmol) and crude azido acid **13** (51 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL). After 10 mins, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 x 15 mL). The aqueous washes were extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield the desired pentamer **16** (132 mg, 63 % from **14**).

$[\alpha]_D^{25}$: -4.6° (c 0.22, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3424, 2987, 2937, 2103, 1747, 1664, 1529, 1211, 1087; **m/z**: HRMS (ES+) found 872.4246; $C_{38}H_{62}N_7O_{16}$ $[M+H]^+$ requires 872.4248.

^{1}H (700 MHz, 5.6 mM in benzene-d_6 @ 7.15 ppm) & ^{13}C (175 MHz, benzene-d_6 @ 128.0 ppm)

Residue	Position		δ_H (ppm)	Multiplicity	*J* (Hz)	δ_C (ppm)
A	C-1		-	-	-	168.5
	C-2		4.31	d	8.2	76.8
	C-3		4.21	ddd	8.1, 4.9, 2.6	79.2
	C-4	4	3.44	dd	13.4, 2.6	52.2
		4’	3.17	dd	6.0, 2.7	
B	C-1		-	-	-	170.5
	C-2		4.06	d	7.9	79.7
	C-3		4.11	ddd	15.0, 7.2, 4.6	77.8
	C-4	4	4.16	dd	3.8, 1.8	41.6
		4’	3.22	ddd	13.4, 7.1, 3.5	
	NH		7.62	dd	7.5, 3.1	-
C	C-1		-	-	-	170.5
	C-2		4.01	d	1.9	79.7
	C-3		4.04	dd	7.6, 3.9	77.8
	C-4	4	4.14	dd	5.9, 3.7	41.6
		4’	3.15	dd	7.4, 3.5	
	NH		7.68	dd	7.9, 3.2	-
D	C-1		-	-	-	170.4
	C-2		3.93	d	7.7	78.9
	C-3		4.00	ddd	7.7, 6.2, 2.9	77.7
	C-4	4	4.04	dd	7.6, 3.9	41.4
		4’	3.18	dd	9.0, 4.4	
	NH		7.45	dd	7.4, 3.5	-
E	C-1		-	-	-	170.2
	C-2		4.15	d	7.0	77.2
	C-3		4.28	ddd	5.1, 3.5, 2.1	77.8
	C-4	4	3.57	ddd	13.9, 6.9, 5.2	40.8
		4’	3.44	dd	13.4, 2.6	
	NH		6.80	t	5.9	-
Others	C*H*$(CH_3)_2$		4.97	sept	6.3	69.1
	^{i}Pr Me		1.04 (3H)	d	6.3	21.6
	^{i}Pr Me		1.01 (3H)	d	6.3	21.5
	Isopropylidene q*C*$(CH_3)_2$		-	-	-	111.5, 111.3, 110.8, 110.7, 110.6
	Isopropylidene CH_3 groups		1.45, 1.44, 1.36, 1.35, 1.32, 1.29, 1.24, 1.20, 1.20, 1.16	s	-	27.0, 26.9, 26.8, 26.1, 25.9, 25.9, 25.7, 25.5

(4*S*,5*R*)-Isopropyl 5-(((4*R*,5*S*)-5-(((4*S*,5*R*)-5-(((4*R*,5*S*)-5-(((4*S*,5*R*)-5-(((4*R*,5*S*)-5-(azidomethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (17)



DIPEA (40 μL, 0.24 mmol) and TBTU (56 mg, 0.18 mmol) were added to a stirred solution of crude amino ester **14a** (80 mg, 0.12 mmol) and crude azido acid **13** (40.5 mg, 0.12 mmol) in CH_2Cl_2 (0.25 mL). After 10 mins, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 x 15 mL). The aqueous washes were extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield the desired hexamer **17** (85 mg, 59 % from **14**).

