Synthesis and Biology of Resolvins D3, E1 and Hybrids

and

Synthesis of Bridge-substituted Bicyclo[1.1.1]pentanes

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Synthesis and Biology of Resolvins D3, E1 and Hybrids and Synthesis of Bridge-substituted Bicyclo[1.1.1]pentanes

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This thesis consists of two projects, the first describes the development of a modular and enantioselective total synthesis of resolvins D3 and E1 using cyclic dimethyl alkenylsiloxanes. These potent anti-inflammatory polyenes are an integral part of the mammalian immune response, yet their structure-activity relationship remains poorly understood, a short coming that this work sought to address. The molecules were split into three fragments and three strategies have been examined for their unification. First, leveraging the different rate of transmetallation between 5- and 6-membered cyclic dimethyl alkenylsiloxanes; second, leveraging the different rate of transmetallation between 5-membered cyclic dimethyl alkenylsiloxanes and acyclic benzyldimethylsilanes and third, using the different rate of oxidative insertion into C-Br and C-I bonds. Ultimately, the latter strategy proved successful and was applied to the synthesis of resolvins D3 and E1 and hybrids.

The second project describes a novel synthesis of bridge-substituted bicyclo[1.1.1]pentanes (BCPs). Bridge-substituted BCPs offer unique opportunities in drug design and molecular engineering, as the bridge-substituents are placed at a dihedral angle relative to the linear 1,3-substituents, that cannot be achieved by current molecular scaffolds. Bridge-substituted BCPs were thought to arise from carbene insertion into 2-substituted bicyclo[1.1.0]butanes. These molecules are poorly precedented and three strategies were examined for their synthesis. First, via the synthesis or 2,3-disubstituted cyclobutanones; second, through a novel bis 3-exo-tet alkylation strategy and third, via the sequential synthesis of the respective cyclopropane, followed by a ring-closing alkylation. The last strategy proved successful and the examined 2-substituted bicyclo[1.1.0]butane was indeed a viable substrate for dichlorocarbene insertion which resulted in a proof of concept of the described strategy.

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I would like to extend my gratitude to the following people, without whom this enterprise would never have been completed, or indeed even begun.

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List of abbreviations

AT	aspirin-triggered
ATRA	atom transfer radical addition
BCB	bicyclo[1.1.0]butane
BCO	bicyclo[2.2.2]octane
BCP	bicyclo[1.1.1]pentane
BLT1	leukotriene B4 receptor
ChemR23	chemerin receptor 23
COX	Cyclooxygenase
dba	dibenzylideneacetone
DHA	docosaheaenoic acid
DIBAL-H	di-*i*-butylaluminium hydride
ECC-DOSY	external calibration curve diffusion ordered spectroscopy
EPA	eicosapentaenoic acid
Eq.	equation
eq.	equivalents
GPR32	G protein-coupled receptor 32
HDHA	hydroxydocosaheaenoic acid
HLM CL_{int}	intrinsic clearance in human liver microsomes
HpDHA	hydroperoxydocosaheaenoic acid
HPLC	high pressure liquid chromatography
IC_{50}	half maximal inhibitory concentration

KC	chemokine ligand 1
KOTMS	potassium trimethylsilanolate
LiHMDS	lithium hexamethyldisilazide
LLS	longest linear sequence
logD	partition coefficient
LT	leukotriene
MCP1	monocyte chemoattractant protein 1
NaHMDS	sodium hexamethyldisilazide
NOE	nuclear Overhauser effect
NSAID	non-steroidal anti-inflammatory drugs
PBMC	peripheral blood mononuclear cell
PMN	polymorphonuclear neutrophils
RCM	ring-closing metathesis
Rv	resolvin
SAE	Sharpless asymmetric epoxidation
SPM	specialised pro-resolving mediator
TASF	tris(dimethylamino)sulfonium difluorotimethylsilicate
TBAF	tetrabutyl ammonium fluoride
TCP	tricyclo[1.1.1^{1,3}]pentane
TNFα	tumor necrosis factor α
TS	total steps

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Synthesis and Biology of Resolvins D3, E1 and Hybrids

1 Introduction

1.1 Resolution of Inflammation

Localised acute inflammation is part of the host's protective response to tissue injury and infection, with the ultimate goal of destroying the invading pathogens and repairing any damaged tissue.[1–5] The state of acute inflammation is host protective but unsustainable and can result in a wide range of acute, chronic and systemic inflammatory disorders if left uncontrolled. Excessive, uncontrollable or chronic inflammation is the unifying symptom of some of the most common and difficult to treat diseases, including cardiovascular disease, rheumathoid arthritis, periodontal disease, asthma, diabetes and inflammatory bowel disease, as well as neurological disorders such as Alzheimer's disease and age-related macular degeneration. Typically, the therapeutic treatment of such conditions involves the inhibition of pro-inflammatory mediators, which is not very effective in many cases. Furthermore, non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and aspirin act to a varying degree on both COX-1 (maintenance and protection of gastrointestinal tract) and COX-2 (regulation of pain and inflammation via biosynthesis of pro-inflammatory prostaglandins). More selective COX-2 inhibitors such as valdecoxib and rofecoxib were shown to significantly increase the risk of heart attacks and had to be taken off the market. At the same time, common NSAIDs acting on the same receptor (e.g. ibuprofen, aspirin) received a warning on their label.

The isolation of specialised pro-resolving mediators (SPMs) created alternative therapeutic paradigms based on resolving acute inflammation before the onset of chronic inflammation. In 2002, Serhan published his initial findings on the first family of endogenous anti-inflammatory lipid mediators, which were termed resolvins for promoting the resolution of inflammation.[6] Resolvins reduce inflammation at nM or even pM concentrations by stimulating cellular resolution events, thus they are acting on a complementary pathway to conventional NSAIDs and COX-2 inhibitors which block the synthesis of pro-inflammatory prostaglandins. Their high potency goes hand in hand with low natural abundance, which makes these compounds interesting targets for total synthesis. Initial efforts led to the establishment of their structure, yet their structure activity relationship remains poorly explored.

The Anderson group has recently developed a convenient Lindlar hydrogenation protocol to access cyclic alkenylsiloxanes from alkynylsilanes. These compounds serve as coupling

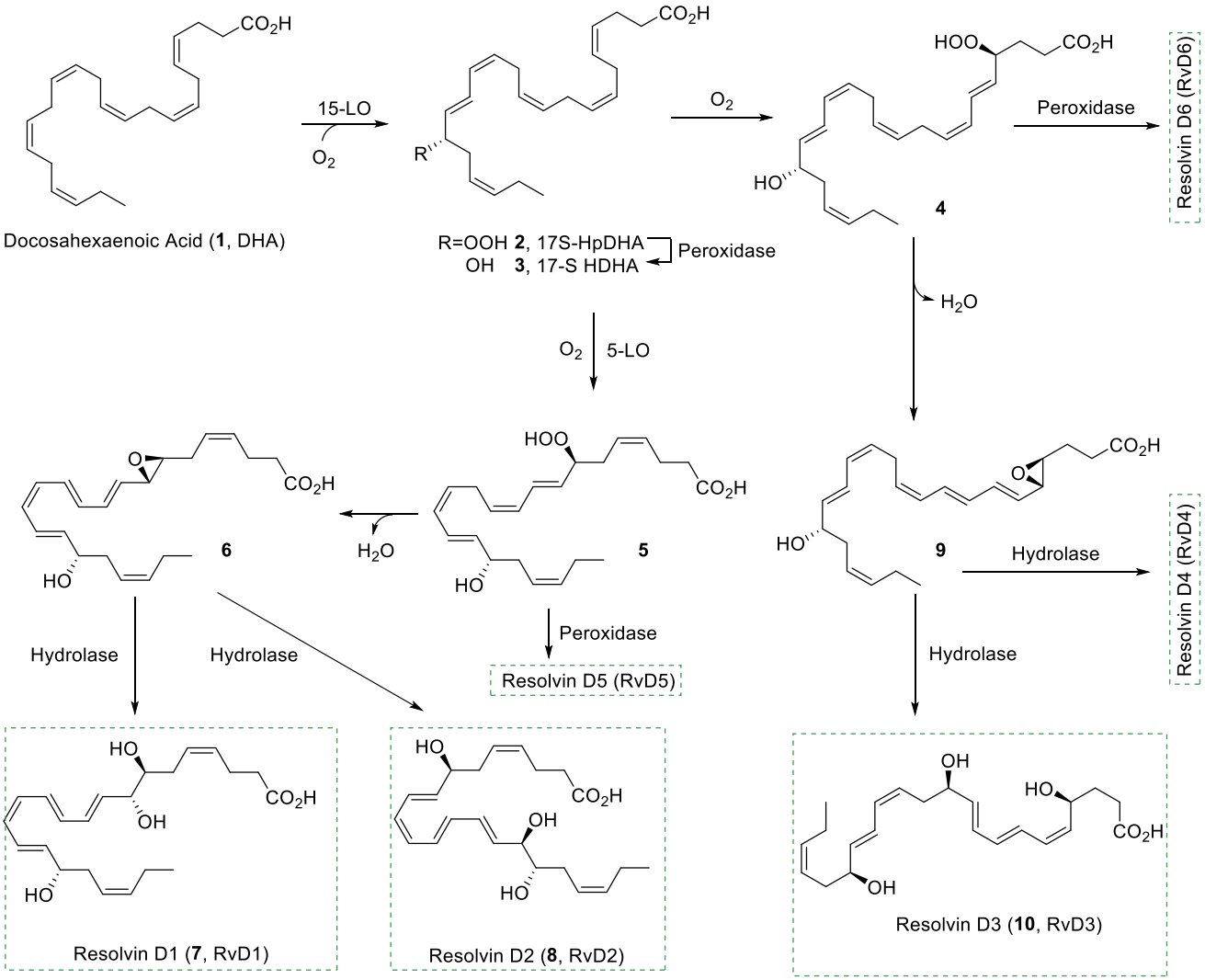
partners that reveal (*Z*)-allylic and homoallylic alcohol motifs on Hiyama-Denmark cross coupling.[7] This thesis will examine a modular and enantioselective synthesis of resolvins D3 and E1 via Hiyama-Denmark coupling of cyclic siloxanes. Particular emphasis is placed on leveraging the tantalising prospect of ring-size dependent selectivity in the transmetallation step of 5- and 6-membered cyclic siloxanes.

The following chapter will provide an introduction to the biology of lipid mediators, the synthesis of cyclic siloxanes and their application in total synthesis, and previous work within the group.

1.2 Resolvins D3 and E1

1.2.1 Resolvin D3

The biosynthesis of RvD3 (**10**) commences with the action of 15-LO on docosaheaenoic acid (**1**, DHA) to yield 17-*S* hydroperoxydocosaheaenoic acid (**2**, 17*S*-HpDHA) which is subsequently reduced to 17-*S* hydroxydocosaheaenoic acid (**3**, 17*S*-HDHA) (Scheme 1). Further oxygenation transforms this molecule into an epoxide which is subsequently hydrolysed and, depending on the regioselectivity of the epoxidation and hydrolysis, yields either RvD1, RvD2, RvD3 or RvD4. RvD5 and RvD6 result from the direct reduction of the respective peroxides. Aspirin triggered (AT) lipoxygenations are known and yield the respective 17*R* epimers (or AT-Rv).[8]



Scheme 1: Biosynthesis of D-Resolvins

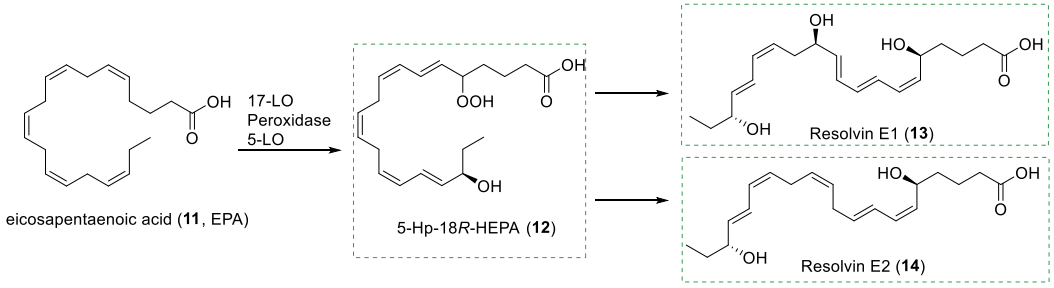
Resolvin D3 is uniquely placed in the timeframe of resolution. Its concentration remains elevated up to 72 h after the maximum concentration of polymorphonuclear neutrophils (PMNs) has been reached, which is in stark contrast to, for instance, RvD1, RvD2 or RvD5 which fade away much more rapidly during the resolution event.[9] The potency of Resolvin D3 is equally remarkable. At a dose of 10 ng/mouse, both RvD3 and AT-RvD3 reduce the number of transmigrated neutrophils into the peritoneal cavity by 43%. The same dose brings about a 65% reduction in PMN transmigration of TNF-α induced acute inflammation while also strongly reducing inflammatory signals like MCP1 (by 70%) or KC (by 50%). Again, both RvD3 and AT-RvD3 were of similar potency. RvD3 also impacts the eicosanoid biosynthesis. At 10 ng/mouse, the concentration of pro-inflammatory LTB_4 was reduced by 80%, PGD_2 was reduced by 67% and PGE_2 concentration was increased 3-fold. In human leukocytes, RvD3 reduces PMN transmigration by 25% at concentrations as low as 10^{-11} M. Both RvD3 and AT-RvD3 increase macrophage phagocytosis of zymosan by

30% at 10^{-9} M. Thus, both RvD3 and AT-RvD3 display potent anti-inflammatory actions characteristic of SPMs. This bioactivity is remarkable and RvD3 is one of the most potent resolvins isolated so far. Both RvD3 and AT-RvD3 act on G protein-coupled receptor 32 (GPR32) (as do RvD1 and RvD5), which upregulates phagocytic activity.

Another study examined the impact of the metabolically more stable AT-RvD3 on the recovery of lung tissues after acute lung injury.[10] This type of injury leads to loss of normal epithelial and endothelial barrier functions, edema and ultimately an impairment of gas exchange. Mouse lungs were exposed to HCl and the recovery monitored. At doses of 10 ng AT-RvD3/mouse the concentration of PMNs was reduced 3-fold after 6 h and still 2-fold after 72 h, the concentration of macrophages was reduced 2-fold after 6 h and showed no significant change to the control after 72 h. This beneficial impact was traced back to the action of AT-RvD3 on multiple pathways, such as the increased sodium channel γ expression and lymphatic vasculature, limitation of the infiltration of proinflammatory leukocytes into the lung, and NFκB activation (nuclear factor kappa-light-chain-enhancer of activated B cells) accelerating the recovery of epithelial barrier integrity and function by promoting proliferation of epithelial cells.

1.2.2 Resolvin E1

The biosynthesis of RvE1 (**13**) is similar to the Resolvins of the D series (Scheme 1) and, starting from eicosapentaenoic acid (**11**, EPA), involves a series of lipoxygenations, reductions (**14**, RvE2) or an epoxide formation/hydrolysis sequence (**13**, RvE1, Scheme 2).[2]



Scheme 2: Synthesis of E-Resolvins (Resolvin E3 omitted)

Total synthesis of RvE1 permitted access to larger quantities of this potent anti-inflammatory agent for the first time (*vide infra*) and biological tests in mouse models could be carried out. A dosage of 100 ng/mouse decreased PMN-infiltration in TNFα induced

dorsal air pouches by 50 – 70%.[11] For a similar response 10 mg/mouse of dexamethasone or 1 mg/mouse of aspirin was needed. Another inflammation model supports this trend. In zymosan induced peritonitis 100 ng/mouse of RvE1 gave 50 – 60% inhibition of leukocyte recruitment, whereas indomethacin, another commonly used anti-inflammatory drug, gave only a 25% reduction at 100 ng/mouse.[12]

A limited structure activity relationship study has been published, which shows that 18*S*-RvE1, also endogenously produced, has similar activity to the 18*R* epimer. Furthermore, the all-*trans* analogue of RvE1 shows slightly reduced potency (70% of RvE1).[13]

Biological actions of RvE1 include protection of pro-inflammatory gene expression, protection against colitis,[14] promotion of macrophage ingestion of apoptotic PMNs,[15] protection against osteoclast-mediated bone destruction and prevention of periodontitis,[16] selective counterregulation of platelates and leukocytes,[17] and reduction of inflammatory pain.[18]

So far, the receptors ChemR23[12] and BLT1[19] have been identified as molecular targets for RvE1 *via* tritium labelling studies. [^{3}H] RvE1, prepared *via* tritiation in the final alkyne reduction (Scheme 3, *vide infra*), was shown to bind to an apparent single site on ChemR23 transfectants with high affinity, K_d=11.3 ± 5.4 nM. The ChemR23 receptor is expressed at mRNA level in leukocytes, gastrointestinal, testis, prostate, heart, aorta, brain, kidney, liver, and lung. However, the role of RvE1 in these tissues remains to be elucidated. [^{3}H] RvE1 was equally shown to bind to LTB_4 receptor BLT1 with K_i=70nM which might explain the observed suppression of LTB_4 stimuli *via* competitive inhibition. The resolvin precursors EPA and DHA did not compete for any specific [^{3}H] RvE1 binding.

1.2.3 Metabolic Inactivation of Resolvin E1

Sparse details on the RvD3 metabolome exist;[2] however, the degradation of RvE1 has been studied in some detail and may provide insights on the metabolism of poly(enol)s in mammalian tissue (Figure 1). So far, 4 pathways for the inactivation of resolvin E1 (**13**) have been identified.[20] Oxidation to **17** and **18** or reduction to **19** lead to biologically inactive RvE1 derivatives whereas ω-oxidation leads to **16** which retains some properties of RvE1. This highlights that not all metabolites are necessarily inactive, further complicating the analysis of the activity of RvE1 and its metabolome.

However, these studies enabled the design of RvE1 analogues with improved metabolic stability. One particularly successful modification consists of the appendage of a p-fluorophenoxy motif (compound **15**) to RvE1 which does not impact anti-inflammatory and pro-resolving properties but does block inactivation via metabolites **17** and **18**.[21] Taken together, these findings might enable the development of RvE1 based therapeutics as agonists of resolution. Furthermore, the study of the RvE1 metabolome may help to identify biomarkers relevant to ω-3 supplementation studies in humans.

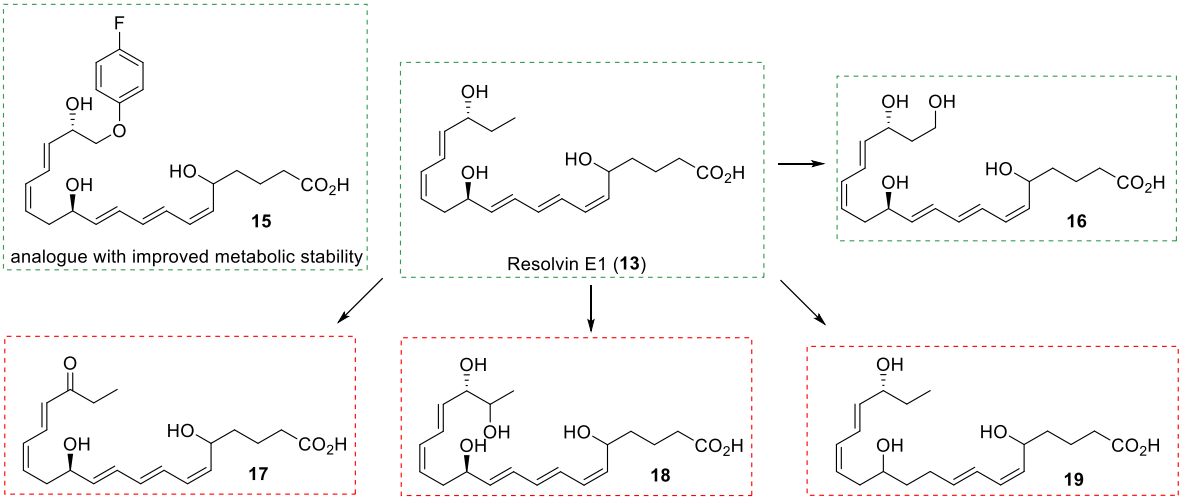


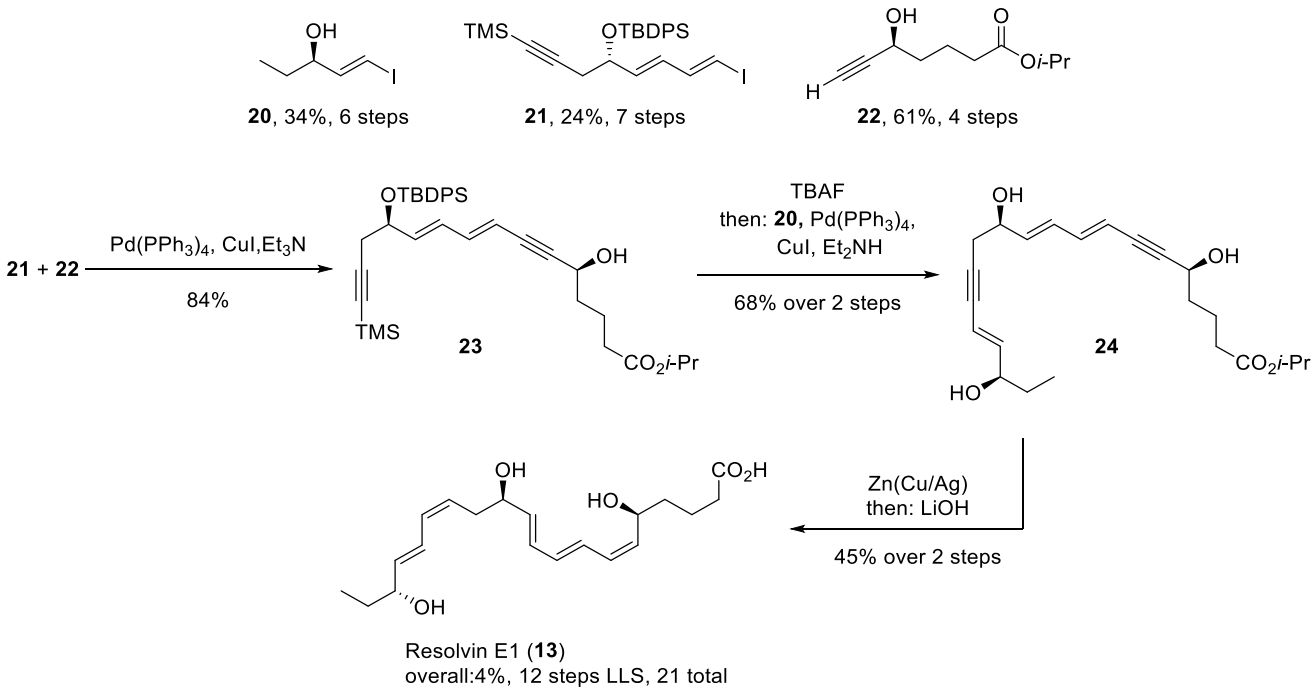
Figure 1: Resolvin E1 metabolome

1.2.4 Previous Syntheses of RvE1 and RvD3

The structure and stereochemistry of RvD3 and RvE1 were confirmed by Petasis and Serhan *via* total synthesis. The synthetic sample exhibited identical properties to the enzymatically prepared natural sample by GC-MS, UV-VIS, LC-MS and in biological tests since the low natural abundance of RvD3 and RvE1 did not allow for correlation by NMR spectroscopic techniques.[12,22,23] Their initial route was further optimised and scaled up by Schwartz to prepare 1.8 g of RvE1 for *in vivo* testing.[24] This synthesis is representative of all hitherto reported approaches to resolvins and will be summarised in Scheme 3. The reader is referred to the following references for reports on the synthesis of resolvins D1 – D6 and E1 – E3 that relied on identical disconnections.[25–37]

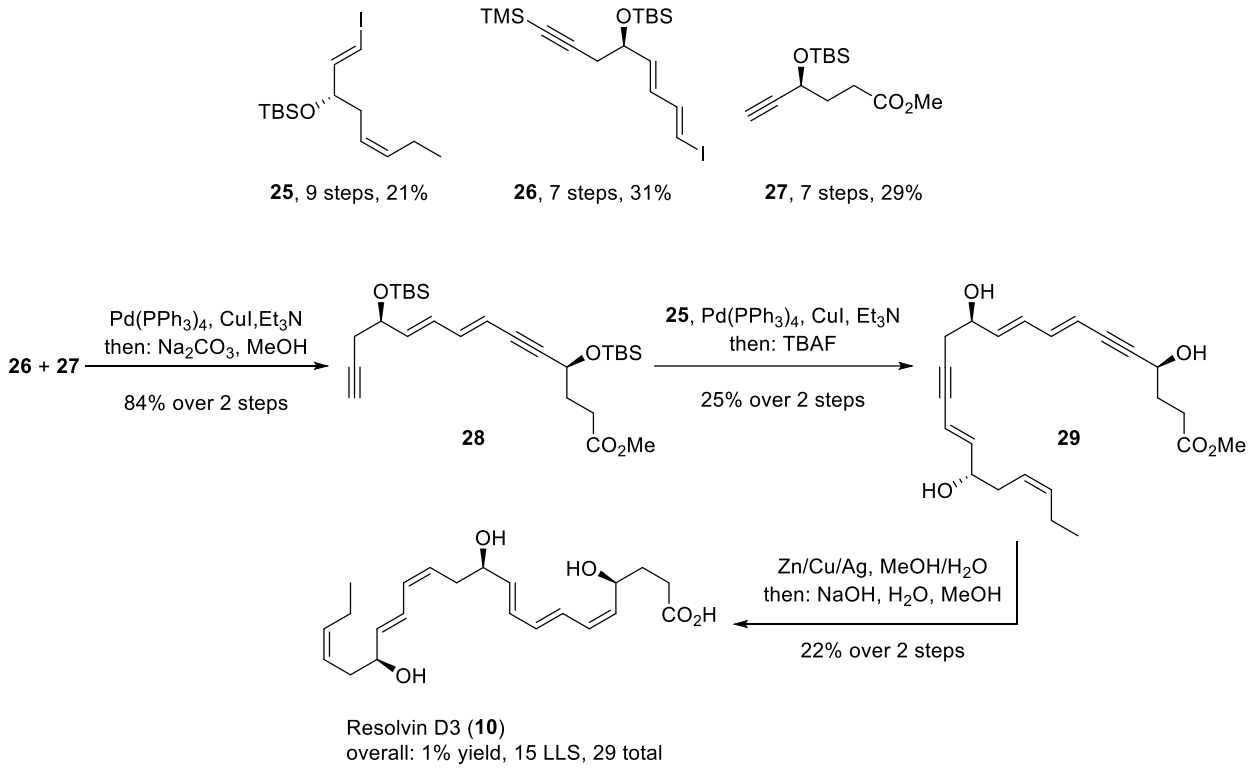
The RvE1 route relied on the union of 3 key fragments **20** – **22** via Sonogashira coupling. Starting from glutaric anhydride, **20** was synthesised in 61% yield over 4 steps. **21** was prepared from enantiopure (*S*)-glycidole and was obtained in 24% over 7 steps. A similar route delivered **22** in 34% yield over 6 steps. Subsequent Sonogashira coupling of **21**, **22**

and **20**, afforded polyenyne **24** in 57% yield (3 steps) which was subjected to (*Z*)-selective alkyne reduction using Boland's conditions.[38] The triene unit was found to be prone to isomerisation upon exposure to light or acid, but sufficiently stable when handled with care. Finally, hydrolysis of the isopropylester gave resolvin E1 in 21 steps (12 LLS) and 4% overall yield. The main issue associated with this route is the reliance on the Takai olefination which requires large amounts of chromium dichloride and results in significant amounts of waste. The synthesis of fragment **20** has since been revised and improved,[39] however the synthesis of **21** has solely employed Takai olefination to this date.



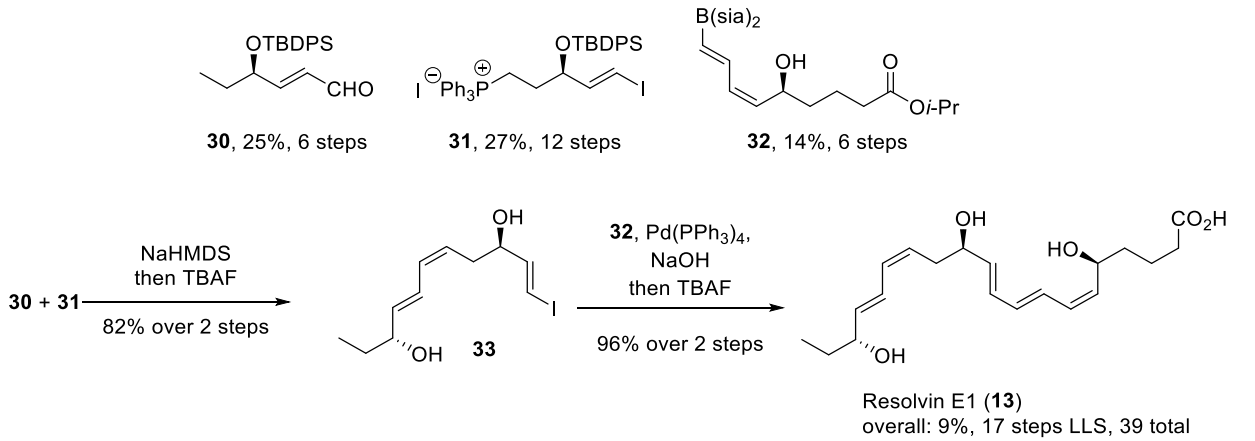
Scheme 3: Schwartz' gram-scale total synthesis of resolvin E1 (following Petasis synthesis)

Petasis also prepared resolvin D3 (**10**) in a similar fashion (Scheme 4). Both syntheses (resolvin D3 and E1) are characterised by a modular and enantioselective approach that relies mostly on chiral pool starting materials. The step count seems appropriate for the complexity of the molecule and hence allows for convenient access of the natural products. The only drawback is the high reliance on the Takai olefination which could impede scale-up.



Scheme 4: Petasis' synthesis of resolvin D3

A conceptually different approach to resolvin E1 (**13**) was disclosed by Kobayashi who introduced the (*Z*)-configured double bonds via Suzuki coupling of (*Z,E*)-alkenyl bromide **33**, and by a Wittig reaction (Scheme 5).[37] This synthesis is quite lengthy but was reported to afford resolvin E1 (**13**) in an astounding 9% yield over 17 steps, an average yield of 87% per step.



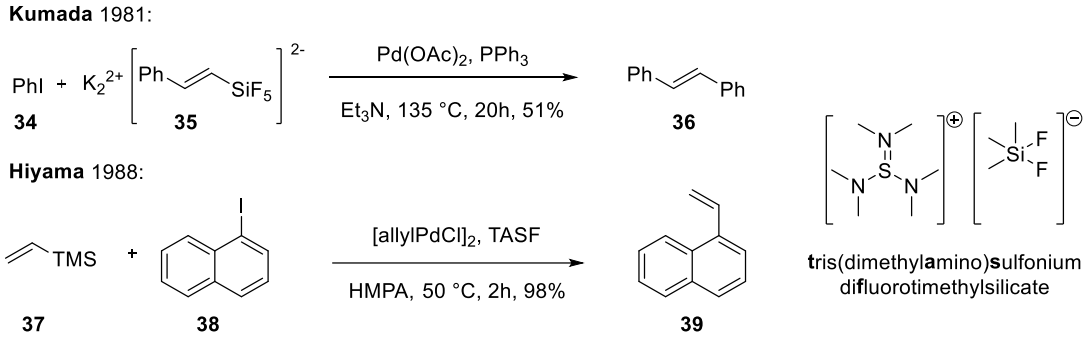
Scheme 5: Kobayashi's synthesis of resolvin E1

1.3 Introduction to Hiyama-Denmark Couplings

1.3.1 Definition and Development

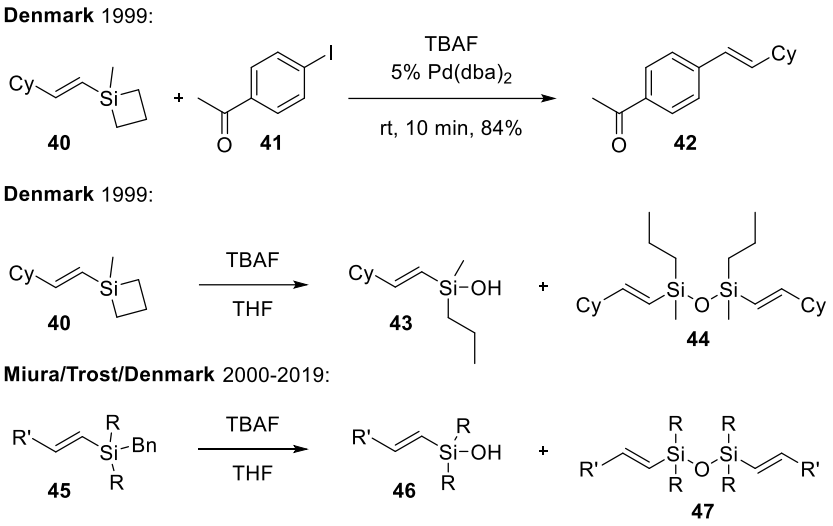
The term Hiyama cross-coupling denotes the union of organosilicon compounds with organohalides and is one of the most recently developed classes of cross-couplings; a variant employing silanols instead of silanes is typically referred to as Hiyama-Denmark cross-coupling.[40] The key challenge of this type of reaction lies in the low polarity of the C-Si bond which requires a suitable activator (typically KOTMS or TBAF) to allow for transmetallation of the organosilicon compound *via* the respective silicon-ate complex.[41] This stability combined with their generally non-toxic and inexpensive nature makes organosilanes a very attractive alternative to more traditional cross-couplings.[40,42]

The first example of a cross-coupling involving silicon as the organometallic component was reported by Kumada in 1981 in the reaction of pentafluorosilicate **35** and iodobenzene (**34,** Scheme 6).[43] The main drawback of preforming a high valent silicate species was mitigated by Hiyama in 1988 who achieved *in situ* activation of stable and readily available vinyltrimethylsilane (**37**) by tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) in the synthesis of **39**.[44] This finding greatly improved the applicability and scope of this cross-coupling reaction.



Scheme 6: The first examples of Hiyama cross-coupling

In 1999, Denmark introduced a siletane **40** as organosilane species whose high coupling efficiency was at first attributed to a 'strain release Lewis acidity' (Scheme 7).[45] Subsequent studies however identified rapid ring-opening of siletane **40** to silanol **43** and siloxane **44** in presence of TBAF, which led Denmark to investigate the performance of these more stable species.[45] Other all-carbon substituted silicon precursors to silanols are known, and the most popular is benzyldimethylsilane which displays both high stability to various conditions and ready conversion to the silanol in presence of fluoride sources.[46,47]



Scheme 7: Development of silanol based cross-coupling by Denmark

In 1989, Tamao discovered the high coupling efficiency of mono-, di- or trialkoxysilanes under mild conditions[48] which led to the development of a large variety of silanol, silanoate and disiloxane reagents as the organometallic compound in cross-couplings (Figure 2). These reagents undergo cross-coupling under both fluoride-promoted and fluoride-free conditions (alkoxide, hydroxide or carbonate as activator) due to their increased C-Si bond polarisation when compared to organosilanes.[49] The activation with oxygen anions represents a significant advantage of the methodology as it enables the tolerance of common silyl ether protecting groups, and improves compatibility with industrial processes (price and avoidance of glass corrosion). Further improvements were made by Denmark through the introduction of pre-formed silanolates which can increase the scope with base sensitive substrates (e.g. the halide itself).

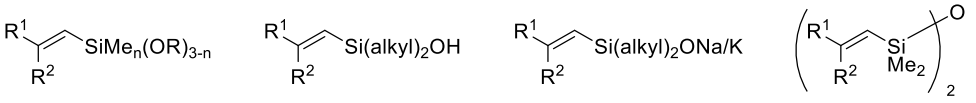
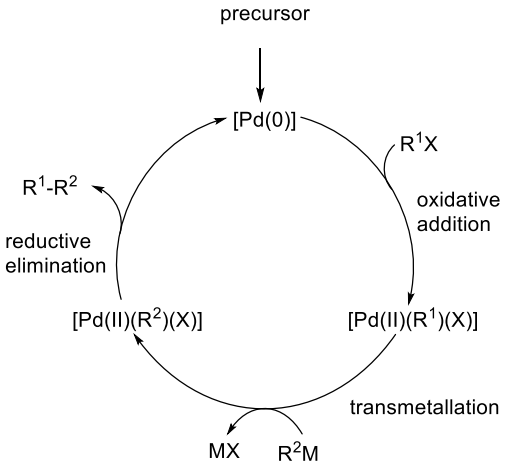


Figure 2: Commonly used vinylorganosilanes with one or more oxygen substituents (reproduced from [50])

1.3.2 The Mechanism of Hiyama-Denmark Cross-couplings

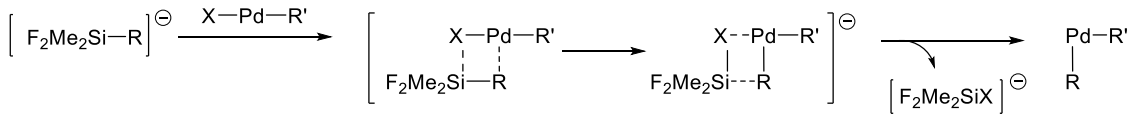
The catalytic cycle of the Hiyama-Denmark cross-coupling begins with oxidative addition of an organohalide to palladium, followed by rate-determining transmetallation of the organo-silicon species and concludes with the reductive elimination of the two carbon

ligands on palladium to form the desired product (Scheme 8). Oxidative addition and reductive elimination are similar across all branches of cross-couplings,[51] however the transmetallation step varies with the metal and in case of silicon, mechanistic differences can even be observed for different silanes. The following introduction will focus on the cross-coupling of alkenylsilanes.



Scheme 8: general mechanism of palladium catalysed cross-couplings

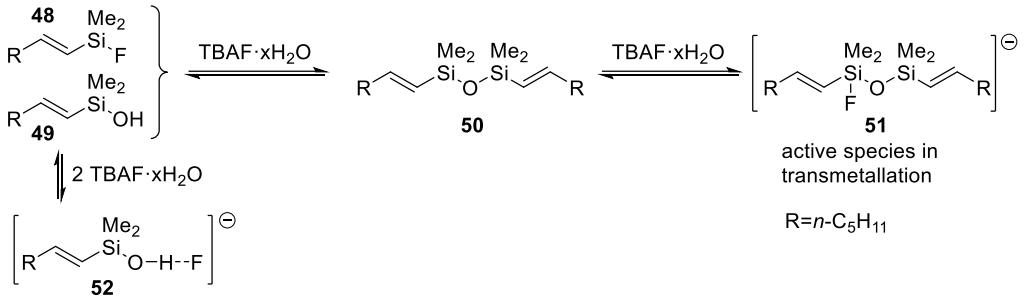
In 1982, Hiyama found that mono- and difluoroalkenylsilanes were effective in fluoride-promoted cross-couplings with aryl iodides, while trifluorosilanes were inactive.[52] He suggested that the latter was able to form a hexacoordinate and hence coordinatively saturated silicon species in the presence of fluoride, which makes the organosilicate unavailable for transmetallation. Pentacoordinate silicates (formed from mono- or difluoroalkenylsilanes) were therefore proposed to be active in a 4-membered transition state where the R group on silicon was transferred to palladium concomitantly as the halogen was transferred from Pd-X to the silicon (Scheme 9). In this context X is either I, from the oxidative addition, or F, after ligand exchange (*vide infra*).[53,54]



Scheme 9: Transmetallation of organosilanes according to Hiyama (1982), X is F or I

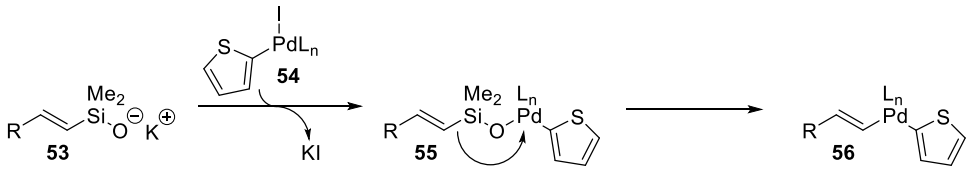
In 2004, Denmark investigated the transmetallation of silanols **49**, disiloxanes **50** and fluorosilanes **48** in the presence of TBAF as the activator, and uncovered an intricate web of chemical equilibria (Scheme 10).[55] Studies by ^{1}H, ^{19}F and ^{29}Si NMR revealed that initial

action of TBAF on either of the above species would convert them into the respective disiloxane **50**. Further exposure to TBAF·xH_2O would convert this species to siliconate ion **51** which is active in the transmetallation, or silanol **52** whose alcohol proton is subject to a hydrogen bond to fluoride. It was found that low and high fluoride concentration result in little conversion which can be explained by the position of the respective equilibria: at low concentrations of fluoride species **48** – **51** are dominant, whereas at high concentrations **52** would be the major reaction component. Usually 2 equivalents of TBAF·3H_2O are employed in these types of reaction which in this context would be a medium (most effective) concentration of TBAF (low is <2 and high is >2 equivalents of TBAF).



Scheme 10: The fate of silanols in fluoride mediated transmetallations

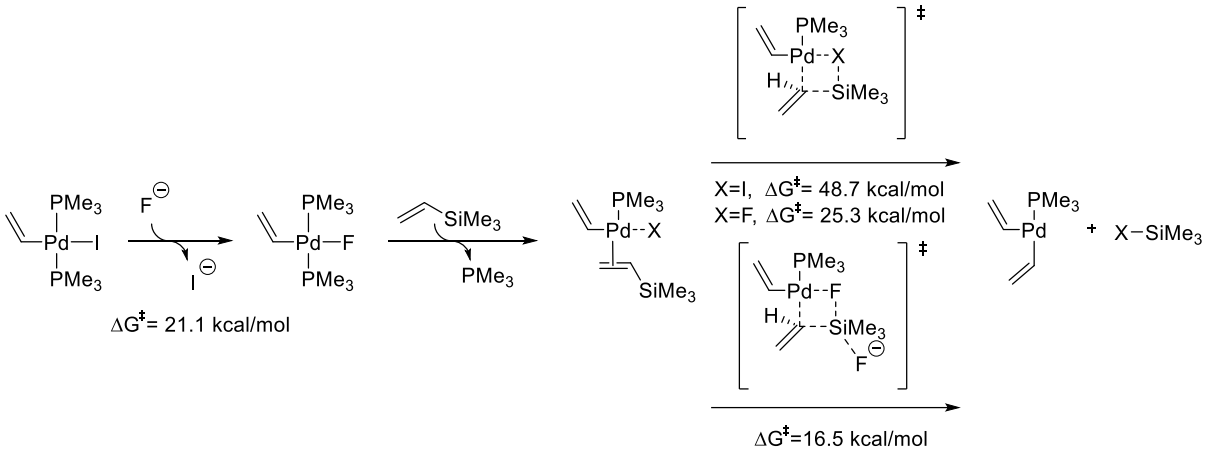
Also in 2004, Denmark reported a distinct mechanism for the transmetallation of potassium alkenylsilanoates in the absence of fluoride (Scheme 11).[56] The coupling of 2-iodothiophene and alkenylsilanoate **53** was proposed to proceed through complex **55**, where the silanoate oxygen acts as a ligand of palladium. This Si-O-Pd complex then allows for intramolecular transmetallation without further activation of the siloxane as its respective -ate complex. This transmetallation proceeds thus appears to proceed through a tetravalent Si species!