$[\alpha]_D^{25}$: -12.6° (c 0.475, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3471, 2987, 2935, 2103, 1747, 1656, 1530, 1212, 1085; **m/z**: HRMS (ES+) found 1046.5250; $C_{45}H_{76}N_9O_{19}$ $[M+NH_4]^+$ requires 1046.5252.

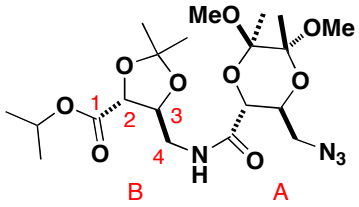
^{1}H (700 MHz, 5.6 mM in benzene-d_6 @ 7.15 ppm) and ^{13}C (125 MHz, benzene-d_6 @ 128.0 ppm)

Residue	Position		δ_H (ppm)	Multiplicity	*J* (Hz)	δ_C (ppm)
A	C-1		-	-	-	170.1
	C-2		4.30	d	8.2	76.8
	C-3		4.22	dd	4.8, 2.6	79.2
	C-4	4	3.46	dd	13.5, 2.6	52.2
		4’	3.19	dd	13.5, 4.8	
C	C-1		-	-	-	170.5
	C-2		4.04	d	8.3	79.7
	C-3		4.06-4.09	m	-	77.8
	C-4	4	4.16-4.19	m	-	41.6

Residue	Position		δ_H (ppm)	Multiplicity	*J* (Hz)	δ_C (ppm)
		4’	3.15-3.18	m	-	
	NH		7.74	dd	7.6, 3.6	-
B*	C-1		-	-	-	170.5
	C-2		4.01-4.03	m	-	79.7
	C-3		4.27-4.29	m	-	77.8
	C-4	4	4.13-4.15	m	-	41.6
		4’	3.13-3.16	m	-	
	NH		7.64	m	-	-
D*	C-1		-	-	-	170.4
	C-2		4.02-4.04	m	-	78.9
	C-3		4.06-4.08	m	-	77.7
	C-4	4	4.11-4.14	m	-	41.4
		4’	3.23-3.26	m	-	
	NH		7.64	m	-	-
E	C-1		-	-	-	170.4
	C-2		3.99	d	7.8	79.7
	C-3		4.02-4.04	m	-	77.8
	C-4	4	4.06-4.08	m	-	41.5
		4’	3.23-3.26	m	-	
	NH		7.51	dd	7.6, 3.3	-
F	C-1		-	-	-	170.1
	C-2		4.15	d	7.0	77.2
	C-3		4.27-4.29	m	-	77.8
	C-4	4	3.56-3.60	m	-	41.4
		4’	3.41-3.44	m	-	
	NH		6.82	t	6.0	-
Others	C*H*$(CH_3)_2$		4.97	sept	6.3	69.1
	^{i}Pr Me		1.04 (3H)	d	6.3	21.6
	^{i}Pr Me		1.01 (3H)	d	6.3	21.5
	Isopropylidene q*C*$(CH_3)_2$		-	-	-	111.5, 111.3, 110.9, 110.8, 110.8, 110.6
	Isopropylidene CH_3 groups		1.47, 1.44, 1.43, 1.42, 1.37, 1.37, 1.35, 1.33, 1.31, 1.31, 1.25, 1.21	s	-	27.1, 27.0, 27.0, 26.9, 26.8, 26.1, 26.0, 26.0, 25.9, 25.8, 25.8, 25.6

*Due to resonance overlap, unambiguous sequence-specific assignments were not possible (though each individual spin system can be identified) and so these are tentative assignments based on the available data. Consequently, the sequence of these residues may be reversed.

(4*R*,5*S*)-Isopropyl 5-(((2*R*,3*S*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (20)



DIPEA (160 μL, 0.92 mmol) and TBTU (221 mg, 0.69 mmol) were added to a stirred solution of crude amino ester **9** (100 mg, 0.46 mmol) and crude azido acid **19** (127 mg, 0.46 mmol) in CH_2Cl_2 (1.0 mL). After 10 mins, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 x 15 mL). The aqueous washes were extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield the desired dimer **20** (112 mg, 58 % from **8**).