Scheme 11: Transmetallation of silanols mediated by oxygen anions

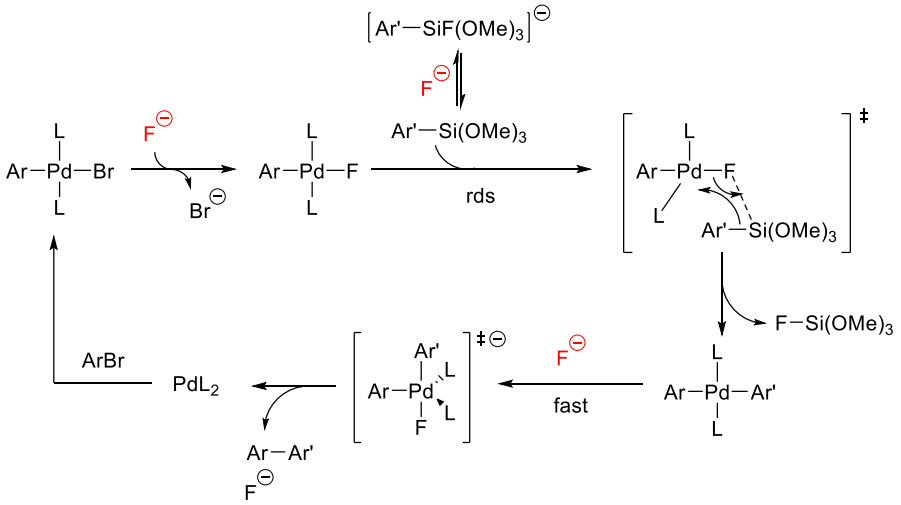
In 2008, Hiyama investigated the role of fluoride on the transmetallation of vinyl silanes computationally (DFT/BS-II) (Scheme 12). These calculations revealed that there was no preformation of fluorosilicate complexes from trimethylvinyl silane. Instead it was found that a ligand exchange on palladium from iodide to fluoride drastically lowered the

activation barrier of transmetallation with trimethylvinyl silane from 48.7 kcal/mol (Pd-I) to 25.3 kcal/mol (Pd-F), at least in part accounted for by the formation of a stronger Si-F bond instead of a Si-I bond. Furthermore, nucleophilic attack of fluoride on silicon in the 4-membered transition state reduced the activation barrier of transmetallation further to 16.5 kcal/mol. These findings suggest that the rate limiting step of the transmetallation is in fact the ligand exchange on palladium with an activation energy of 21.1 kcal/mol. If fluoride was replaced with hydroxide in the calculation, the exact same route was found to be preferable and no evidence of a distinct pathway (Denmark, *vide supra*) could be located. Lastly, phosphine ligands inhibited the transmetallation in all calculated scenarios which is consistent with experimental observations; in practice Hiyama-Denmark cross-couplings are performed in absence of any phosphine ligands.



Scheme 12:The role of fluoride in the transmetallation of vinyltrimethylsilane - a computational study

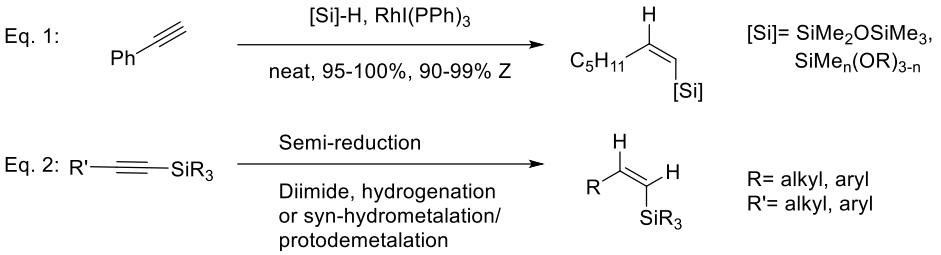
In 2014, Jutand applied cyclic voltammetry to identify the role of fluoride in the transmetallation of organosilanes (Scheme 13). Its role seems to be three-fold.[57] Firstly, ligand exchange on the palladium from Pd-Br to Pd-F is enabling for the transmetallation. Interestingly, it is proposed to proceed through a Pd-F-Si interaction which bears great similarity to the Pd-O-Si ligation proposed by Denmark (*vide supra*). Secondly, coordination of fluoride to palladium facilitates reductive elimination. Lastly, high fluoride concentration was found to inhibit transmetallation by forming pentavalent silicates as off-cycle products.



Scheme 13: The role of fluoride in the transmetallation of aryltrimethoxysilane – studied by cyclic voltametry

1.3.3 Synthesis of Vinyl Silanes

In general, Hiyama-Denmark couplings proceed with a high degree of stereochemical retention,[58] thus the stereo- and regioselective preparation of the required organosilanes is paramount for the overall efficiency of the reaction sequence. Many methods allow for the introduction of alkenylsilanes with diverse geometries and substitution patterns of which 1,2-disubstituted vinyl silanes are perhaps the most useful building block in the context of polyene synthesis.[59] In contrast to (*E*)-vinyl silanes, the (*Z*)-isomers are more difficult to access. This is in part due to the *syn*-stereospecificity of most hydrosilylation protocols, but also because of their propensity to light or heat mediated isomerisation to their more stable *E*-form. A few reports of *anti*-hydrosilylation of terminal alkynes exist (Scheme 14): Chang reported the use of $[RuCl_2(p\text{-cymene})]_2$ as catalyst for the synthesis of all-carbon substituted vinyl silanes[60] and Hiyama disclosed the use of cationic rhodium complexes for the synthesis of mono- and dialkoxysilanes and siloxanes (Eq. 1).[61] Nevertheless, these methods do not seem to be readily applicable in practice, as even 20 years after their disclosure the semi-reduction of alkynylsilanes remains the method of choice (Eq. 2). This *syn*-hydrogenation is usually achieved via diimide reduction[62] or via *syn*-hydrometalation followed by protodemetalation using dicyclohexylborane[63] or DIBAL-H.[64] The classical Lindlar hydrogenation proceeds often sluggishly or with poor stereoselectivity,[65] an issue that recent work within the Anderson group addressed.[7]

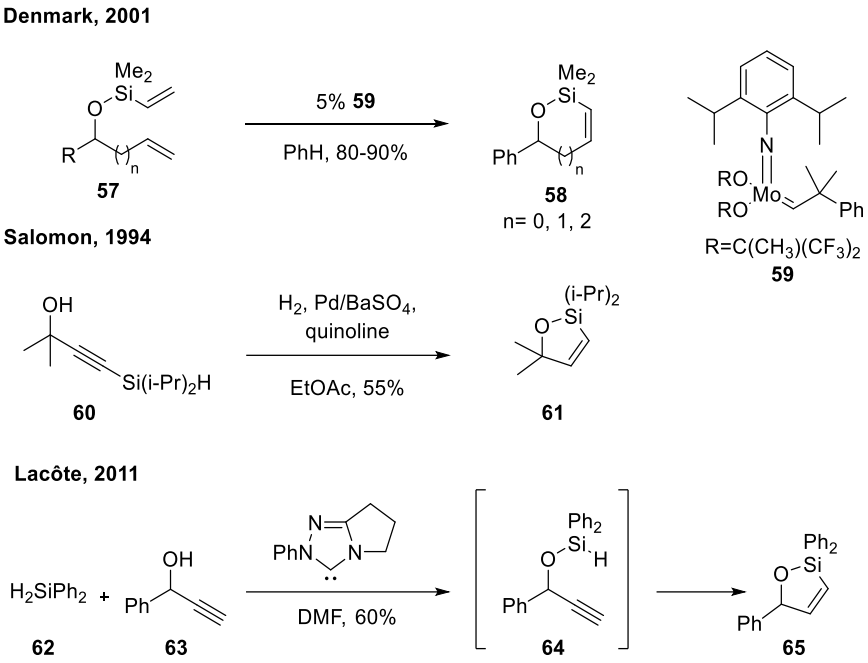


Scheme 14: Selected examples of 1,2-disubstituted (*Z*)-vinyl silane syntheses (reproduced from [50])

1.3.4 Synthesis of Cyclic Alkenylsiloxanes

Cis-alkenylsiloxanes can undergo ring formation with proximal alcohols, giving rise to cyclic siloxanes. This cyclisation is useful to upgrade the stereochemical purity of the vinyl siloxane. Furthermore, the cyclic nature prevents isomerisation of the vinyl siloxane in downstream processing, serves as a protecting group for the alcohol, and potentially enables a stereocontrolled synthesis of (*Z*)-alkenes bearing allylic or homoallylic alcohols.

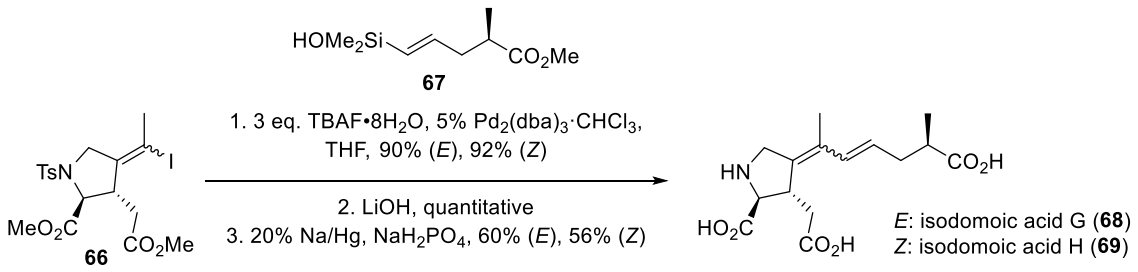
Pioneered by Grubbs, the main route to accessing cyclic siloxanes has been *via* ring-closing metathesis (RCM) of vinyl silanes (**57**), which has been used to synthesise 5-,6- and 7-membered rings (**58**, Scheme 15). However, this strategy requires the use of air- and moisture sensitive Schrock catalyst (**59**) to overcome the steric hindrance of the bulky substituents on silicon.[66,67] Denmark studied this approach comprehensively[68,69] and applied it to the synthesis of macrocyclic polyenes;[70,71] the application to brasilenyne will be discussed below. Further isolated reports exist on the synthesis of cyclic siloxanes, however without any scope: In 1994, Salomon found that Lindlar hydrogenation of **60** gave **61** in moderate yield,[72] while in 2011 Lâcote and co-workers reported that an N-heterocyclic carbene (NHC) catalyst could affect trans-hydrosilylation across propargylic alcohol **63** to yield **65** *via* the intramolecular hydrosilylation of an alkoxysilane intermediate (**64**).[73]



Scheme 15: Synthesis of cyclic alkenylsiloxanes

1.3.5 Application of Acyclic Vinyl Silanes in Total Synthesis

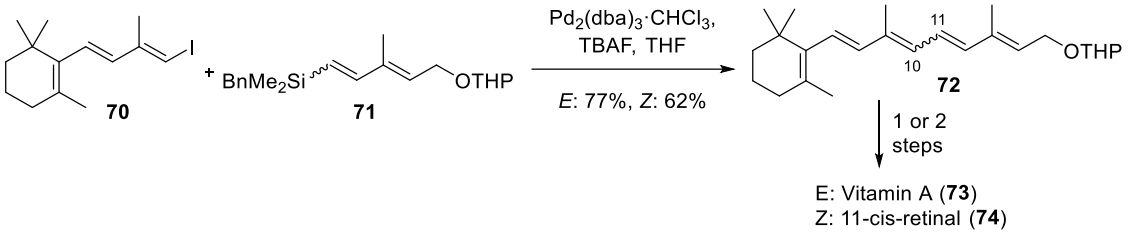
Mild reaction conditions and excellent stereochemical retention make Hiyama-Denmark couplings a valuable tool for practitioners of total synthesis.[58] In 2009 Denmark reported the synthesis of isomeric neuroexcitatory agents isodomoic acids G and H (**68** and **69**, Scheme 16).[74] Both the *E* and *Z* isomer (**66**) coupled with silanol **67** in excellent yields to construct the diene, yielding the natural product after ester hydrolysis. The authors noted that the hydration level of TBAF was critical for the success of this Hiyama cross-coupling, and TBAF·8H_2O provided the best results.



Scheme 16: Synthesis of iodomoic acid G and H by Denmark

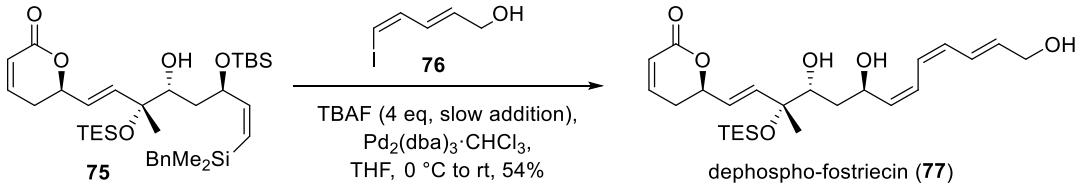
In 2009, López demonstrated the application of Hiyama-Denmark cross-couplings to the synthesis of retinoids.[75] Earlier work of the same group on a Suzuki cross-coupling approach flagged up stability issues of the respective boronic acid synthon which could be

overcome by several silicon-based reagents, of which **71** is presented (Scheme 17).[76] The coupling efficiency is high, and this report substantiates the benefits of Hiyama couplings on the synthesis of polyenes.



Scheme 17: López synthesis of retinoids

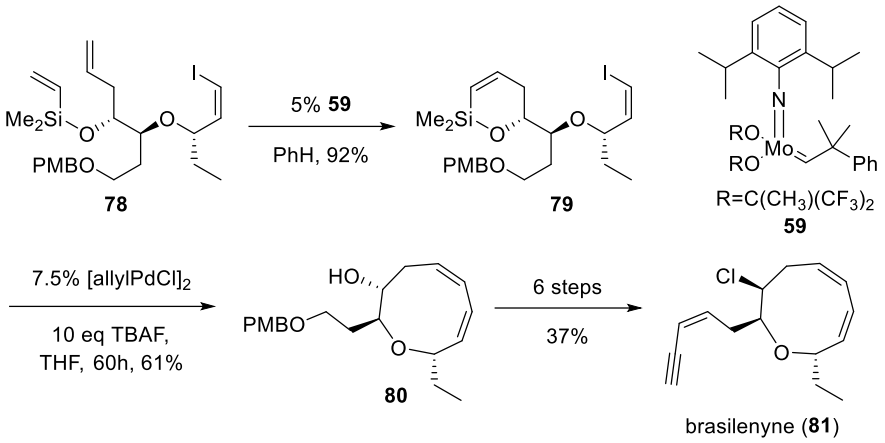
Another example was reported by Trost in 2005 in the synthesis of dephospho-fostriecin (**77**) where treatment of **75** with TBAF in the presence of **76** and $Pd_2(dba)_3$ afforded the product in moderate yield (Scheme 18).[62] Although not noted by the authors, this coupling could well proceed *via* a cyclic alkenylsiloxane.



Scheme 18: Synthesis of dephospho-fostriecin by Trost

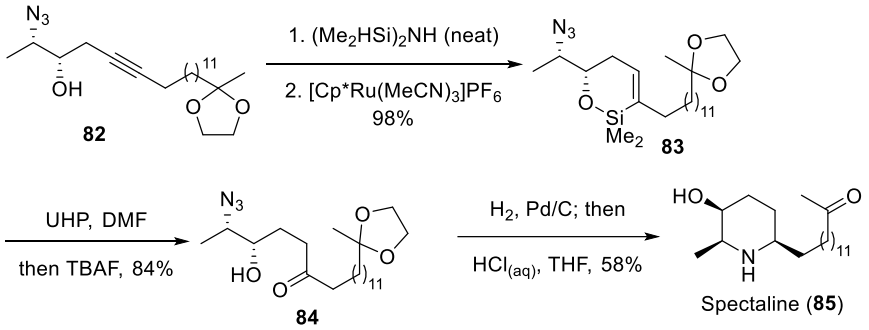
1.3.6 Applications of Cyclic Alkenylsiloxanes in Total Synthesis

Cyclic siloxanes have been applied in a number of natural product total syntheses. For example, the intramolecular cross coupling between the cyclic siloxane and the vinyl iodide in **79** enabled construction of the 9-membered cyclic ether **80** en route to brasilenyne (**81**, Scheme 19).[70] **79** was prepared via RCM of acyclic vinyl siloxane **78**, a process that left the vinyl iodide moiety intact. The subsequent intramolecular Hiyama-Denmark cross-coupling succeeded in forming the medium-sized ring in moderate yield, albeit requiring high catalyst and fluoride loadings and extended reaction times.



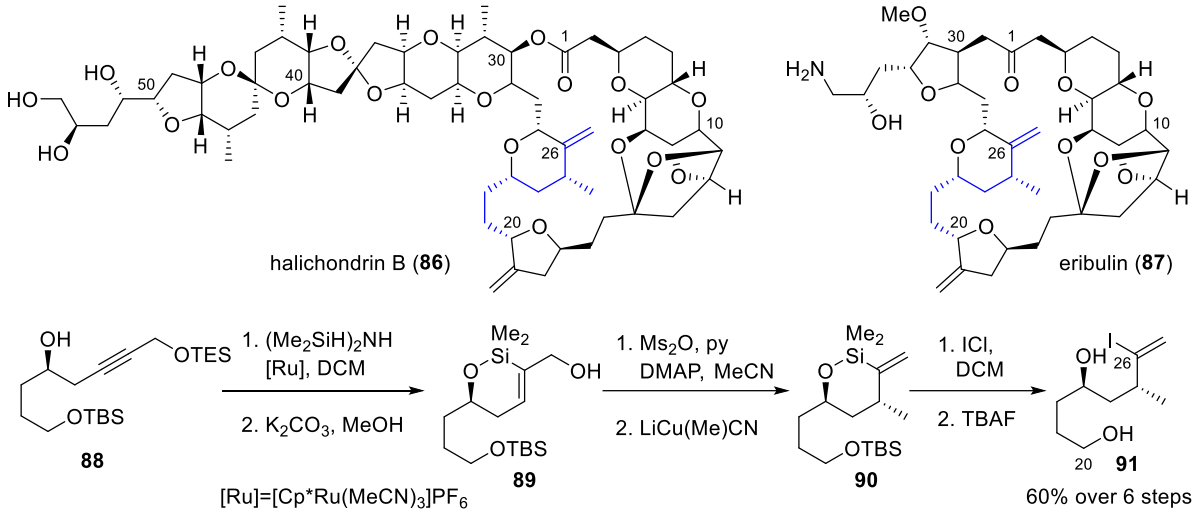
Scheme 19: Synthesis of brasilenyne by Denmark

In 2005, Trost employed cyclic siloxane **83** in the synthesis of the antifungal piperidine alkaloid spectaline (**85**), where it featured as an intermediate in a 3-step intramolecular alkyne hydration (Scheme 20).[77] This elegant sequence enabled the selective formation of 1,4 hydroxy-ketone **84** from homopropargylic alcohol **82**. **84** was then carried through to spectaline in two steps.



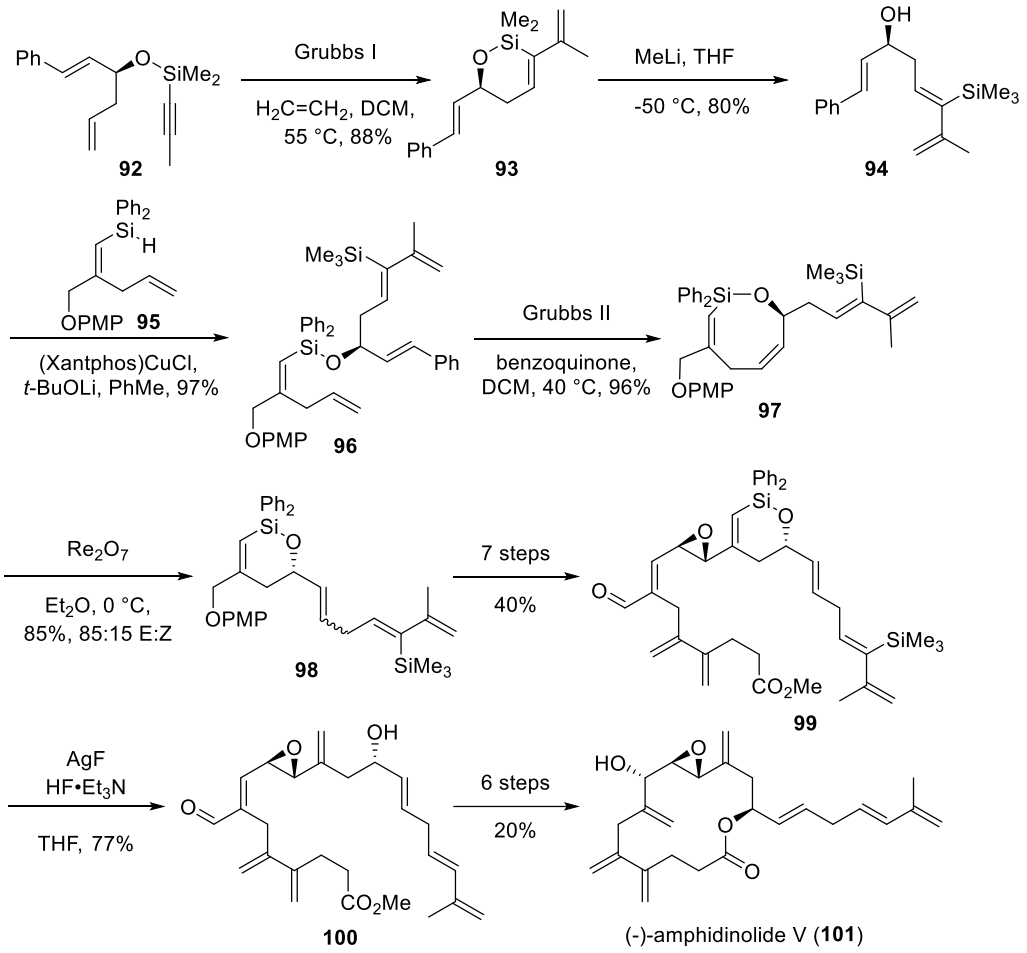
Scheme 20: Synthesis of spectaline by Trost

Kishi made use of cyclic siloxane **89** in his landmark total synthesis of the halochondrins and related natural products when synthesising building block **91** (Scheme 21),[78] which for instance is found in the C23-26 portions of natural product halichondrin B (**86**) and anti-cancer drug eribulin (**87**, Halvaren®).[79] The 6-membered siloxane was assembled by Trosts' intramolecular hydrosilylation methodology, and then used to set the C-25 stereocentre in a highly selective conjugate addition, before being iododesilylated using iodine monochloride and TBAF to yield building block **91**.



Scheme 21: Synthesis of halichondrin B and eribulin by Kishi

In 2013, Lee applied his ene-yne RCM strategy for cyclic siloxane formation to the synthesis of (-)-amphidinolide V (**101**, Scheme 22).[80] Notably, the less reactive Grubbs catalyst is sufficiently reactive to bring about RCM of **92** to **93** whereas ene-ene RCM required Schrock's catalyst (Scheme 19).[81,82] The cyclic siloxane was then opened with methyllithium, a complex silyl ether was appended, and **96** underwent RCM to **97**. Rhenium oxide-catalysed ring contraction afforded another 6-membered cyclic siloxane (**98**), which served as a protecting group (survived: iodo benzoic acid-oxidation, Horner-Wadsworth-Emmonsreaction, DIBAL-reduction, Sharpless asymmetric oxidation, Parikh-Doering-Oxidation, Proline aldol reaction). **99** was later desilylated to reveal the 1,1 disubstituted alkene along with the homoallylic alcohol.



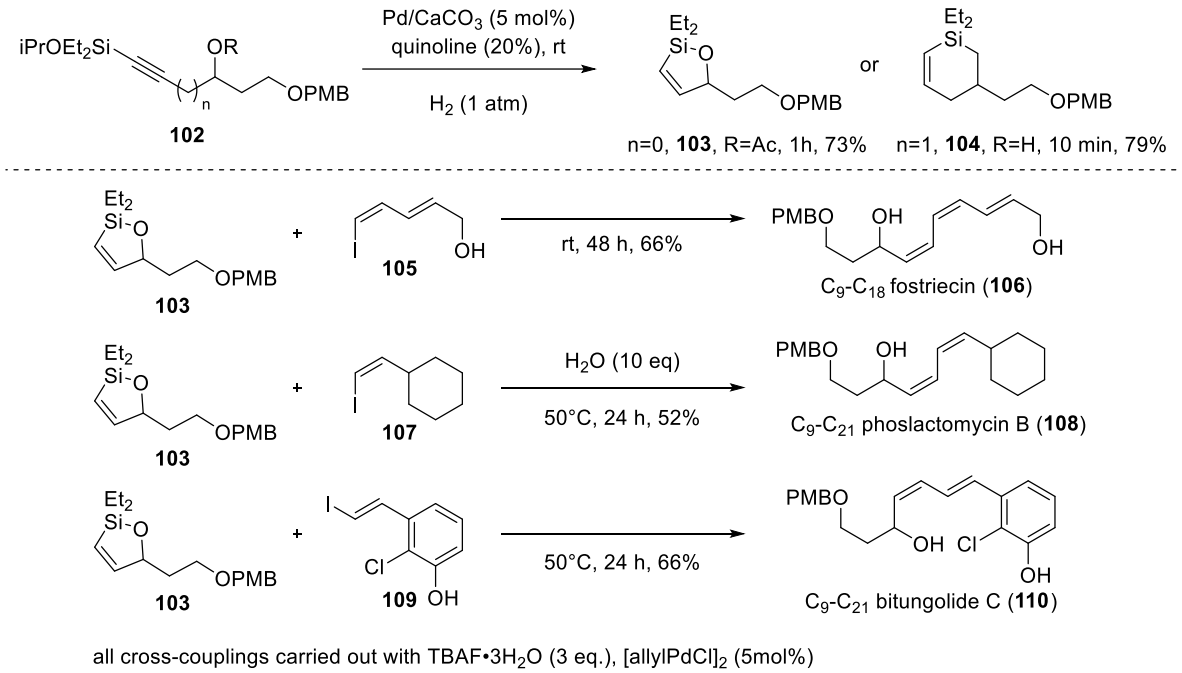
Scheme 22: Synthesis of (-)-amphidinolide V by Lee

1.4 Studies of Cyclic Siloxanes in the Anderson group

1.4.1 Synthesis of Cyclic Alkenylsiloxanes by Semihydrogenation

The versatility of cyclic siloxanes in total synthesis attracted the attention of our research group, which disclosed a convenient route into unsubstituted cyclic siloxanes.[7,50] This motif is particularly useful since it gives specific control over the stereochemistry of a (*Z*) alkene by virtue of the cyclic structure of the siloxane. Polyenes containing α- or β- hydroxy (*Z*)-alkenes are common in bioactive natural products and the efficient synthesis of these motifs is therefore an important goal. To this end, previous DPhil student Elbert developed a Lindlar hydrogenation protocol of isopropoxydiethylsilanes **102** to access both 5- and 6-membered diethyl cyclic siloxanes, which smoothly underwent Hiyama-Denmark cross-coupling to afford a variety of natural product fragments (Scheme 23).[7,50] When coupling **103** with vinyl iodides **107** or **109** heating to 50 °C was required to induce the desired reaction. Furthermore, the water content of the TBAF was found to be important, and in

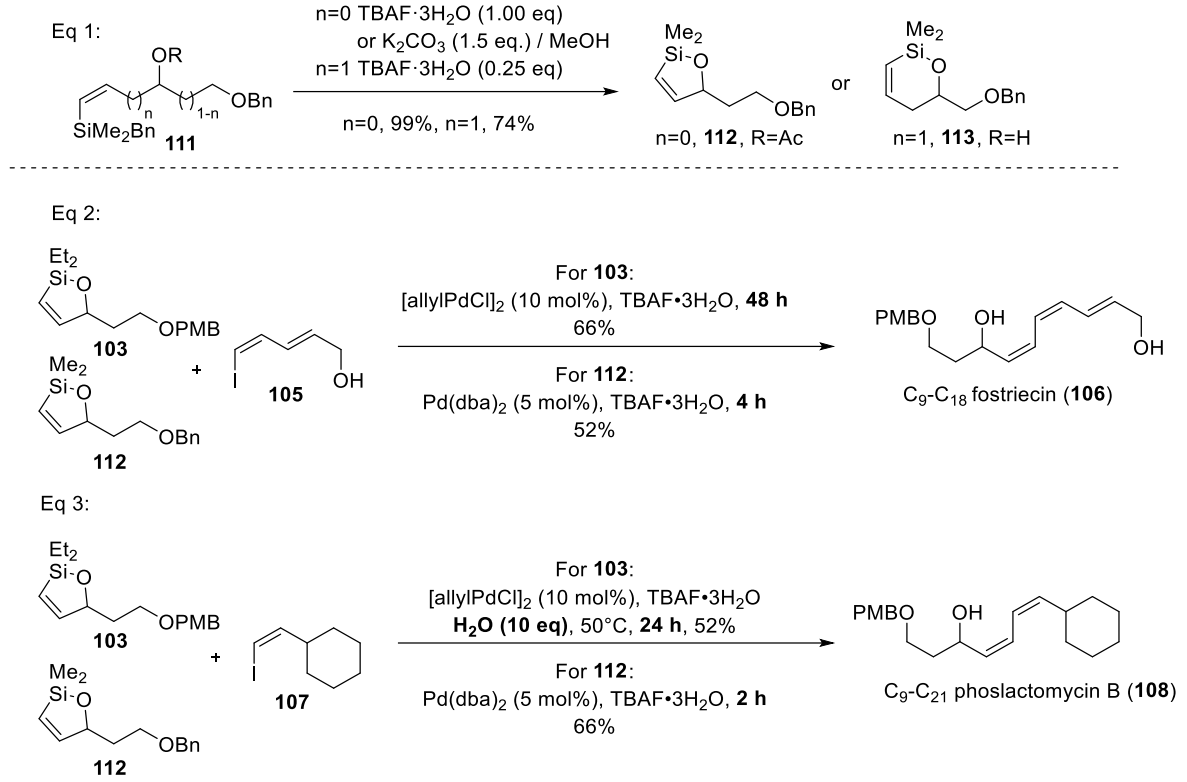
the absence of free alcohols additional water had to be added to reduce the basicity of the fluoride and prevent protodesilylation.[50] However, elevated water concentrations (>10 eq. of water/TBAF) completely inhibited the reaction.



Scheme 23: Lindlar hydrogenation approach for the synthesis of cyclic diethylsiloxanes

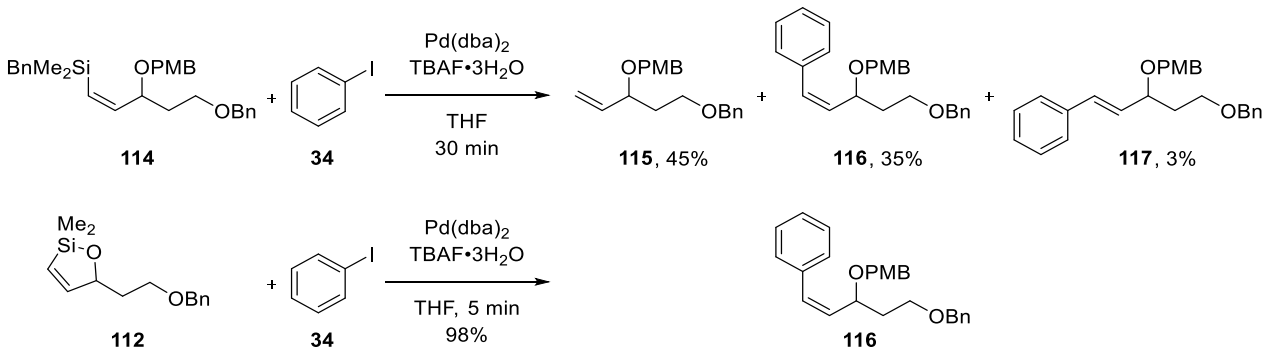
One drawback of this methodology is the somewhat low reactivity of the cyclic diethylsiloxanes in the Hiyama cross-coupling, which manifests itself in long reaction times or the need to heat the reaction to get useful degrees of conversion. A lower degree of steric crowding around the silicon atom might alleviate this problem; however, using the above described methodology for the synthesis of dimethylsiloxanes proved unsuccessful since the corresponding alkynyl isopropoxydimethylsilane is highly hydrolytically sensitive.[50] Subsequent work by Kuper and Gudmundsson addressed this issue: Benzyldimethylsilyl alkynes are more stable than the previously employed alkynyl isopropoxydimethylsilanes and thus readily handled. Furthermore, they proved stable under Lindlar hydrogenation conditions, but the latent silanol could be revealed under a variety of conditions in the case of the 5-membered ring, or via the more traditional TBAF in the case of the 6-membered ring.[83] This discovery paved the way to synthesising both 5- and 6-membered dimethyl cyclic siloxanes, which display remarkably high reactivity (Eq. 1, Scheme 24). It is useful to compare this reactivity of the dimethylsiloxanes to their diethyl analogues: In general, the reaction time is shorter, e.g. 4 h compared to 48 h (Eq 2), and

in the case of coupling to vinyl iodide **107** (Eq 3) neither heating nor the addition of water is required whereas diethylsiloxanes required additional water to avoid protodesilylation.



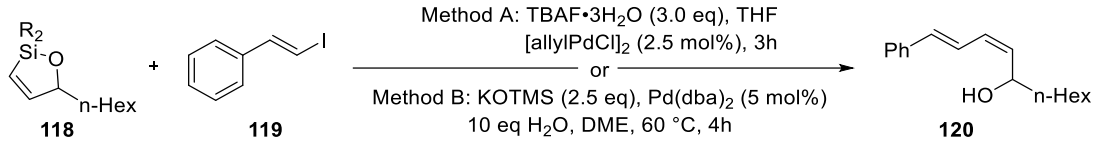
Scheme 24: The synthesis of cyclic dimethylalkenylsiloxanes and comparison of their reactivity

Perhaps surprisingly, it was found that the cyclic nature of the siloxane greatly aided the reaction. In the case of acyclic benzyldimethylsilane **114** the optimised conditions resulted in significant amounts of protodesilylation (45%) along with the desired (*Z*, 35%) and isomerised (*E*, 3%) product, compared to 98% yield of the desired product after 5 minutes in the case of the cyclic siloxane **112** (Scheme 25).



Scheme 25: Control experiment: is the cyclic structure important?

Further investigations into how the substituents on silicon influence the reactivity reiterated the stated trend: a higher degree of steric bulk lessens reactivity irrespective of whether TBAF or KOTMS is used as the activator (Scheme 26).

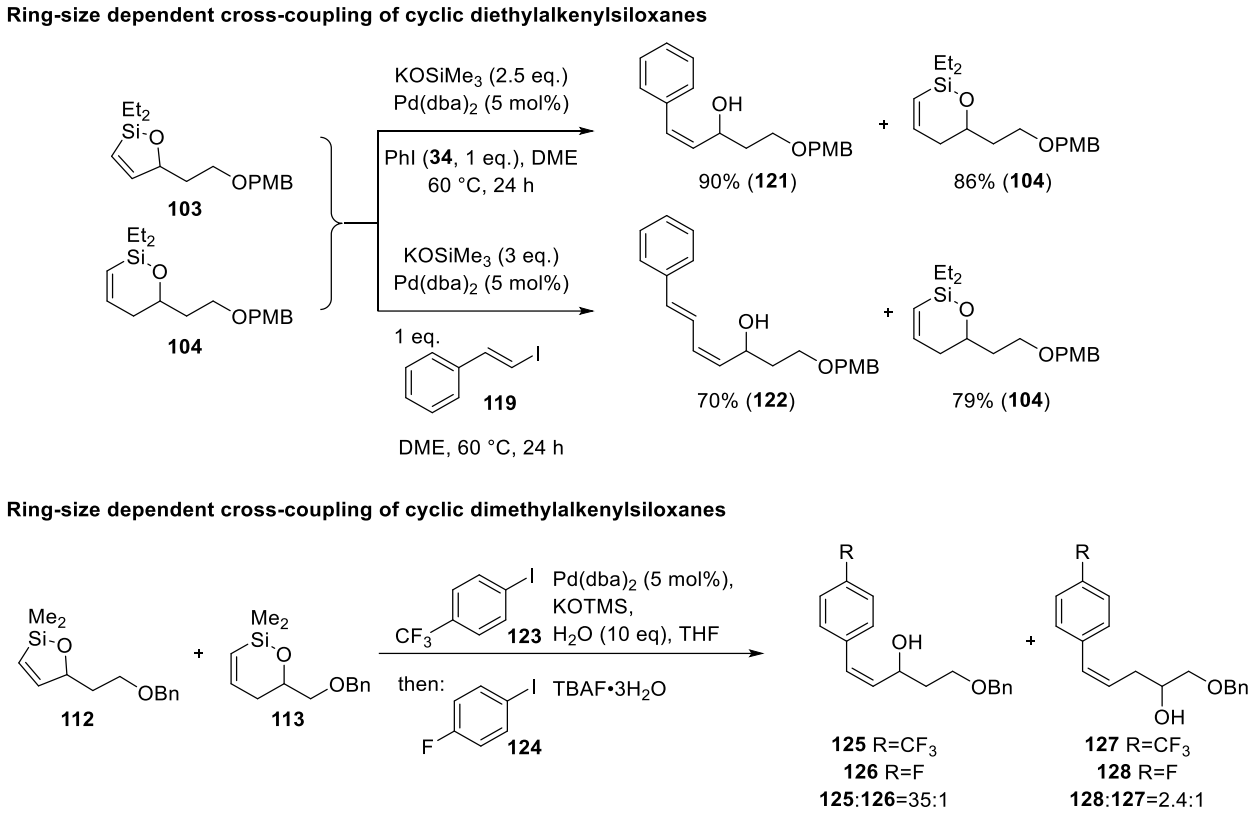


R	Yield (method A)	Yield (method B)
Me	61% (3 h)	43 % (4 h)
Et	60% (24 h)	54 % (24 h)
i-Pr	33% (24 h)	25% (24 h)

Scheme 26: Comparison of the reactivity of cyclic dialkylsiloxanes with different dialkyl groups

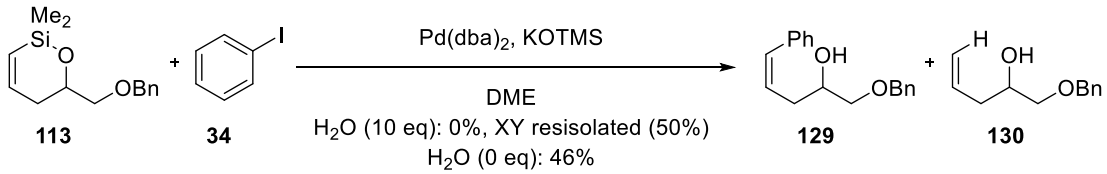
1.4.2 Ring-size Dependent Cross-coupling

Earlier investigations of the diethylsiloxanes found that 5- membered siloxane **103** cross-coupled selectively with either **34** or **119** in the presence of its 6-membered homologue to afford **121** and **122** as the only products, while the 6-membered siloxane could be reisolated in good yield (Scheme 27).[7] Further work by Kuper seemed to confirm this selectivity for the respective cyclic dimethylsiloxanes, although both five- and six-membered dimethylsiloxanes were reactive in the presence of KOTMS and water (10 eq). Still, the 5-membered siloxane transmetallated at a higher rate than its 6-membered homologue, giving rise to a 35:1 selectivity of **125** to **126**, indicating full consumption of the 5-membered siloxane before addition of the second aryl iodide. Addition of TBAF and a second aryl iodide then led to some product formation in modest selectivity **128** : **127** = 2.4 :1. This NMR study highlighted the feasibility of this concept although no isolated yields were obtained.



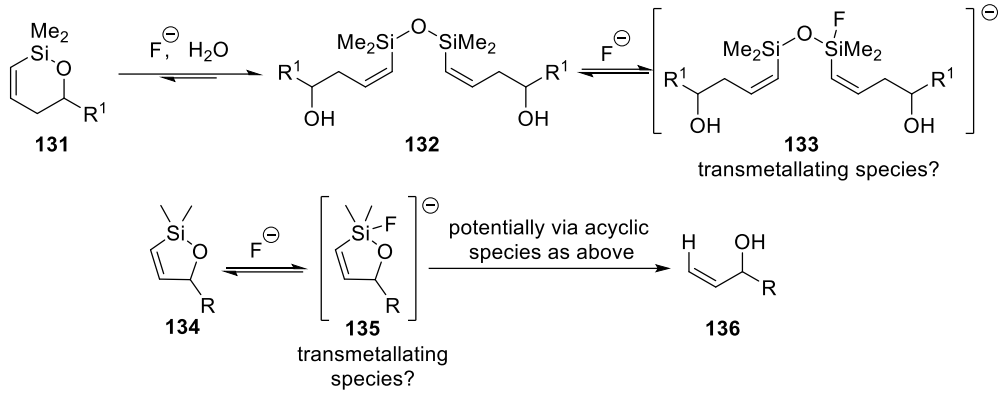
Scheme 27: Ring-size dependent cross-coupling of cyclic dimethyl- and diethylsiloxanes

The cross-coupling of the 6-membered dimethylsiloxane **113** with KOTMS activator was studied in further detail and revealed a strong dependency on the water concentration (Scheme 28): with no added water yields of 46% were achieved, while additional water lowered the yield until the reaction completely shut down at 10 equivalents of water. In the presence of 10 equivalents of water, starting material **113** could be reisolated in 50% yield, which is notably lower than in case of the respective diethylsiloxane.



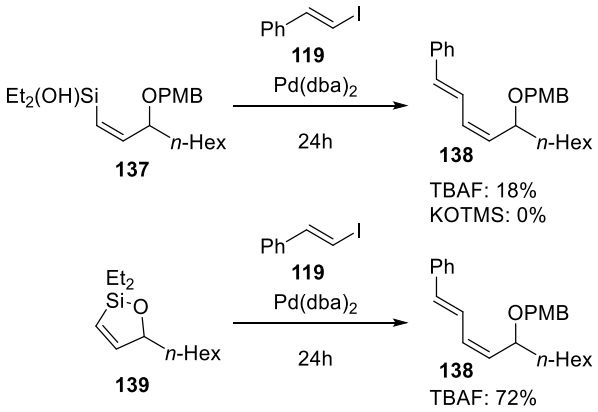
Scheme 28: Impact of water content on the KOTMS mediated cross-coupling of 6-membered cyclic dimethylalkenylsiloxanes

The mechanistic underpinning for the observed selectivity is not entirely clear despite extensive investigation. NMR spectroscopic observations indicate the rapid establishment of an equilibrium of cyclic and acyclic siloxane species in case of the 6-membered dimethylsiloxane. ECC-DOSY (External Calibration Curve Diffusion Ordered SpectroscopY) experiments showed the acyclic siloxane to be disiloxane **132** for 6-membered siloxane **131**. In the case of 5-membered **134**, this experiment was unsuccessful because of rapid (on ECC-DOSY timescale) desilylation of the (a)cyclic silanol and/or disiloxane (Scheme 29).



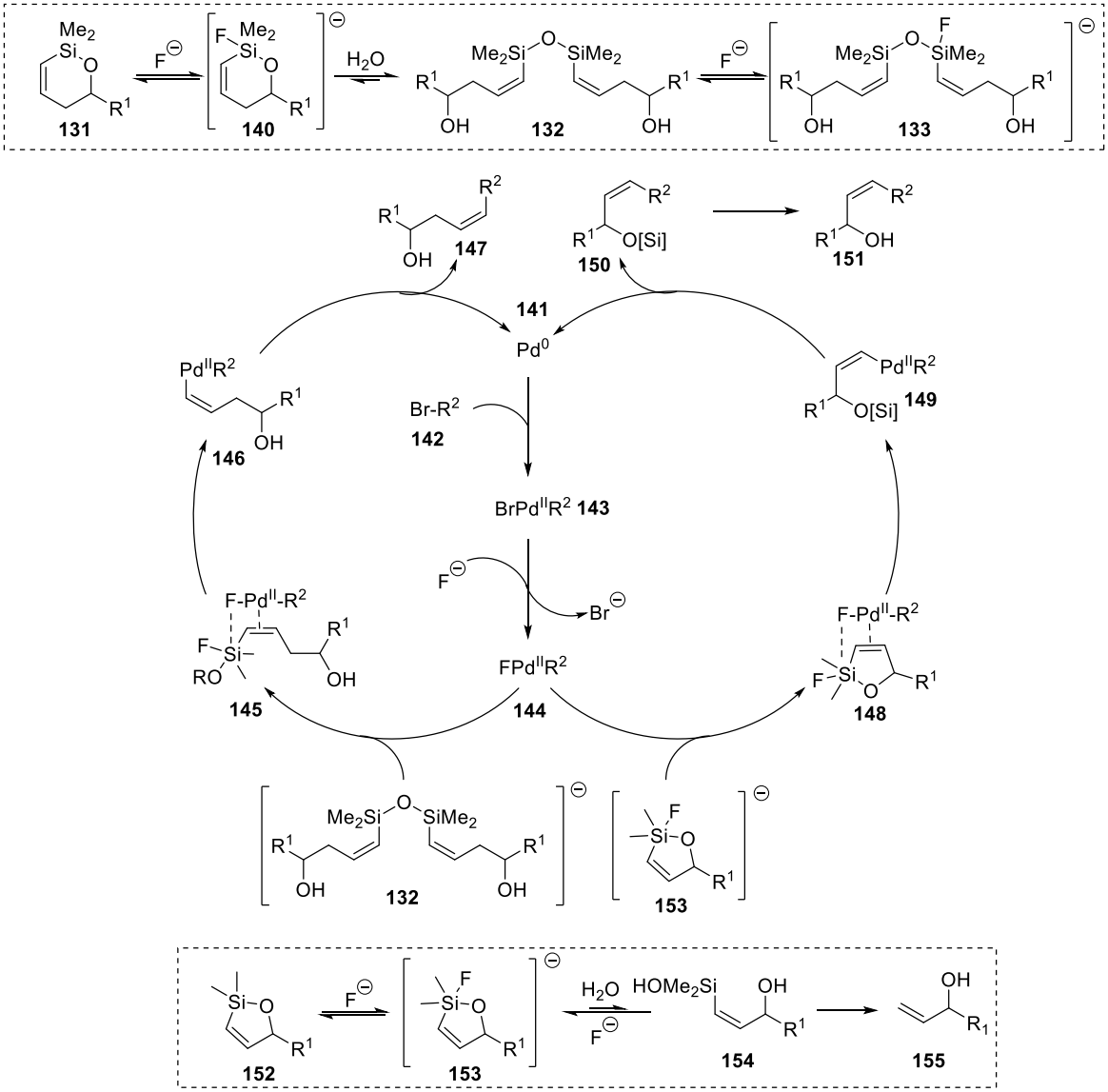
Scheme 29: Possible transmetallating species for 5- and 6-membered cyclic dimethylsiloxanes

Based on control experiments using a necessarily acyclic (*Z*)-alkenylsilanol, a cyclic ate species is thought to be the active transmetallating species in the Hiyama-Denmark cross-coupling of cyclic 5-membered dialkylsiloxanes (Scheme 30):[83,84] Coupling of **137** in the presence of TBAF proceeds sluggishly (18% yield) and with KOTMS not at all (similar to the respective dimethyl species, Scheme 25), whereas coupling of the cyclic diethylsiloxane species is high yielding (24 h, 72%).



Scheme 30:Control experiment: is the cyclic structure important?

Based on the above evidence, it was suggested that the species involved in the transmetallation process are (5-membered ring ate) **153** and (6-disiloxane acyclic ate) **133** (Scheme 31). The 5-membered ate complex was proposed since it forms readily in presence of TBAF and should be more reactive than the uncharged cyclic siloxane (Denmark's NMR studies, see 1.4.4). Transmetallation via the acyclic disiloxane was ruled out due to the poor reactivity of the (*Z*)-alkenylsilanol (Scheme 25 and Scheme 30). In the case of the 6-membered dialkylsiloxane, rapid ring-opening and formation of disiloxane **132** was observed, hence transmetallation via its respective ate complex was proposed. Selectivity in transmetallation could then be accounted for by virtue of the cyclic 'ate' complex's higher reactivity compared to the acyclic one. Arguments for this are for instance the stronger electron withdrawing character of the oxygen in the cyclic siloxane (1 O/1 Si vs 1O/2Si) and the forced cyclic conformation resulting in poorer orbital overlap than in the acyclic case ($\pi_{C\text{-}C} \rightarrow \sigma^*_{C\text{-}O}$) making the alkene relatively electron-rich and thus facilitating transmetallation. Critically though, no ate complex whether cyclic or acyclic could ever be experimentally identified. Whether ate complexes are actually involved in the transmetallation (as proposed by Denmark, chapter 1.3.2) or whether the uncharged species transmetallates (suggested by Hiyama and Jutand, 1.4.4) is unknown. The arguments made are true regardless of this detail and the suggested mechanism is a good working hypothesis to explain the observed selectivity.

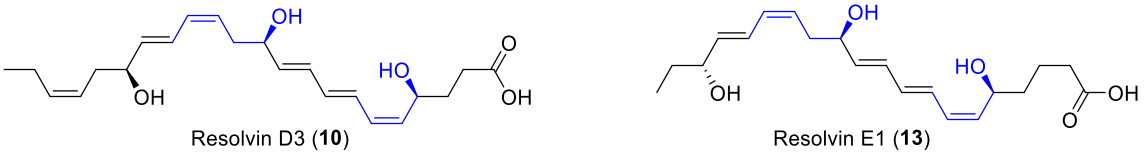


Scheme 31: Mechanistic proposal for the cross-coupling of cyclic dimethylsiloxanes by Kuper

However, it should be pointed out that alternative mechanisms have not been disproven. For instance, direct transmetallation of the 6-membered cyclic siloxane **131** (which is in equilibrium with disiloxane **132**) and not its disiloxane derivative with a R-Pd-F complex is also possible. Finally, the reactivity of the acyclic alcohol of the 5-membered siloxane might be distinct from the PMB-protected surrogate investigated in Scheme 25 and Scheme 30. Productive Hiyama-Denmark cross-couplings of alkenylsiloxanes are known (chapter 1.4.5) and a ring-opened species of the 5-membered siloxane might yet play a role in this transformation.

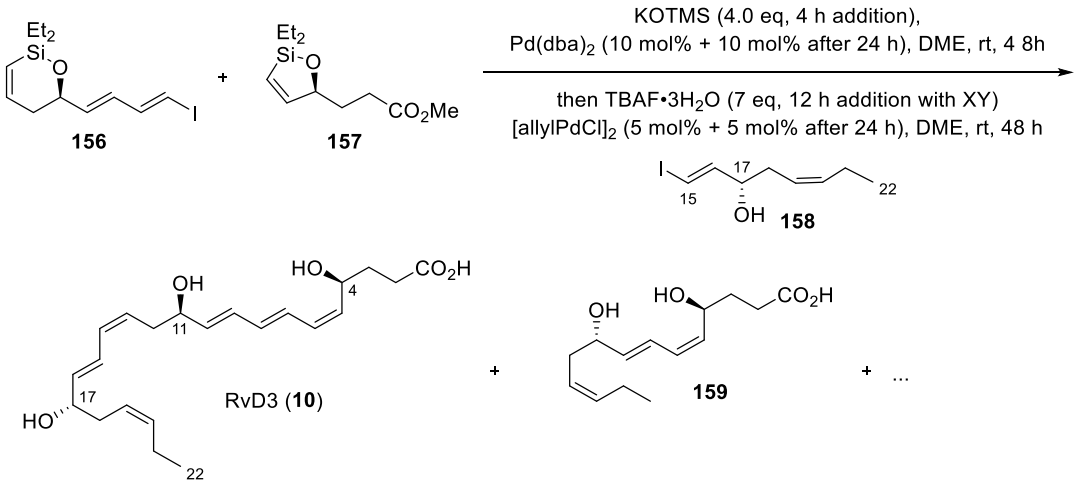
1.5 Aim of the Project

We wanted to test the ring-size dependent cross-coupling of cyclic siloxanes in the arena of natural product synthesis. Resolvins D3 (**10**) and E1 (**13**) presented themselves as ideal targets as they contain both (*Z*) allylic and homoallylic alcohol motifs, which could be derived from 5- and 6-membered cyclic siloxanes respectively (Scheme 32).[50]



Scheme 32: Structure of resolvins D3 and E1

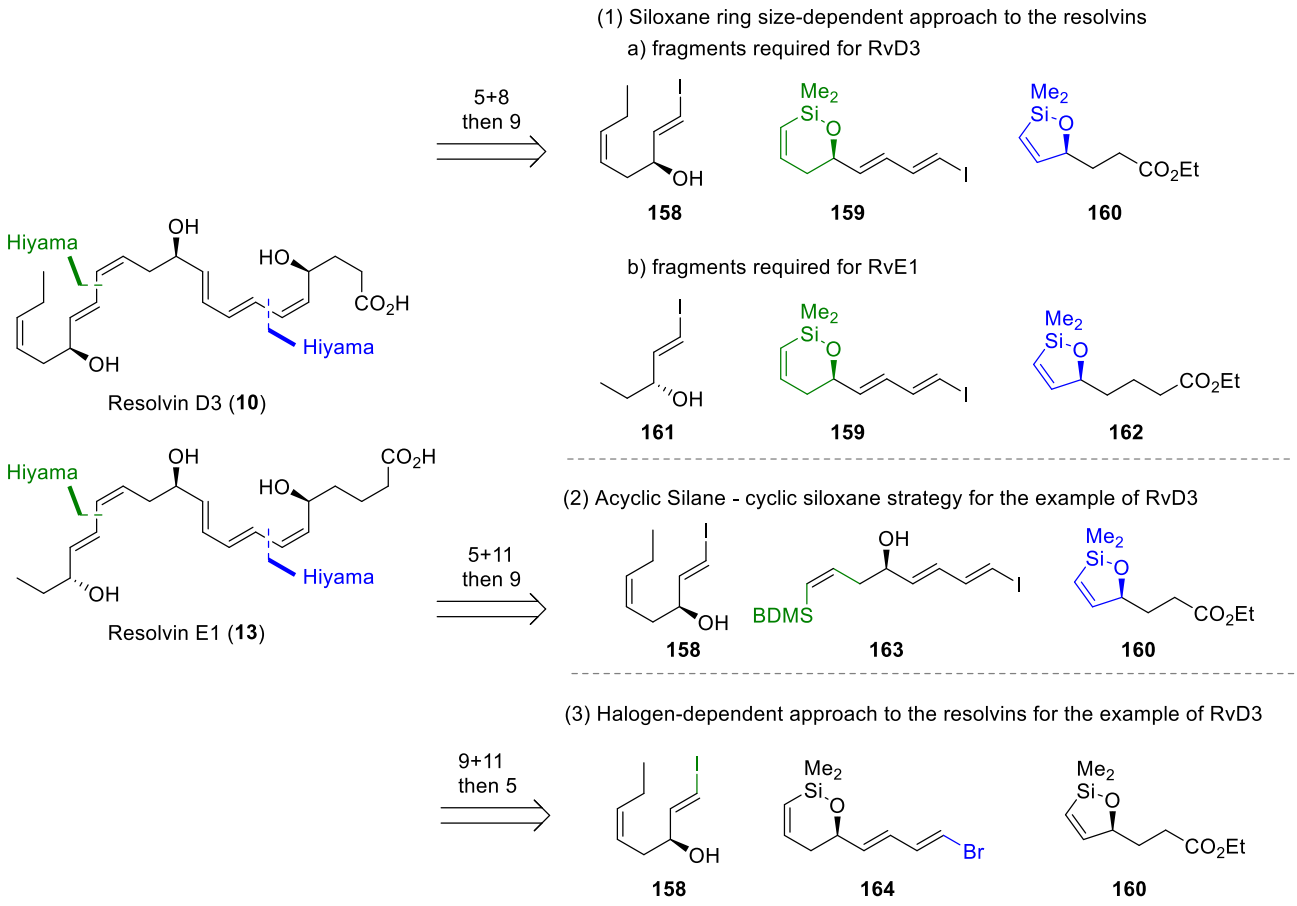
The main appeal of this approach lies in the possibility of a one-pot fragment union in the last step, which would allow for a more convergent synthesis than previous work in the field. In earlier group work, an attempt at synthesising resolvin D3 (**10**) using diethylsiloxanes was made by Elbert.[50] Initially, 5-membered siloxane **157** and 6-membered siloxane **156** were prepared and subjected to cross-coupling promoted by KOTMS to effect formation of the C6/C7 bond, before adding fragment **158** and TBAF to couple the 6-membered siloxane in the same pot (Scheme 33). Due to the presence of numerous impurities, including excess amounts of TBAF, analysis of the reaction mixture was inconclusive, and it is uncertain as to whether RvD3 was formed.



Scheme 33: Elbert's attempt at the synthesis of resolvin D3 using cyclic diethylsiloxanes

Since Elbert's work on cyclic diethylsiloxanes, DPhil students Gudmundsson and Kuper developed cyclic dimethylsiloxanes as a higher yielding and more reactive alternative.[83,84]

These developments prompted a re-examination of the syntheses of RvD3 (**10**) and RvE1 (**13**). We anticipated there to be chemoselectivity differences in the *transmetallation* of cyclic (5 or 6-membered) and acyclic dimethylalkenylsiloxanes, and the following strategies for the construction of resolvins were envisaged (Scheme 34): (1) selective coupling of the 5-membered cyclic siloxane **160** with vinyl iodide **159** and (2) selective coupling of **160** with the acyclic silane **163**. An alternative "fall-back" strategy (3) would exploit the established chemoselectivity differences of a vinyl iodide and bromide in oxidative addtion.[85–89]



Scheme 34: Proposed syntheses of resolvins D3 and E1

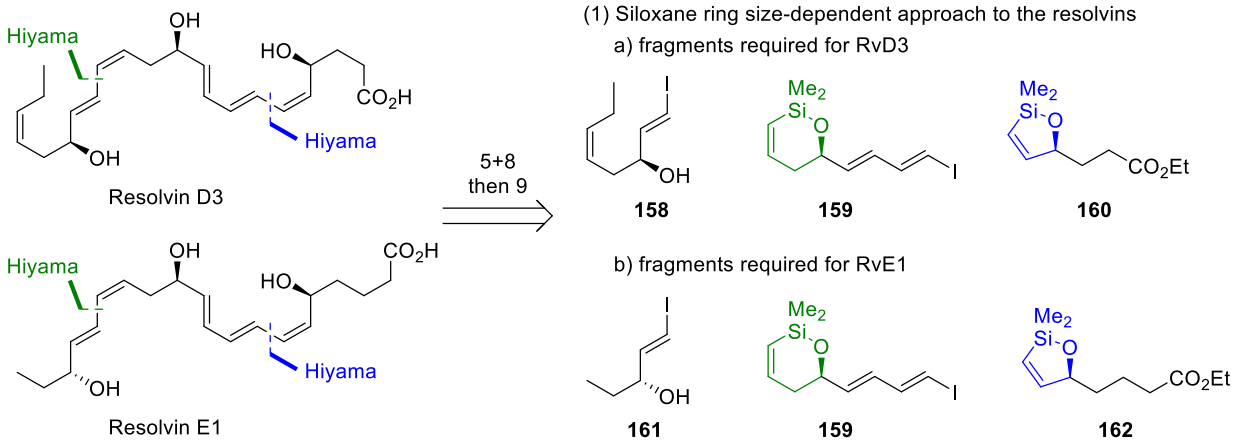
The modularity of the depicted synthetic approach would allow for the combination of different fragments and could provide a library of resolvin analogues that could be screened in biological assays. As was noted in section 1.2, very subtle differences in the chain lengths and the degree of hydroxylation greatly impact the potency of these lipid-mediators. The preparation of resolvins that contain an odd-number of carbons would be interesting, as these have not been synthesised to date and are not accessible via biosynthesis. Furthermore, a systematic study of the stereochemistry of the different

alcohols and their impact on the anti-inflammatory activity is yet to be carried out. Only in the case of RvE1 and RvD3 it is known that the C17-epimers AT-RvE1 and AT-RvD3 possess similar activity.

2 Synthesis of Resolvin D3

2.1 Ring-size Dependent Cross-coupling

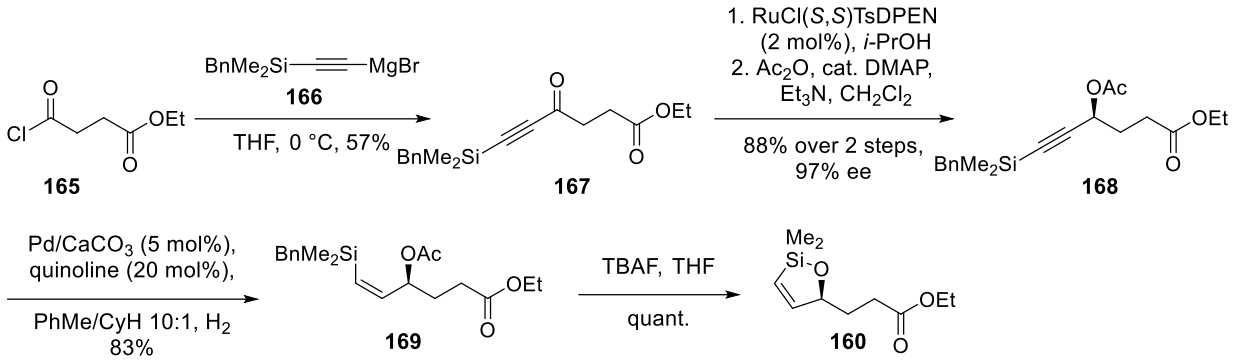
This chapter focusses on establishing a viable strategy for resolvin synthesis. The first tactic to be studied involved a ring-size dependent cross-coupling (Scheme 35), whereby the rate of transmetallation of the 5-membered cyclic siloxane **160** to palladium was anticipated to outcompete that of the 6-membered analogue **159**.



Scheme 35: Ring-size dependent cross-coupling

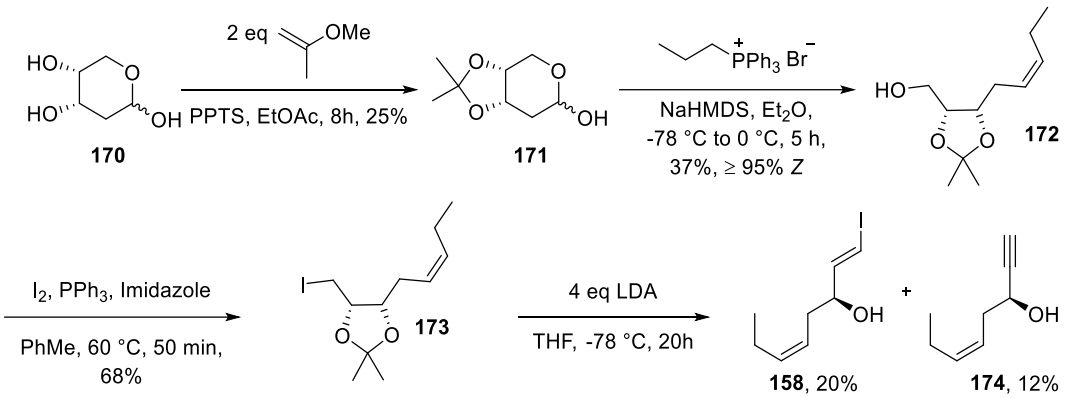
2.1.1 Preparation of Right-hand, Middle and Left-hand Fragments for Resolvin D3

The synthesis of right-hand fragment **160** began with reaction of alkynyl Grignard **166** (prepared from the alkyne using MeMgBr) with acid chloride **165** to give ketone **167** in 57% yield (Scheme 36). This was converted to the enantioenriched propargylic acetate **168** through Noyori asymmetric transfer hydrogenation (97% *ee*)[90] and esterification of the resulting alcohol, which is crucial for achieving high (*Z*)-selectivity in the subsequent Lindlar reduction.[7,91] In the event, semi-hydrogenation to the (*Z*)-benzyldimethylalkenylsilane **169** proceeded with high yield and selectivity (83%, *Z*:*E* > 20:1). The alkenylsilane was then treated with TBAF, which effected debenzylation, *in situ* deacetylation and cyclisation to give the cyclic 5-membered siloxane **160** in quantitative yield. Only an aqueous work-up was required for purification of the silacycle **160**, which is unstable to chromatography.



Scheme 36: Synthesis of 5-membered siloxane **160**

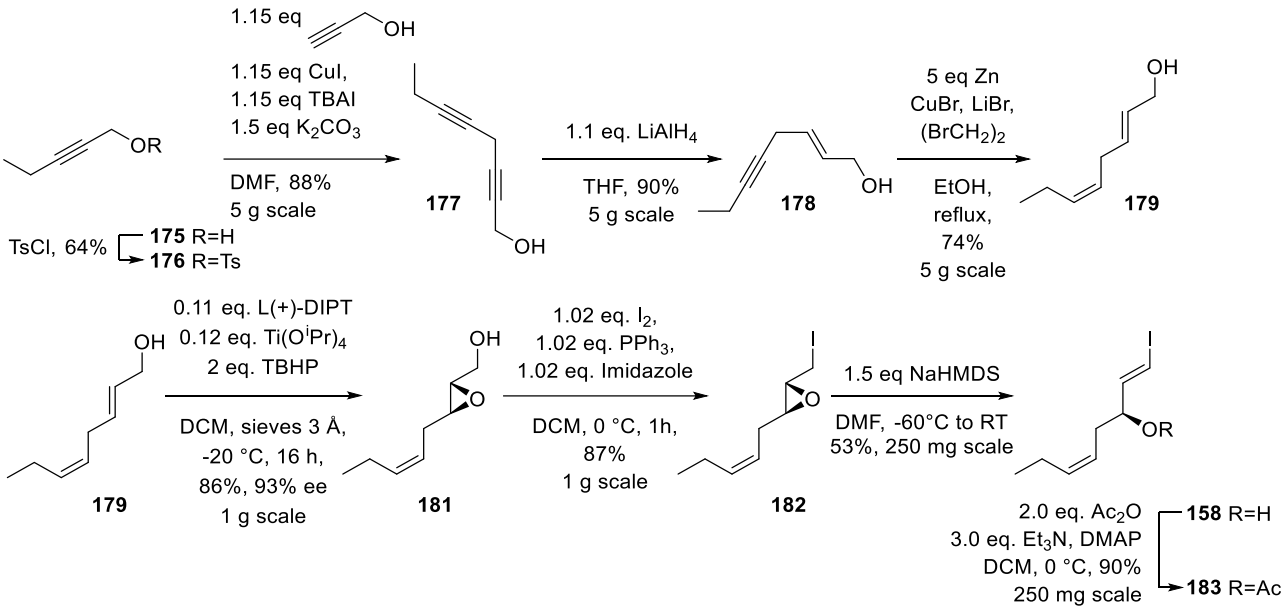
The synthesis of the left-hand fragment **158** followed a previous report by Spur (Scheme 37).[25] Readily available 2-desoxyribose **170** was protected as its acetonide **171**, and subsequently reacted with a non-stabilised propyl ylide to afford (*Z*)-configured alcohol **172** as the only product. An Appel reaction transformed **172** into the corresponding iodide **173,** which underwent elimination to the corresponding vinyl iodide **20** when treated with LDA. Building block **20** was obtained in 1% overall yield over 4 steps.



Scheme 37: Synthesis of **158** using Spur's strategy

To continue our studies, we required ready access to large amounts (up to 1 g) of fragment **158**. Unfortunately, the original route described by Spur (Scheme 37) was not effective on large scale. This was attributed to a low yielding final step (**173** to **158**), whereby alkyne **174** was observed to form from **173** and was difficult to separate from **158**. A further drawback is that the chiral pool starting material is only available in one enantiomeric series. We therefore envisaged an alternative procedure in which the absolute configuration could be controlled using Sharpless asymmetric epoxidation (SAE). This strategy was previously reported by Spur in his RvD6 synthesis, and we embarked on investigating the scalability of this route.[34,92]

The synthesis of iodide **158** now instead began with a copper-catalysed substitution of tosylate **176** with propargyl alcohol to afford the skipped diyne **177** in 88% yield (on up to 5g scale, Scheme 38).[34] The subsequent reduction using $LiAlH_4$ was chemo- and stereoselective for the formation of (*E*)-allylic alcohol **179** (>20:1 dr).[93] In contrast, the reported Lindlar reduction to transform the remaining alkyne into the (*Z*)-alkene was not fully selective, a result that has also been observed by other researchers.[94] Fortunately, Brandsma's activated-zinc reduction gave the (2*E*,5*Z*) product **180** exclusively.[95] Sharpless epoxidation proceeded in good yield and enantioselectivity (determined by HPLC analysis of the benzoate, assignment of enantiomeric series in analogy to previous reports),[34] and the resulting alcohol **181** was transformed into the corresponding iodide **182** via an Appel reaction. Finally, NaHMDS mediated isomerisation of iodoepoxide **182** afforded the desired product **158** in moderate yield.[92] Acetate **183** was also prepared for use in later studies.

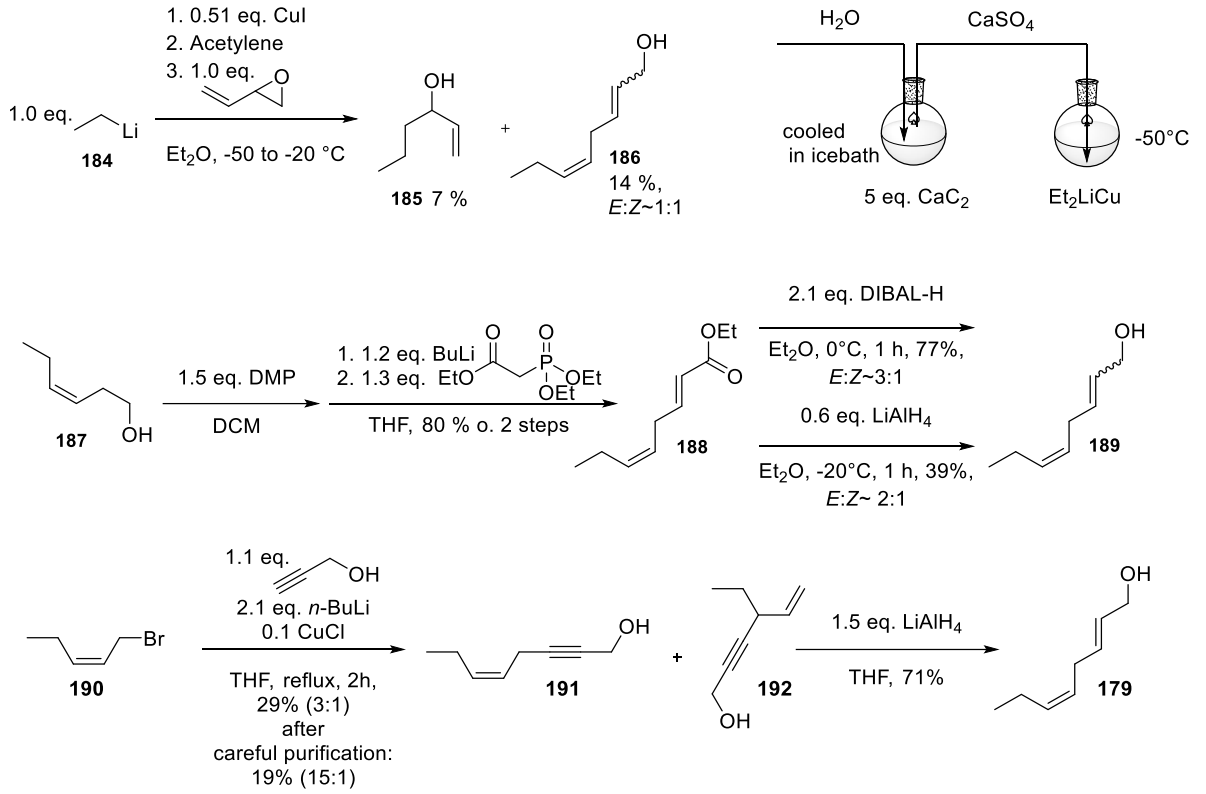


Scheme 38: Synthesis of **158** via iodoepoxide fragmentation

Other ways of synthesising the skipped diene **179** are known; however, they proved either impractical or lower yielding (Scheme 39). Carbocupration of acetylene, followed by S_N2' opening of 3,4-epoxy-1-butene, is an attractive, one-step procedure for the preparation of **179**;[96] however, departmental safety regulations prohibited direct access to acetylene. An alternative, *in situ* generation of acetylene from calcium carbide according to the experimental arrangement in Scheme 39 was attempted, but the reported results could not be replicated under these conditions.

Meshram obtained **179** by reduction of ethyl ester **188**, prepared by HWE reaction of 3-hexanal (**187**).[97] The reported conditions for this reduction led to partial isomerisation of the indicated alkene (*E*:*Z*=3:1) and employing $LiAlH_4$ did not improve this ratio (*E*:*Z*=2:1). It is possible that solvent variation and/or lower temperatures would have afforded the stereochemically pure product, but this reaction was not investigated further.

Finally, methylmagnesium chloride/copper chloride mediated nucleophilic substitution of alkenyl bromide **190** by propargyl alcohol led to a mixture of S_N2 (**191**) and S_N2' (**192**) products in a 3:1 ratio (29%).[98] This ratio could be enhanced by careful purification by column chromatography (15:1, 19%) and finally reduction of the acetylenic alkene (by $LiAlH_4$ afforded the desired product.



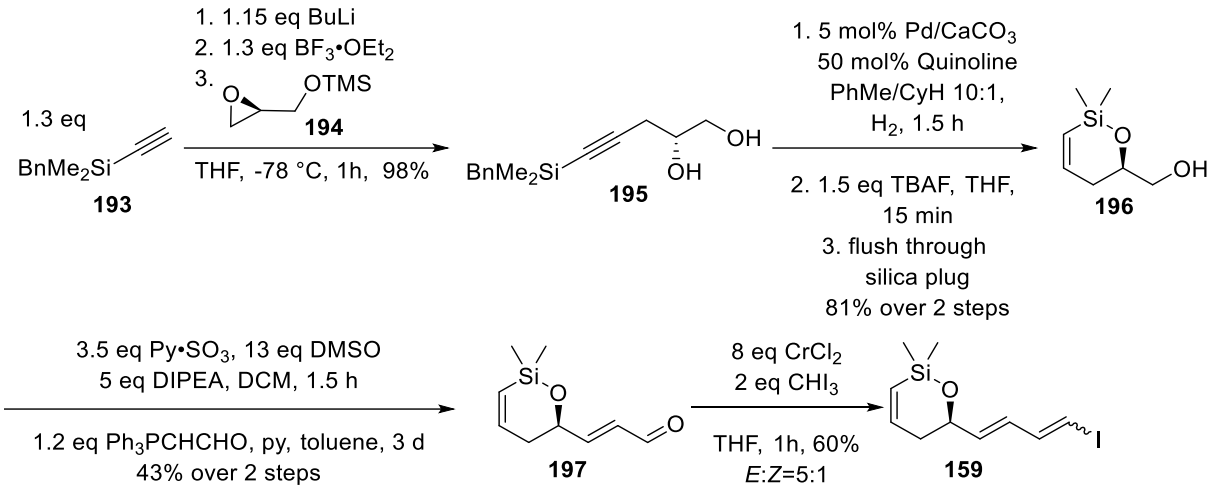
Scheme 39: Alternative routes for the preparation of **179**

For the synthesis of middle fragment **159**, a variation of a previous route by Elbert was employed, starting with temporary protection of (*S*)-glycidol as the TMS ether **194**.[50] At low temperature, this silyl ether was stable to addition of the BF_3 complex of benzyldimethylacetylide,[99] but was readily cleaved upon acidic workup to diol **195** in excellent yield (Scheme 40). Lindlar hydrogenation of the resulting alkyne (**195**) in presence of 50 mol% quinoline provided the alkene (**196**) in good diastereoselectivity (Z:E=15:1). The catalyst was filtered off and the crude reaction mixture stirred with 1.5

equivalents of TBAF to yield cyclic alkenylsiloxane **196** in 81% yield over 2 steps. Although the cleavage of benzyldimethylsilanes is typically catalytic in fluoride (Scheme 24), it was found that, in this case, substoichiometric amounts of TBAF led to sluggish cyclisation and concomitant desilylation. Whereas the slow conversion can be likely traced to coordination of fluoride to the diol resulting in a decrease of its nucleophilicity,[100] the origins of desilylation remain unclear, although it can be speculated that the extended reaction time contributes to this observation.

Parikh-Doering oxidation of **196** afforded its aldehyde, which was unstable to silica gel and used directly in a Wittig olefination to give enal **197**, which displayed greater stability and could be purified by chromatography. Here, a serendipitous discovery was made – residual pyridine from the oxidation step improved the yield of the olefination from 32% to 52% (43% from **196**). The homologation to the α,β-unsaturated aldehyde **196** required precise amounts of (Triphenylphosphoranylidene)-acetaldehyde and the consumption of the starting material was monitored by ^{1}H-NMR spectroscopy of aliquots (0.05 ml). Additional portions of the Wittig reagent were added until the starting material was consumed to afford a 1:0.07 mixture of the desired product (only *E*) and separable bis-homologated aldehyde. Whilst the Wittig reaction provided excellent control over the geometric isomers, the subsequent Takai-olefination afforded an inseparable 5:1 *E*:*Z* mixture of vinyl iodide **159** in 60 % yield.

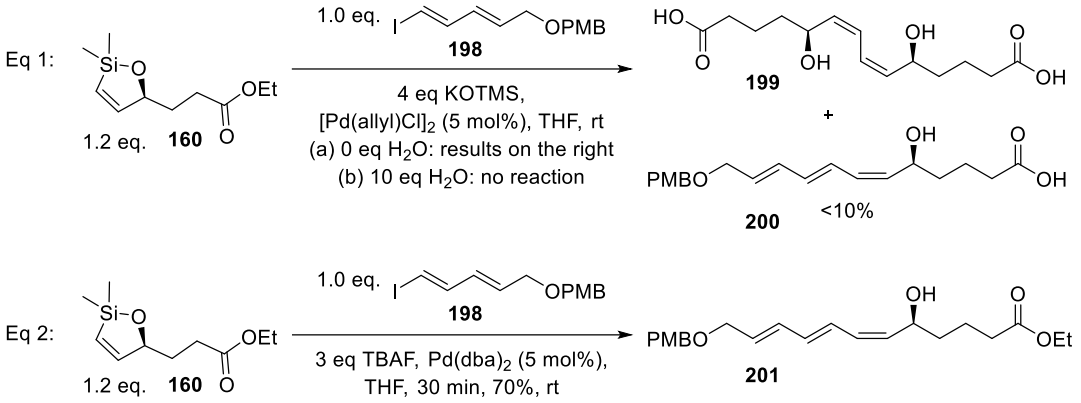
All 6 membered cyclic alkenylsiloxane compounds prepared here were slightly unstable to silica gel, resulting in streaking on the column and a reduced yield by about 20-30% per chromatographic separation. This was noted especially in case of aldehyde **197**, which was difficult to purify from its ‘double-Wittig’ homologue and could require multiple chromatographic purifications. Neither different solvent systems nor the addition of triethylamine could circumvent this problem. Thus, the reaction mixture was used crude whenever possible or was eluted quickly through as short a silica column as possible.



Scheme 40: Synthesis of **159** from (*S*)-TMS-glycidol

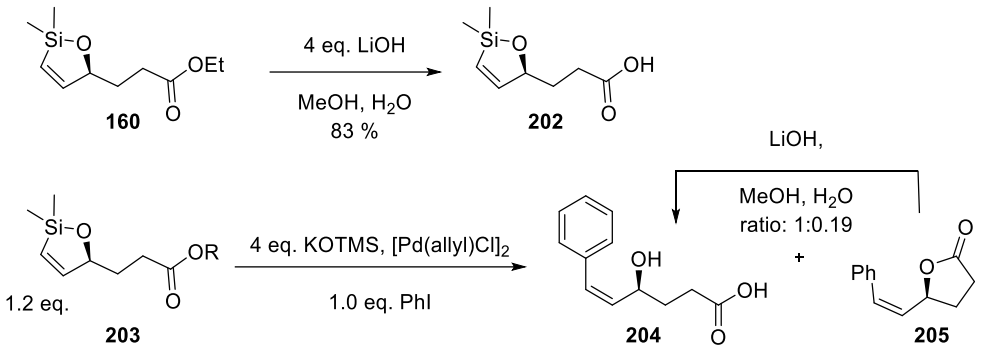
2.1.2 Cross-coupling of Middle Fragment 159 and Right-hand Fragment 160

Before studying the coupling of middle fragment **159** with the right-hand fragment **160**, we first wanted to study the reactivity of **160** separately. A model coupling between the 5-membered cyclic siloxane **160** and the vinyl iodide **198**, using KOTMS as the activator (Eq 1 (a)), afforded a mixture of silane homocoupling product **199** and the hydrolysed cross-coupling product (**200**) in low yield; evidently, the ester was readily hydrolysed under the reaction conditions (Scheme 41). Earlier studies suggested (Scheme 27) that the addition of 10 eq water would be necessary to achieve ring-size dependent selectivity in the cross-coupling step. However, this caused the reaction to stall completely even though the ester hydrolysis seemed to be suppressed (Eq 1 (b)); the 5-membered cyclic siloxane was unchanged, as judged by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Finally, the desired cross-coupling was achieved using TBAF as the activator in 70% yield (experiment carried out by DPhil student Sear). However, for this activator no conditions were identified that induce a rate-difference in the transmetallation of 5- against 6-membered cyclic siloxanes.



Scheme 41: Cross-coupling of **160** with dienyliodides using KOTMS as activator (Eq 2 by C. Sear)

Given that hydrolysis of the ethyl ester of **160** was observed when using KOTMS as activator, we investigated how a carboxylic acid functionality would influence the efficiency of the coupling and prepared **202** by hydrolysis (Table 1). In this case, coupling of **203** with iodobenzene, with KOTMS as activator and $[Pd(allyl)Cl]_2$ as catalyst proceeded well with or without 10 eq water (this amount was shown to be necessary to achieve ring-size dependent cross-coupling for aryl iodides);[83] however, in case of the carboxylic acid **202**, additional water was required. Concomitant lactonisation was observed to a similar degree in all cases, with <10% formation of **205** generally observed. It is confusing why the cross-couplings of **203** with iodobenzene proceeded well when using KOTMS as the activator, yet vinyl iodides are not well tolerated under those conditions (see Scheme 41). Potential issues could be: differences in speed of the elementary steps of the catalytic cycle (oxidative addition, transmetallation, reductive elimination) or elimination side-reactions of the vinyl halide.

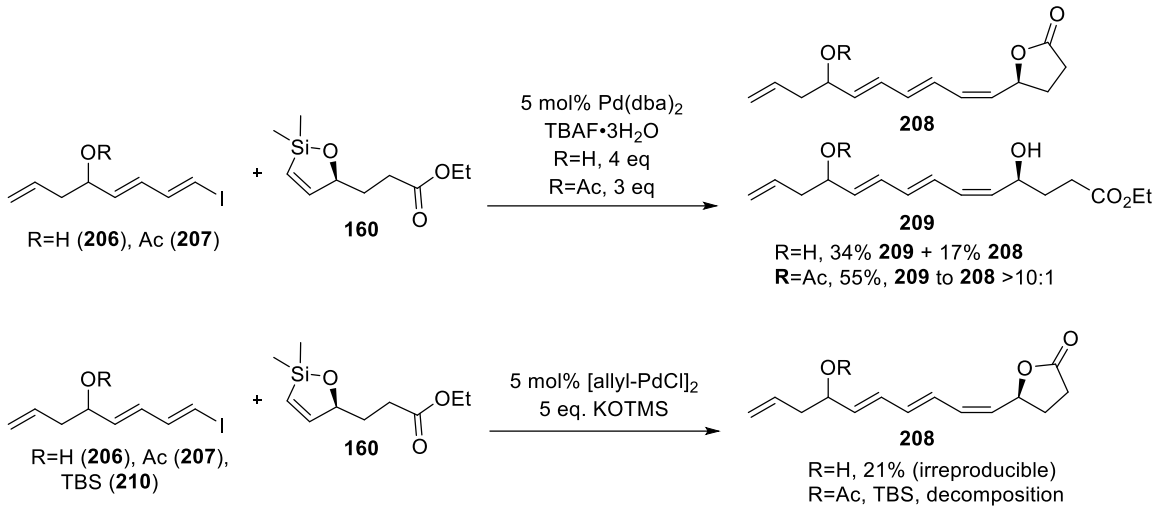


R	Added water	Yield	Ratio of products
Et	0	82%	1: 0.07
	10 eq	70%	1:0.12
H	0	26%	1:0.03
	10 eq	61%	1:0.07

Table 1: KOTMS mediated cross-coupling of **203** with iodobenzene

Tolerance of unprotected alcohols is important for the synthesis of resolvins by ring-size dependent cross-coupling, as the sequential opening of cyclic siloxanes would reveal those functionalities. This aspect was next examined in the cross-coupling of dienyl iodides **206** and **207** and 5-membered siloxane **160** (Scheme 42). In case of the free alcohol **206**, we obtained the product in moderate yield but, much to our surprise, as a 2:1 mixture of the desired product (**208**) and its γ-lactone (**209**). While we knew that PMB would impart the necessary selectivity on the reaction (Scheme 41), it is an unsuitable protecting group in polyene synthesis because the strongly oxidising conditions required for its removal impact the integrity of polyenes.[99] Protection of the alcohol as an acetate was tested, as this would easily be removed in the last step of the synthesis. In the event, the acetyl protecting group proved beneficial for the Hiyama coupling and **209** was obtained in 55% yield with little γ-lactone by-product (<10%).

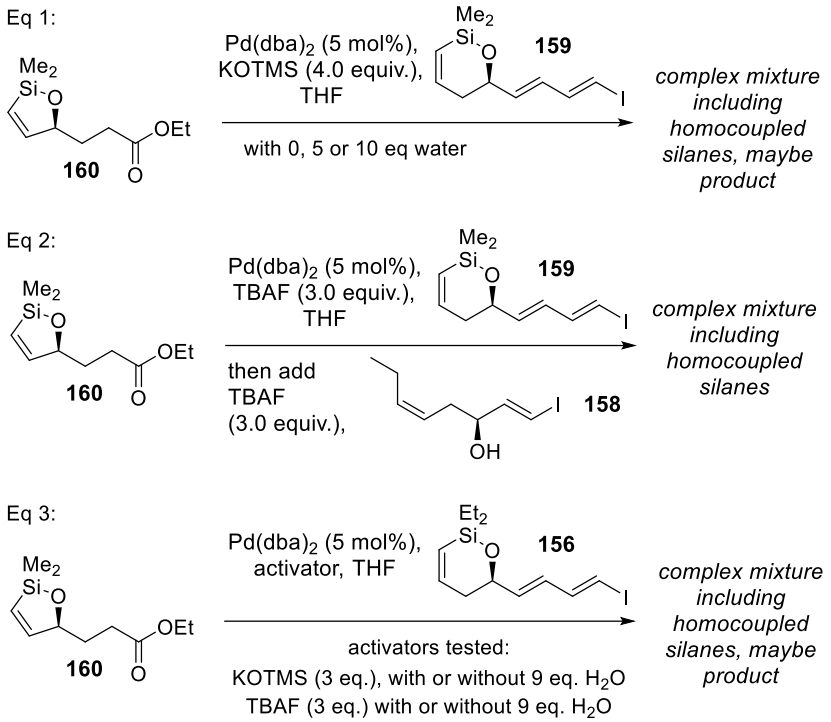
The cross-coupling of vinyl iodides **206**, **207** and **210** with siloxane **160** under KOTMS conditions started out by isolating **208** in 21% yield. Subsequent attempts to improve or even just to reproduce this result ended in failure and it is not clear which parameters were responsible for the initial success. Regardless, a successful protocol could not be established by varying catalyst or activator loading, or water content. Protecting the alcohol as either acetate or silylether was briefly investigated but could not alter the outcome.



Scheme 42: Cross-coupling of (*E*,*E*)-dienyliodides with **160**

The model systems had revealed the successful cross-coupling of 5-membered cyclic siloxane **160** with vinyl iodides **198** and **207** under TBAF activation whereas KOTMS activation (with and without 10 eq water) failed to achieve this. Nevertheless, the initially proposed approach was examined (Scheme 43). First, the cross coupling of **160** and **159** was tested under KOTMS activation (Eq 1, Scheme 43); however, this resulted in a complex mixture of products that included homocoupled silanes, which is consistent with the results presented above. Second, since the TBAF-mediated conditions were highly effective in coupling (Eq. 2, Scheme 41), we questioned whether a rate difference could be discerned between the reactions of the 5- and 6-membered siloxanes **160** and **159** (cognisant that both are activated by TBAF).

Unfortunately, this proved not to be the case and a complex mixture was obtained (Eq 2, Scheme 43); again, only homocoupling products were identifiable in this mixture. The reactions (1) and (2) were repeated twice and (1) was studied with various amounts of added water (0, 5 or 10 eq), however none of these conditions yielded any hints of the desired product. Since the transmetallation rate difference between 5- and 6-membered dimethylsiloxanes could not be turned into a ring-size dependent cross-coupling, we hypothesised that the less reactive diethylsiloxanes could enable selectivity in the studied system. To this end, diethylsiloxane **156** was prepared via Elbert's route[50] and submitted to test reactions with the (presumably more reactive) dimethylsiloxane **160**. Once again, however, none of the activators screened (TBAF or KOTMS) with or without additional water brought about any productive reaction.



Scheme 43: Ring-size dependent cross-coupling towards RvD3 (Eq 3 performed by Sear)

2.1.3 Conclusion

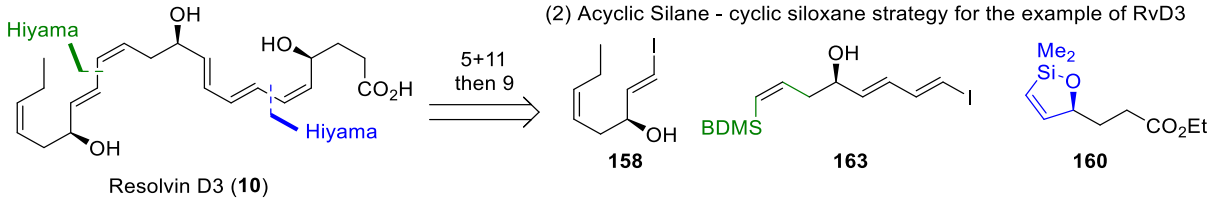
The ring-size selective cross-coupling, which was observed in previous studies in the competitive cross-coupling of 5- and 6-membered cyclic siloxanes with β-bromostyrene (diethylsiloxane) and with aryl iodides (dimethylsiloxane and diethylsiloxane) (Scheme 27) could not be translated to the total synthesis of resolvins. For their synthesis, the competitive cross-coupling of 5- and 6-membered cyclic siloxanes with vinyl iodides was envisaged; however, these substrates did not yield the desired product in the coupling of right-hand fragment **160** with KOTMS as the activator. The coupling was successful with TBAF as the activator but the selective activation of 5- and 6-membered cyclic dimethylsiloxanes was not achieved.