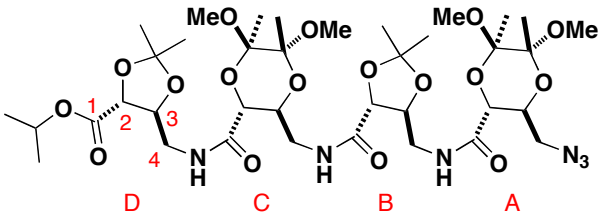
$[\alpha]_D^{25}$: -30.7° (c 0.28, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3426, 2987, 2997, 2097, 1753, 1678, 1524, 1206, 1097; **m/z**: HRMS (ES+) found 475.2395; $C_{20}H_{34}N_4O_9$ $[M+H]^+$ requires 475.2399.

^{1}H (500 MHz, 5.6 mM in benzene-d_6 @ 7.15 ppm) and ^{13}C (125 MHz, benzene-d_6 @ 128.0 ppm)

Residue	Position		δ_H (ppm)	Multiplicity	*J* (Hz)	δ_C (ppm)
A	C-1		-	-	-	168.4
	C-2		4.31	d	10.2	69.9
	C-3		3.96	ddd	10.0, 7.4, 2.4	70.3
	C-4	4	3.66	ddd	7.6, 2.3, 1.4	51.7
		4’	3.52	dd	13.2, 7.4	
B	C-1		-	-	-	170.1
	C-2		4.23	d	4.5	77.2
	C-3		4.20-4.25	m	-	78.0
	C-4	4	3.68-3.72	m	-	40.2
		4’	3.25-3.29	m	-	
	NH		7.02	dd	6.5, 4.5	-
Others	C*H*$(CH_3)_2$		4.94	sept	6.2	68.9
	^{i}Pr Me		0.98 (3H)	d	6.3	21.6
	^{i}Pr Me		0.99 (3H)	d	6.3	21.5

Residue	Position	δ_H (ppm)	Multiplicity	*J* (Hz)	δ_C (ppm)
	Isopropylidene q*C*$(CH_3)_2$	-	-	-	111.3
	Isopropylidene CH_3 groups	1.24, 1.20	s	-	17.5, 17.4
	C(*CH*$_3$)(OCH_3)	1.36, 1.34	s	-	27.0, 25.8
	C(CH_3)(O*CH*$_3$)	3.02, 2.89	s	-	47.9
	C(CH_3)(OCH_3)	-	-	-	99.5, 99.0

(4*R*,5*S*)-Isopropyl 5-(((2*R*,3*S*,5*R*,6*R*)-3-(((4*R*,5*S*)-5-(((2*R*,3*S*,5*R*,6*R*)-3-(azidomethyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamido)methyl)-5,6-dimethoxy-5,6-dimethyl-1,4-dioxane-2-carboxamido)methyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (23)



DIPEA (54 μL, 0.32 mmol) and TBTU (75 mg, 0.24 mmol) were added to a stirred solution of crude amino ester **21** (70 mg, 0.16 mmol) and crude azido acid **22** (67 mg, 0.16 mmol) in CH_2Cl_2 (1.0 mL). After 10 mins, the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (2 x 15 mL). The aqueous washes were extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (EtOAc) to yield the desired tetramer 23 (75 mg, 59 % from dimer azido ester).

$[\alpha]_D^{25}$: -51.7° (c 0.145, $CHCl_3$); **ν_{max}/cm^{-1} (film)**: 3426, 2989, 2943, 2097, 1753, 1673, 1523, 1209, 1115; **m/z**: HRMS (ES+) found 863.4237; $C_{37}H_{62}N_6O_{17}$ $[M+H]^+$ requires 863.4244.