Mechanistically, there could be a wide range of potential issues in their competitive cross-coupling: mismatched relative rates of the elementary steps of the catalytic cycle (oxidative addition, transmetallation, reductive elimination) compared to the successful aryl iodides or elimination side-reactions of the vinyl halide. Identifying the problem(s) is further complicated by a complex set of equilibria between open and closed siloxanes, their disiloxanes and potentially even mixed disiloxanes of the 5- and 6-membered dimethylsiloxane (Scheme 31).

The synthetic application of a previous observation revealed an insufficient mechanistic understanding of the processes involved. Several model couplings of 5- and 6-membered cyclic dimethylsiloxanes with vinyl iodides with two different activators (KOTMS, TBAF) with or without water were screened but no suitable conditions were identified. The silver lining consisted in identifying successful conditions for the coupling of the right-hand side fragment of resolvin D3 with a dienylioidide model substrate of its middle fragment.

2.2 Acyclic siloxane – siloxane Strategy

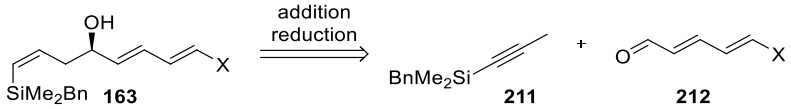
The competitive experiments using the 5- and 6-membered siloxane fragments **160** and **159** had demonstrated a distinct lack of selectivity in coupling. However, silane differentiating selectivity might yet be obtained through the combination of acyclic benzyldimethylsilane **163** and the 5-membered dimethylsiloxane (**160**, Scheme 44); after all, the competitive cross-coupling of silanols and benzyldimethylsilanes has precedence.[101] In our case, it was speculated that the fluoride mediated benzyl-cleavage would be a slower process than the cross-coupling of the highly reactive cyclic siloxane.



Scheme 44: Retrosynthesis RvD3 according to the acyclic silane - cyclic siloxane strategy

2.2.1 Preparing the Middle Fragment 163

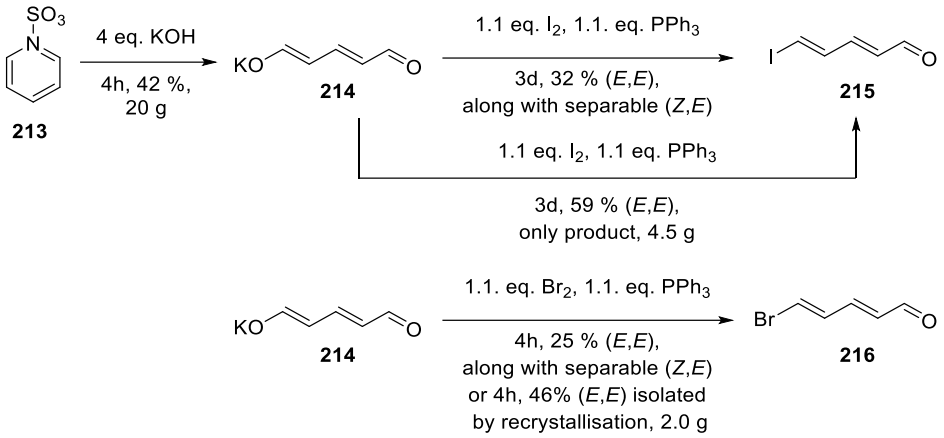
With both right-hand and left-hand side fragments **160** and **158** in hand, the synthesis of **163** was addressed. It was proposed that it could be assembled via the addition of benzyldimethylsilylpropyne **211** into (*E*,*E*)-5-halopentadienal **212**, followed by reduction (Scheme 45).



Scheme 45: Retrosynthesis of middle fragment **163**

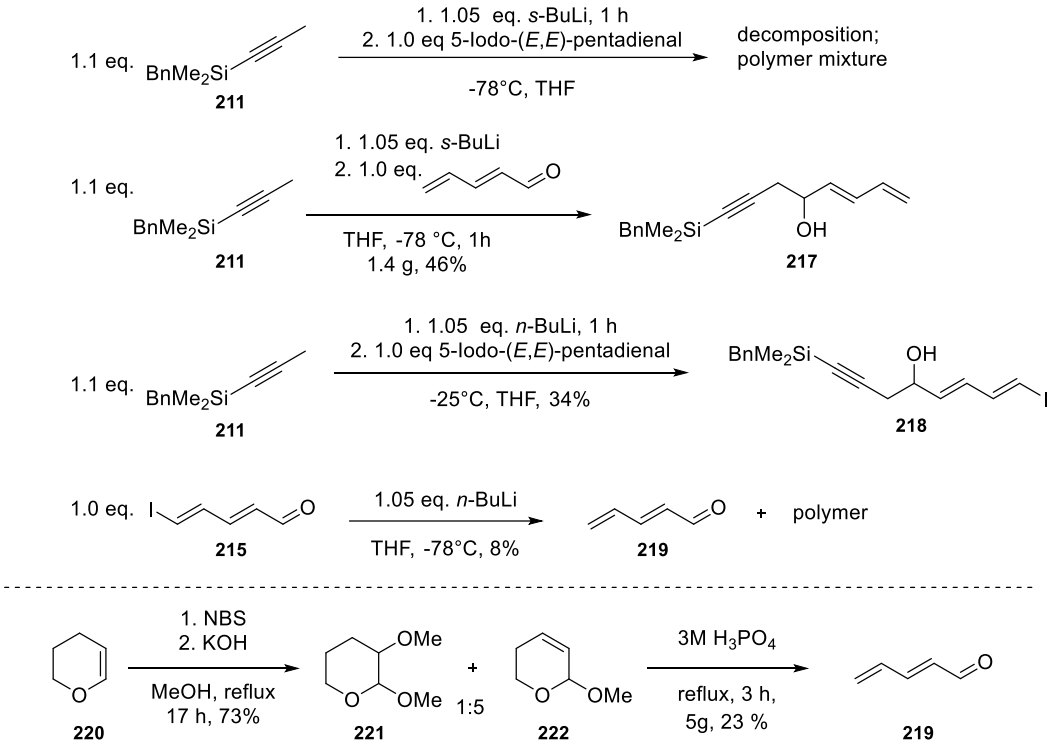
Dienylhalides **215** and **216** were first prepared according to a procedure by Duhamel (Scheme 46).[102] Hydrolysis of the SO_3·pyridine complex (**213**) with potassium hydroxide afforded glutaconaldehyde potassium salt **214** in 42% yield[103] and this compound was further reacted with either bromine or iodine in the presence of triphenylphosphine to afford the desired 5-halopentadienals in 25% and 32% yield respectively. This reaction affords a ~1:1 mixture of the (2*E*,4*E*) and (2*E*,4*Z*) dienes which needed to be separated by painstaking column chromatography.[102] To avoid this, a significantly improved recrystallisation procedure was developed that allowed for the almost quantitative isolation

of pure (*E*,*E*)-bromopentadienal **216** (46%). It was important to melt the mixture of isomers, and triturate with hot heptane (60 °C), which caused selective precipitation of the desired (*E*,*E*) isomer. Simple heating of the mixture with heptane only enriched the mixture to 10:1 (*E*,*E*):(*E*,*Z*). Extension of this protocol to 5-iodopentadienal was not investigated; in one instance, the exclusive formation of (*E*,*E*)-5-iodopentadienal was observed under, on paper, the exact same conditions, but this proved irreproducible.



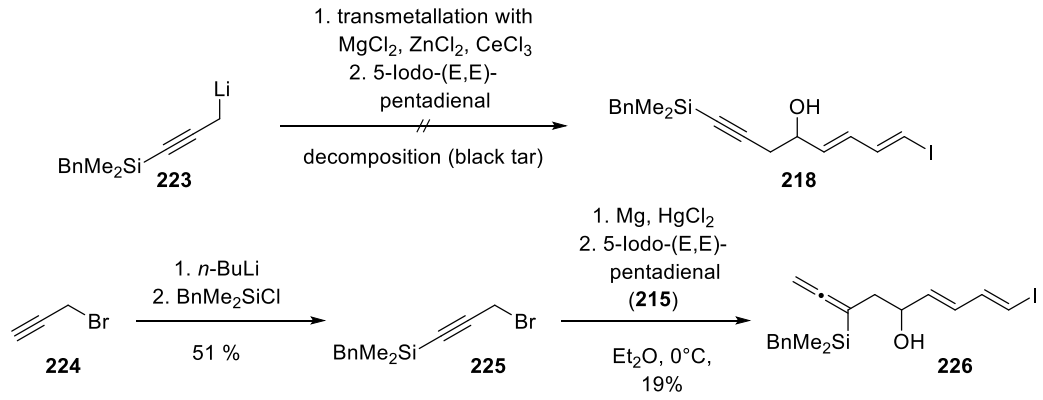
Scheme 46: Synthesis of (*E*,*E*)-5-halopentadienals

Addition of the propargyllithium species of **211** (prepared by deprotonation with *s*-butyllithium) into (*E*,*E*)-5-iodopenta-2,4-dienal resulted in unidentifiable polymeric compounds (Scheme 47). However, addition of lithium benzyldimethylsilylpropylide to penta-2,4-dienal (**219**) proceeded in 46% yield.[104] Curiously, the addition of the propargyllithium into (*E*,*E*)-5-iodopenta-2,4-dienal (**215**) succeeded in a respectable 34% yield when the deprotonation was carried out with *n*-butyllithium. It is not clear why this is the case; in both cases the *n*- or *s*-butyllithium solution was titrated to ensure correct molarity, and the same batch of aldehyde was used. It can be speculated that in case of *s*-butyllithium deprotonation was not complete after one hour, and that residual *s*-butyllithium degraded the aldehyde **215**. Indeed, direct addition of alkyllithium species resulted in lithium halogen exchange, and the formation of degradation products.



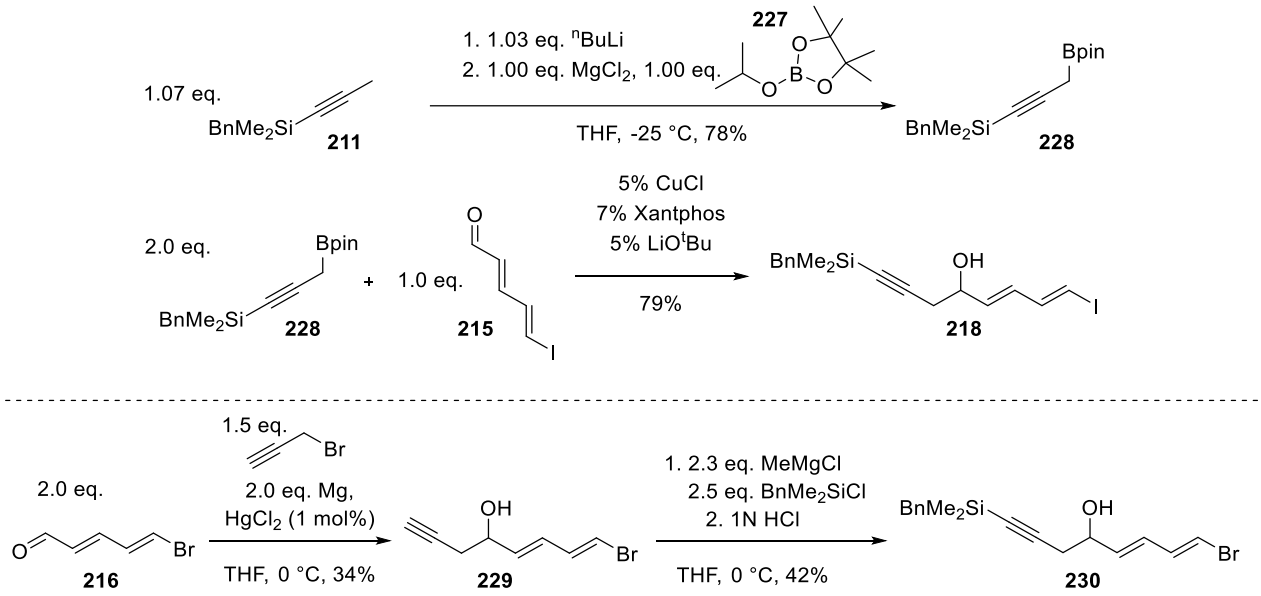
Scheme 47: Addition of Organolithiums into (*E*,*E*)-5-Iodopentanal

Given the moderate efficacy of propargyllithium addition, the suitability of other organometallics was next investigated (Scheme 48). Attempts at increasing the yield through transmetallation of propargyllithium species **223** to the magnesium, zinc, or cerium species proved unproductive. An alternative approach via the propargylic bromide was also attempted; this bromide was prepared by deprotonation of propargyl bromide (**224**) and quenching with benzylchlorodimethylsilane. The Grignard reagent was prepared at low temperature by reaction with a magnesium amalgam, but addition to **215** afforded allene **226** in modest yield. Terminal allenes are common byproduct in related reactions with aldehydes.[105,106]



Scheme 48: Addition of propargyl Grignard reagent into **215**

Inspired by a recent report by Fandrick, we investigated the use of propargylboronate esters for the synthesis of **218** (Scheme 49).[107] The required pinacolboronate ester was conveniently synthesised via deprotonation of benzyldimethylpropylsilane, addition into boronate **227** in presence of magnesium chloride, and subsequent anhydrous work-up with acetyl chloride.[108] We were delighted to find that Fandrick's protocol produced **218** in excellent yield and selectivity. Finally, bromide **230** was accessed by a mercury-catalysed propargylation, followed by a bis-silylation/ silyl ester hydrolysis.



Scheme 49: Successful preparation of **218** via addition of organoboron species **228** into **215**, and synthesis of **230**

With **218** in hand, attention turned to the semi-reduction of alkyne **218** to alkene **163** (Figure 3). Lindlar hydrogenation was not successful and resulted in the concomitant reduction of the halogen (the same result was obtained for the bromide **230**). Other conditions, for example, using nickel-boride[109] or hydroboration followed by protodeborylation[110] led only to decomposition of the starting material; the previously successful lithium aluminium hydride reduction[111] or DIBAL-H reduction[112] showed no conversion. Finally, a titanium-mediated reduction proved successful affording the product in 24% yield on 1 mg scale.[113,114]

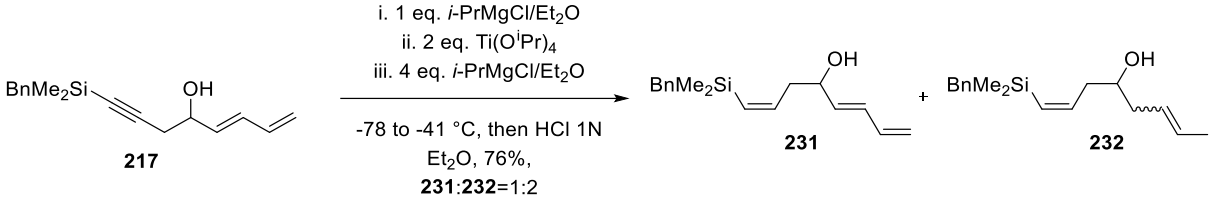
conditions	result
$Pd/CaCO_3$, quinoline, cyclohexene/toluene, H_2, 4 h	dehalogenation
$Ni(OAc)_2$, $NaBH_4$, EtOH, 70 °C, 1 d	Baseline material
Cy_2BH, o.n., then AcOH	Unidentified products
$LiAlH_4$, Et_2O, o.n.	No reaction
DIBAL-H, Et_2O, o.n.	No reaction
10 eq. Ti(O*i*-Pr)$_4$ + 20 eq. *i*-PrMgCl, -50 to -30 °C, 2 h	24%, 1 mg

Figure 3: Semi-reduction of alkyne **218**

This initial result was obtained with an excess of reducing agent (10 eq. Ti(O*i*-Pr)$_4$ + 20 eq. *i*-PrMgCl) while the original publication suggested that 1 equivalent should be sufficient.[114] However, reducing the equivalents of reagent to 2 or 4 equivalents led to no the desired the reaction (Figure 4). After extensive experimentation, including various temperatures and reverse addition of reagents, we found that none of the aforementioned variables was at the cause of the problem; instead the THF solvent of the commercial *i*-PrMgCl was identified as the culprit. When a solution of *i*-PrMgCl in Et_2O was used instead, **218** was obtained in 45% yield on 100 mg scale using 2 equivalents of reducing agent, which was found to be optimal. Interestingly, the iodine atom serves to protect the diene motif, as non-halogenated diene **217** was reduced to the vinyl silane in only 25% yield, with competing reduction of the diene moiety observed (Scheme 50).

conditions	result
10 eq. Ti(O*i*-Pr)$_4$ + 20 eq. *i*-PrMgCl, -50 to -30 °C, Et_2O:THF=12:1, 2 h	24%
2.2 eq. Ti(O*i*-Pr)$_4$ + 4.4 eq. *i*-PrMgCl, -50 to -30 °C, Et_2O:THF=5:1, 2 h	No conversion
1 eq. *i*-PrMgCl, then: 2.0 eq. Ti(O*i*-Pr)$_4$ + 4.0 eq. *i*-PrMgCl, -30 to -50 °C, Et_2O, 2 h	45%

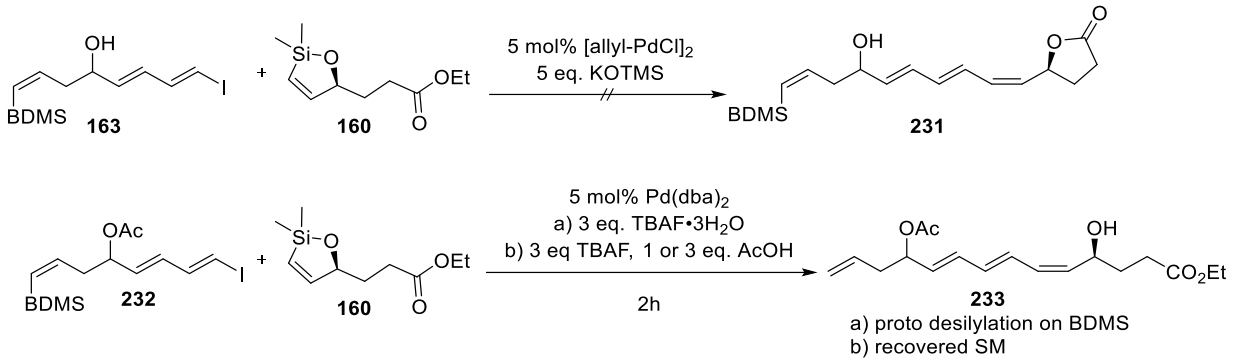
Figure 4: Optimisation of Titanium-mediated semireduction of alkyne **218**



Scheme 50: Titanium-mediated semi-reduction of **217**

2.2.2 Acyclic Silane-Siloxane Strategy

With vinyl silane **163** in hand, we turned to the proposed cross-coupling and found that KOTMS mediated conditions were unsuccessful (Scheme 51). Attempted coupling of **232** and **160**, using TBAF·3H_2O led to a complex mixture of products, of which the polyene **233** was tentatively identified in the ^{1}H NMR spectrum of the crude mixture. The presence of a terminal alkene was identified by key resonances in the 5-6 ppm region, which was attributed to protodesilylation of the BDMS group during the reaction. Attempts to mitigate this issue using TBAF·AcOH were unsuccessful, with the starting materials returned in quantitative yield.



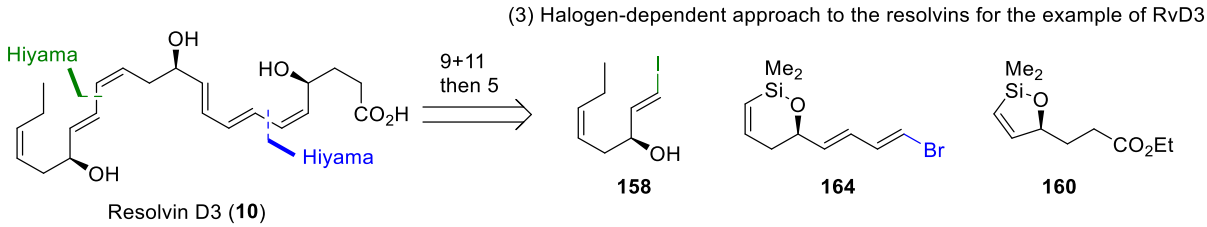
Scheme 51: The acyclic siloxane - cyclic siloxane strategy

2.2.3 Conclusion

These studies showed that the acyclic silane strategy failed because of unproductive differentiation of the silane environments. In this case, successful coupling of the right-hand side fragment **160** with the middle fragment **163** was achieved which verified the initial hypothesis of faster rate of transmetallation of the 5-membered siloxane **160** compared to the benzyldimethylsilane **163**; however, at the same time proto desilylation of the benzyldimethylsilane moiety could not be suppressed under coupling conditions. On a positive note, an alternative method to achieve reduction of the silylalkyne to a vinyl silane was identified using low-valent titanium species. In the face of these issues, the next section will focus on establishing selectivity through the choice of halogen atom.

2.3 Halogen Dependent Cross-coupling

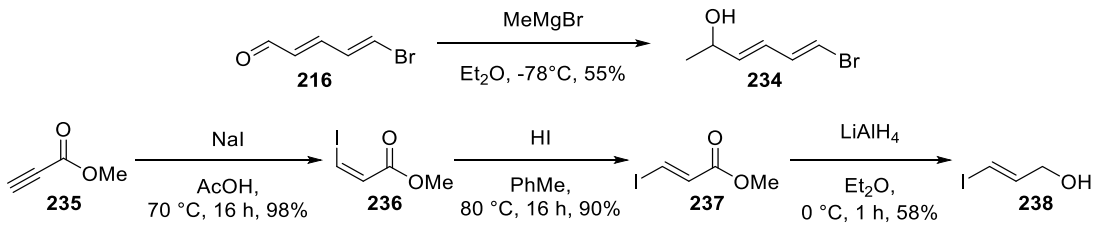
It is well known that the rate of oxidative addition of Pd(0) into R-X decreases in the order R-I > R-Br > R-Cl for R=Ar, and although pertinent kinetic data for R=vinyl has not been disclosed it is reasonable to assume that the same trend holds true.[85–89] In our three-fragment resolvin assembly we sought to exploit the reactivity difference of carbon-bromine and carbon-iodine bonds to introduce selectivity between the different fragments (Scheme 52). This approach would require vinyl iodide **158**, vinyl bromide **164** and siloxane **160**. Any selectivity issues of competing transmetallation between species **160** and **164** would be avoided by reacting vinyl iodide **158** with the 6-membered cyclic siloxane **164** before introducing the right-hand fragment **160**.



Scheme 52: The halogen differentiation strategy

2.3.1 Verification of the Strategy through Model Couplings

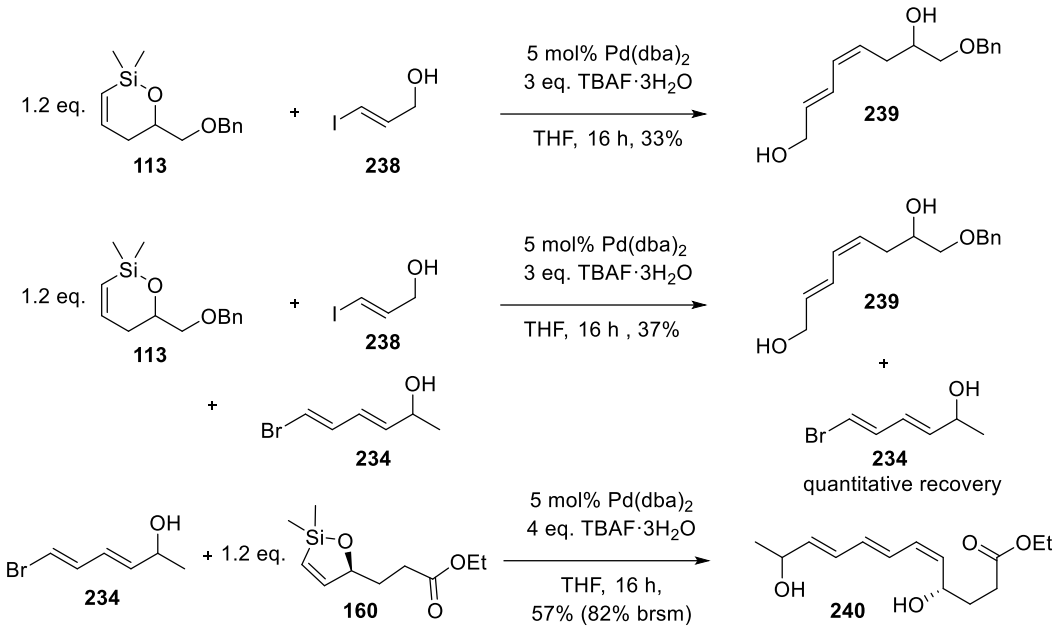
A set of model substrates was prepared to verify the feasibility of the strategy (Scheme 53). Thus, addition of methylmagnesium bromide into **216** afforded **234** in 55% yield, while alcohol **238** was prepared in a 3-step sequence from methyl propiolate (**235**) in 52% yield.[115]



Scheme 53: Preparation of model substrates **234** and **238**

First **113** was submitted to cross-coupling with **238** which afforded **239** in 33% yield (unoptimized, Scheme 54). The halogen-dependent strategy was tested by cross-coupling **113** with iodide **238** in presence of **234**, and again affording **239** while recovering **234** in

quantitative yield. Its own reactivity was subsequently verified in a reaction with the 5-membered siloxane **160** which afforded the desired product **240** in 57% yield (82% brsm).



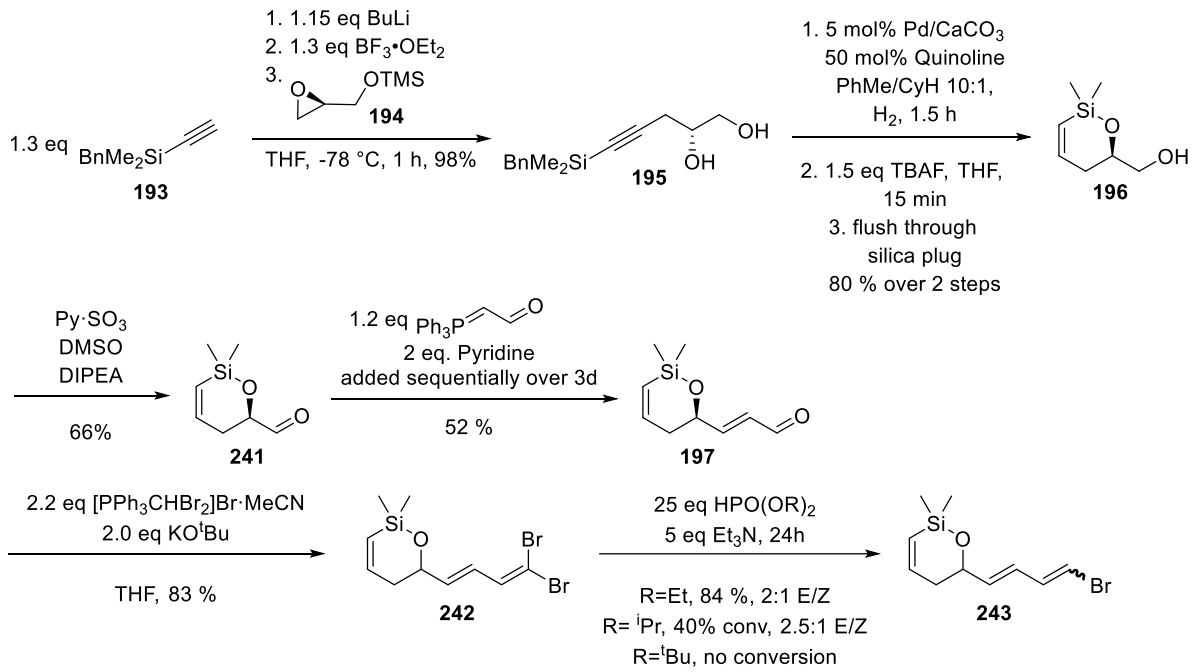
Scheme 54: model couplings verifying a halogen-dependent cross-coupling approach

Together these results lent credibility to the outlined approach and the synthesis of the 6-membered siloxane **164** will be discussed next.

2.3.2 Synthesis of Middle Fragment 164

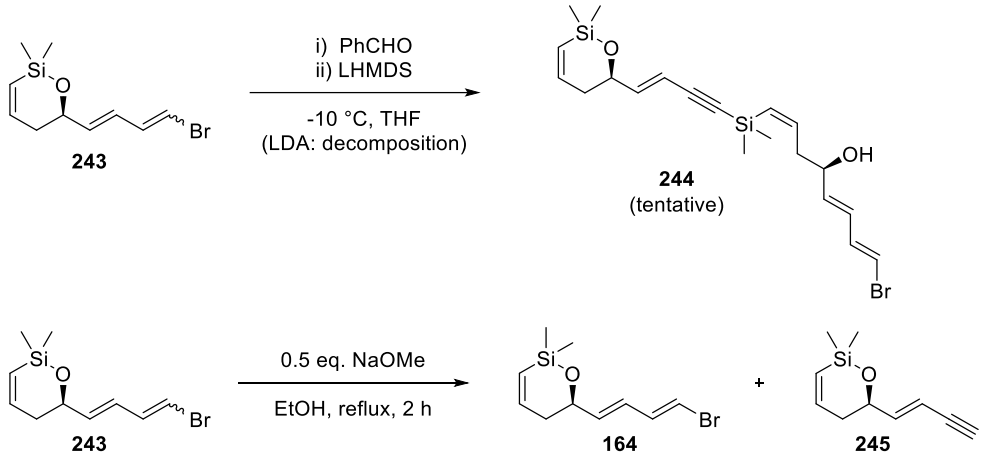
Access to vinyl iodide **158** and 5-membered siloxane **160** was already previously established (chapter 2.1.1) and our attention turned towards 6-membered siloxane **164**. The route which successfully delivered iodide **159** (Scheme 40) was employed in our quest to bromide **164** (Scheme 55). Aldehyde **197** was obtained through the previously described sequence of epoxide opening, Lindlar hydrogenation, Parikh-Doering oxidation and Wittig homologation. Whereas the Takai olefination has a sound reputation for the synthesis of vinyl iodides from aldehydes, an equivalent procedure for the preparation of vinyl bromides yields poor results.[116] A 2-step procedure consisting of Ramirez olefination[117,118] and Hirao reduction[119,120] has been developed and generally performs much better. In our case, Ramirez olefination afforded dibromide **242** in 83% yield, and subsequent Hirao reduction with diethyl phosphite yielded the desired *E*-vinyl bromide **243** in good yield but with moderate selectivity (84%, 2:1 *E*:*Z*). This result is in line with previous reports where

dibromodienes display lower selectivity than dibromoalkenes.[120] We sought to improve the selectivity of the reaction by increasing the bulk of the phosphite reagent and, indeed, di-*i*-propyl phosphite offered a marginal improvement of selectivity at the expense of reactivity (40% conversion after 24 h, 2.5:1 *E*:*Z*) whereas di-*t*-butyl phosphite failed to affect any reaction. Neither conducting the reaction at 0 °C nor employing DMF as the solvent improved the selectivity any further, and hence diethylphosphite (neat, 25 eq.) and triethylamine remained the reagent combination of choice to effect monodebromination.



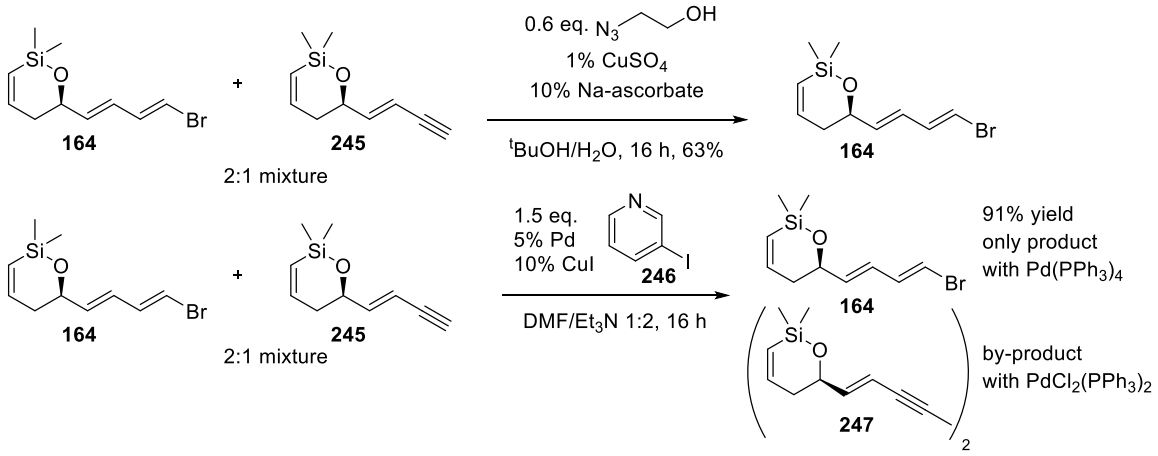
Scheme 55: Synthesis of **243** from (*S*)-glycidol

Separation of the *E*/*Z* mixture **243** proved very difficult and was only successful on one occasion on 10 mg scale. A more effective way of removing the undesired (*Z*)-isomer was needed, and elimination to the alkyne came to mind, where the (*Z*)-isomer should eliminate more quickly than its (*E*)-counterpart because of the availability of a favourable anti-periplanar arrangement of the C-H and C-I bonds. Interestingly, when **243** was treated with LiHMDS in the presence of benzaldehyde to scavenge the resulting lithium acetylide a product tentatively assigned as **244** was isolated (Scheme 56). It seems that the siloxane is much more electrophilic than benzaldehyde. When the same reaction was carried out with LDA alone, decomposition was observed. We turned to a report by Hayashi where the successful elimination of a (*Z*)-vinyl bromide in presence of its (*E*)-isomer was achieved by refluxing with sodium ethoxide in ethanol.[121] It came as a pleasant surprise that the cyclic siloxane withstood these conditions and the (*E*)/(*Z*)-vinyl bromide mixture **243** was transformed into a mixture of (*E*)-vinyl bromide **164** and alkyne **245**.



Scheme 56: selective elimination of (*Z*) vinyl bromide in presence of (*E*) vinyl bromide

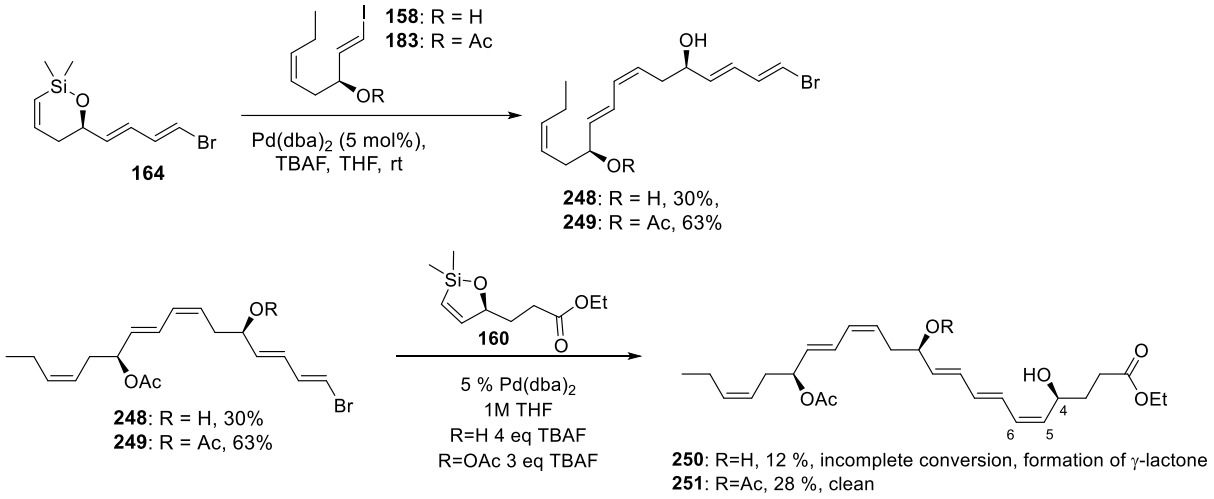
These two compounds were still inseparable by column chromatography but at least the alkyne functionality would allow for further chemistry to remove it from the product mixture. Thus, a [1,3]-dipolar cycloaddition with 2-azidoethanol successfully removed the triazole after column chromatography and 63% of the (*E*)-bromide (**164**) was recovered (Scheme 57).[122–124] A Sonogashira reaction with 3-iodopyridine (**246**) was also tested and using $Pd(PPh_3)_4$ as catalyst gave the desired bromide **164** in 91% yield whereas the use of $(PPh_3)_2PdCl_2$ led to the formation of inseparable diyne **247** as byproduct.[125]



Scheme 57: Chemical separation of (*E*) vinyl bromide **164** from alkyne **245**

2.3.3 Synthesis of Resolvin D3 through Halogen Dependent Cross-coupling

The synthesis of **164** paved the way for testing the halogen dependent cross-coupling strategy. As before (see Scheme 42), we observed that the presence of a free alcohol in **158** led to incomplete conversion alongside a by-product, tentatively assigned as homocoupling of iodide **158** (**248**:**158**-homocoupling=6:1), even with slow addition of the silane (Scheme 58). However, reaction of the allyl acetate derivative of the allylic alcohol (**249**) proceeded to full conversion and delivered product **249** in higher yield (63%) and without isomerisation. The benefit of acetylation was reinforced when acetylated **249** cross-coupled successfully with five-membered siloxane **160** to afford the diacetylated ethyl ester of RvD3 (**251**) cleanly in 28% yield.



Scheme 58: Halogen-dependent cross-coupling strategy for the synthesis of resolvin D3

The impact of acetylation is quite remarkable and is best illustrated by examination of ^{1}H-NMR spectra of the products **248** and **249** (Figure 5). For the reaction of **158** and **164**, minor impurities appear (spectrum 1), however careful column purification allows for their removal (spectrum 2). The product of the cross-coupling of the acetate **183** shows sharp peaks with no sign of isomerisation (spectrum 3). This result is curious given previous studies of the group where free alcohols were tolerated when coupling with either 5- or 6-membered cyclic siloxanes (chapter 1.4);[83,84] the present case does not show this to be generally true. These observations indicate another reason why the initially targeted ring-size dependent cross-coupling strategy would have been problematic.

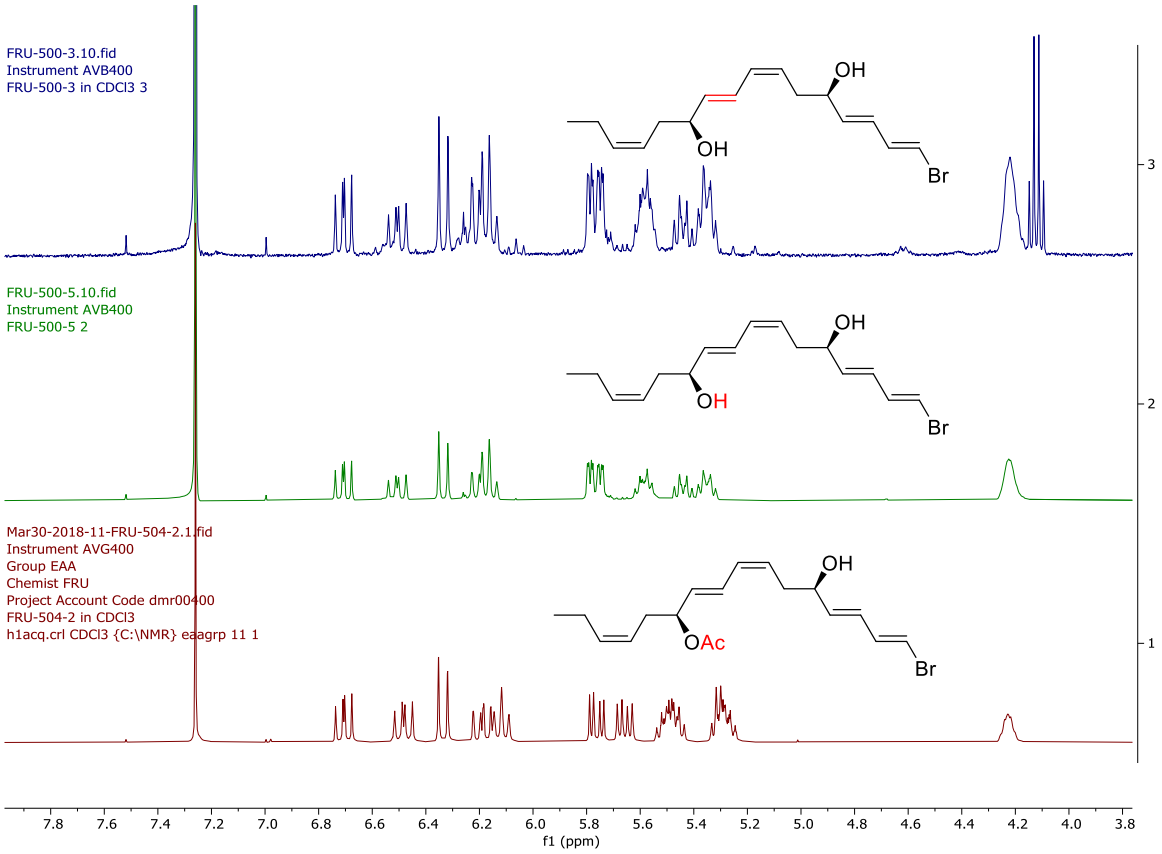


Figure 5: Comparison of TBAF mediated cross-coupling of **164** and **158** with and without acetate protection

The impact of acetylation on the reaction of **160** with **248** was quite different in nature. Examination of the ^{1}H-NMR spectrum of **250** (Figure 6) revealed that the H5-H6 coupling constant of the product and byproduct were around 10 Hz, indicating a (*Z*)-alkene, but that the chemical shift of H4, H5 and H6 in the byproduct had increased significantly. Together, these data support the formation of a γ-lactone. However, much to our surprise (compare to Scheme 42), some erosion of stereochemistry of the C5-C6-(*Z*)-alkene of the γ-lactone (spectrum 3, Figure 6) was observed. It can be speculated that an intramolecular Tsuji-Trost reaction with the lactone carboxylate as leaving group could lead to this outcome. Acetylation increased yield (from <10 to 28%), conversion (~50% to full conversion) and purity of the ^{1}H-NMR spectrum (spectrum 1 and spectrum 2, Figure 6).