^{1}H (700 MHz, 5.6 mM in benzene-d_6 @ 7.15 ppm) and ^{13}C (175 MHz, benzene-d_6 @ 128.0 ppm)

Residue	Position		δ_H (ppm)	Multiplicity	J (Hz)	δ_C (ppm)
A	C-1		-	-	-	168.4
	C-2		4.41	d	10.1	69.6
	C-3		4.14	ddd	9.9, 7.3, 2.3	70.3
	C-4	4	3.86	dd	13.1, 2.2	52.0
		4’	3.63	dd	13.1, 7.3	
B	C-1		-	-	-	169.9
	C-2		3.98	d	7.9	79.9
	C-3		3.92	ddd	7.9, 7.8, 3.8	77.9
	C-4	4	4.20	dd	8.8, 4.5	41.4
		4’	3.14	ddd	13.2, 7.7, 2.9	
	NH		7.93	dd	7.9, 2.5	-
C	C-1		-	-	-	169.0
	C-2		4.25	d	3.2	71.9
	C-3		3.90-3.92	m	-	69.2
	C-4	4	4.02	ddd	13.7, 5.8, 4.0,	40.6
		4’	3.68	dd	7.4, 3.8	
	NH		7.30	t	6.2, 6.2	-
D	C-1		-	-	-	170.1
	C-2		4.27	d	6.7	53.3
	C-3		4.23	dd	7.0, 4.0	77.2
	C-4	4	3.72	dd	9.6, 4.3	40.4
		4’	3.32	td	13.9, 4.5	
	NH		7.06	dd	7.1, 4.7	-
Others	C*H*$(CH_3)_2$		4.95	sept	6.2	69.0
	^{i}Pr Me		1.00 (3H)	d	6.3	21.6
	^{i}Pr Me		0.98 (3H)	d	6.3	21.5
	Isopropylidene q*C*$(CH_3)_2$		-	-	-	111.4, 110.5
	Isopropylidene CH_3 groups		1.38, 1.35, 1.27, 1.25	s	-	27.1, 27.0, 26.0, 25.8
	C(*C*H_3)(OCH_3)		1.46, 1.32, 1.23, 1.20	s	-	17.6, 17.5, 17.5, 17.4
	C(CH_3)(O*C*H_3)		3.21, 3.08, 3.04, 2.90	s	-	48.4, 47.9
	C$(CH_3)(OCH_3)$		-	-	-	99.0, 99.0

Residue	Position	NOE's to
A	H-2	3A, 4A, 4'A
	H-3	2A, 4A, 4'A
	H-4	2A, 3A, 4'A
	H-4'	2A, 3A, 4A
B	H-2	3B, 4B, 4'B
	H-3	2B, 4B, 4'B
	H-4	2B, 3B, 4'B
	H-4'	2B, 3B, 4B
	NH^{B}	$H_2{}^{A}$, $H_3{}^{A}$, $H_2{}^{B}$, $H_3{}^{B}$, $H_4{}^{B}$, $H_{4'}{}^{B}$
C	H-2	3C, 4C, 4'C
	H-3	2C, 4C, 4'C
	H-4	2C, 3C, 4'C
	H-4'	2C, 3C, 4C
	NH^{C}	$H_2{}^{B}$, $H_3{}^{B}$, $H_2{}^{C}$, $H_3{}^{C}$, $H_4{}^{C}$, $H_{4'}{}^{C}$
D	H-2	3D, 4D, 4'D
	H-3	2D, 4D, 4'D
	H-4	2D, 3D, 4'D
	H-4'	2D, 3D, 4D
	NH^{D}	$H_2{}^{C}$, $H_3{}^{C}$, $H_2{}^{D}$, $H_3{}^{D}$, $H_4{}^{D}$, $H_{4'}{}^{D}$