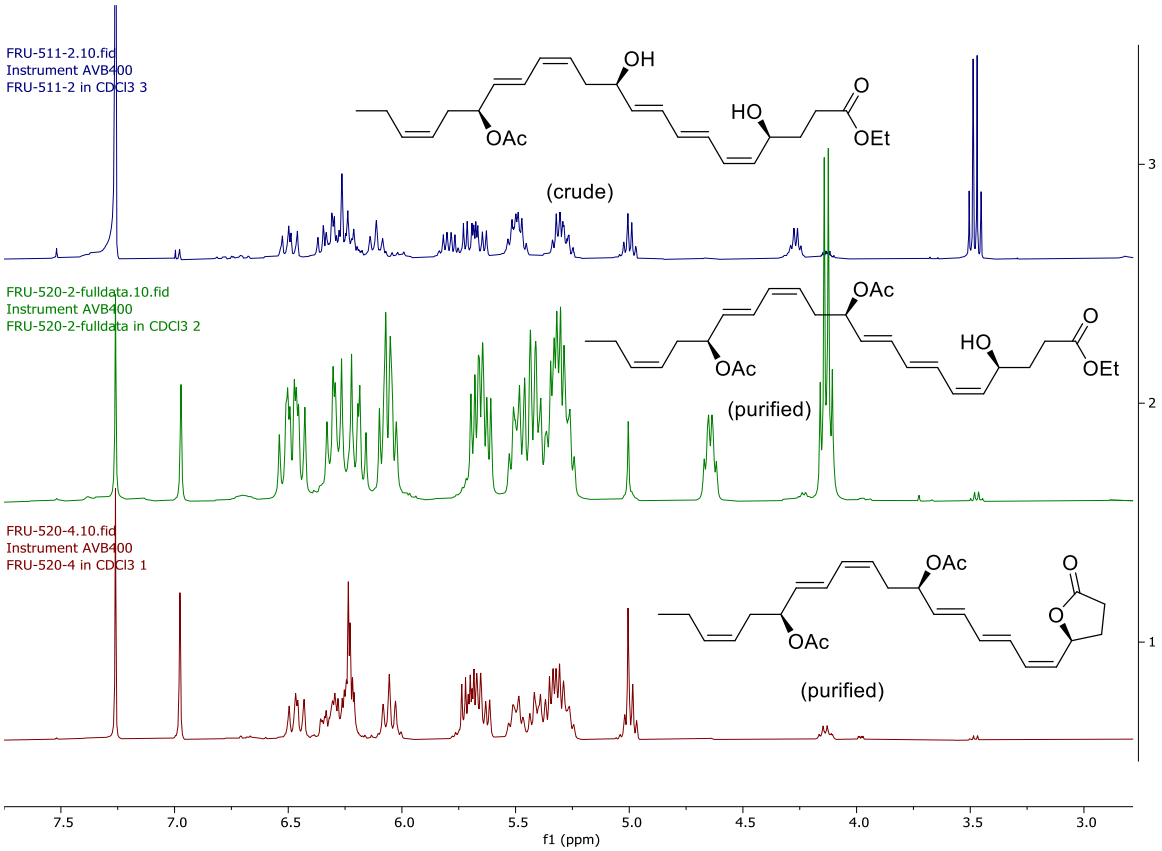


Figure 6: ^{1}H-NMR spectra of **250** and **251**, mono- and diacetylated RvD3 (spectrum 1 and 2)

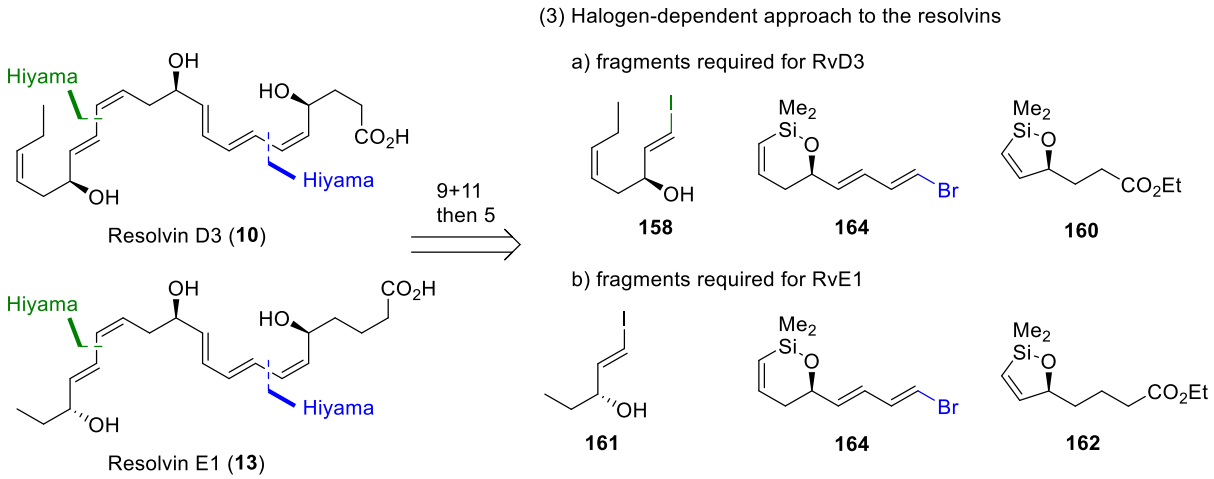
Together, these findings show that while Hiyama-Denmark couplings of cyclic siloxanes can proceed with unprotected alcohols, they perform much better when these are acetylated (other protecting groups were not examined in this study). Problems that are induced by free alcohols were not consistent in all cases but may manifest as scrambling of double bond geometry (Eq.1, Scheme 58), γ-lactone formation (Scheme 42) or sluggish conversion (Eq. 2, Scheme 58).

2.3.4 Conclusion

The halogen dependent cross-coupling strategy succeeded in providing diacetylated ethyl RvD3. It was found that free alcohols lead to partial isomerisation of double-bond geometry, sluggish conversion and γ-lactone formation during the Hiyama-Denmark cross-coupling process, which necessitates their protection. This finding also rules out any prospect of ring-size dependent cross-coupling as was initially attempted. The above results permitted the completion of the synthesis of resolvin D3 and E1, which will be discussed in the next chapter.

3 Synthesis of Resolvins D3, E1 and Hybrids

Utilising the different rate of oxidative addition of vinyl halides to introduce selectivity into our modular synthesis proved a successful strategy in assembling resolvin D3 diacetate ethyl ester from vinyl iodide **158** and cyclic siloxanes **164** and **160**. This chapter will extend this concept to the synthesis of resolvin E1 (Scheme 59), and the assembly of unnatural hybrids by combining fragments of resolvin D3 and E1.



Scheme 59: Retrosynthesis Resolvin D3 (**10**) and E1 (**13**)

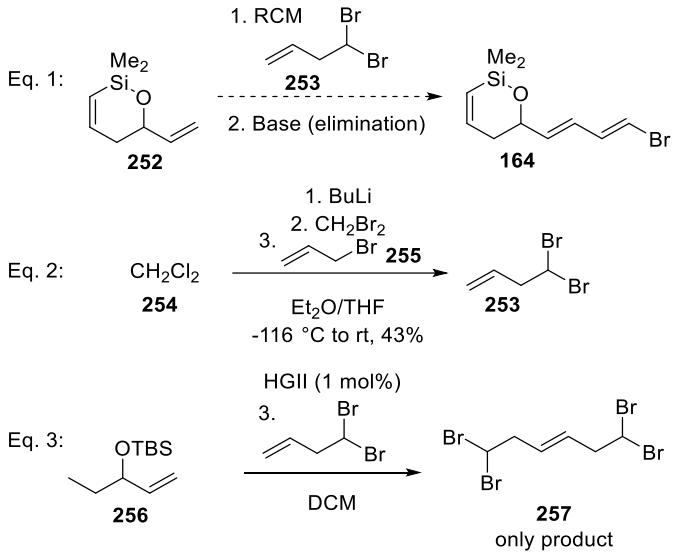
3.1 Synthesis of Left-hand and Right-hand Fragments for Resolvin E1

To follow through with the synthesis of resolvin E1, the preparation of its left-hand and right-hand side fragments **161** and **162** was carried out, using the strategies presented in chapters 2.1.1 for resolvin D3. Furthermore, two ideas for improving access to the common middle fragment **164** were investigated. The first consisted of a refined vinyl bromide synthesis while the second would depart from the initial goal of highlighting our Lindlar hydrogenation approach[7] in a total synthesis context and instead utilise Grubbs' and Denmark's RCM strategy[66,68] to assemble the cyclic siloxanes.

3.1.1 Other Syntheses of 164 using Lindlar-Hydrogenation

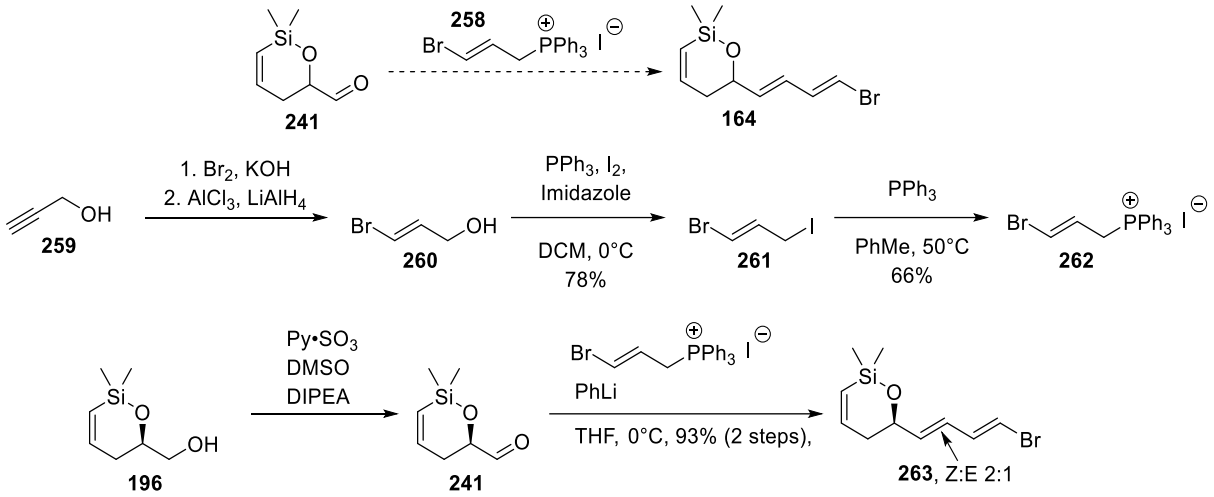
We first considered appending the (*E*,*E*)-dienyl bromide via intermolecular crossmetathesis, an idea based on precedent by Hoveyda who showed that TBS protected

allylic alcohols undergo (*E*) selective cross-metathesis with terminal olefins catalysed by Hoveyda-Grubbs II catalyst.[126] To investigate the suggested route (Eq. 1, Scheme 60), a model system was prepared. Dibromide **253** was synthesised via low-temperature deprotonation of dibromomethane by dichlormethyl lithium and alkylation with allylbromide (Eq. 2).[127] However, in our hands, cross-metathesis did not proceed productively, and we instead obtained the dimer of **257** alongside consumption of the starting material in an unknown and unproductive manner.



Scheme 60: Synthesis of **164** – an intramolecular cross-metathesis approach

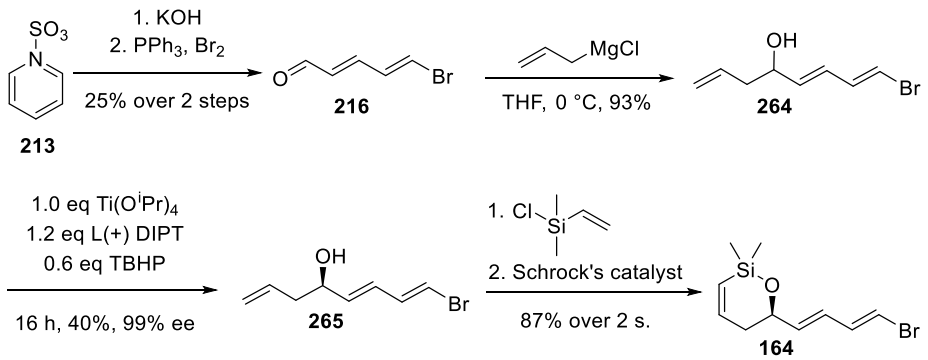
We also investigated a Wittig reaction of **241** with novel ylide **258** which, if successful, would significantly lower the step count (Scheme 61). The Wittig reagent was conveniently prepared from propargylic alcohol (**259**) via bromination and alane reduction,[128] iodination and nucleophilic substitution with triphenylphosphine. Parikh-Doering oxidation of alcohol **196** afforded the unstable aldehyde **241**, which was used immediately in the subsequent Wittig reaction to give diene **263** in 93% yield but as a 2:1 mixture of (*Z*)-:(*E*)-isomers. The poor *E*-selectivity is unfortunate but not unexpected given that **258** is a nonstabilised ylide.[129] However, the yield is remarkable and it is quite conceivable that if this reaction were to proceed with higher (*Z*)-selectivity at lower temperature, this might offer a convenient access into the (*Z*,*E*)-isomer, if desired. However, the synthesis of the (*E*,*E*)-isomer seems unachievable and was not pursued further.



Scheme 61: Synthesis of **164** via Wittig reaction

3.1.2 Synthesis of 164 using Ring-closing Metathesis

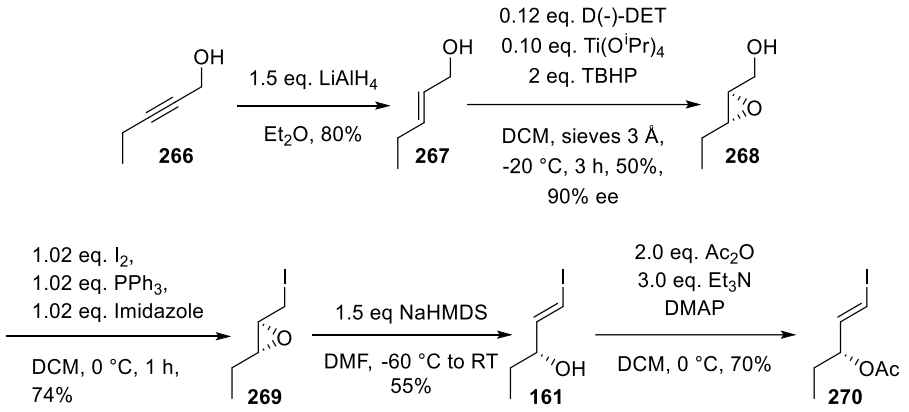
Due to the problems of stereocontrolled dienyl bromide synthesis, a conceptually different approach was examined that took recourse to Grubbs' and Denmark's RCM to dimethylsiloxanes (Scheme 62).[66,68] (*E*,*E*)-5-bromopentadienal **216** was readily accessed from SO_3·pyridine complex (**213**) by alkaline hydrolysis and subsequent bromination (Scheme 46).[19] Addition of allylmagnesium bromide, followed by Sharpless resolution (98% *ee*, determined by HPLC analysis), afforded enantioenriched alcohol **265**. Formation of an intermediate vinyldimethylsilyl ether set the stage for ring-closing metathesis mediated by the Schrock catalyst, which proceeded in excellent yield (87% over two steps). This is the shortest synthesis of **164** although the two resolution events (purification of a 1:1 (*E*,*E*):(*E*,*Z*) mixture and Sharpless resolution of the racemate) preclude a high overall yield. **164** was thus obtained in 6 steps but only 8% yield.



Scheme 62: Synthesis of **164** via intramolecular RCM strategy (route scouting and racemic synthesis by me, enantioselective route by P Streatfeild)

3.1.3 Synthesis of RvE1's Left-hand Fragment 161

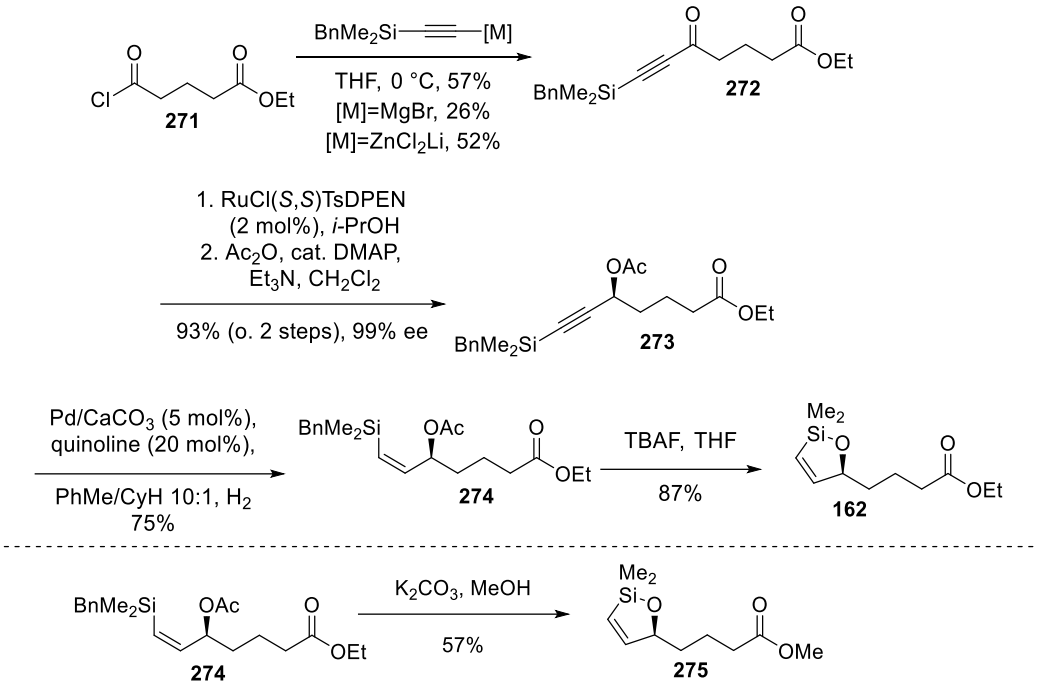
Fragment **161** was synthesised by analogy to iodide **158** by base-mediated isomerisation of iodoepoxide **269** (Scheme 63). The synthesis began with reduction of propargylic alcohol **266** by lithium aluminium hydride, since commercial **267** strangely contained 3% epoxide **268** in its racemic form thus lowering the enantiomeric access of **268** after Sharpless epoxidation. Allylic alcohol **267** underwent by Sharpless epoxidation (50%, 90% ee determined by HPLC analysis of the benzoate) and the volatile epoxide was carried through to iodide **269** (74% yield) and then treated with NaHMDS to reveal **261** in good yield. This route is an interesting alternative to previous reports.[24,39,130]



Scheme 63: Synthesis of left-hand fragment **161** (RvE1)

3.1.4 Synthesis of RvE1's Right-hand Fragment 162

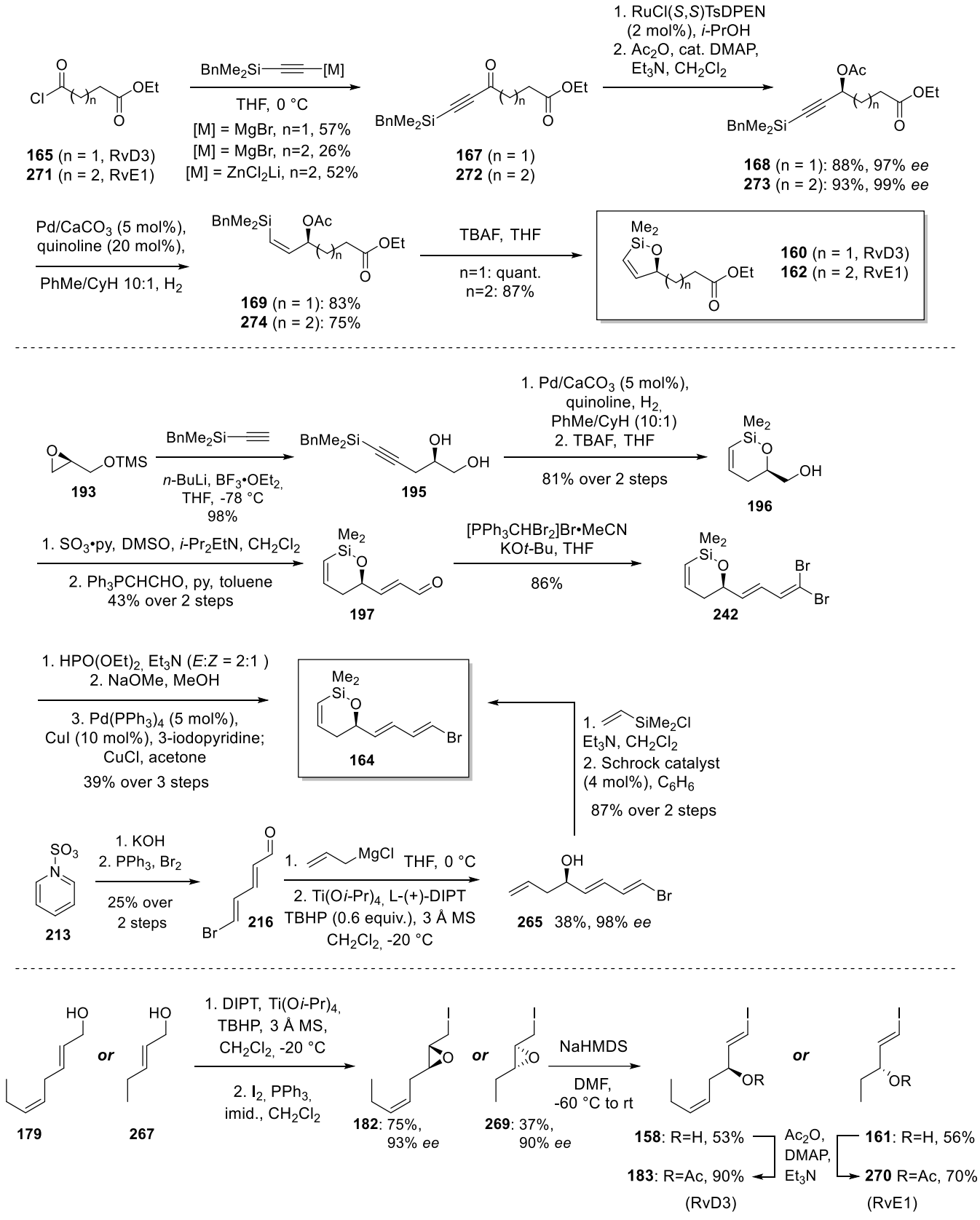
The synthesis of the C1–C7 fragment **162** of RvE1 (Scheme 64) proceeded in analogy to the synthesis of **160** (Scheme 36). However, the reaction of alkynyl Grignard (prepared from the alkyne using MeMgBr) with acid chloride **271** gave ketone **272** in only 26% yield (compare to **167**, 52% yield, Scheme 36). The remedy came in the form of the benzyl(ethynyl)dimethylsilane zincate species which generated the desired ketone in 52% yield.[131,132] **272** was converted to the enantioenriched propargylic acetate **273** through Noyori asymmetric transfer hydrogenation (99% *ee*)[90] followed by esterification. Semi-hydrogenation to the (*Z*)-benzyldimethylalkenylsilane **274** proceeded with high yield and selectivity (75%, *Z*:*E* > 20:1) and the alkenylsilane was then treated with TBAF to effect debenzylation, *in situ* deacetylation, and cyclisation to the cyclic 5-membered siloxane **162** in 87% yield. Alternatively, deacetylation of **274** could be carried out by K_2CO_3 in methanol in moderate yield and with concomitant transesterification at the terminal ester group.



Scheme 64: Synthesis of fragment **162**

3.2 Summary of Routes for the Synthesis of RvE1 and RvD3 Fragments

The following scheme summarises the synthesis of fragments for resolvins D3 and E1 (Scheme 65).

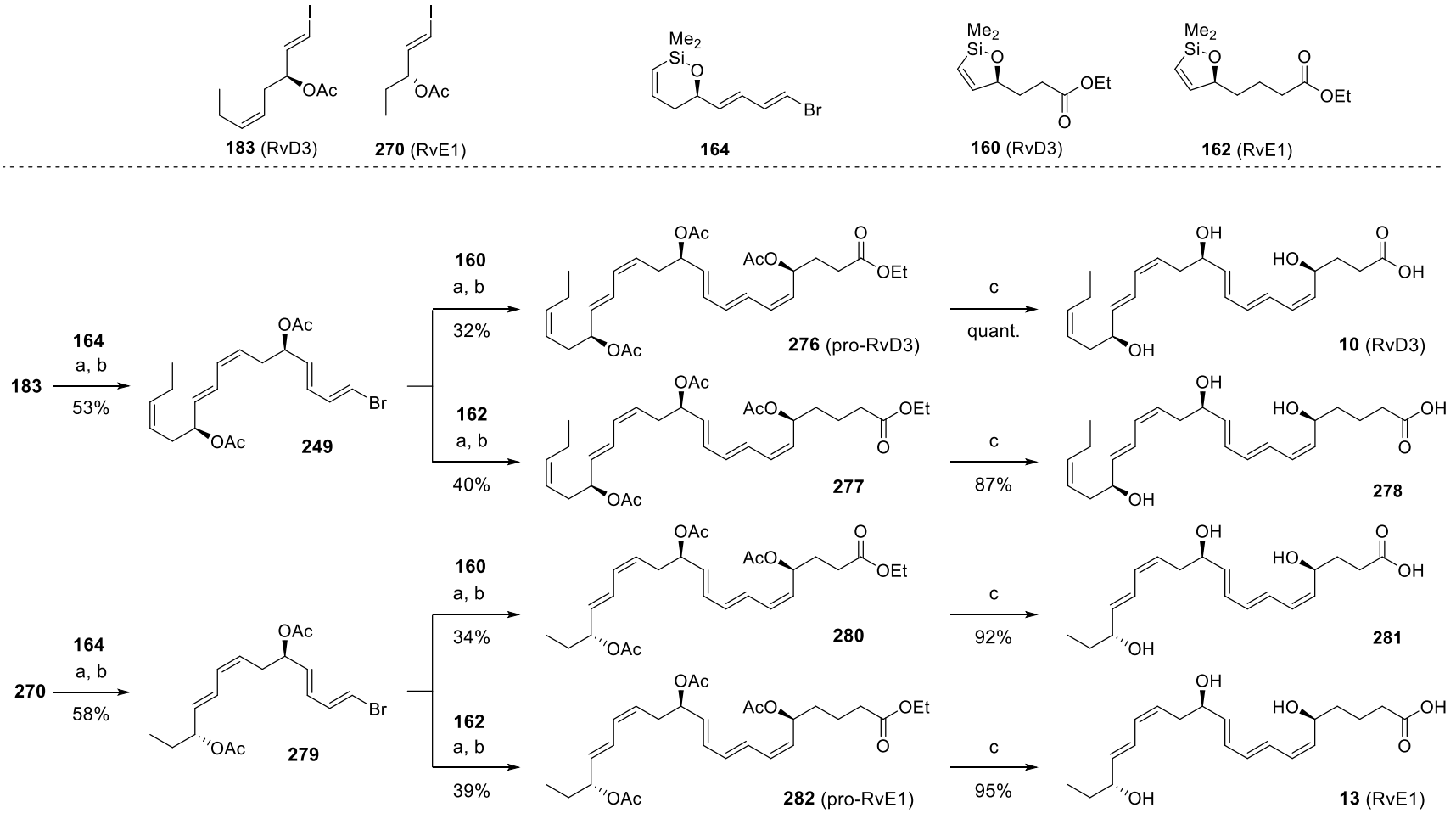


Scheme 65: Summary of fragment synthesis **160**, **162**, **164**, **183** and **270** for RvD3 and RvE1

3.3 Synthesis of Resolvin D3, E1 and Hybrids

Coupling of **183** and **164** (Scheme 66), followed by acetylation, afforded dienyl bromide **249** (53%). This was coupled with siloxanes **160** and 1**62** to give product alcohols that were immediately acetylated (**276** and **277**, 32-40%). This acetylation helped purification of **276** and **277** from a γ-lactone formed from cyclization of the γ-hydroxyester head group (see chapter 2.3.3); in case of **280** the respective δ-lactone was never observed. Furthermore, the per-acetylated ethyl esters displayed significantly higher stability than the natural product and allowed for HPLC purification (carried out at UCB by Dr. J. Llaveria) in preparation for biological testing and long-term storage. Resolvin D3 (**10**) and the RvD3/E1 hybrid **278** were revealed in near quantitative yield on treatment with lithium hydroxide. Similar coupling of **164** with iodoalkene acetate **270** gave the tetraene **279** after acetylation (58%). Coupling with the two head group siloxanes and acetylation now afforded RvE1 triacetate **282**, and hybrid **280**. Again, these could be saponified in high yield on treatment with aqueous lithium hydroxide to afford resolvin E1 (**13**) and the RvE1/D3 hybrid **281**.

In conclusion, our work afforded RvD3 in 2% yield (13 LLS, 24 TS) and RvE1 in 2% yield (11 LLS, 20 TS) along with two hybrids which is slightly shorter than the literature precedent (RvD3 was prepared by Petasis in 1% yield (15 LLS, 29 TS),[23] RvE1 was synthesised by Schwartz in 4% yield (12 LLS, 21 TS)[24]). Unfortunately, the relatively low-yielding synthesis of the middle-fragment **164** and the need for protection of the hydroxyl-groups, which added 3 additional steps to the longest linear sequence, prevented us from making a bigger impact on the field. Nevertheless, the present work is an efficient and enantioselective synthesis that may find application.



Scheme 66: Synthesis of resolvins D3, E1 and hybrids. Reagents and conditions: a) $Pd(dba)_2$ (5 mol%), TBAF (3 eq.), THF, b) Ac_2O, DMAP, Et_3N, DCM; c) LiOH, THF/ H_2O (1:1)

3.4 Comparison of Spectroscopic Data

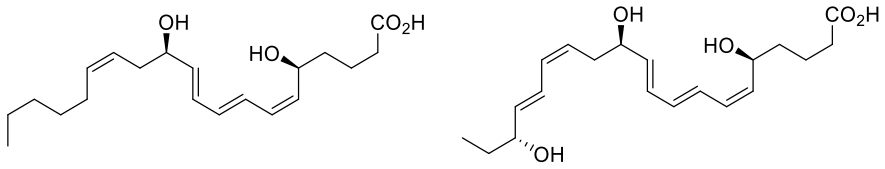
The data of our synthetic products was in reasonable agreement with the reported data (Table 2),[23,24] although the ^{13}C-shift of the carboxylic acid and its α-carbon displayed a rather significant disparity (>1 ppm). Whether this is due to the water content of the solvent or a concentration effect could not be elicited.

Table 2: comparison of ^{13}C NMR chemical shifts of our synthesised natural products to the reported data

Resolvin D3			Resolvin E1		
Serhan	Our data	Δ	Schwartz	Our data	Δ
182.5	177.7	-4.7	182.9	178.7	-4.2
137.5	137.9	0.3	138.0	137.8	-0.2
137.5	137.5	0.0	137.7	137.8	0.1
135.5	135.2	-0.3	135.7	135.3	-0.4
134.8	134.8	0.1	134.9	135.0	0.1
134.6	134.6	0.0	131.9	131.5	-0.4
131.8	131.5	-0.2	131.2	131.1	-0.1
131.0	131.1	0.1	130.5	130.6	0.1
130.3	1307	0.4	129.2	129.0	-0.2
129.2	128.8	-0.4	128.2	128.1	-0.1
128.2	128.1	-0.1	126.8	126.7	-0.1
126.6	126.6	0.0	74.8	74.6	-0.2
125.5	125.5	0.0	73.2	73.0	-0.2
73.2	73.2	0.0	68.5	68.4	-0.1
73.1	73.0	-0.1	39.1	38.2	-0.9
68.9	67.8	-1.0	38.9	36.7	-2.2
36.7	36.7	0.0	36.8	35.8	-1.0
36.2	36.2	0.0	31.3	31.2	-0.1
35.4	33.8	-1.6	23.7	22.4	-1.3
35.3	31.2	-4.1	10.3	10.2	-0.1
21.7	21.7	0.0			
14.5	14.5	0.0			

3.5 Biology of Resolvins D3, E1 and Hybrids

Subtle differences in chain lengths and degree of hydroxylation greatly impact the potency of these lipid mediators (chapter 1.1). For instance, leukotriene B4 (**283**) is pro-inflammatory whereas resolvin E1 (**13**) is anti-inflammatory (Figure 7). Odd-numbered resolvins are completely unknown and our synthesis of odd-numbered resolvin analogues might reveal surprising effects on their efficacy.



Leukotriene B4 (**283**) *Resolvin E1* (**13**)

Figure 7: Leukotriene B4 and Resolvin E1

To address these questions, we embarked on a collaboration with Prof. D. Gilroy at University College London (UCL) and our initial goal was to establish a screen that might quantify the anti-inflammatory response of the resolvins. Those assays have been disclosed and rely mostly on *in vivo* experiments (chapter 1) but Prof. Gilroy suggested to start with a Ca^{2+}-release assay, a quick *in vitro* test. This test measures the intracellular concentration of Ca^{2+} in peripheral blood mononuclear cells (PBMCs) where Ca^{2+} acts as a signalling molecule mediating neutrophil interactions with both the host and pathogens.[133,134] The assay was carried out by Edmond Toma who found that neither our compounds nor the commercially purchased resolvins (for comparison) elicited any response. An exemplary response curve of our resolvin E1 is included below (Figure 8). This observation is actually in agreement with the literature, Serhan notes “In general, SPMs do not utilise intracellular calcium (Ca^{2+}) mobilisation in neutrophils for signal transduction but instead activate phosphorylation.”[1] Other publications[2,35] suggest that the resolution of zymosan A induced inflammation is a better suited model for measuring the bioactivity of resolvins. This *in vivo* assay requires a more complex set-up, however, and work is currently ongoing. Once a suitable assay is established, we will investigate the bioactivity of our synthesised resolvins D3 and E1, and their unnatural analogues.

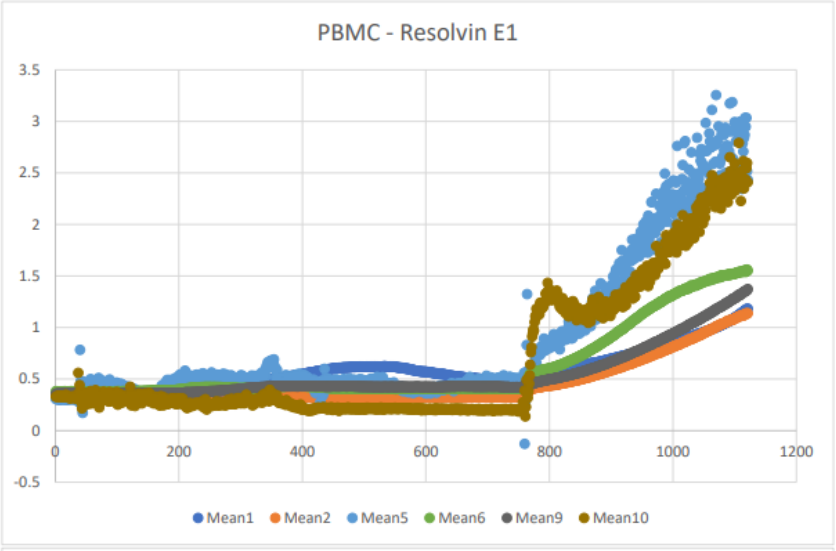


Figure 8: Response of resolvin E1 to Ca^{2+}-release assay (fluorometric assay using PBMCs, any opening of Ca^{2+} channels should result in a peak, endpoint: Ca^{2+}-channel opened with ionomycin to show that cells are alive)

This concludes the biological work that has been carried out on the resolvins. While the research hypotheses are still of interest, they cannot be verified until a reliable assay has been established. To this end, work is currently ongoing in the Gilroy lab and we eagerly await its completion.

4 Conclusion and Future Work

This project examined the group's previous finding of ring-size dependent transmetallation of cyclic siloxanes in the context of the total synthesis of resolvins D3 and E1. This concept states that 5-membered siloxanes transmetallate faster than their 6-membered homologues under TBAF activation and are uniquely reactive under KOTMS activation. Previous work showed this concept to work moderately well with aryl iodides, however it could not be successfully extended to the vinyl halides of the present study.

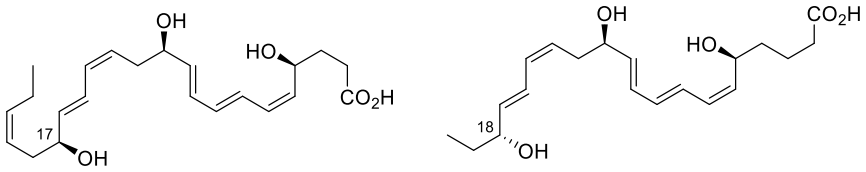
5-Membered cyclic siloxanes react remarkably quickly in Hiyama couplings and to investigate the difference in reactivity further, we looked at the competition of benzyldimethylvinyl silane, (a masked silanol), and the 5-membered siloxane, the most reactive member of the family. Again, neither TBAF nor KOTMS activation could levy the potential of this approach; additionally, we found the first example where unprotected alcohols are not well tolerated in the cross-coupling process and induce loss of stereochemistry at the newly formed C-C bond.

The failure of ring-size dependent transmetallation or indeed silane differentiating transmetallation necessitated a change of approach and we turned towards the well-known difference in rate of oxidative addition of vinyl halides. The tail fragment was thus equipped with a vinyl iodide, while the middle fragment bore a vinyl bromide. Coupling of these two fragments proceeded selectively and appendage of the head siloxane was achieved as well. This strategy allowed for synthesis of resolvins D3, E1 and hybrids. We are applying our modular synthesis to structure-activity questions of these lipid-mediators. Therefore, a collaboration with Prof. D. Gilroy (UCL) was initiated and work is currently underway to identify suitable biological assays for our studies.

Future work could help to identify necessary structural features for a resolvin molecule to possess for a positive anti-inflammatory response *in vivo*. This would then extend to a consideration of diastereomeric and enantiomeric analogues of the natural resolvins, effects of chain length, position and configuration of alkenes, increased saturation and the role of the carboxylic acid and its lactone.

For example, in the case of RvE1 and RvD3, it is known that the AT-RvE1 and AT-RvD3 analogues possess similar activity (Figure 9) but no data on other epimers or diastereomers has been reported. The modularity of the developed synthesis would allow for the free combination of building blocks, which each contain one stereogenic centre,

and thus allow to vary each of the 3 stereocentres of resolvins D3 or E1 individually. The resulting 8 diastereomers could then be evaluated for their anti-inflammatory properties to address this basic question of structure-activity relationship.



17- (S)=*Resolvin D3* (**10**) (depicted)
17-(R)=AT-Resolvin D3 (**284**)

18- (R)=*Resolvin E1* (**13**) (depicted)
18-(S)=AT-Resolvin E1 (**285**)

Figure 9: Resolvin D3 and E1

Synthesis of Bridge-substituted Bicyclo[1.1.1]pentanes

5 Introduction

5.1 Linear Spacer Units

Linear spacer units alter the distance between functionalities without affecting the overall geometry of the molecule. Thus, they are important linkers in the molecular tool box and have seen application in medical and material sciences, for instance as bioisosters (see chapter 5.4).[135] Classically, conjugated hydrocarbons such as alkynes and benzenes have been used as linear spacer units, as they can be easily incorporated through cross-coupling reactions.[136,137] More recently, non-conjugated rigid hydrocarbons have been investigated for this role.[135] This group of molecules is characterised by being rigid, linear (arrangement of functionalities in 180° angle) and non-conjugated (sp^3 hybridised carbons interrupt conjugation, only partially true, *vide infra*). Non-conjugated rigid hydrocarbons comprise of highly strained molecules like cubane and bicyclo[1.1.1]pentane (BCP) and more common ones like bicyclo[2.2.2]octane (BCO).[138,139]

This introduction will focus on BCPs and familiarise the reader with its properties, synthesis and bonding situation.

5.2 Properties of Bicyclo[1.1.1]pentane

5.2.1 Inter-bridgehead distance

X-ray diffraction, electron diffraction and other spectroscopic techniques allowed for determination of the inter-bridgehead distance of common linear spacer units (Figure 10). It is shortest in acetylene (**300**, 1.20 Å), and increases through BCP (**301**, 1.85 Å), BCO (**302**, 2.60 Å) and cubane (**303**, 2.72 Å) to *p*-substituted benzene (**304**, 2.79 Å). While the C-C distance in cubane is very similar to benzene, in BCP it is only slightly longer than the longest observed C-C single bond length (1.70 Å).[140]

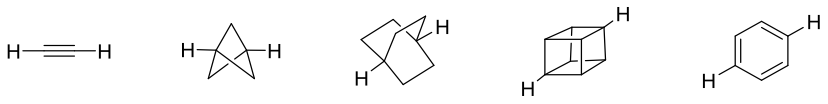
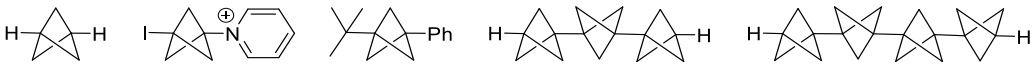


Figure 10: C-C bond length of various linear spacer units

The internal C-C distance of the highly strained BCP is strongly influenced by steric and electronic effects (Figure 11). It increases for electron-donating substituents, e.g. **306**,[141] and decreases for electron-withdrawing groups, e.g. pyridinium salt **305**.[142] Notably, the length of the number of BCP units in staffane impacts the length of the internal C-C distance as well: it is 1.87 Å in [3]staffane (**307**) and 1.89 Å in [4]staffane (**308**).[143] The sensitivity of the internal C-C distance to substituents has been attributed to slightly different hybridisations of the bridgehead carbon depending on its substituent. For instance, electron withdrawing groups would result in a higher degree of s-character in the bridgehead carbon bond towards them (Bent's rule).

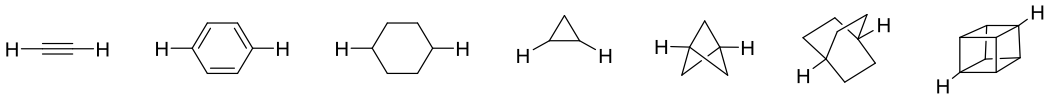


301	**305**	**306**	**307**	**308**
1.85 Å	1.80 Å	1.89 Å	1.87 Å	1.89 Å

Figure 11: Bond length in BCP depending on bridge substituents

5.2.2 Hybridisation and Orbital Interactions in BCP

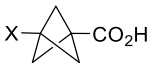
The bridgehead hybridisation is not only important for the electronic communication across the bridge but also influences the reactivity of the compound. A direct way to establish the degree of hybridisation is by analysing $J_{C\text{-}H}$ which can be determined by NMR spectroscopy (Figure 12).[144] $J_{C\text{-}H}$ and the derived s-character (s%=$J_{C\text{-}H}$/5) of BCP (**301**), cubane (**303**), BCO (**302**) and reference molecules are summarised in Figure 12. Whereas BCO is relatively close to the parent cyclohexane (sp^3),[145] the s-character of BCP and cubane is much closer to benzene (sp^2).[146,147] This results both in p-rich cage C-C orbitals and a high kinetic acidity of the exocyclic C-H bond. The kinetic acidity of cubane has been measured and supports the NMR-spectroscopic results. Cubane is ~7,000 times less acidic than benzene but also ~6,000 times more acidic than cyclohexane[148] and hence comparable to cyclopropane.[149] This is equally reflected in the similar degree of hybridisation (s-character: 32% (cyclopropane) vs 31% (cubane)).



	300	**304**	**309**	**310**	**301**	**302**	**303**
$J_{(C\text{-}H)}$	249 Hz	158 Hz	127 Hz	162 Hz	168 Hz	134 Hz	154 Hz
s-character	50%	33%	25%	32%	34%	27%	31%

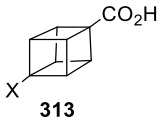
Figure 12: Analysis of s-character of C-H bonds in various hydrocarbons

The close internal C-C distance in non-conjugated rigid hydrocarbons results in their interaction having both a through bond and through space component. This electronic communication can be analysed based on the acidity of differently substituted carboxylic acids and will be discussed for the BCP (**311**), BCO (**312**) and cubane (**313**) scaffold (Figure 13).[150–153] The influence of the bridgehead substituent is more pronounced the shorter the internal C-C distance, as evidenced by comparison of chloro-substituted BCO ($\Delta(pK_A)$= 0.82) and chloro-substituted BCP ($\Delta(pK_A)$= 0.94) with their parent compound. Furthermore, the through bond and through space correlation were analysed for 3- and 4-substituted BCOs where, lacking the internal bridgehead interaction, the 3-substituted BCO had a markedly lower impact on acidity than the 4-subsituted one.[154] Wiberg showed, that the influence of the substituents is correlated to a field effect where the acidity of the bridge-carboxylic acid is linearly dependent on the C-X dipole (Figure 13).[154]



311

312



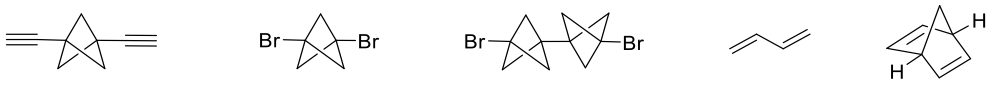
313

X	pK_A	pK_A	pK_A
H	5.63	6.54	5.94
Cl	4.69	5.72	
F	4.84		
CF_3	4.75	5.79	
CH_3		6.50	
Br			5.32

Figure 13: Substituent effect on acidity of non-conjugated rigid hydrocarbon carboxylic acids

Another measurement for the interaction between occupied MOs is their energy difference, the orbital splitting energy ΔI_n. This interaction can take place either through space or through bonds (*via* σ-system). Considering Koopmans theorem, these interactions can be observed by photoelectron spectroscopy (PE) and quantified by interpretation of the respective bands.[155] Cubane,[156] cubane derivatives[157] and BCO[158] show very small splitting of the HOMO and next highest occupied molecular orbital which is indicative of a weak interaction (0.10 – 0.20 eV). On the other hand, BCP shows a strong splitting: The π-MOs of **314** showed a split of 0.67 eV and the same order of magnitude was observed

for the ionisation energies of **315** (0.72 eV) and **316** (0.45 eV) (Figure 14).[159] This shows the strong interaction of the backlobes of the exocyclic hybrid orbitals and further illustrates the stabilising effect within staffanes where individual BCP subunits are elongated (cf Figure 11). While the observed effects are much smaller than in conjugated systems (butadiene, **317**, 2.5 eV) and slightly smaller than in homoconjugated cases (norbornadiene, **318**, 0.86 eV), they still show a good relay effect.



314 ΔI_{π}~ 0.67 eV | **315** ΔI_{n}~ 0.72 eV | **316** ΔI_{n}~ 0.45 eV | **317** ΔI_{π}~ 2.5 eV | **318** ΔI_{π}~ 0.86 eV

Figure 14: Orbital energy splitting of BCPs and standards[159]

The electronic communication between the two bridgehead carbons could be further substantiated by electron transmission spectroscopy which revealed strong through bond coupling of π*-orbitals.[160] The π* splitting in **314** was determined to 1.1 eV which complements the previously described PE studies.