CHAPTER 4: REFERENCES

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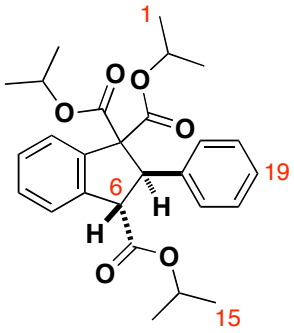
CHAPTER 5: APPENDIX

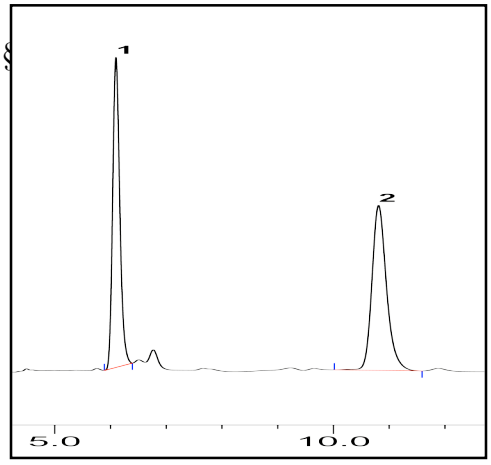
1. HPLC Data:

(2*R*,3*S*)-Tri*iso*propyl 2-phenyl-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (128)



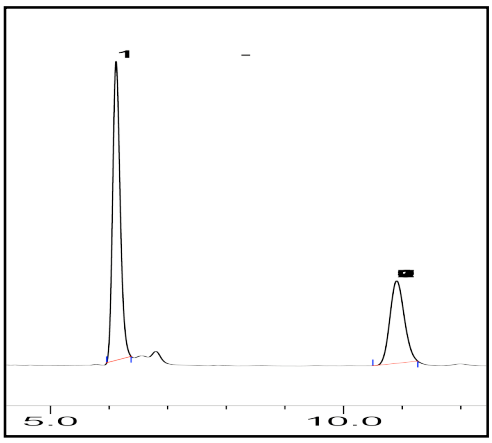
Chiral HPLC (Chiralpak OD, 2.5 % IPA, 97.5 % hexane, 1.0 mL.min^{-1}, λ = 210)

Racemic



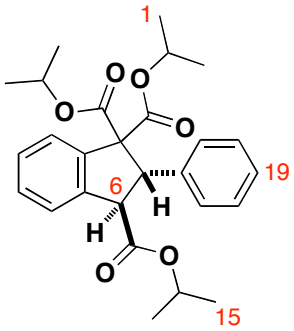
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	6.10	293.511	43.445	47.85
2	10.81	156.239	47.352	52.15

Asymmetric



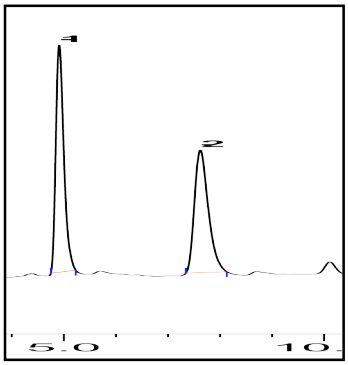
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	6.12	748.048	111.155	65.58
2	10.91	206.616	58.334	34.42

(2*S*,3*R*)-Tri*iso*propyl 2-phenyl-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (136)



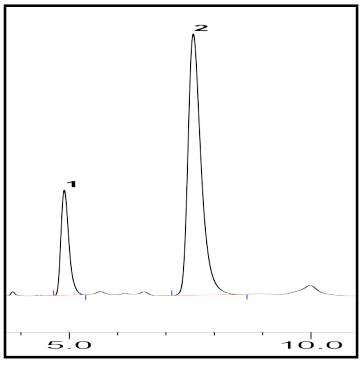
Chiral HPLC (Chiralpak OD, 2.5 % IPA, 97.5 % hexane, 1.0 mL.min^{-1}, λ = 210)

Racemic



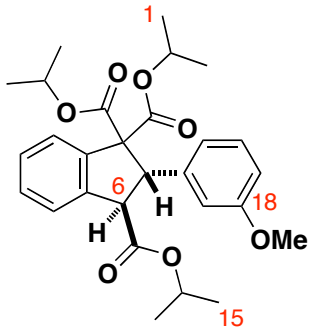
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	4.91	197.152	35.169	51.84
2	7.62	106.498	32.673	48.16

Asymmetric



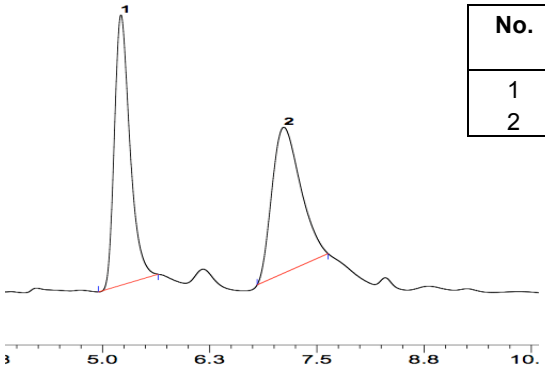
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	4.90	289.850	55.111	19.52
2	7.57	720.137	227.206	80.48

(2*S*,3*R*)-Tri*iso*propyl 2-(3-methoxyphenyl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (138)



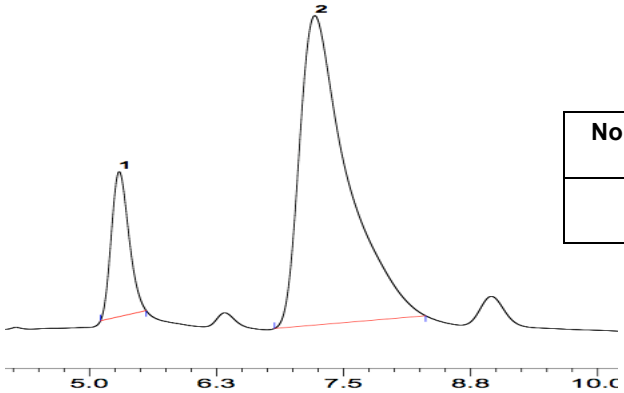
Chiral HPLC (Chiralpak OD, 2.5 % IPA, 97.5 % hexane, 1.0 mL.min^{-1}, λ = 210)

Racemic



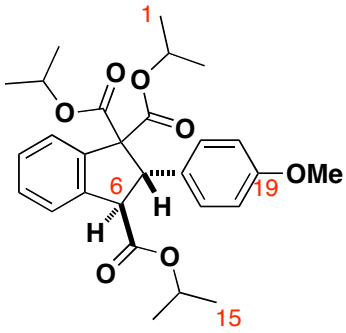
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.21	526.586	110.692	50.13
2	7.11	284.195	110.123	49.87

Asymmetric



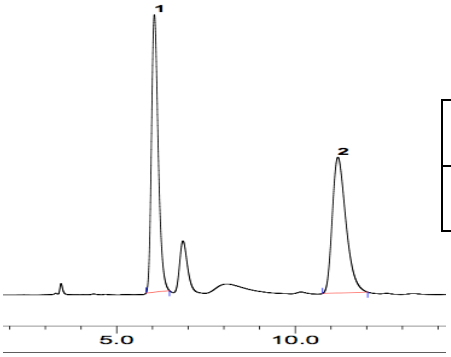
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.29	194.443	38.911	14.70
2	7.22	415.098	225.798	85.30

(2*S*,3*R*)-Tri*iso*propyl 2-(4-methoxyphenyl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (137)