5.2.3 Ring Strain of BCP

Strain in cyclic molecules is a combination of angle strain, torsional strain and transannular strain. In small molecules such as BCP and cubane and their monocyclic analogues angle strain is the dominating factor. Cyclopropane is the most strained single ring system with a strain of 27.7 kcal/mol and while cyclobutane has a similar strain energy, the strain per C-C bond is markedly lower and cyclohexane is strain free by definition (Table 3).[161,162] In terms of the bicyclic compounds, both BCP and cubane are more highly strained in terms of strain energy per C-C bond, with cubane being the most strained molecule of them. If one considers cubane to be constituted of 6 cyclobutanes the strain energy is however somewhat lower than expected. Furthermore, it is important to point out that strain energy does not necessarily correlate with thermodynamic stability, as cubane is remarkably stable (e.g. to temperatures up to 220 °C) due to the lack of decomposition pathways.[163] The same can be said about BCP which is kinetically stable up to 280 °C.[164]

Compound	Strain energy [kcal/mol]	Strain energy per C-C bond [kcal/mol]
Cyclopropane	27.7	9.1
Cyclobutane	26.3	6.6
Cyclohexane	0	0.0
BCP	68.0	11.3
Cubane	161.5	13.5
BCO	7.4	0.8

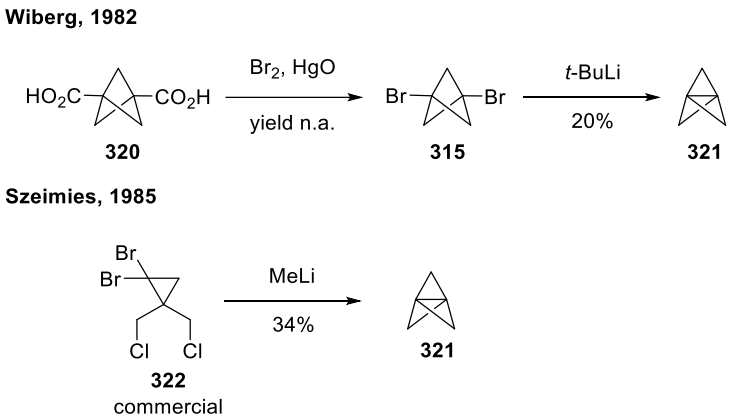
Table 3: Strain energy of BCP, cubane, BCO and reference compounds

5.3 Synthesis of Bicyclo[1.1.1]pentane

5.3.1 Tricyclo[1.1.1.0^{1,3}]pentane (TCP) Route

5.3.1.1 Synthesis and Properties of TCP

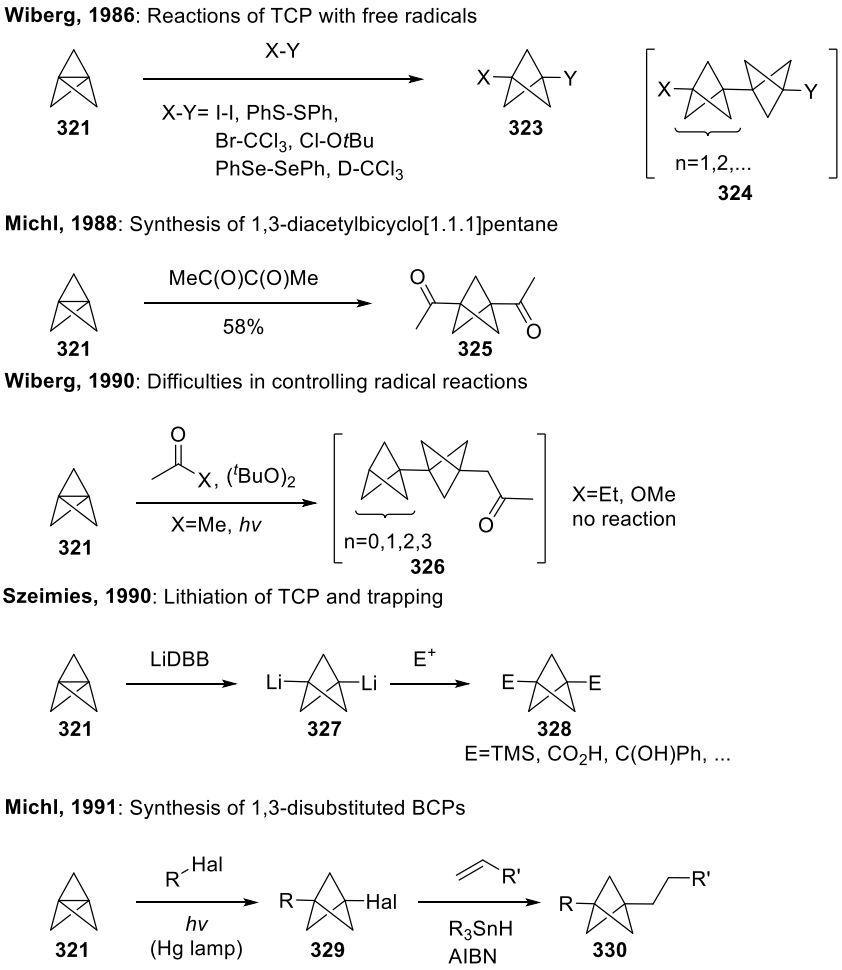
Tricyclo[1.1.1.0^{1,3}]pentane (**321**, TCP) consists of three cyclopropane rings fused along a common C-C axis. Although highly strained (~100 kcal/mol), its remarkable geometric arrangement confers a surprising amount of stability and it can be stored over months as a solution in ether at 0 °C.[139,165] TCP was first synthesised by Wiberg in 1982[166] but is more readily accessed using Szeimies' approach which has since been optimised further by several groups (Scheme 67).[167–169]



Scheme 67: Synthesis of tricyclo[1.1.1^{1,3}]pentane

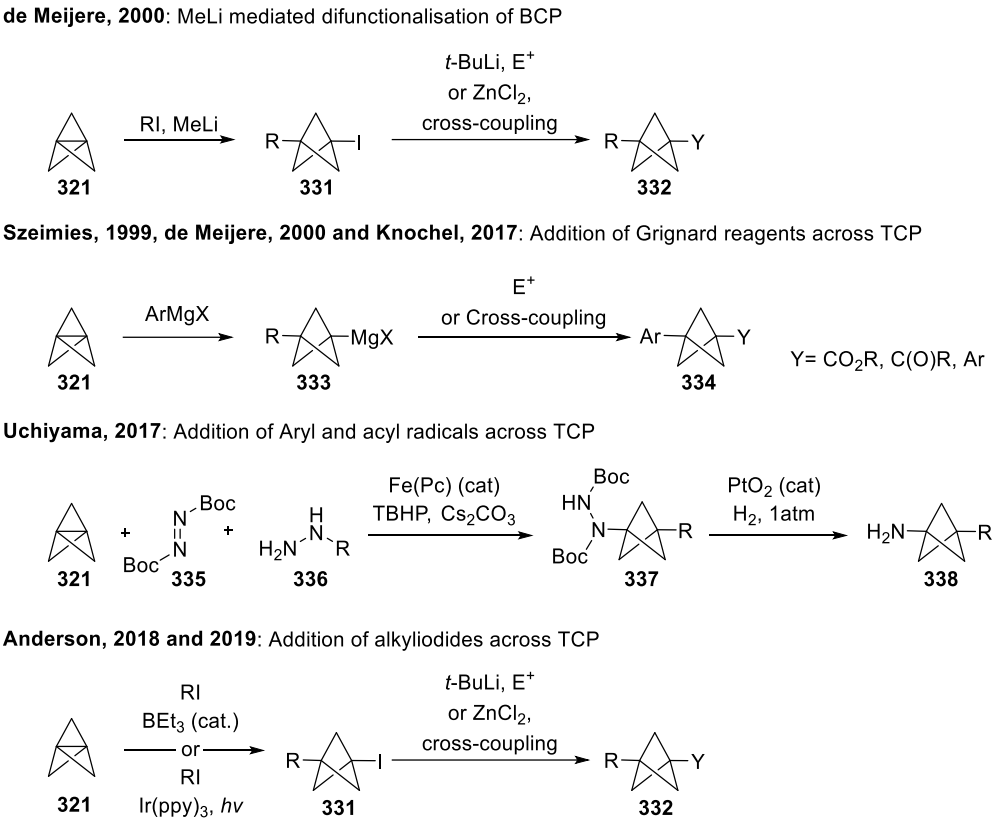
5.3.1.2 Reactivity of TCP

Initial studies focussed on reaction of TCP with suitable radicals, a very facile reaction aided by a significant strain-release of 30 kcal/mol when breaking the C_1-C_3 bond.[139,165] A variety of molecules such as iodine, diphenyl disulfide, bromoform and *tert*-butylhypochlorite were shown to open TCP in Wiberg's seminal study (Scheme 68).[170] Further researchers reported on the addition of acyl radicals,[171] ketones[165] and organohalides[172] across TCP and even on its lithiation.[173] A common problem consists in the formation of staffanes, when the bicyclopentylradical reacts with another TCP molecule before propagating the chain process.[165,174] This process is dependent on the radicals employed and can sometimes be avoided.[165] For instance, radicals derived from cyanogen bromide, acetone, methyl propiolate and THF led to staffane formation, whereas iodine, chloroform or thiophenol formed monomeric BCPs.



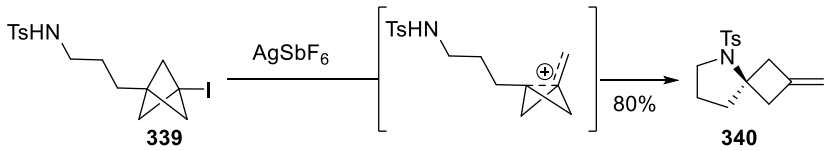
Scheme 68: Typical additions of radicals across TCP

A recent review described the synthesis of bicyclo[1.1.1]pentanes (BCP) from tricyclo[1.1.1]pentane (TCP) to be the "most promising approach".[175] Indeed, recent research enlarged the scope of TCP functionalisation significantly, and unsymmetrically substituted BCPs are now available via a variety of methods (Scheme 69 for select examples). Szeimies, de Meijere and Knochel investigated the ionic addition of organometallic compounds across TCP which allowed for subsequent Negishi cross-coupling to afford a wide variety of BCPs.[141,176,177] Uchiyama disclosed a convenient access into aminated BCPs and Anderson reported a mild atom transfer radical addition (ATRA) for the synthesis of versatile BCP iodides (**332**).[178–180]



Scheme 69: Select examples for the synthesis of difunctionalised BCPs

While radical and anionic BCPs are reasonably stable intermediates and feature in numerous transformations (*vide supra*), the analogous BCP cations are unstable and undergo rapid rearrangement to cyclobutanes (for a recent example see Scheme 70).[180]

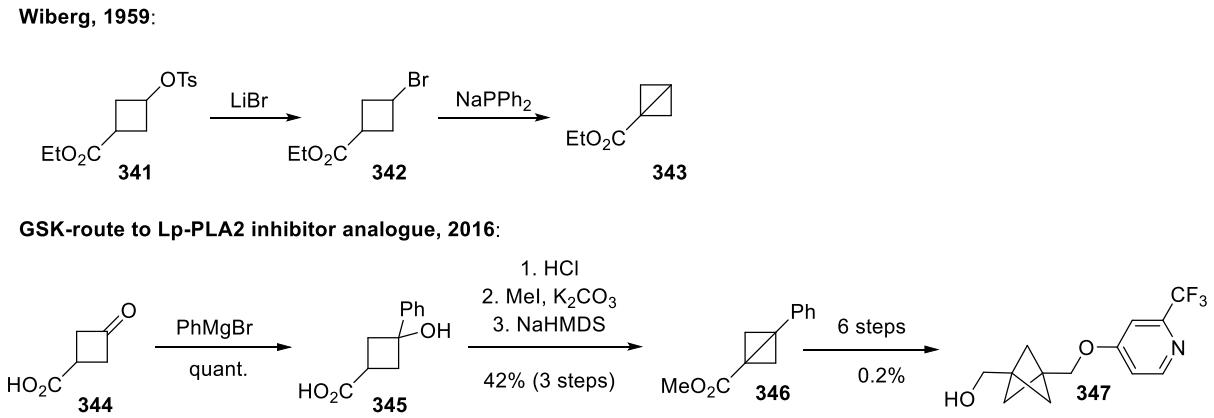


Scheme 70: Synthesis of spirocyclic cyclobutane **340** via rearrangement of BCP iodide **339**

5.3.2 BCB Carbene Route

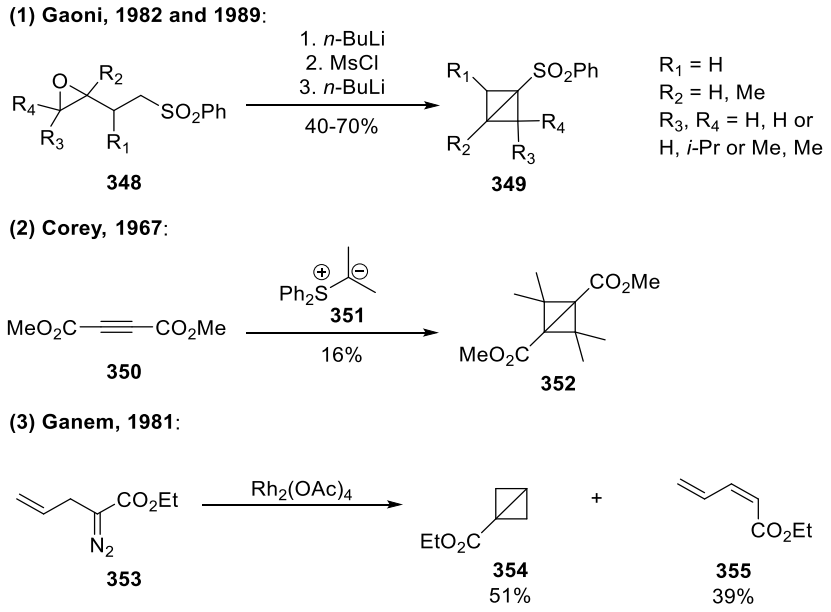
5.3.2.1 Synthesis of Bicyclobutanes

The structure and reactivity of Bicyclo[1.1.0]butanes (BCB) have been extensively studied since the 1960s,[181,182] when the first BCB **343** was synthesised by Wiberg *via* bromination of 1,3-disubstituted cyclobutane **342** and subsequent base-mediated cyclisation (Scheme 71).[183] Formation of BCBs *via* transannular nucleophilic substitution allows access to a wide variety of 1,3 substituted structures and has been widely employed since. For instance, in GlaxoSmithKline's synthesis of a Lp-PLA2 inhibitor analogue (**347**) the desired BCP **346** was prepared from cyclobutane **345**, itself accessible from commercial **344**.[184]



Scheme 71: Synthesis of BCB via transannular nucleophilic substitution

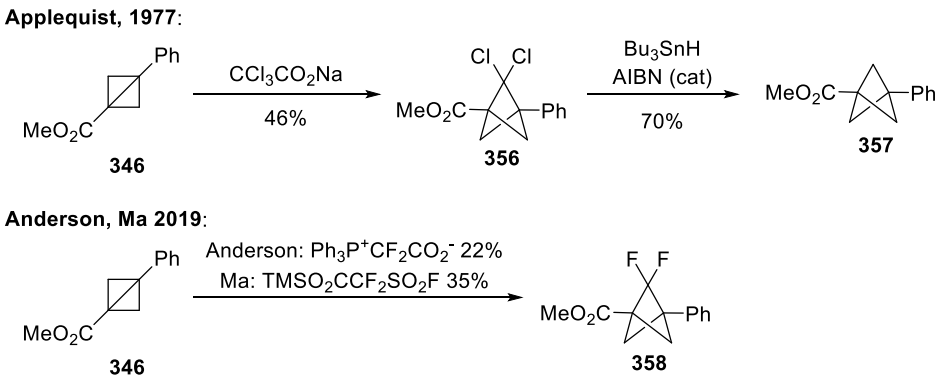
Other routes have been explored but remain highly specific and have not been adopted for the incorporation of a wider variety of substituents (Scheme 72). BCB sulfones (e.g. **349**) can be synthesised via intramolecular epoxide opening followed by nucleophilic substitution,[185,186] while *gem*-dimethyl bridge-substituted BCBs are available via double Corey-Chaikovsky reaction on electron poor alkynes.[187] Rhodium catalysed carbene insertions were also shown to afford BCBs in moderate yield.[188–190]



Scheme 72: Other Syntheses of BCBs

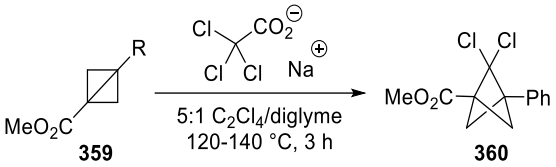
5.3.2.2 Carbene Insertion into BCB

A BCB consists of two cyclopropane rings fused along a common C-C axis, which increases its ring strain to more than twice that of cyclopropane (BCB: 67 kcal/mol, cyclopropane: 27 kcal/mol). Its central bond is nearly only p in character, arising from an enforced σ interaction between two unhybridized p orbitals.[191] Taken together, the high ring strain and p-character of the central bond result in pseudo-olefinic reactivity. The well precedented dichlorocarbene addition[192] was translated to BCBs by Applequist who first achieved synthetically useful yields for carbene insertions into the central bond of **346**.[193] Recently, together with Chan in the Anderson group, we identified phosphonium difluoroacetate (PDFA) as an efficient reagent for the difluorocarbene insertion (Scheme 73).[194] At the same time, Ma reported trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate (TFDA) as the most successful reagent of this type.[195]



Scheme 73: Carbene insertion into BCB, second equation: work by R. Chan

The successful carbene insertion requires BCBs of the general structure **359** and is highly dependent on the polarisation of the central C-C bond (Figure 15).[193,194] For instance, Chan found that the dichlorocarbene insertion proceeds in much higher yield for phenyl and *p*-methoxy phenyl than for *o*-difluorophenyl substituents and that aliphatic substituents did not give any productive conversion at all.[194] The same holds true for difluorocarbene insertion and the respective BCB-sulfones cannot be converted to BCPs via carbene insertion.



R	Yield
Ph	40%
p-$MeOC_6H_4$	34%
o,*o*-$F_2C_6H_3$	6%
n-Bu	--

Figure 15: Dichlorocarbene insertion into BCB-esters

5.4 Applications of BCP

BCPs have found application as bioisosteric surrogates for aryl,[196–201] alkynyl[177] and *tert*-butyl[202] motifs in medicinal chemistry where they can improve pharmacokinetic properties, binding affinity and selectivity of drug candidates. For example, replacing the alkyne in mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (**363**, MPEP) resulted in reduced non-specific binding (Figure 16).[177] BCPs have also seen application in materials chemistry as rod-like one-dimensional polymers,[203] supramolecular spacer units,[204] liquid crystals[205] and to biological probes as DEL fragments[201] and in FRET sensor molecules.[206]

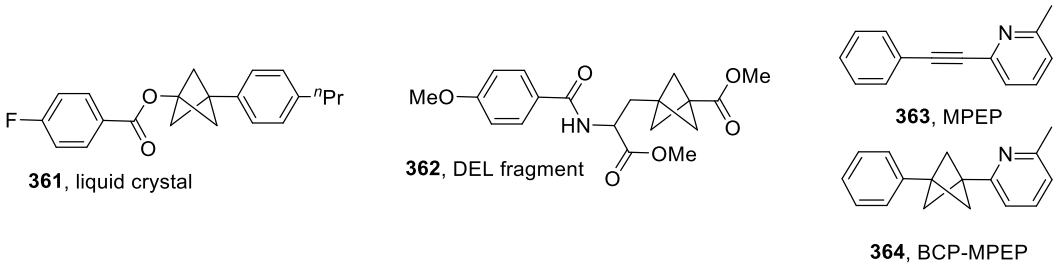
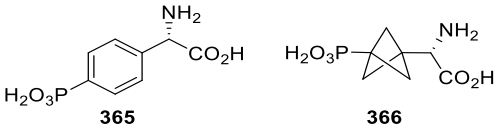


Figure 16: Applications of BCPs

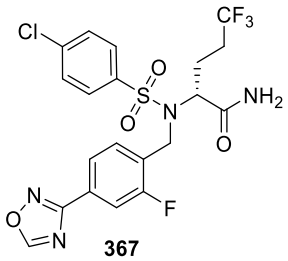
The application of BCPs in drug discovery was recently reviewed in detail.[207] Two examples will be presented to familiarise the reader with typical findings. In 2006, Pelliciarri compared the selectivity of glutamate receptor agonist **365** and its BCP analogue (**366**, Figure 17).[208] The latter maintained its activity against mGluR4 while lowering its half maximal effective concentration (EC_{50}) against mGluR6 and mGluR7, which resulted in improved group III mGluR subtype selectivity (mGluR4) over its group II subtypes.



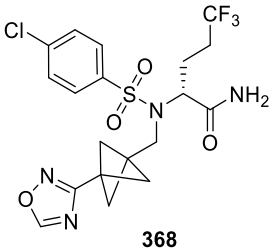
Receptor	EC_{50} [µM]	EC_{50} [µM]
mGluR4	5.3±0.1	4.2±2.0
mGluR6	4.7	66±28
mGluR7	185	>1000

Figure 17: Binding affinity of glutamate receptor agonist **365** and its BCP analogue

Recent studies by Stepan of the γ-secretase inhibitor avagacestat (**367**, drug against Alzheimers disease) showed the incorporation of BCP to result in stark improvements of pharmacokinetic properties while maintaining potent bioactivity (Figure 18).[196] For instance, logD and rate of metabolic degradation decreased and cell permeability, kinetic and thermodynamic solubility increased.



367



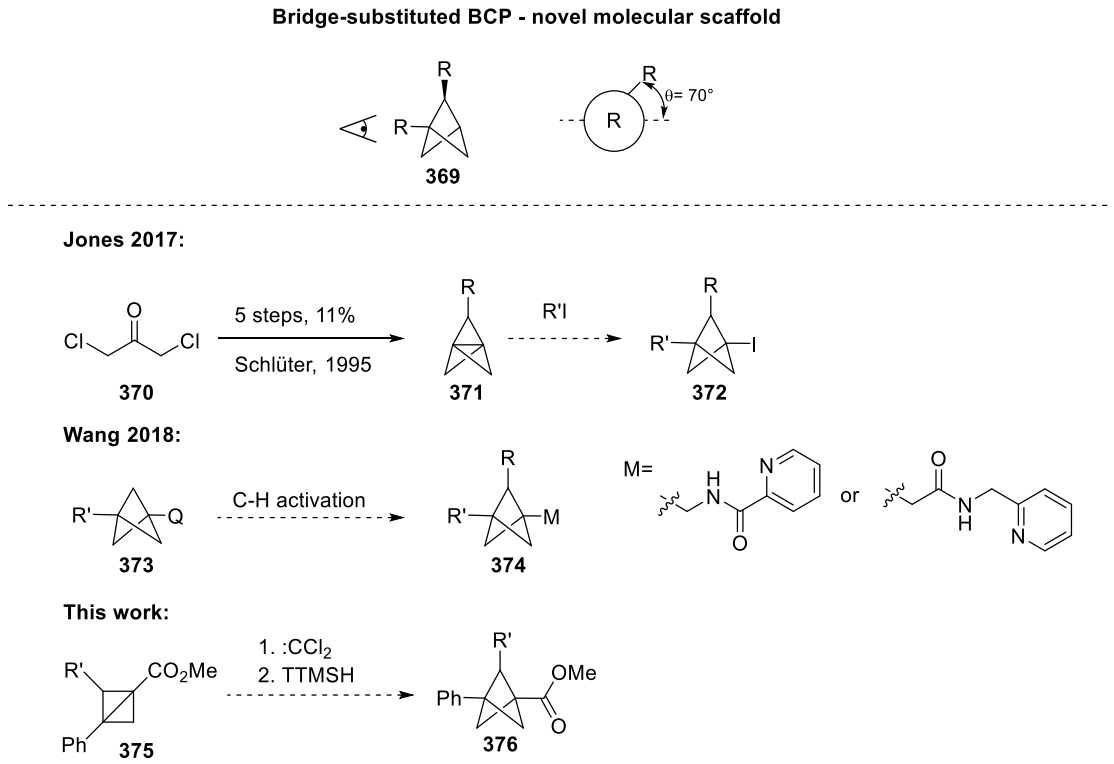
368

Properties	Avagacestat	BCP-Avagacestat
IC_{50} ($A\beta_{42}$, nM)	0.225	0.176
logD (pH=7.4)	4.7	3.8
Kinetic solubility (pH=6.5, µM)	0.6	216
Thermod. solubility (pH=6.5, µM)	1.7	19
HLM CL_{int} (mL/min/kg)	<16.2	<8.2

Figure 18: Comparison of pharmacokinetic properties of avagacestat **367** and its BCP analogue **368**

5.5 Aim of the Project

Bridge-substituted BCPs offer unique opportunities in molecular engineering, as the bridge-substituents are placed at a 70° dihedral angle (simulated on Chem3DUltra version 18.1.2.18, exact angle depends on the substitution pattern) to the linear 1,3-substituents, a relationship that cannot be achieved by current molecular scaffolds. Access to new chemical space, both in terms of new substitution vectors and new handles for the introduction of chirality, is of high interest to medicinal chemists, material scientists and others. Combined with BCPs known beneficial properties, it can be expected that these molecules would not just satisfy chemical curiosity but also find practical application. The challenge of synthesising bridge-substituted BCPs (**369**) has been a recent goal of our group (Scheme 74). Several routes have been scouted by previous members.[209,210] First, the application of ATRA reactions to bridge-substituted TCPs, introduced by Schlüter in the context of polymer synthesis,[211] was investigated but ultimately failed because Schlüter's synthesis proved difficult to reproduce.[209] Second, Wang briefly researched the possibility of C-H activation on the BCP bridge but could not identify suitable directing groups in a brief screen.[210] We questioned whether it would be possible to introduce a bridge substituent into bicyclobutane and form the bicyclobutane by carbene insertion (chapter 5.3.2).



Scheme 74: Previous attempts and our approach to bridge-substituted bicyclopentane

Our proposal would require the synthesis of a 1,2,3-substituted bicyclobutane which is poorly precedented. Known structures are mostly symmetrically substituted and hence not amenable to carbene insertion (Figure 19).[212–214] Also, 1,2-substituted bicyclobutanes featuring an ester at C1 are accessible via intramolecular rhodium-catalysed carbene insertion.[189,190] In order to succeed in the project, our first goal was thus to prepare a suitably substituted bicyclobutane.

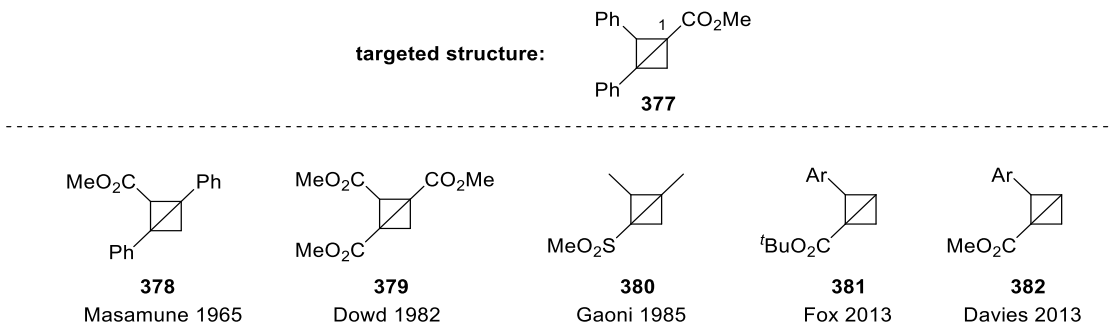
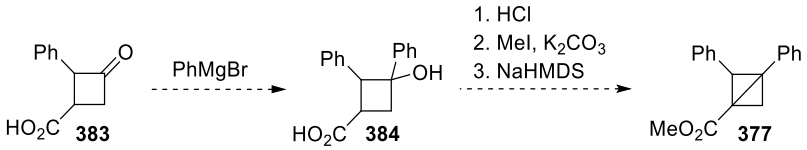


Figure 19: 1,2,3 substituted Bicyclobutanes - target and precedence

6 Synthesis of Bridge-substituted Bicyclo[1.1.1]pentanes

6.1 Synthesis of 2,3-Substituted Cyclobutanones

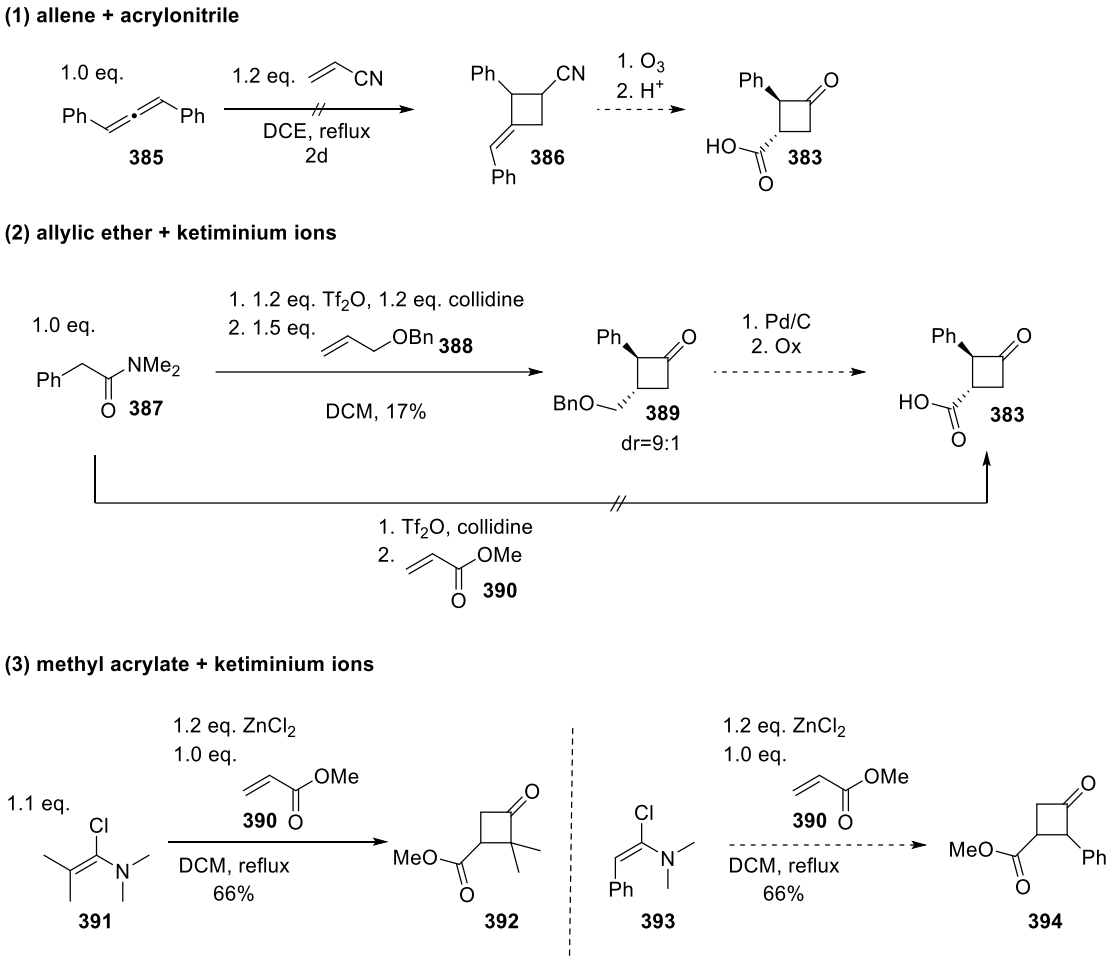
The project began by finding ways of making 2-phenyl 3-carboxy-cyclobutanone **383** which was anticipated to yield the desired 2,3-diphenylbicyclo[1.1.0]butane-1-carboxylic acids in analogy to GSKs Lp-PLA2 inhibitor synthesis (Scheme 75, see also Scheme 71).[184]



Scheme 75: Proposed synthesis of 2,3-diphenylbicyclo[1.1.0]butane-1-carboxylic acids

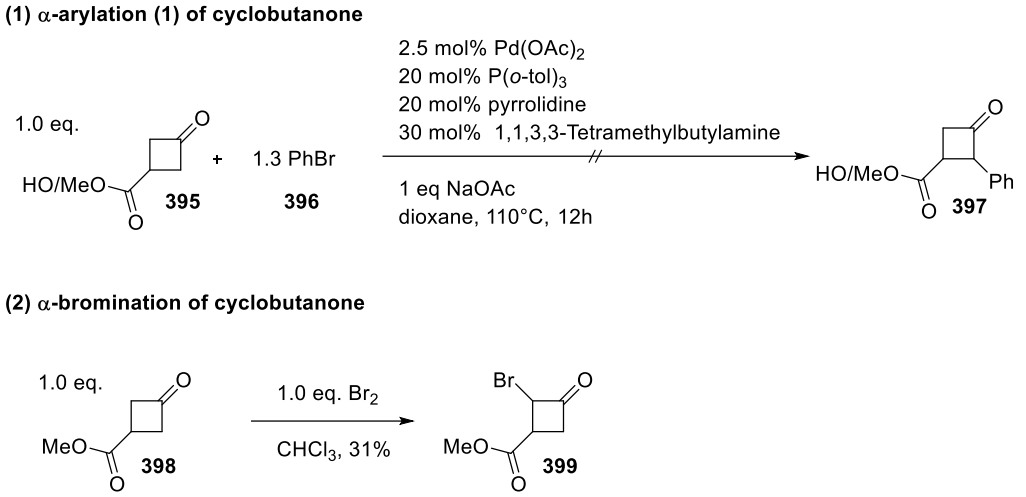
First, the [2+2]-cycloaddition of various alkenes was investigated (Scheme 76). In analogy to the literature route for the preparation of 3-oxocyclobutane-1-carboxylic acid **383** from allene and acrylonitrile at high pressure (>40 atm),[215,216] 1,2-diphenylallene[217] was heated (to 84 °C) with acrylonitrile (bp= 77 °C) at ambient pressure (Eq. 1). It was hoped that the phenyl substituents might reduce the required activation energy sufficiently, but no reaction was observed. Since our laboratory is not equipped for high pressure chemistry, this route had to be abandoned.

Looking at more activated alkene acceptors in [2+2] cycloadditions, ketiminium ions were next investigated (Eq. 2).[218,219] The relatively electron-poor allyl ether **388** did react with the ketiminium triflate of **387**, conveniently generated *in situ* from amide **387** and triflic anhydride.[220] The use of **389** would result in a rather lengthy route for the synthesis of **383** but it also was not possible to extend the above reaction to methylacrylate (**390**). On the other hand, the reaction of electron-poor olefins is well precedented in zinc(II) catalysed reactions, where the ketiminium ion is formed by chloride abstraction from iminoylchloride by Zn(II) salts.[221,222] In our hands, the reaction performed well (Eq. 3) but we were unable to prepare iminoyl chloride **393**, required for the synthesis of cyclobutanone **394**, in analogy to Ghosez' procedure for **392**. The preparation of iminoyl chlorides other than **391** is a known limitation of the field as these species tend to be highly hydrolytically sensitive and unstable. Thus, the [2+2] approach had to be abandoned.



Scheme 76: [2+2] cycloaddition for the synthesis of 2-substituted cyclobutanones

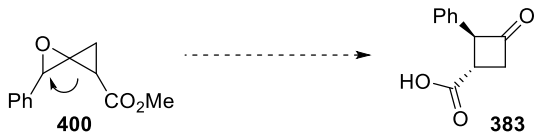
We briefly considered the α-functionalisation of cyclobutanone **395** by palladium-catalysed α-arylation (Scheme 77, Eq. 1). No methods for the α-arylation of cyclobutanones existed at the time of investigation,[223] and a couple of recent methods were surveyed (an example is depicted in equation 1) but did not bring about any reaction.[224] α-Bromination followed by nucleophilic substitution or cross-coupling was considered next.[225,226] The respective bromide **399** was obtained in an unconvincing 31% yield after screening both acid and methylester **398** under various conditions, and efforts for α-functionalisation were halted at this point.[225,227]



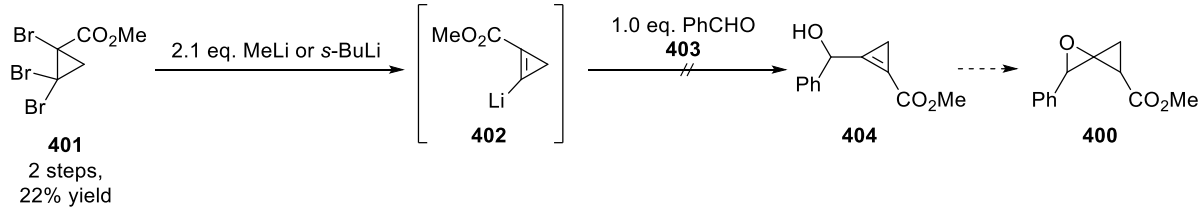
Scheme 77: α-functionalisation of cyclobutanone

Another method for the quick assembly of cyclobutanone **383**, consists in the rearrangement of highly strained spiroepoxide **400** under acidic conditions, a reaction that is precedented for a variety of similar molecules (Scheme 78).[228–230] The key to this approach relied upon a rapid synthesis of spiroepoxide **400** for which 3 routes were investigated.

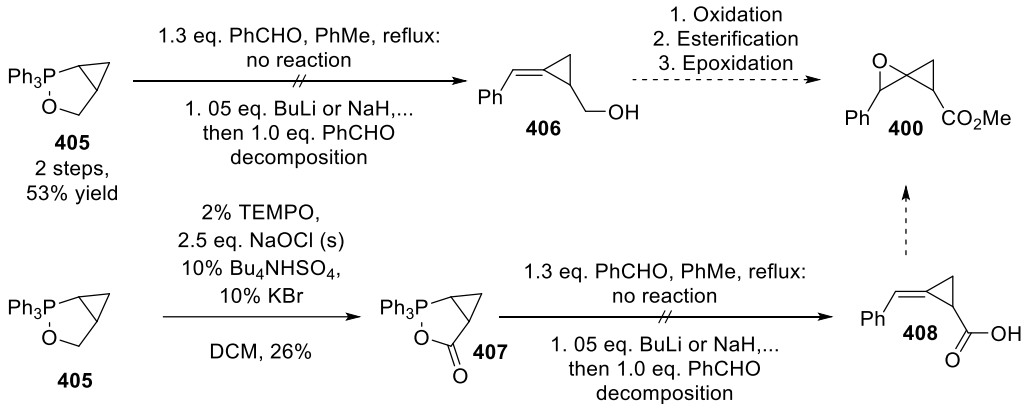
First, a domino cascade consisting of lithiation of tribromocyclopropane **401**, followed by addition of the cyclopropenyllithium species **402** into benzaldehyde (**403**) and conjugate addition of the resulting alcohol(ate) **404** into the cyclopropene was envisaged but ultimately failed because of the incompatibility of the pendant methylester.[231] The second approach consisted of a Wittig reaction of the cyclic phosphonium salt **405** with benzaldehyde (**403**), a known reaction which we were unable to reproduce despite some experimentation.[232,233] The analogous phosphonium carboxylate **407** did not result in the desired Wittig reaction either. Finally, lithiation of **409**[234] followed by acylation failed due to polymerisation of the lithium species of **409**, likely due to significant strain relief of methylenecyclopropane species during anionic polymerisation. At this point, the efforts at synthesising spiroepoxide **400** were halted.



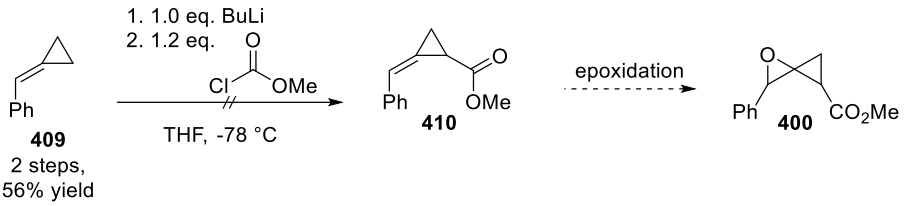
(1) cyclopropene-lithium addition, conjugate addition domino cascade



(2) methylenecyclopropene-epoxidation: Wittig approach

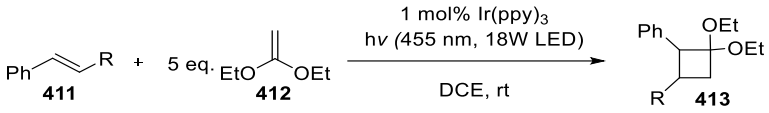


(3) methylenecyclopropene-epoxidation: acetylation approach



Scheme 78: Synthesis of cyclobutanone **383** via rearrangement of spiroepoxide **400**

Instead, a direct photoredox reaction of acceptor-substituted styrenes **411** and 1,1-diethoxyethene **412** was conceived and turned out to be a promising lead (Figure 20).[235,236] Conversion was best for cinnamic acid (75% after 11 hours) but other acceptors (the methylester and aldehyde were also tested) also performed well. Although the initial attempts at this route were promising, general scalability[237] and the cost of the photocatalyst (>£100/g of **413**) were causes for concern, especially considering that, in the GSK Lp-PLA2 inhibitor patent (Scheme 71), the yield of the BCP was 5% from the respective cyclobutanone.[184]

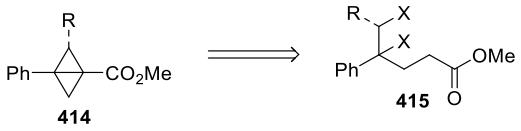


R	Conversion after 5h	Conversion after 11h
CO_2Me	41%	45%
CO_2H	67%	75%
CHO	45%	53%

Figure 20: Synthesis of Cyclobutanones by photoredox reaction, reaction carried out in an Evoluchem™ PhotoRedOx box using an Evoluchem™ 455 nm 18W LED, conversion determined by integration of characteristic peaks of starting material **411** vs product **413**

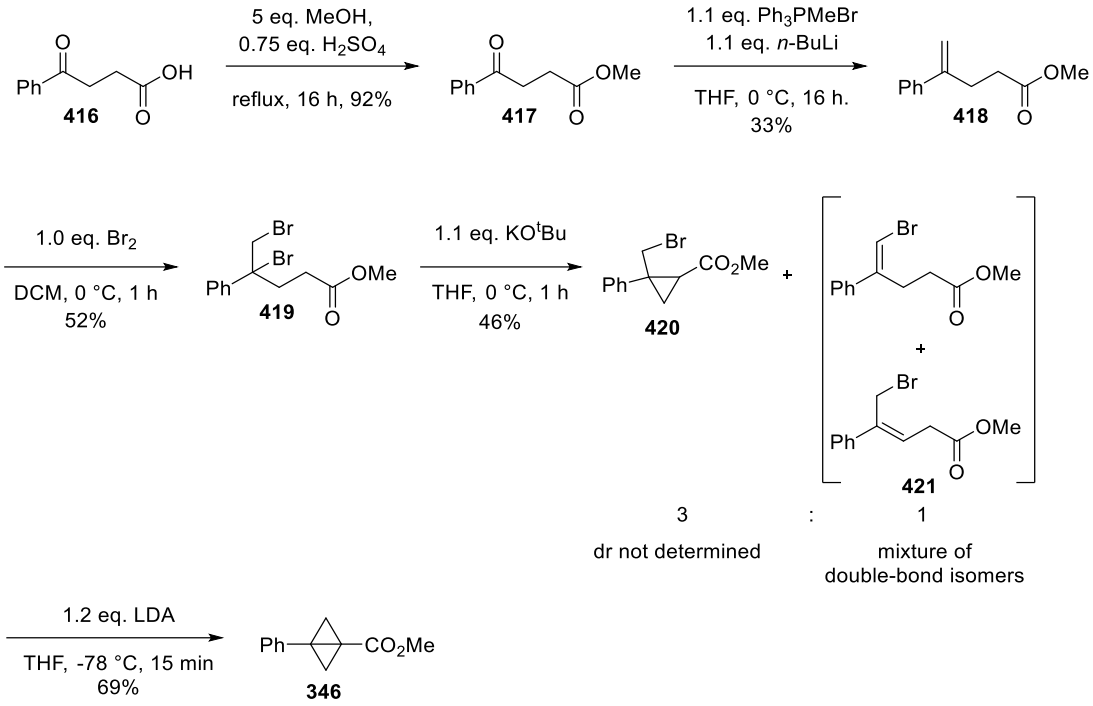
6.2 Scalable Route for the Synthesis of Bicyclo[1.1.0]butanes

No convenient synthesis of 2,3-disubstituted cyclobutanones was identified and their utility as starting materials for the preparation of bridge substituted BCBs remained thus unexplored. A major limitation of this approach is that at least 4 additional steps are required for the conversion of the cyclobutanone to the bicyclobutane (Scheme 71). Therefore, another approach was targeted. Instead of forming the cyclobutane ring first, followed by a cyclisation to afford bicyclobutane, we hypothesised that the same structure could arise from two sequential 3-exo-tet alkylation events. In this case, bridge-substitution could be incorporated directly from the starting material (**415**, Scheme 79).



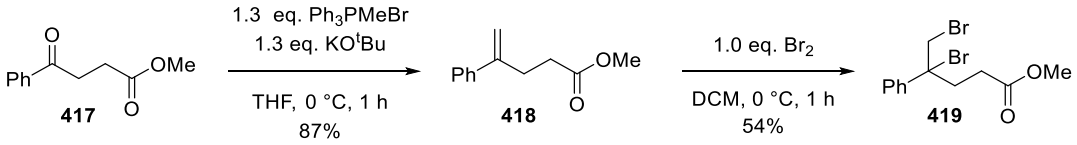
Scheme 79: Retrosynthesis of bicyclo[1.1.0]butane

The proposed synthesis worked well, and a first proof of concept was obtained within a week of investigating this novel disconnection. Thus, esterification of 3-benzoylpropionic acid (**416**) afforded methyl ester **417** in 92% yield (Scheme 80). **417** was subsequently subjected to Wittig methylenation (33%) and the resulting styrene **418** brominated (52%). A small set of bases (NaH, LiHMDS, KO*t*-Bu) was screened at 0 °C of which only potassium *tert*-butoxide afforded cyclopropane **420** as the major component (46%, 3:1 mixture with elimination by-products). Cyclopropane **420** was subsequently cyclised to bicyclobutane **346** with LDA in 69% yield.



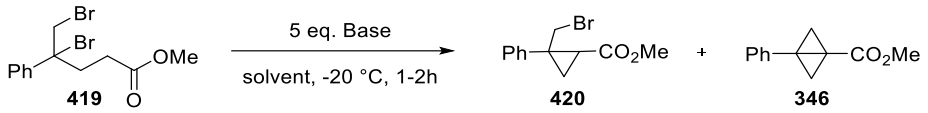
Scheme 80: Proof of concept synthesis of bicyclo[1.1.0]butane

Subsequent optimisations showed that the Wittig methylenation proceeded best when 1.3 equivalents of preformed ylide were added to phenyl ketone **417** (Scheme 81). Reverse order of addition led to only 50% conversion, potentially due to competitive deprotonation of the methyl ester by the ylide, resulting in its inactivation. Furthermore, *n*-butyllithium was replaced with the easier to handle potassium *tert*-butoxide. The outcome of the subsequent bromination could not be improved by decreasing the reaction temperature to -20 °C or changing the concentration of the reaction mixture or reagent.



Scheme 81: Optimisation results of Wittig methylenation and bromination

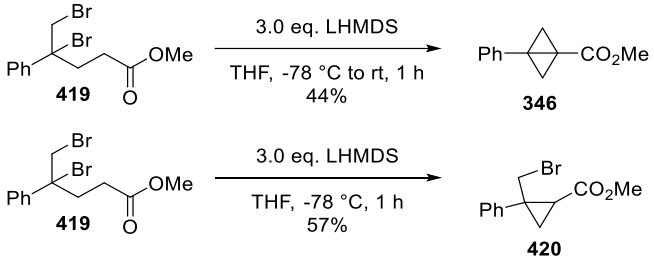
The intramolecular alkylation of **419** was investigated next. An array of bases, in various solvent systems was screened at -20 °C (unless otherwise stated) but mostly led to decomposition (Table 4). An exception was the previously identified potassium *tert*-butoxide which afforded the cyclopropane. Much to our delight, LiHMDS directly afforded the desired BCB without any elimination by-products when added at -78 °C whereas NaHMDS afforded the BCB together with elimination by-products in a 3:1 ratio.



Base	Decomposition	Other outcome
KO*t*-Bu	PhMe, PhMe+Et_3N, *t*-BuOH, DMSO	THF: formation of cyclopropane
LDA	-78 °C: THF, hexanes + Et_3N	
LiO*t*-Bu	hexanes + Et_3N	
KOH	0 °C: DMSO	
NaH	THF	
LiHMDS	hexanes (no reaction) Et_2O, TBME	hexanes + Et_3N, THF (-20 °C: BCB:elimination 3:1), THF (-78°C to rt, clean)
NaHMDS		THF (-78 °C, BCB:elimination 3:1)
$NaNH_2$	THF	

Table 4: Base screening for the cyclisation of dibromide **419** to BCB **346**, ratios determined by ^{1}H-NMR spectroscopy

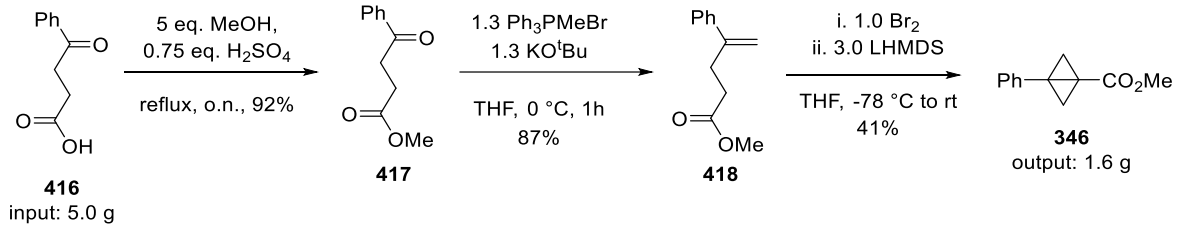
Further optimisation showed that the addition of 3.0 equivalents (more are not detrimental to the yield) of LiHMDS to dibromide **419** afforded BCB **346** in 44% yield (Scheme 82). The intermediate cyclopropane (**420**) was isolated in 57% yield when the reaction temperature was kept at -78°C. This identifies the first reaction as the lower yielding alkylation of the two.



Scheme 82: Optimisation results for LiHMDS mediated cyclisation of **419**

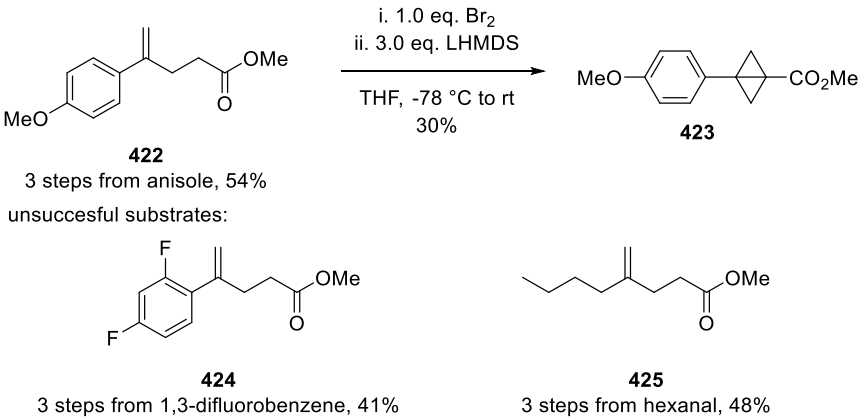
Finally, bromination and cyclisation of **418** could be conducted in one pot in 41% yield, a significant improvement over the 24% two step procedure (Scheme 83). The final route is

summarised below and affords bicyclobutane **346** in 3 steps and 33% yield on gram scale (1.6 g prepared) from 3-benzoylpropionic acid **416**. This route compares favourably to previous syntheses, e.g. GSKs Lp-PLA2 inhibitor synthesis, where BCB **346** was prepared in 42% yield from cyclobutanone **344** in 4 steps; **344** being prepared in 54% yield from readily available di-*i*-propylmalonate.[238]



Scheme 83: Gram-scale synthesis of bicyclobutane **346**

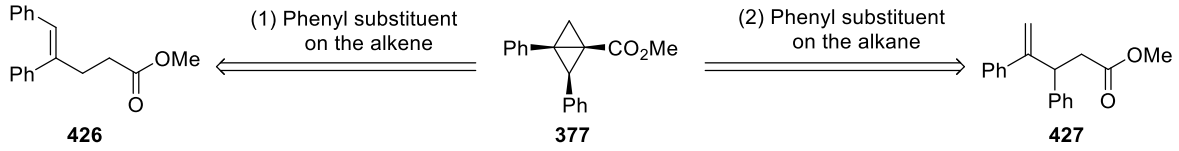
The scope of the established reaction was briefly investigated (Scheme 84). The p-methoxy derivative afforded the respective BCB **423** in 30% yield, whereas the electron deficient di-fluoroderivative **424** and the aliphatic butyl derivative **425** only led to decomposition after successful bromination. The aryl substituted alkenes were prepared in analogy to the parent phenyl compound (Scheme 83) and butyl substituted alkene **425** through a known procedure.[239]



Scheme 84: Scope of BCB-synthesis

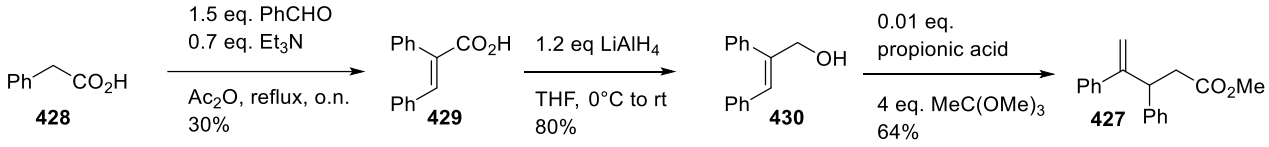
6.3 Bridge-substituted BCB via One-pot Dialkylation

The successful synthesis of BCB **346** enabled us to investigate the option of introducing bridge-substitution on the BCB (Scheme 85). This could either take place through substitution on the alkene (1) or on the aliphatic chain (2).



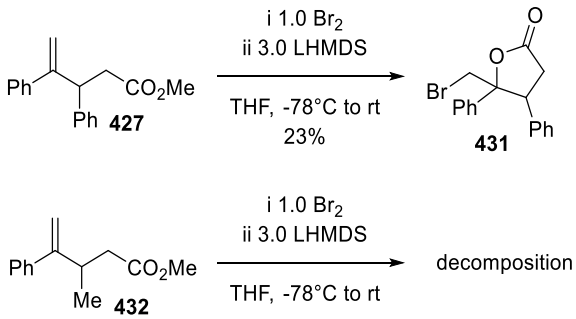
Scheme 85: Proposed synthesis of bridge-substituted BCBs

Alkene **427** was first targeted and could be obtained through sequential aldol-condensation, lithium aluminium hydride reduction and Johnson-Claisen rearrangement (Scheme 86).



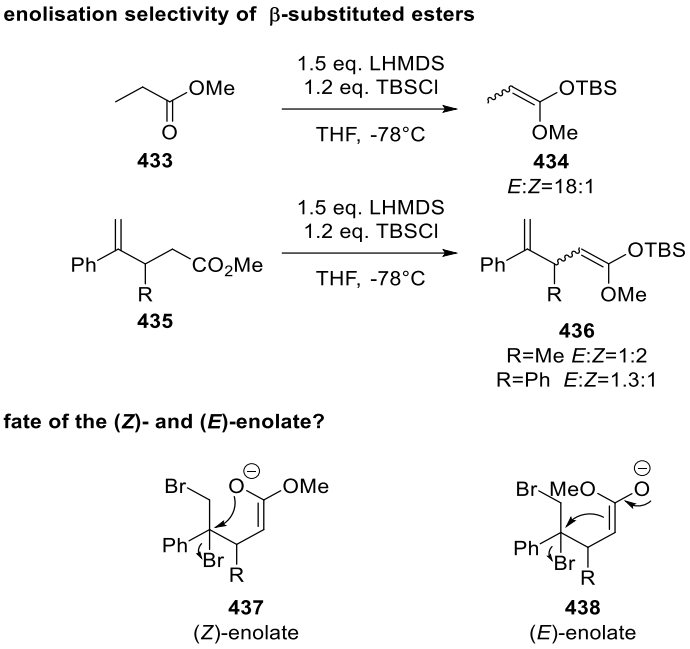
Scheme 86: Synthesis of alkene **427**

Surprisingly, the reaction of alkene **427** under the optimised conditions yielded lactone **431** as the only isolable product in 23% yield (Scheme 87). Questioning whether a smaller substituent would fare better (reduced Thorpe-Ingold effect), the allylic phenyl group was replaced with a methyl group (**432**, prepared in analogy to Scheme 86). However, when treated with bromine and LiHMDS a large number of unidentified products was formed.



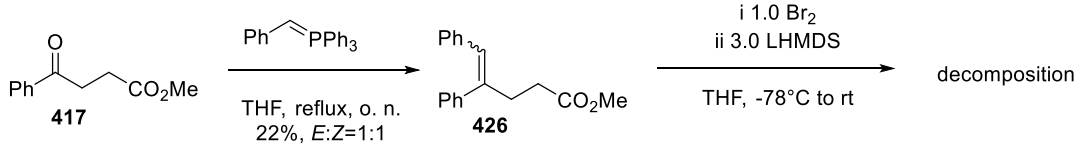
Scheme 87: Attempted cyclisation of alkenes substituted in allylic position

The successful bromination of **427** and **432** was verified in separate control experiments which left the cyclisation of the dibromide as the problematic step. The enolisation selectivity of **427** and **432** was compared to the unsubstituted case and, indeed, a rather large (*Z*)-proportion of the ester (*Z*)-enolate was trapped by TBSCl and identified by ^{1}H-NMR- spectroscopy of the crude reaction mixture (Scheme 88). This variation in enolate geometry could well be at the cause of the moderate yield of lactone **431**, which is formed via O-alkylation, but does not offer any definite confirmation.



Scheme 88: Enolisation of β-substituted esters

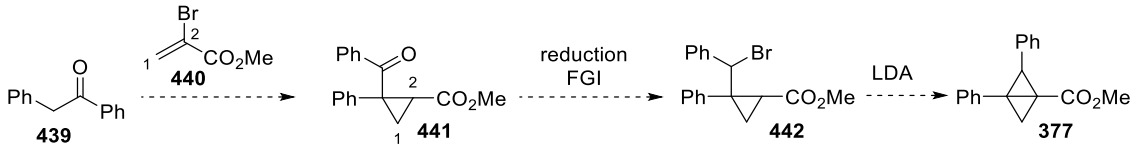
The performance of the phenyl-substituted alkene (**426**) was investigated next. This was prepared by Wittig olefination of ketone **417** and was obtained as a 1:1 *E*:*Z* mixture, which was subjected to the bromination-cyclisation conditions (Scheme 89). Again, no signs of BCB were identified while the bromination performed well and thus, the reaction was abandoned.



Scheme 89: Investigation of phenylsubstituted alkenes in bromine-LiHMDS cyclisation protocol

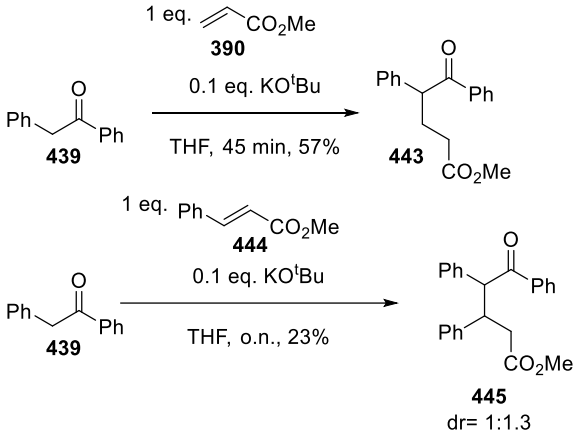
6.4 Bridge-substituted BCB via Sequential Alkylations

At this point, it seemed likely that the first alkylation event which leads to the formation of cyclopropane **420** was the cause of our troubles (Scheme 82). Indicators for this were the low tolerance of the reaction against variations of the substitution pattern on the alkene (Scheme 84 and Scheme 89) and next to it (Scheme 87). This hypothesis could be verified by separating the two alkylation events and a new approach was conceived (Scheme 90). Thus, cyclopropane **441** would be prepared via sequential conjugate addition and intramolecular alkylation, a similar reaction of phenyl acetaldehyde has precedence,[240] and subsequent reduction, bromination and cyclisation would afford the desired bridge-substituted bicyclobutane **377**.



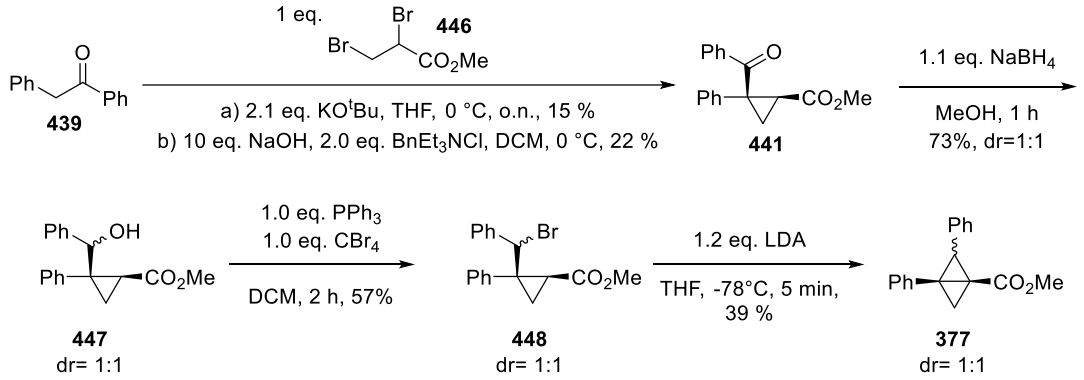
Scheme 90: Synthesis of bridge-substituted BCBs via two separate intramolecular alkylations

Investigations started by adding methyl methacrylate (**390**) to phenylacetophenone (**439**) in 57% yield catalysed by 10% potassium *tert*-butoxide (Scheme 91).[241] The reaction proceeded much slower with methyl cinnamate (**444**) as the acceptor but afforded a respectable 23% yield and the prospect of double bridge-substitution (Scheme 90).



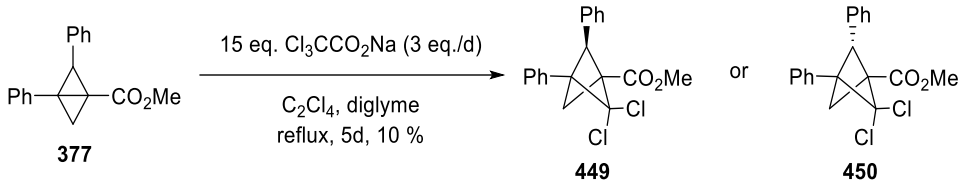
Scheme 91: Addition of methylacrylate and methylcinnamate to phenyl acetophenone

Although sluggish, the reaction between methyl α-bromoacrylate (which is polymerisation prone and was generated *in situ*) and phenyl acetophenone in the presence of potassium *tert*-butoxide afforded the desired product in 15% yield as the *syn*-isomer (determined by NOE correlations) (Scheme 92). The reaction was also conducted using phase-transfer catalysis, but the high affinity of bromide for ammonium salts necessitated the stoichiometric use of benzyltriethylammonium chloride.[242,243] Nevertheless, the reaction profile was much cleaner (only cyclopropane **441** detected by TLC) and the product was obtained in 22% yield. It is possible that ester hydrolysis was the cause for this surprisingly low yield, but time constraints prevented a thorough optimisation of this step. The ketone was subsequently reduced to yield a mixture of separable diastereomeric alcohols **447**, which were converted into the bromides **448** via Appel reaction. When a 10:1 diastereomeric mixture of alcohol **447** was subjected to these bromination conditions, the bromide **448** was obtained in a 3:1 ratio of its diastereomers consistent with a 35% S_N1-pathway (or full S_N1-pathway if 3:1 is thermodynamic ratio). The bromide **448** was cyclised on treatment with LDA to give the bridge-substituted BCB **377** in 39% yield, a reaction that proceeds without loss of stereochemical information (a 3:1 mixture of bromides yielded a 3:1 mixture of products).



Scheme 92: Synthesis of bridge-substituted BCB

The above procedure allowed for access of 200 mg of bicyclobutane **377** which was subjected to dichlorocarbene insertion (Scheme 93).[193] The reaction proceeded very slowly and required multiple addition of sodium trichloroacetate but afforded the desired bridge-substituted bicyclo[1.1.1]pentane (**449**/ **450**) in 10% yield, an important proof of concept. This product appears to be a single diastereomer based on aliphatic ^{1}H-NMR-signals; however, the aromatic region is not well resolved, and further analysis is required. Time constraints prevented further optimisations and the reduction of the *gem*-dichloride on the bridge.



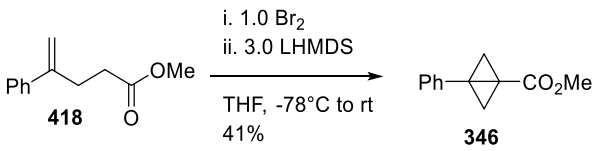
Scheme 93: Synthesis of bridge-substituted bicyclo[1.1.1]pentane

7 Conclusion and Future Work

This project was designed to find an entry into bridge-substituted bicyclo[1.1.1]pentanes, an intriguing molecular scaffold with potential application in medicinal chemistry, material sciences and others.

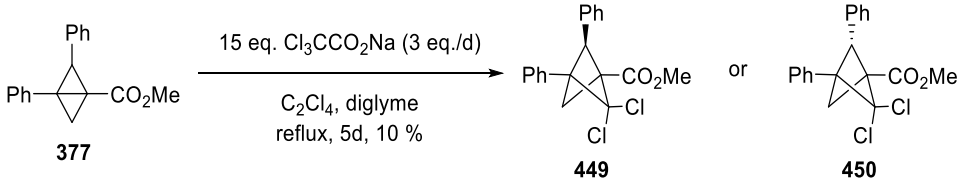
First, the synthesis of 2,3-substituted cyclobutanones as precursors to 1,2,3-substituted BCBs was examined. Of the many approaches, a photoredox reaction of 1,1-diethoxyethene and cinnamic acid showed some promise but had to be abandoned because of cost and scale-up concerns (Figure 20).

Second, a novel intramolecular double alkylation of *vic*-dibromides was developed and optimised which resulted in a scalable synthesis of BCB **346** (Scheme 83, Scheme 94). The scope of the reaction was briefly investigated, phenyl was successfully replaced by *p*-methoxybenzene (30% yield), but *o,p*-difluorobenzene and *n*-butyl were not tolerated and led to decomposition (Scheme 84). Unfortunately, this approach was also unsuccessful for the incorporation of bridge substituents as the respective *vic*-dibromides decomposed in presence of LiHMDS (Scheme 87, Scheme 89).



Scheme 94: Gram-scale synthesis of bicyclobutane **346**

Finally, bridge-substituted BCB **377** was obtained by a modified route consisting of domino conjugate addition and intramolecular alkylation, reduction, bromination and cyclisation (Scheme 92). Dichlorocarbene insertion into **377** was slow but ultimately successful and afforded bridge-substituted bicyclo[1.1.1]pentane **449**/ **450** (Scheme 95).

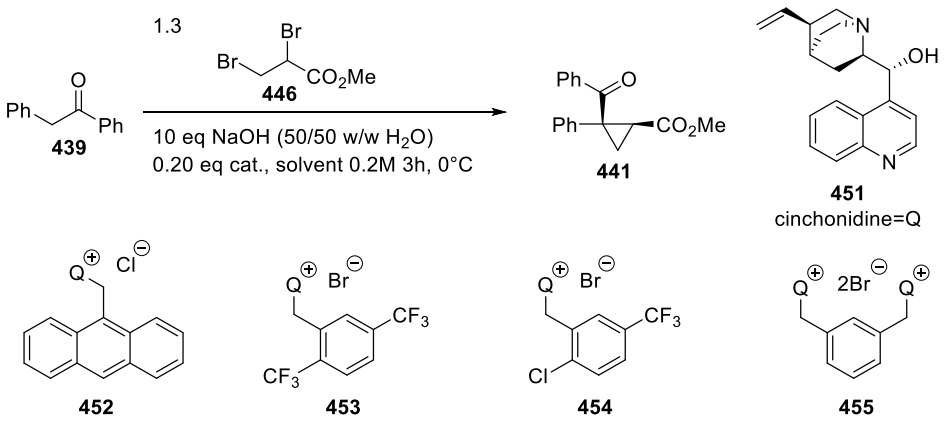


Scheme 95: Synthesis of bridge-substituted bicyclo[1.1.1]pentane

This exploratory study highlights a number of issues and opportunities that should be addressed in future work.

First, the developed BCB synthesis (Scheme 83, Scheme 94) is characterised by a short step-count, cheap reagents and good yield. Substrates of this type find application in the pharmaceutical industry (chapter 5.4) and interest in a convenient methodology for accessing them can be expected. So far, the scope of our reaction sequence has not been thoroughly explored (Scheme 84) and preliminary results suggest that further modifications might be required to accommodate a larger range of substituents.

Second, the ultimately successful approach towards bridge-substituted BCBs has not been optimised due to time constraints (Scheme 92). The first step in particular requires attention as it proves the bottle neck of our synthesis in terms of yield. The use of phase-transfer catalysis was a huge step forward in improving the reaction profile. Furthermore, it offers the prospect of introducing chirality in the synthesis via asymmetric versions.[244] a limited survey has been carried out as part of our studies (biscinchonidine catalyst **455** performed best)[245] and may serve as a basis for further investigations (Figure 21).



solvent	Yield (ee)	Yield (ee)	Yield (ee)	Yield (ee)
PhMe	50% (0%)	18% (0%)	7% (0%)	11% (0%)
DCM	93% (1.5%)	100% (2.7%)	8% (n.d.)	89% (8.1%)
DCE	99% (3.4%)	100% (2.8%)	72% (2.0%)	n.d.

Figure 21: Screening of some phase-transfer catalysts for the asymmetric synthesis of **441**, ee and yields determined by HPLC analysis (yields: internal standard (1,3-dimethoxybenzene))

Third, our approach might extend to double bridge-substitutions, if dibrominated cinnamic acid derivatives are employed instead of methyl 2,3-dibromopropionate **446**. A test reaction showed lowered reactivity and some optimisation might be required (Scheme 91).

Finally, the entire strategy of synthesising bridge-substituted BCPs from 2-substituted BCBs stands and falls with the efficiency of insertion of carbene or carbenoids into the central BCB bond. Dichlorocarbene insertion followed by reduction is the classic approach but maybe it is possible to find a more convenient and higher yielding alternative. Options could be the conjugate addition of a methane carbenoide,[189] the insertion of a highly active aluminium carbenoide[246] or copper-mediated insertion of diazomethane.[247]

Experimental and References

8 Experimental

8.1 General Considerations

Reagents and solvents: All reagents, obtained from Acros, Aldrich, Fluka, Lancaster, Strem and Fluorochem fine chemicals suppliers, were used directly as supplied. Solvents were either used as commercially supplied, or as purified by standard techniques. Dichloromethane (DCM), tetrahydrofuran (THF), toluene (PhMe) and methanol (MeOH) were obtained anhydrous from solvent dispenser units having been passed through an activated alumina column under argon. 1,2-dimethoxyethane (DME) and propane-1,3-diol were distilled over calcium hydride under reduced pressure prior to use. Diethylamine was distilled under nitrogen over 3 Å molecular sieves. Anhydrous dimethyl sulfoxide (DMSO) was purchased from Fisher Scientific and used as received. Petroleum ether ether refers to the fraction of petroleum ethereum ether which boils in the range 40-60 ºC. Tetrabutylammonium fluoride (TBAF) solution was obtained by dissolving tetrabutylammonium fluoride trihydrate in anhydrous THF. TBAF·$3H_2O$, and potassium trimethylsilanolate was weighed out in a glove box under nitrogen. Potassium trimethylsilanolate was purchased from CombiBlocks.

Reaction techniques: Unless otherwise stated, non-aqueous reactions were performed in oven dried apparatus under nitrogen atmospheres at room temperature.

Reactions were monitored by thin layer chromatography on pre-coated aluminium-backed plates (Merck Kieselgel 60 with fluorescent indicator UV254). Spots were visualised by quenching of UV fluorescence or by staining with potassium permanganate or vanillin, and retention factors are reported with the solvent system in parentheses. Flash column chromatography was performed on silica gel obtained from Macherey Nagel (MN 60, 230–400 mesh) under positive nitrogen pressure, using the solvent system quoted in parentheses.

NMR Spectroscopy: ^{1}H NMR spectra were recorded at 200, 250, 400 or 500 MHz on a Bruker DPX 200, Bruker DPX 250, Bruker DPX 400, Bruker DQX400, Bruker AVN 400, Bruker DRX500 or Bruker AVII 500, respectively. ^{13}C NMR spectra were recorded at 101 MHz or 125 MHz on a Bruker DQX 400, Bruker AVN 400, Bruker DRX500 or a Bruker ACII 500 with ^{13}C cryoprobe, respectively. Proton, carbon and phosphorus chemical shifts (δ_H, δ_C, δ_P) are quoted in ppm. ^{1}H NMR spectra were recorded using an internal

deuterium lock for the residual protons in $CDCl_3$ (δ 7.26). ^{13}C NMR Spectra were recorded using an internal deuterium lock using solvents $CDCl_3$ (δ 77.16). Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HMBC, HSQC and/or NOESY experiments. Peak multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, spt = septet, m = multiplet, br. = broad; and coupling constants (*J*) are reported to the nearest 0.1 Hz.

Infrared Spectroscopy: Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer with the sample being prepared as a thin film on a diamond ATR module. Absorption maxima (v_{max}) are quoted in wavenumbers (cm^{-1}).

Mass Spectrometry: Low resolution mass spectra were recorded on a Micromass LCT Premier Open Access using electrospray ionisation (ESI). Accurate mass (HRMS) data was determined under conditions of ESI on a Bruker MicroTOF. High resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

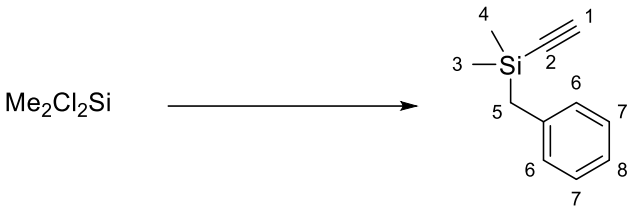
Melting Points: Melting points were obtained using a Griffin melting point apparatus and are uncorrected.

Specific Rotation: Optical Rotations were recorded on a Perkin Elmer 241 or 341 polarimeter with a path length of 1 dm (using sodium D line, 589 nm). $[\alpha]_D$ are reported in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are reported in g/100mL. Temperatures are reported in °C.

High performance liquid chromatography: HPLC was performed on an Agilent 1200 Series running in normal phase under UV detection using a ZORBAX RX-SIL (150 mm x 4.6 mm ID).

8.2 Synthesis of BDMS-alkynes

Benzyl(ethynyl)dimethylsilane, 193



FRU-555

A solution of benzylmagnesium chloride was prepared from slow addition of benzyl chloride (35.5 mL, 308 mmol, 1.0 eq.) and diethyl ether (250 mL) on an excess of magnesium (10.48 g, 431 mmol. 1.4 eq.) in diethyl ether (50 mL). The reaction mixture was stirred at room temperature for 2 hours, then the etheral layer was decanted into a dropping funnel and added dropwise within 10 minutes to neat dimethyldichlorosilane (52.0 mL, 400 mmol, 1.4 eq.) at 0 °C under argon. After 15 minutes the ice bath is removed and stirring continued for 1 h at room temperature, a white salt precipitates. The suspension is settled, and the supernatant decanted into a flask that was previously inerted (vacuum/argon). The solvent and excess of dimethyldichlorosilane were removed by concentration *in vacuo* to afford crude benzyldimethylchlorosilane as a pale yellow oil.

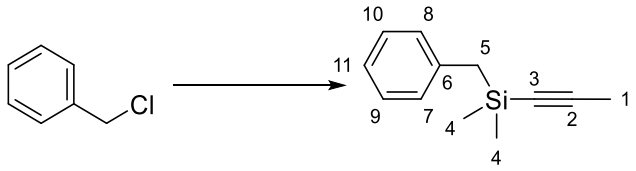
To a solution of crude benzyldimethylchlorosilane in THF (250 mL) at 0 °C was added dropwise (45 min) a solution of ethynyl magnesium bromide (800 mL, 0.5 M in THF, 400 mmol, 1.3 eq.). The reaction mixture was warmed at room temperature, stirred overnight, quenched at 0 °C with saturated 2 N HCl (100 mL) and diluted with water (100mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 x 100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petroleum ether) gave ethynylbenzyldimethylsilane (42.01 g, 79 %) as colorless oil.

The physical data were found to be in agreement with previous reported (*JACS* **2005**, *127*, 3666.

^{1}H NMR (400 MHz, $CDCl_3$) 7.28-7.20 (m, 2H, H-7), 7.16-7.06 (m, 3H, H-6, H-8), 2.44 (s, 1H, H-1), 2.25 (s, 2H, H-5), 0.18 (s, 6H, H-3, H-4);

^{13}C NMR (101 MHz, $CDCl_3$) 138.7, 128.5 (2C), 128.4 (2C), 124.6, 94.5, 88.7, 26.0, –2.2.

Benzyldimethyl(prop-1-yn-1-yl)silane, 211



FRU-175

A solution of benzylmagnesium chloride was prepared from slow addition of benzyl chloride (16.0 mL, 139 mmol, 1.0 eq.) and Et_2O (120 mL in a different funnel) to an excess of magnesium (4.74 g, 195 mmol, 1.4 eq.) in Et_2O (20 mL). The reaction mixture was heated at reflux for one hour. After cooling at room temperature, this solution is added dropwise to dimethyldichlorosilane (24.0 mL, 199 mmol, 1.4 eq.). After heating at reflux for one hour, the mixture is cooled to room temperature. The solvent and excess dimethyldichlorosilane were removed by concentration *in vacuo*. The crude residue was redissolved in THF, filtered under nitrogen and the salt washed with anhydrous ether to yield crude benzyldimethylchlorosilane as a pale-yellow oil.

To a solution of crude benzyldimethylchlorosilane in THF (240 mL) at 0°C was added dropwise (15 min) a solution of ethynyl magnesium bromide (304 mL, 0.5 M in THF, 152 mmol, 1.3 eq., relative to benzyl chloride). The reaction mixture was warmed to room temperature, refluxed for one hour, before being quenched at 0°C with saturated NH_4Cl (50 mL) and water (100mL). The aqueous layer was extracted with Et_2O (3 x 50mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give crude ethynylbenzyldimethylsilane (21.5 g, 124 mmol, 89%).

n-Butyllithium (61.0 mL of a 2.5 M solution in hexanes, 152 mmol, 1.2 eq.) was added dropwise to a solution of crude ethynylbenzyldimethylsilane (21.5 g, 124 mmol, 1.0 eq.) in THF (240 mL) at –78 °C. The solution immediately turned pale red and was stirred for 10 minutes at –78 °C. Then, methyl iodide (12.4 mL, 199 mmol, 1.4 eq.) was added to the alkynyl lithium at –78 °C which caused the red colour to disappear. The solution was stirred for a further 10 minutes at this temperature, warmed to 0°C, and stirred for 30 minutes. It was subseq.uently concentrated *in vacuo* and the residue taken up in 50 mL of water and 30 mL Et_2O. The aqueous layer was extracted with Et_2O (2 x 30 mL) and

the combined organic phase dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (19:1)) gave benzyldimethyl(prop-1-yn-1-yl)silane (19.9 g, 114 mmol, 76%) as colourless oil.

Rf 0.80 (petroleum ether);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 2H, H7 to H-11), 7.14 – 6.90 (m, 3H, H7 to H-11), 2.18 (s, 2H, H-5), 1.89 (s, 3H, H-1), 0.10 (s, 6H, H-4).

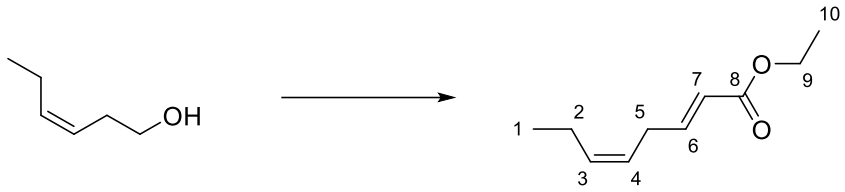
^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 128.5 (2C), 128.3 (2C), 124.4, 104.5, 82.4, 26.6, 5.1, –1.9 (2C).

IR (thin film, ν_{max} / cm^{-1}) 3026, 2960, 2182, 1493, 1250, 836, 698.

HRMS (EI^+) not found.

8.3 Synthesis of Left-hand Side Fragments for RvD3 and RvE1

Ethyl (2*E*,5*Z*)-octa-2,5-dienoate, 188



FRU-101

Dess-Martin periodinane (6.36 g, 15.0 mmol, 1.5 eq.) was added portion wise to a vigorously stirred solution of (*Z*)-3-hexenol (1.2 mL , 10 mmol, 1.0 eq.) in DCM (20 mL) at room temperature over 10 minutes. The solution was stirred for 3 hours and subseq.uently filtered. The filtrate was washed with 40 mL saturated $NaHCO_3$. The aqueous phase was extracted three times with 25 mL Et_2O. The combined organic phase was dried ($MgSO_4$) and concentrated (T=30°C, p>400mbar) to yield crude (*Z*)-3-hexenal.

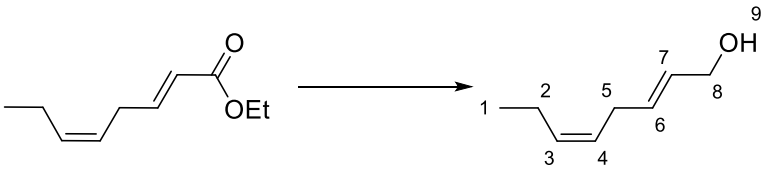
n-Butyllithium (7.5 mL of a 1.6 M solution in hexanes, 12 mmol, 1.2 eq.) was added dropwise to a solution of triethyl phosphonoacetate (2.6 mL, 13 mmol, 1.3 eq.) in THF (5 mL) at 0 °C. After stirring the pale-yellow solution for 10 minutes, the crude aldehyde in 7mL THF was added. The solution immediately turned yellow and was stirred for one hour at 0 °C. The reaction was quenched at 0 °C with 15 mL saturated NH_4Cl. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phase washed was dried ($MgSO_4$). Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (30:1 to 20:1)) gave the ester (1.32 g, 7.20 mmol, 72%) as colourless oil.

The analytical data matched the reported data (*Synth. Commun.* **2013**, *43*, 1145):

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 15.6, 6.3 Hz, 1H, H-6), 5.94 – 5.73 (m, 1H, H-3/H-4/H-7), 5.68 – 5.47 (m, 1H, H-3/H-4/H-7), 5.34 (dddd, *J* = 14.0, 7.2, 3.2, 1.6 Hz, 1H, H-3/H-4/H-7), 4.17 (q, *J* = 7.1 Hz, 2H, H-9), 2.93 (dddd, *J* = 8.0, 6.3, 2.7, 1.3 Hz, 2H, H-5), 2.15 – 1.98 (m, 2H, H-2), 1.28 (t, *J* = 7.1 Hz, 3H, H-10), 1.03 – 0.88 (m, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 147.4, 134.6, 123.6, 121.5, 60.3, 30.0, 20.7, 14.4, 14.3.

(2*E*,5*Z*)-Octa-2,5-dien-1-ol, 179



FRU-102

(2*E*,5*Z*)-Octa-2,5-dien-1-ol was prepared following a procedure reported in the literature (*Synth. Commun.* **2013**, *43*, 1145).

DIBAL (16.4 mL of a 1.0 M solution in hexanes, 16.4 mmol, 2.1 eq.) was added dropwise to a solution of ethyl (2*E*,5*Z*)-octa-2,5-dienoate (1.31 g, 7.8 mmol, 1.0 eq.) in Et_2O (12 mL) at 0 °C. After stirring for one hour at 0°C the reaction was quenched in the cold with 10 mL aqueous ethanol (EtOH/H_2O 1:3). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic phase was dried ($MgSO_4$). Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (2:1 to 1:1)) gave the alcohol (750.3 mg, 6.00 mmol, 77%, 3:1 E:Z mixture at C6/C7 in the above numbering) as a colourless oil.

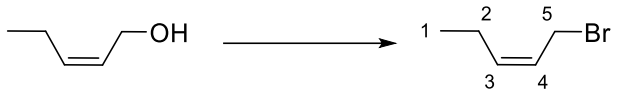
The analytical data matched the reported data (*Synth. Commun.* **2013**, *43*, 1145):

Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 – 5.51 (m, 2H, H-3/H-4/H-6/H-7), 5.49 – 5.38 (m, 1H, H-3/H-4), 5.36 – 5.17 (m, 1H, H-3/H-4/H-6/H-7), 4.09 (t, *J* = 3.4 Hz, 2H, H-8), 2.78 (dd, *J* = 7.4, 4.4 Hz, 2H, H-2), 2.11 – 1.84 (m, 2H, H-5), 1.63 – 1.44 (s, br, 1H, H-9), 0.97 (t, *J* = 7.4 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.0, 131.5, 129.3, 126.1, 63.8, 30.0, 20.6, 14.4.

(*Z*)-1-Bromopent-2-ene, 190



FRU-177/FRU-182

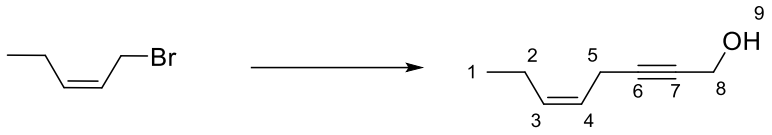
Phosphorous tribromide (2.20 mL, 23.3 mmol, 0.4 eq.) was added to a solution of (*Z*)-2-pentenol (5.9 mL, 58 mmol, 1.0 eq.) in Et_2O (100 mL) at 0°C. The ice bath was removed and the solution was stirred for 1 hour at room temperature before being quenched with 10 mL water. The aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure (T=40°C, p>200 mbar) to afford the highly volatile product (6.71 g, 45.0 mmol) in 78% yield.

The analytical data matched the reported data (*ACIE*, **2010**, 1583):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 – 5.65 (m, 1H, H-4), 5.60 (dt, *J* = 10.6, 7.4 Hz, 1H, H-3), 4.00 (d, *J* = 8.2 Hz, 2H, H-5), 2.16 (app pd, *J* = 7.4, 1.4 Hz, 2H, H-2), 1.02 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 124.8, 27.4, 20.4, 13.9.

(*Z*)-oct-5-en-2-yn-1-ol, 191



FRU-183

A procedure was adapted from the literature (Org. Lett., 2010, 4204) as follows:

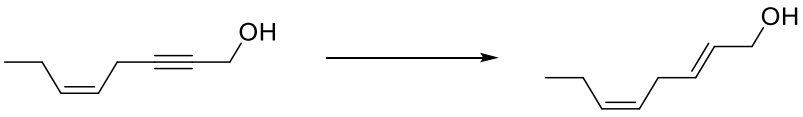
n-Butyllithium (66.0 mL of a 1.6 M solution in hexanes, 105 mmol, 2.1 eq.) was added dropwise to a solution of propargyl alcohol (3.20 mL, 55.0 mmol, 1.1 eq.) in THF (100 mL) at 0 °C. After stirring the yellow solution for 30 minutes, copper iodide (952.5 mg, 5.0 mmol, 0.1 eq.) was added in one portion and the solution was stirred vigorously for another 30 minutes after which a clear, yellow solution resulted. (*Z*)-1-bromopent-2-ene (7.40 g, 50.0 mmol, 1.0 eq.) in THF (100 mL) was added dropwise over 15 minutes. The solution turned orange and was stirred for 30 minutes at 0 °C. Then, the ice bath was removed, and the reaction stirred for 24 hours at room temperature. The reaction was quenched with saturated NH_4Cl (30 mL) and water (10 mL) and vigorously stirred for 10 minutes. The aqueous layer was extracted with 3x40 mL Et_2O and the combined organic phase was washed with brine (30 mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (4:1)) gave the desired alcohol (1.14 g, 9.20 mmol, 19%) as acolourless oil.

The analytical data matched the reported data (*Journal of the Indian Chemical Society*, **1989**, 169):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 (app dtt, *J* = 10.2, 6.9, 1.4 Hz, 1H, H-3/H-4), 5.37 (app dtt, *J* = 10.2, 6.9, 1.4 Hz, 1H, H-3/H-4),4.40 – 4.04 (m, 2H, H-8), 3.08 – 2.79 (m, 2H, H-5), 2.05 (app pd, *J* = 6.9, 1.3 Hz, 2H, H-2), 1.75 (t, *J* = 6.0 Hz, 1H, H-9), 0.97 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8, 123.2, 84.9, 78.1, 51.5, 20.6, 17.2, 14.1.