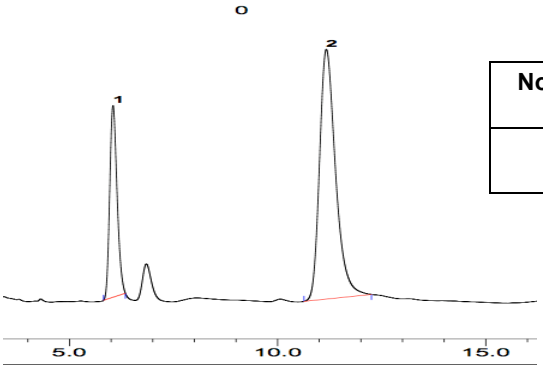
Chiral HPLC (Chiralpak OD, 2.5 % IPA, 97.5 % hexane, 1.0 mL.min^{-1}, λ = 210)

Racemic



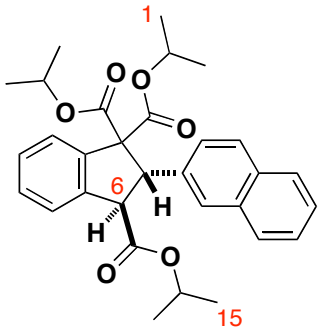
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	6.05	882.691	193.053	50.24
2	11.19	431.908	191.236	49.76

Asymmetric



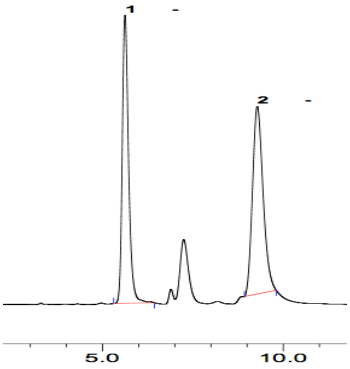
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	6.05	102.967	21.010	26.02
2	11.17	134.103	59.738	73.98

(2*S*,3*R*)-Tri*iso*propyl 2-(naphthalen-2-yl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (139)



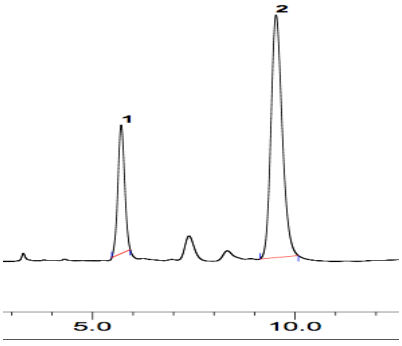
Chiral HPLC (Chiralpak OD, 2.5 % IPA, 97.5 % hexane, 1.0 mL.min^{-1}, λ = 210)

Racemic



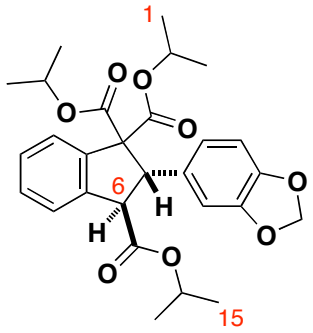
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.62	734.466	147.920	47.61
2	9.28	478.209	162.760	52.39

Asymmetric



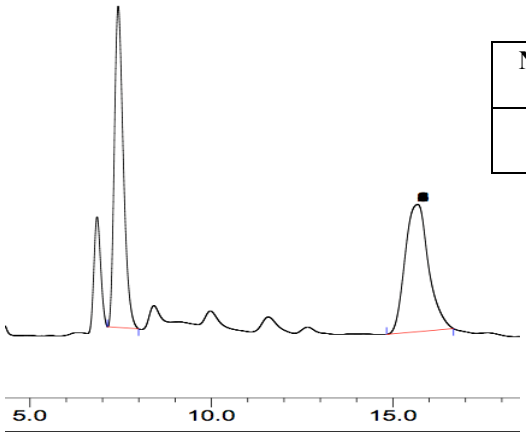
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	5.71	125.073	24.084	24.10
2	9.53	236.054	75.868	75.90

(2*S*,3*R*)-Tri*iso*propyl 2-(benzo[d][1,3]dioxol-5-yl)-2,3-dihydro-1H-indene-1,1,3-tricarboxylate (140)



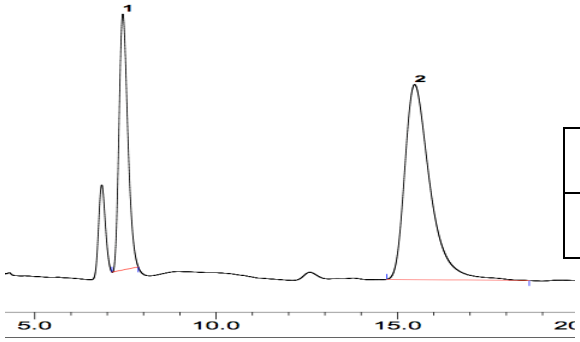
Chiral HPLC (Chiralpak OD, 2.5 % IPA, 97.5 % hexane, 1.0 mL.min^{-1}, λ = 210)

Racemic



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	7.43	102.730	29.623	49.22
2	15.68	40.750	30.563	50.78

Asymmetric



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	7.43	154.573	43.270	31.20
2	15.47	117.827	95.411	68.80

2. X-ray crystallography Data

(*Z*)-(2-bromo-2-nitrovinyl)benzene

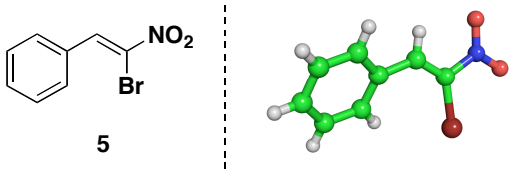


Table 5.1: Key data and refinment for the crystal structure MS0703

Identification code	MS0703
Empirical formula	$C_8H_6BrNO_2$
Formula weight	228.05
Temperature	180(2) K
Crystal system	Orthorhombic
Space group	pbca
Unit cell dimensions	a = 11.4061(3) Å α = 90°
	b = 7.3133(2) Å β = 90°
	c = 19.5573(4) Å γ = 90°
Volume	1633.06(7) $Å^3$
Z	8
Density (calculated)	1.855 Mgm^{-3}
Absorption coefficient	4.987 mm^{-1}
F (000)	896
Reflections collected	15191
Independent reflections	2831 [R(int) = 0.0770]
Final R indices [I>2sigma (I)]	R1 = 0.0427, wR2 = 0.0906
R indices (all data)	R1 = 0.0659, wR2 = 0.1015

(*E*)-3-(3-oxohex-1-en-1-yl)-2*H*-chromen-2-one

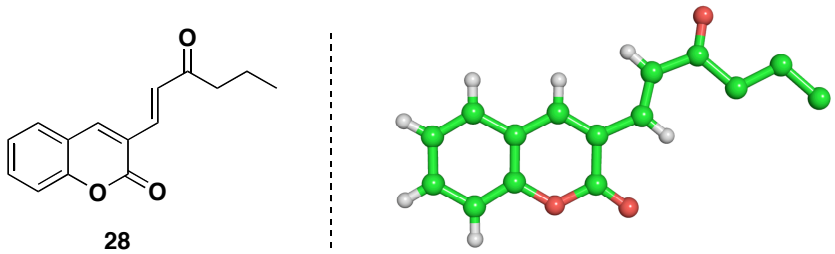


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Table 5.2: Key data and refinment for the crystal structure MS0716

Identification code	MS0716
Empirical formula	$C_{15}H_{14}O_3$
Formula weight	242.26
Temperature	180(2) K
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 5.0697(2) Å α = 90°
	b = 28.6462(1) Å β = 94.93(2)°
	c = 7.5162(2) Å γ = 90°
Volume	1203.36(5) $Å^3$
Z	4
Density (calculated)	1.337 Mgm^{-3}
Absorption coefficient	0.093 mm^{-1}
F (000)	512
Reflections collected	6365
Independent reflections	2307 [R(int) = 0.0319]
Final R indices [I>2sigma (I)]	R1 = 0.0524, wR2 = 0.1311
R indices (all data)	R1 = 0.0729, wR2 = 0.1443