(2*E*,5*Z*)-Octa-2,5-dien-1-ol, 179



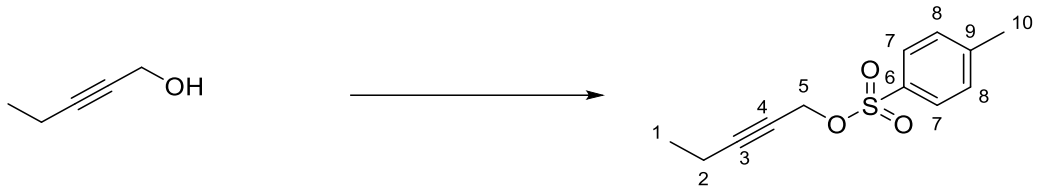
FRU-185

A procedure was adapted from the literature (OL, 2010, 4204) as follows:

(*Z*)-oct-5-en-2-yn-1-ol (1.12 g, 8.99 mmol, 1.0 eq.) in 2 mL THF was carefully added to a suspension of $LiAlH_4$ (513.0 mg, 13.5 mmol, 1.5 eq.) in 15 mL THF at 0°C. The ice bath was removed and stirring was continued for 17 hours. The reaction was quenched with saturated 1N HCl (10 mL) and vigorously stirred. $MgSO_4$ was added and the solid filtered off. Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (3:1)) gave the desired alcohol (799.1 mg, 6.34 mmol, 71%) as a colourless oil.

Analytical data see p. 107

Pent-2-yn-1-yl 4-methylbenzenesulfonate, 176



FRU-399-4 (data), FRU-400-3 (yd)

Over 10 minutes TsCl (13.6 g, 71.3 mmol, 1.2 eq.) was added portionwise to a solution of pent-2-yn-1-ol (5.5 mL, 59.4 mmol, 1.0 eq.) in Et_2O (120 mL) at 0 °C. The ice bath was removed, and the reaction mixture gradually warmed to room temperature over 30 minutes. The reaction was diluted with H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic phases washed with brine (10 mL), and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (9:1 to 4:1)) gave the tosylated alcohol (9.00 g, 37.8 mmol, 64%) as colourless oil along with 1-chloropent-2-yne (1.6 g, 15.7 mmol, 27%).

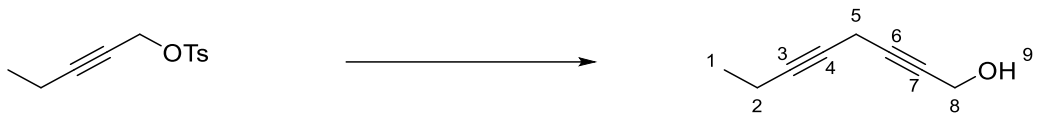
The analytical data matched the reported data (*Synthetic Communications*, **2017**, *47*,. 1848):

Rf 0.23 (petroleum ether / Et_2O (9:1));

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.63 (m, 2H, H-7), 7.40 – 7.30 (m, 2H, H-8), 4.69 (t, *J* = 2.2 Hz, 2H, H-5), 2.44 (s, 3H, H-10), 2.28 – 1.89 (m, 2H, H-2), 1.01 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 133.5, 129.8, 128.3, 91.9, 71.3, 58.9, 21.8, 13.3, 12.5.

Octa-2,5-diyn-1-ol, 177



FRU-402-4 (data), FRU-411 (yd)

CuI (15.64 g, 82.1 mmol, 1.15 eq.), TBAI (30.3 g, 82.1 mmol, 1.15 eq.) and K_2CO_3 (14.8 g, 107.1 mmol, 1.50 eq.) were dissolved in DMF (142 mL) and the flask cooled to 0 °C. Propargyl alcohol (4.8 mL, 82.1 mmol, 1.15 eq.) was added, causing the formation of a solid. After stirring for 30 minutes, a solution of pent-2-yn-1-yl 4-methylbenzenesulfonate (17.0g, 71.4 mmol, 1.00 eq.) in DMF (10 mL) was added. The reaction was stirred for 1 day and quenched by the addition of $NH_4Cl/NH_4OH/H_2O$ (100 mL, 1:1:1 v:v:v) and left to stir for a further day. The blue solution was further diluted with H_2O (100 mL), and extracted with EtOAc (150 mL, then 3 x 50 mL) and the combined organic phases washed with 5% $NaCl/H_2O$ (3x 120 mL), brine (50 mL), and dried ($MgSO_4$). Purification by column chromatography on silica gel (Et_2O) gave the diynol (7.73 g, 62.3 mmol, 88%) as a colourless oil.

The use of 1-bromopent-2-yne instead of pent-2-yn-1-yl 4-methylbenzenesulfonate afforded the product in 64 % yield on 3.7 g scale.

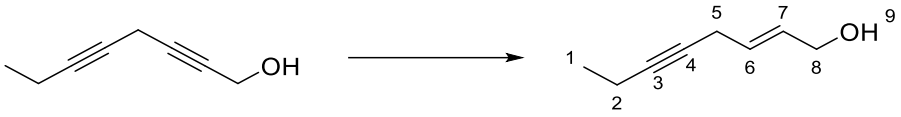
The analytical data matched the reported data (*Tetrahedron Letters* **1992**, 5757):

Rf 0.3 (petroleum ether / Et_2O (3:1));

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (t, *J* = 2.3 Hz, 2H, H-8), 3.18 (app p, *J* = 2.3 Hz, 2H, H-5), 2.17 (qt, *J* = 7.5, 2.3 Hz, 2H, H-2), 1.11 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 82.6, 81.0, 78.5, 72.8, 51.4, 14.0, 12.5, 10.0.

(*E*)-oct-2-en-5-yn-1-ol, 178



FRU-408-1 (data), FRU-420 (yield)

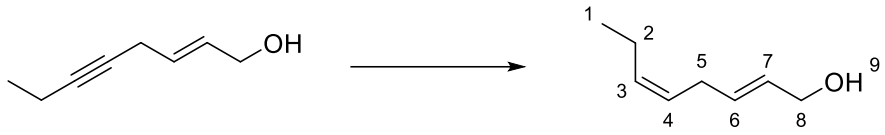
Lithium aluminium hydride (3.93 g, 104 mmol, 1.10 eq.) was placed in an oven dried flask. The flask was evacuated and backfilled with nitrogen. Diethyl ether (150 mL) was added and the supsension cooled to 0 °C. Over the course of 20 minutes, a solution of oct-2,5-diyn-1-ol (11.5 g, 94.1 mmol, 1.0 eq.) in Et_2O (20 mL) was added dropwise and the flask and syringue rinsed with Et_2O (10 mL). The reaction was stirred over night and quenched by slow addition of Rochellles salt (50 g in 200mL water). The resulting suspension was vigorously stirred for 6 hours, separated, and the aqueous layer extracted with Et_2O (3 x 100 mL). the combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$) to give the alcohol (10.47 g, 84.3 mmol, 90%) as colourless oil.

The analytical data matched the reported data (*Synthetic Communications*, **2017**, *47*, 1848):

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 – 5.82 (m, 1H, H-6), 5.70 (dtt, *J* = 15.3, 5.3, 1.5 Hz, 1H, H-7), 4.14 (app td, *J* = 5.7, 1.4 Hz, 2H, H-8), 2.93 (ddd, *J* = 5.2, 3.9, 2.4 Hz, 2H, H-5), 2.19 (qt, *J* = 7.5, 2.4 Hz, 2H, H-2), 1.40 – 1.34 (m, 1H, H-9), 1.13 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 130.4, 127.5, 84.3, 76.1, 63.4, 21.9, 14.4, 12.6.

(2*E*,5*Z*)-octa-2,5-dien-1-ol, 179



FRU-419-1

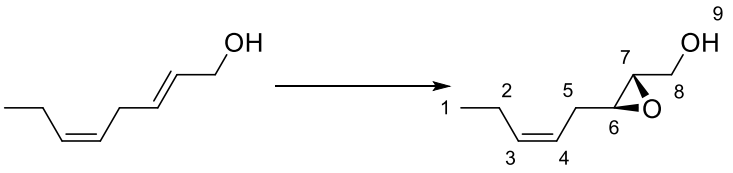
To a supsension of zinc (1.47 g, 22.3 mmol, 5.00 eq.) in EtOH (2.5 mL) under argon was added dibromoethane (0.10 mL, 1.12 mmol, 0.25 eq.). The mixture was brought to reflux and a further portion of dibromoethane (0.10 mL, 1.12 mmol, 0.25 eq.) was added through the reflux condenser, causing vigorous gas evolution. The reaction was brought to 50 °C and a solution of LiBr (195.5 mg, 2.25 mmol, 0.50 eq.) and CuBr (322.9 mg, 2.25 mmol, 0.50 eq.) in THF (3 mL) was added. The reaction was stirred for 10 minutes at that temperature, the starting material in 1 mL ethanol (rinse with 0.5 mL) was added and reation mixture brought to reflux and stirred at 50 °C over night. The suspension was filtered, rinsed with Et_2O (30 mL) and quenched with halfsaturated NH_4Cl solution (30 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$) to give the alcohol (403.4 mg, 3.19 mmol, 71%) as colourless oil.

The analytical data matched the reported data (*Tetrahedron*, **2015**, 5589):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 – 5.51 (m, 2H, H-3/H-4/H-6/H-7), 5.48-5.38 (m, 1H, H-3/H-4), 5.36 – 5.17 (m, 1H, H-3/H-4/H-6/H-7), 4.09 (app t, *J* = 3.4 Hz, 2H, H-8), 2.78 (dd, *J* = 7.3, 4.4 Hz, 2H, H-5), 2.11 – 1.84 (m, 2H, H-2), 1.63 – 1.44 (s, br, 1H, H-9), 0.97 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.0, 131.5, 129.3, 126.1, 63.8, 30.0, 20.6, 14.4.

((2*S*,3*S*)-3-((*Z*)-pent-2-en-1-yl)oxiran-2-yl)methanol, 181



FRU-187

((2*S*,3*S*)-3-((*Z*)-pent-2-en-1-yl)oxiran-2-yl)methanol was prepared following a procedure reported in the literature (Synth. Commun. 2013, 43, 1145).

To a cooled (–78 °C) suspension of activated 3 Å MS (0.4 g) in DCM (20 mL) were added $Ti(O^iPr)_4$ (0.19 mL, 0.62 mmol, 0.1 eq.) and L (+)-diisopropyltartrate (0.15 mL, 0.68 mmol, 0.11 eq.). After 5 min, a solution of (2*E*,5*Z*)-Octa-2,5-dien-1-ol (778.7 mg, 6.17 mmol) in DCM (16 mL) was added and then dropwise TBHP (2.24 mL, ~5.5 M in decane, 12.3 mmol) over 5 minutes. The resulting mixture was kept at –20°C for 20 h, then quenched with a cooled solution of $FeSO_4x7H_2O$ (300 mg) and tartaric acid (100 mg) in de-ionized water (5 mL), stirred vigorously for 2 hours, and extracted with ether (2x30 mL). The combined organic layers were treated with a pre-cooled (0 °C) solution of 30% (w/v) NaOH (10 mL) in brine (10 mL) and stirred for 1 h at room temperature. The two layers were separated, and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was chromatographed on silica gel (petroleum ether / Et_2O (1:1) to (1:3)) to give the epoxyalcohol (750.1 mg, 5.27 mmol, 86%) as a colourless oil.

The analytical data matched the reported data (*Synth. Commun.* **2013**, *43*, 1145):

Rf 0.2 (petroleum ether / Et_2O (1:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (dtt, *J* = 10.4, 7.2, 1.5 Hz, 1H, H-3), 5.35 (dtt, *J* = 10.7, 7.4, 1.6 Hz, 1H, H-4), 3.91 (ddd, *J* = 12.6, 5.2, 2.5 Hz, 1H, H-8‘), 3.62 (ddd, *J* = 12.5, 6.9, 4.3 Hz, 1H, H-8), 3.13 – 2.92 (m, 2H, H-6/H-7), 2.47 – 2.26 (m, 2H, H-5), 2.12 – 1.98 (m, 2H, H-2), 1.86 – 1.80 (m, 1H, H-9), 0.97 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 122.4, 61.7, 58.1, 55.4, 29.3, 20.8, 14.3.

ee 92.4% (Chiralpak IC, 1% IPA/^{n}Hex, 1.3 mL/min, *S*,*S* – 11.9 min *R*,*R* – 13.0 min, benzoate derivative of the alcohol)

(2*R*,3*S*)-2-(iodomethyl)-3-((Z)-pent-2-en-1-yl)oxirane, 182

FRU-125/FRU-466 (scale)

To a cooled (0 °C) suspension of triphenyl phosphine (1.35g, 5.2 mmol, 1.02 eq.), imidazole (350.7 mg, 5.2 mmol, 1.02 eq.) and ((2*S*,3*S*)-3-((*Z*)-pent-2-en-1-yl)oxiran-2-yl)methanol (717.8 mg, 5.05 mmol, 1.0 eq.) in DCM (10 mL) was added a solution of iodine (1.31 g, 5.15 mmol, 1.02 eq.) in DCM (15 mL). After 10 minutes, the ice bath was removed and stirring was continued at room temperature for one hour, before being quenched with water (10 mL). The aqueous phase was extracted with Et_2O (3x10 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (1:0 to 15:1)) gave the desired iodide (1.10 g, 4.4 mmol, 87 %) as pale-yellow oil.

Rf 0.90 (petroleum ether / Et_2O (4:1));

$[\alpha]_D^{25}$ +16.2 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (dtt, *J* = 10.4, 7.3, 1.5 Hz, 1H, H-3), 5.34 (dtt, *J* = 10.7, 7.3, 1.6 Hz, 1H, H-4), 3.36 – 3.16 (m, 1H, H-8), 3.10 – 2.99 (m, 2H, H-6/H-7, H-8), 2.84 (td, *J* = 5.4, 1.7 Hz, 1H, H-6/H-7), 2.43 (dddd, *J* = 14.5, 7.1, 5.3, 1.4 Hz, 1H, H-5‘), 2.33 – 2.20 (m, 1H, H-5), 2.14 – 1.95 (m, 2H, H-2), 0.98 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3, 122.0, 61.9, 58.0, 29.4, 20.8, 14.3, 5.0.

IR (thin film, ν_{max} / cm^{-1}) 2963, 1458, 1172, 893.

HRMS (ES^+) calc. for $C_8H_{14}IO$ $[M+H]^+$ 253.0089, found 253.0077.

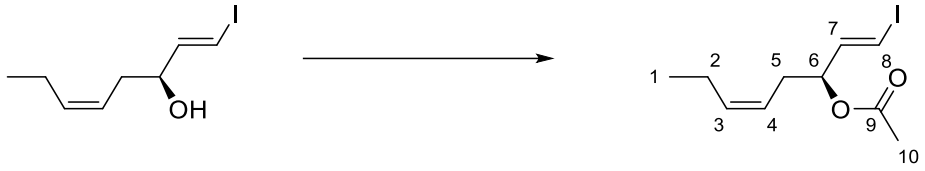
(*S*,1*E*,5*Z*)-1-iodoocta-1,5-dien-3-ol, 158

FRU-130-3

NaHMDS (0.15 mL of a 2.0 M solution in THF, 0.30 mmol, 1.5 eq.) was added dropwise to a solution of (2*R*,3*S*)-2-(iodomethyl)-3-((*Z*)-pent-2-en-1-yl)oxirane (50.0 mg, 0.20 mmol, 1.0 eq.) in DMF (0.16 mL) at –60 °C. After stirring the yellow solution for 15 minutes, the reaction was warmed to –10 °C over the course of 30 minutes. The reaction was quenched with saturated NH_4Cl (1 mL), the aqueous layer was extracted with Et_2O (3 x 1 mL) and the combined organic phase was dried ($MgSO_4$). Purification by column chromatography on silica gel (petroleum ether / Et_2O (9:1 to 4:1)) gave the desired alcohol (26.4 mg, 0.11 mmol, 53 %) as a pale-yellow oil.

The analytical data matched the reported data (*Tetrahedron Letters*, **2012**, 6990):
Rf 0.40 (petroleum ether / Et_2O (4:1));
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (dd, *J* = 14.4, 5.8 Hz, 1H, H-7), 6.37 (dd, *J* = 14.5, 1.3 Hz, 1H, H-8), 5.61 (dddd, *J* = 10.4, 8.8, 5.1, 1.5 Hz, 1H, H-3), 5.33 (app dtt, *J* = 10.8, 7.5, 1.6 Hz, 1H, H-4), 4.25 – 3.93 (m, 1H, H-6), 2.40 – 2.25 (m, 2H, H-5), 2.14 – 2.00 (m, 2H, H-2), 1.73 (d, *J* = 4.3 Hz, 1H, H-9), 0.98 (t, *J* = 7.5 Hz, 3H, H-1).
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 136.3, 122.8, 77.4, 74.0, 34.7, 20.9, 14.4.

(*S*,1*E*,5*Z*)-1-iodoocta-1,5-dien-3-yl acetate, 183



FRU-502-2

Acetic anhydride (0.08 mL, 0.80 mmol, 2.0 eq.) was added to a solution of (*S*,1*E*,5*Z*)-1-iodoocta-1,5-dien-3-ol (100.0 mg, 0.40 mmol, 1.0 eq.), DMAP (2 crystals) and Et_3N (0.17 mL, 1.20 mmol, 3.0 eq.) in DCM (1 mL) at 0 °C. After addition of the anhydride, the mixture was warmed to room temperature and stirred for 2 hours and quenched with H_2O (2 mL). The aqueous layer was extracted with diethyl ether (4 x 1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* column chromatography on silica gel (petroleum ether / Et_2O (19:1)) to give the allylic acetate (111.4 mg, 0.37 mmol, 93%) as a colourless oil.

Rf 0.9 (petroleum ether / Et_2O (7:1)).

$[\alpha]_D^{20}$ –30.2 (*c* 1.0, $CHCl_3$).

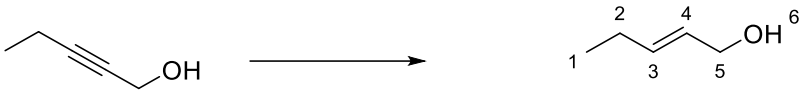
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 14.6, 6.5 Hz, 1H, H-1), 6.41 (dd, *J* = 14.6, 0.8 Hz, 1H, H-8), 5.68 – 5.45 (m, 1H, H-3), 5.34 – 5.22 (m, 1H, H-4), 5.19 (app q, *J* = 6.6 Hz, 1H, H-6), 2.50 – 2.27 (m, 2H, H-5), 2.12 – 1.95 (m, 5H, H-2, H-10), 0.97 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 143.6, 135.6, 122.1, 80.0, 75.3, 31.7, 21.2, 20.9, 14.3.

IR (thin film, ν_{max} / cm^{-1}) 1741, 1231.

HRMS (ES^+) calc. for $C_{11}H_{19}IO_3$ $[M+MeOH+H]^+$ 327.0457, found 327.0461.

(*E*)-Pent-2-en-1-ol, 267



FRU-616-1

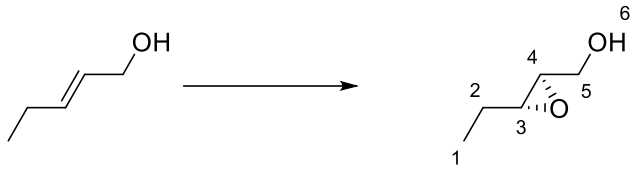
Lithium aluminium hydride (6.93 g, 182.4 mmol, 1.50 eq.) was placed in an oven dried flask. The flask was evacuated and backfilled with nitrogen. Diethyl ether (150 mL) was added and the supsension cooled to 0 °C. Over the course of 20 minutes, 2-pentynol (10.2 g, 121 mmol, 1.0 eq.) was added dropwise and the syringue rinsed with Et_2O (10 mL). The reaction was stirred over night, cooled to 0°C and quenched by slow addition of of 10% H_2SO_4 (250 mL). The layers were separated, and the aqueous layer extracted with Et_2O (2 x 70 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$) to give the alcohol (10.1 g, 97.2 mmol, 80%) as colourless oil.

The analytical data matched the reported data (*JOC*, **1973**, 4263):

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 – 5.70 (m, 1H, H-3/H-4), 5.68 – 5.58 (m, 1H, H-3/H-4), 4.08 (d, *J* = 5.8 Hz, 2H, H-5), 2.20 – 1.95 (m, 2H, H-2), 1.00 (t, *J* = 7.6 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 128.0, 64.0, 25.4, 13.5.

((2*R*,3*R*)-3-ethyloxiran-2-yl)methanol, 268



FRU-619-1

((2*R*,3*R*)-3-ethyloxiran-2-yl)methanol was prepared following a procedure reported in the literature (*JACS*, **1987**, 5765).

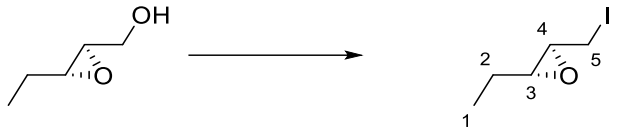
To a cooled (–78 °C) suspension of activated 3 Å MS (4 g) in DCM (200 mL) were added $Ti(O^iPr)_4$ (0.59 mL, 2.0 mmol, 0.1 eq.) and D-(-)-diisopropyltartrate (0.50 mL, 2.4 mmol, 0.12 eq.). After 5 min, a solution of (*E*)-pent-2-en-1-ol (2.5 mL, 20.0 mmol) was added and the solution stirred for 30 minutes before TBHP (7.3 mL, ~5.5 M in decane, 40.0 mmol) was added drop wise over 5 minutes. The resulting mixture was kept at –20°C for 20 h, and then quenched with a cooled solution of $FeSO_4$ x $7H_2O$ (12 g) and tartaric acid (5 g) in de-ionized water (100 mL), stirred vigorously for 2 hours. The layers were separated, and the aqueous layer extracted with DCM (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified on silica gel (petroleum ether / Et_2O (1:1) to (1:3)) to give the epoxyalcohol (1.08 g, 10.0 mmol, 50%) as a colourless oil.

The analytical data matched the reported data (*JACS*, **1987**, 5765):

Rf 0.2 (petroleum ether / Et_2O (1:1)).
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (ddd, *J* = 12.5, 5.5, 2.3 Hz, 1H, H-5‘), 3.63 (ddd, *J* = 12.5, 7.1, 4.1 Hz, 1H, H-5), 3.04 – 2.83 (m, 2H, H-3, H-4), 1.79 – 1.67 (m, 1H, H-6), 1.67 – 1.49 (m, 2H, H-2), 1.00 (t, *J* = 7.5 Hz, 3H, H-1).
^{13}C NMR (101 MHz, $CDCl_3$) δ 61.9, 58.2, 57.2, 24.8, 10.0.

ee 89.1% (Chiralpak IC, 2.5% IPA/^{n}Hex, 1.0 mL/min, *R*,*R* – 15.4 min *S*,*S* – 16.2 min, benzoate derivative of the alcohol).

(2*R*,3*S*)-2-ethyl-3-(iodomethyl)oxirane, 269

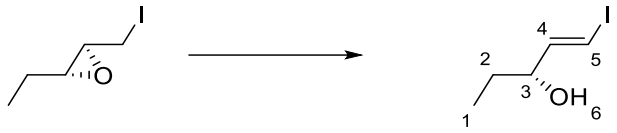


FRU-623-1

To a cooled (0 °C) suspension of triphenyl phosphine (2.66g, 10.1 mmol, 1.02 eq.), imidazole (0.69 g, 10.1 mmol, 1.02 eq.) and ((2*R*,3*R*)-3-ethyloxiran-2-yl)methanol (1.08 g, 9.9 mmol, 1.00 eq.) in DCM (50 mL) was added iodine (2.57 g, 10.1 mmol, 1.02 eq.). After 10 minutes, the ice bath was removed and stirring was continued at room temperature for one hour and then quenched withNaS_2O_3 (20 mL). The layers were separated and the aqueous phase was extracted with DCM (2x20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (19:1)) gave the desired iodide (1.55 g, 7.3 mmol, 74%) as a pale-yellow oil.

Rf 1.0 (petroleum ether / Et_2O (2:1)).
$[\alpha]_D^{25}$ -14.0 (*c* 1.0, $CHCl_3$).
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 – 3.18 (m, 1H, H-5‘), 3.09 – 2.95 (m, 2H, H-4, H-5), 2.79 (td, *J* = 5.6, 1.8 Hz, 1H, H-3), 1.76 – 1.48 (m, 2H, H-2), 1.02 (t, *J* = 7.5 Hz, 3H, H-1).
^{13}C NMR (101 MHz, $CDCl_3$) δ 63.8, 58.3, 24.9, 9.9, 5.2.
IR (thin film, ν_{max} / cm^{-1}) 2967, 1458, 1423, 1172, 886.
HRMS (EI^+) not found.

(*R*,*E*)-1-iodopent-1-en-3-ol, 161



FRU-624-1/628-1 (NMR)

NaHMDS (5.4 mL of a 2.0 M solution in THF, 10.8 mmol, 1.5 eq.) was added dropwise to a solution of (2*R*,3*S*)-2-ethyl-3-(iodomethyl)oxirane (1.52 g, 7.2 mmol, 1.0 eq.) in DMF (72 mL) at –60 °C. After stirring the yellow solution for 15 minutes, the reaction was warmed to –20 °C over the course of 1.5 hours. The reaction was quenched with saturated NH_4Cl (10 mL), and the reaction diluted with water /brine (450 mL, 2:1 (v/v)). The aqueous layer was extracted with PE/Et_2O (3 x 50 mL, 1:1) and the combined organic phase was washed with brine (30 mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (7:1)) gave the desired alcohol (0.84 g, 4.0 mmol, 56%) as a pale-yellow oil.

The analytical data matched the reported data (*TL*, **2011**, 2623):

Rf 0.2 (petroleum ether / Et_2O (4:1)).

$[\alpha]_D^{25}$ +2.0 (*c* 1.0, $CHCl_3$).

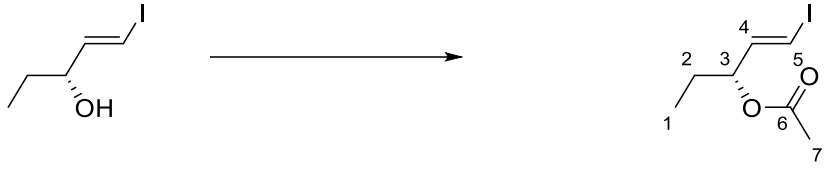
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 14.5, 6.3 Hz, 1H, H-4), 6.35 (dd, *J* = 14.5, 1.2 Hz, 1H, H-5), 4.03 (tdd, *J* = 6.4, 4.4, 1.2 Hz, 1H, H-3), 1.72 – 1.49 (m, 3H, H-2, H-6), 0.94 (t, *J* = 7.4 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6, 77.4, 76.1, 29.7, 9.6.

IR (thin film, ν_{max} / cm^{-1}) 3331, 2964, 2930, 1607, 1460, 1177, 946.

HRMS (EI^+) not found.

(*R*,*E*)-1-iodopent-1-en-3-yl acetate, 270



FRU-627-1

Acetic anhydride (0.76 mL, 8.0 mmol, 2.0 eq.) was added to a solution of (*R*,*E*)-1-iodopent-1-en-3-ol (836.5 mg, 3.95 mmol, 1.0 eq.), DMAP (crystals) and Et_3N (1.6 mL, 12.0 mmol, 3.0 eq.) in DCM (8 mL) at 0°C. After addition of the anhydride, the mixture was warmed to room temperature and stirred for 2 hours and quenched with 1N HCl (10 mL). The layers were separated, the aqueous layer was extracted with DCM (2 x 10 mL), and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (19:1)) to give the allylic acetate (709.1 mg, 2.74 mmol, 70%) as a colourless oil.

Rf 0.6 (petroleum ether / Et_2O (19:1));

$[\alpha]_D^{25}$ +90.2 (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (dd, *J* = 14.6, 6.5 Hz, 1H, H-4), 6.41 (dd, *J* = 14.5, 0.5 Hz, 1H, H-5), 5.12 (app q, *J* = 6.5 Hz, 1H, H-3), 2.06 (s, 3H, H-7), 1.64 (qdd, *J* = 7.3, 6.5, 3.1 Hz, 2H, H-2), 0.90 (t, *J* = 7.4 Hz, 3H, H-1).

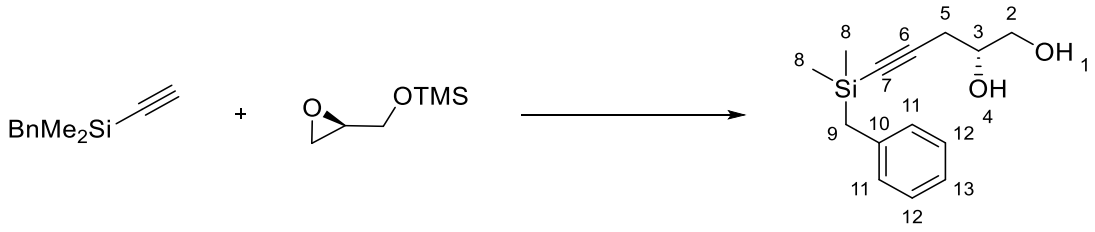
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 143.9, 80.0, 76.9, 26.9, 21.2, 9.4.

IR (thin film, ν_{max} / cm^{-1}) 1739, 1611, 1232.

HRMS (ES^+) not found.

8.4 Synthesis of the Middle-fragments for Resolvins

(*R*)-5-(Benzyldimethylsilyl)pent-4-yne-1,2-diol, 195



FRU-58

n-Butyllithium (4.82 mL of a 2.2 M solution in hexane, 10.60 mmol, 1.4 eq.) was added to a solution of silyl alkyne (1.98 g, 11.35 mmol, 1.5 eq.) in THF (60 mL) at -78 ºC and were stirred at -78 ºC for 30 minutes. $BF_3{\cdot}OEt_2$ (1.40 mL, 11.35 mmol, 1.5 eq.) was added and the mixture stirred for a further 10 minutes before epoxide (1.13 g, 7.63 mmol, 1.0 eq., purity: 98.8%) was added. The mixture was stirred for one hour at –78 °C before being quenched with 1N HCl (10 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL). The combined organic phase was washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The crude was purified *via* flash column chromatography (MeOH/DCM 2% to 6%) to give homopropargylic alcohol (*R*) as a colourless oil (1.84 g, 7.38 mmol, 97%).

Rf 0.20 (MeOH/DCM 2%);

$[\alpha]_D^{25}$ –10.8 (*c* 1.0, $CHCl_3$);

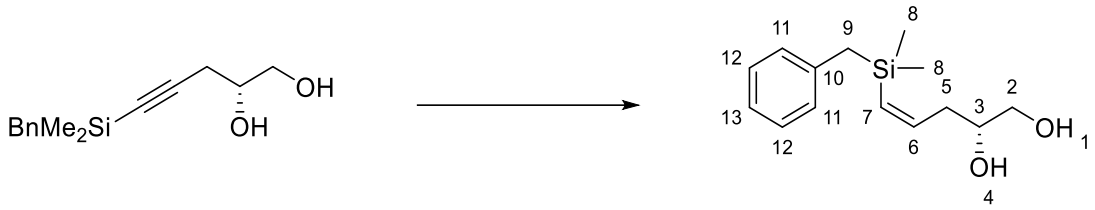
^{1}H NMR (400 MHz, $CDCl_3$) This compound displayed unusual peak doubling in the proton NMR spectrum. δ 7.28 – 7.18 (m, 2H, H-12), 7.15 – 7.02 (m, 3H, H-11, H-13), 4.09 (s, br, 1H, H-2), 3.91 (s,br, 0.5H, H-2), 3.82 (dq, *J* = 8.8, 3.2, 2.5 Hz, 0.5H, H-2), 3.69 (dt, *J* = 9.5, 4.5 Hz, 0.5H, H-3), 3.54 (dt, *J* = 10.8, 5.3 Hz, 0.5H, H-3), 2.58 – 2.48 (m, 1H, H-5), 2.46 (dd, *J* = 6.3, 2.7 Hz, 1H, H-5), 2.26 (d, *J* = 4.8 Hz, 0.5H, H-1), 2.21 – 2.14 (m, 2H, H-9), 1.92 (d, *J* = 5.9 Hz, 0.5H, H-3), 0.14 (s, 3H, H-8), 0.11 (s, 3H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 130.2 (2C), 130.1 (2C), 126.3, 105.7, 88.1, 71.9, 67.4, 28.2, 26.9, 0.0, –0.1.

IR (thin film, ν_{max} / cm^{-1}) 3367 (br), 2958, 2177, 1600, 1493, 1250, 1030, 833.

HRMS (ES^+) calc. for $C_{14}H_{24}O_2NSi$ $[M+NH_4]^+$ 266.1571, found 266.1590.

(*R*,*Z*)-5-(benzyldimethylsilyl)pent-4-ene-1,2-diol



FRU-59

A suspension of palladium on $CaCO_3$ (128.5 mg, 0.06 mmol, 0.05 eq.) in toluene (5 mL) was three times degassed and flushed with hydrogen and stirred for 15 minutes under hydrogen atmosphere.

(*R*)-5-(Benzyldimethylsilyl)pent-4-yne-1,2-diol (300.0 mg, 1.20 mmol, 1.0 eq.) in toluene (1.5 mL), quinoline (0.07 mL, 0.60 mmol, 0.50 eq.) and cyclohexene (0.6 mL) was added to the active palladium catalyst. The reaction was closely monitored by TLC and immediatedly flushed with nitrogen upon complete consumption of the starting material (1.5 hours, varies with catalyst activity). Then the reaction was filtrated on celite and concentrated *in vacuo.* The crude was purified *via* flash column chromatography (MeOH/DCM 5%) to give homopropargylic alcohol (*R*) as a colourless oil (242.9 mg, 0.94 mmol, 79%).

Rf 0.20 (MeOH/DCM 2%);

$[\alpha]_D^{25}$ –9.7 (*c* 1.0, $CHCl_3$);

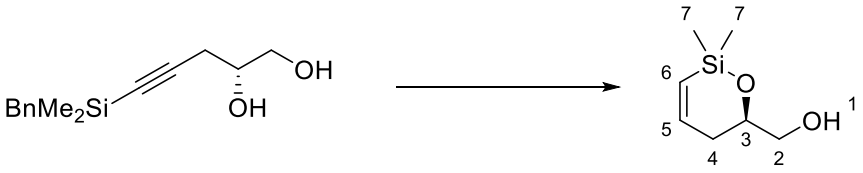
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 2H, H-12), 7.12 – 7.03 (m, 1H, H-13), 7.07 – 6.95 (m, 2H, H-11), 6.35 (dt, *J* = 14.2, 7.4 Hz, 1H, H-6), 5.66 (dt, *J* = 14.1, 1.4 Hz, 1H, H-7), 3.75 – 3.64 (m, 1H, H-3), 3.61 (ddd, *J* = 11.0, 5.6, 3.4 Hz, 1H, H-2), 3.41 (ddd, *J* = 11.2, 6.9, 4.1 Hz, 1H, H-2), 2.22 – 2.15 (m, 2H, H-5), 2.17 (s, 2H, H-9), 2.03 (d, *J* = 3.7 Hz, 1H, H-4), 1.92 (m, 1H, H-1), 0.13 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 140.0, 131.0, 128.4 (2C), 128.3 (2C), 124.2, 71.7, 66.4, 37.4, 26.8, –1.4 (2C).

IR (thin film, ν_{max} / cm^{-1}) 3361 (br), 2361, 2341, 1601, 1493, 1248, 1207, 832.

HRMS (ES^+) calc. for $C_{14}H_{26}O_2NSi$ $[M+NH_4]^+$ 268.1727, found 268.1726.

(*R*)-(2,2-dimethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)methanol, 196



FRU-62/FRU-434 (scale)

The hydrogenation was carried out under identical conditions in 2 flasks:

A suspension of palladium on $CaCO_3$ (462.0 mg, 0.22 mmol, 0.01 eq.) in toluene (48 mL) was three times evacuated under high vacuum and backfilled with hydrogen and stirred for 15 minutes under hydrogen atmosphere.

(*R*)-5-(Benzyldimethylsilyl)pent-4-yne-1,2-diol (2.70 g, 10.8 mmol, 1.0 eq.) in toluene (12 mL), quinoline (0.63 mL, 5.4 mmol, 0.50 eq.) and cyclohexene (6 mL) was added to the active palladium catalyst. The reaction was closely monitored by TLC and immediatedly flushed with nitrogen upon complete consumption of the starting material (45 minutes, varies with catalyst activity).

The material of the two runs was combined, filtered through a pad of celite (wash with Et_2O) and the organic layer washed with 30mL 1N HCl, and 30 mL brine. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo.*

A 1.0 M solution of tetrabutylammonium fluoride in THF (26 mL, 26 mmol, 1.2 eq., freshly prepared from TBAF · $3H_2O$ (8.22g) and THF (26 mL)) was added to a solution of the crude homoallylic alcohol in THF (120 mL) and stirred for 1.5 hours (same TLC as after 15 minutes, there seems to be some UV-active, non cyclisable material remaining (=E?)). The reaction was diluted with water (60 mL), the organic layer separated, and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic phase was washed with brine (50 mL), dried (Na_2SO_4) and concentrated. The crude was quickly filtered through a short plug of silica (flush with ether) to give cyclic alkenylsiloxane as a colourless oil (2.79 g, 17.6 mmol, 81%).

Rf 0.50 (Et_2O);

$[\alpha]_D^{25}$ +24.6 (*c* 0.95, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (ddd, *J* = 14.2, 6.0, 2.3 Hz, 1H, H-5), 5.76 (ddd, *J* = 14.1, 2.9, 1.0 Hz, 1H, H-6), 4.03 (dddd, *J* = 10.4, 6.3, 3.3, 2.7 Hz, 1H, H-3), 3.60 (ddd, *J* = 11.1, 7.6, 3.4 Hz, 1H, H-2), 3.49 (ddd, *J* = 11.2, 6.6, 4.7 Hz, 1H, H-2), 2.34 – 2.14 (m, 2H, H-1, H-4), 2.06 (dddd, *J* = 17.7, 6.0, 2.7, 0.9 Hz, 1H, H-4), 0.20 (s, 3H, H-7), 0.19 (s, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7, 127.1, 71.8, 67.0, 32.2, -0.2, -0.5.

IR (thin film, ν_{max} / cm^{-1}) 3376 (br), 2955, 2919, 2851, 2362, 1589, 1252, 1040, 841, 790.

HRMS (ES^+) calc. for $C_7H_{15}O_2Si$ $[M+H]^+$ 159.0841, found 159.0841.

1N HCl led to dimerisation, could be broken up with TBAF (1.2 eq.)

(*R*)-2,2-Dimethyl-5,6-dihydro-2H-1,2-oxasiline-6-carbaldehyde, 241

FRU-63

Dimethylsulfoxide (1.56 mL, 21.96 mmol, 13.6 eq.) was added to a solution of SO_3·py (834.0 mg, 5.24 mmol, 3.5 eq.) in DCM (4 mL) and stirred for 30 minutes before a solution of diisopropylethylamine (1.56 mL, 8.96 mmol, 5.5 eq.) and (*R*)-(2,2-dimethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)methanol (257.2 mg, 1.62 mmol, 1.0 eq.) in DCM (5.5 mL) was added *via* cannula. After 90 minutes the reaction was quenched with 0.1 N HCl (10 mL), extracted with DCM, dried (Na_2SO_4) and concentrated to give the aldehyde as a yellow oil which was used in the next step without further purification (226.3 mg, 5.3 m% DMSO, 1.37 mmol, 85%).

Rf 0.20 (petroleum ether / Et_2O (9:1));

$[\alpha]_D^{25}$ +59.9 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H, H-1), 6.77 (ddd, *J* = 14.8, 6.5, 3.1 Hz, 1H, H-4), 5.81 (ddd, *J* = 14.1, 2.6, 1.1 Hz, 1H, H-5), 4.33 (dd, *J* = 10.0, 3.7 Hz, 1H, H-2), 2.42 (dddd, *J* = 17.8, 5.2, 3.7, 1.1 Hz, 1H, H-3), 2.31 (ddt, *J* = 17.7, 10.0, 2.7 Hz, 1H, H-3), 0.26 (s, 3H, H-6), 0.23 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 145.2, 128.1, 76.1, 30.6, –0.1, –0.4.

IR (thin film, ν_{max} / cm^{-1}) 3427, 2959, 2924, 2361, 1589, 1252, 1085, 1045, 842, 790.

HRMS (ES^+) calc. for $C_7H_{13}O_2Si$ $[M+H]^+$ 157.0685, found 157.0649.

2-(Triphenyl-l5-phosphanylidene)acetaldehyde

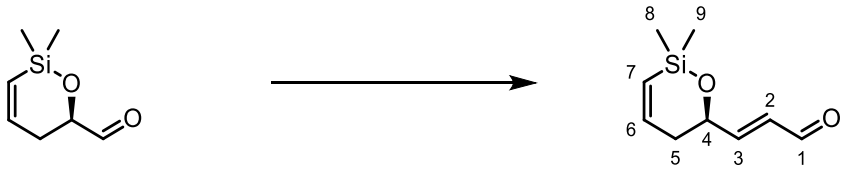
FRU-575-1

Formyl triphenylmethylphosphonium chloride (10.0 g, 29.3 mmol, 1.0 eq.) was dissolved in DCM (150 mL) and shaken with 1N NaOH (33 mL, 33 mmol, 1.1 eq.) for 5 minutes in a separating funnel. The yellow solution quickly turned red. The layers were separated, and the aqueous layer extracted with DCM (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the product as an orange salt (8.94 g, 29.3 mmol, quantitative yield).

The analytical data matched the reported data (*OL*, **2013**, 2708):

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (dd, *J* = 38.2, 3.2 Hz, 1H, H-1-*cis*), 8.26 (dd, *J* = 10.7, 3.5 Hz, 1H, H-1-*trans*), 7.82 – 7.37 (m, 23H, H-3), 4.07 (dd, *J* = 19.4, 10.7 Hz, 1H, H-2-*trans*), 3.78 – 3.44 (m, 1H, H-2-*cis*).

(*R*,*E*)-3-(2,2-Dimethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)acrylaldehyde, 197



FRU-64/FRU-66

Triphenylphosphoranylidene)acetaldehyde (401.8 mg, 1.32 mmol, 1.2 eq.) was added to a solution of crude (*R*)-2,2-Dimethyl-5,6-dihydro-2H-1,2-oxasiline-6-carbaldehyde (238.2 mg, 1.10 mmol, with DMSO) in toluene (11 mL) and stirred overnight in the dark. The crude NMR showed remaining starting material (12%), additional Triphenylphosphoranylidene)acetaldehyde (40.2 mg, 0.13 mmol, 0.12 eq.) was added, and stirred for 24 h when NMR indicated completion. The crude was applied straight to a column and purified by flash column chromatography (Petroleum ether/Ether 9:1 to 6:1) to give pure homologated aldehyde (100.9 mg, 0.55 mmol, 50%).

Rf 0.25 (petroleum ether / Et_2O (5:1));

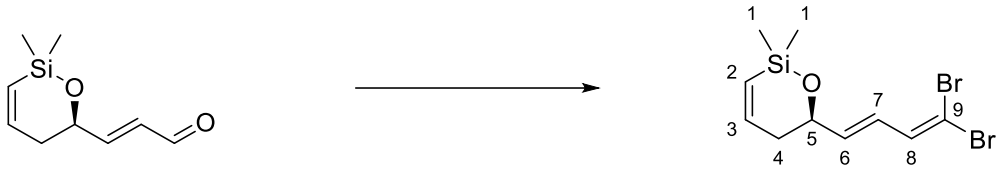
$[\alpha]_D^{25}$ +96.9 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, *J* = 8.0 Hz, 1H, H-1), 6.81 (dd, *J* = 15.6, 3.9 Hz, 1H, H-3), 6.81 – 6.71 (m, 1H, H-6), 6.37 (ddd, *J* = 15.5, 8.0, 1.7 Hz, 1H, H-2), 5.83 (ddd, *J* = 14.1, 2.6, 1.2 Hz, 1H, H-7), 4.77 – 4.66 (m, 1H, H-4), 2.46 – 2.11 (m, 2H, H-5), 0.22 (s, 3H, H-8), 0.22 (s, 3H, H-9), .

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 158.2, 145.8, 130.9, 127.9, 70.3, 35.4, –0.1, –0.5.
IR (thin film, ν_{max} / cm^{-1}) 2992, 2958, 2361, 1691, 1588, 1252, 1101, 971, 958, 844, 790.

HRMS (EI^+) calc. for $C_9H_{15}O_2Si$ $[M+H]^+$ 183.0841, found 183.0808.

(*R*,*E*)-6-(4,4-dibromobuta-1,3-dien-1-yl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline, 242



FRU-438-1

An oven dried flask containing PPh_3CHBr_2Br·MeCN (252.0 mg, 0.45 mmol, 2.20 eq.) was evacuated and backfilled with nitrogen. Potassium tert butoxide (1 M / THF, 0.41 mL, 0.41 mmol, 2.0 eq.) was added and the suspension stirred for 1 hour. (*R*,*E*)-3-(2,2-dimethyl-5,6-dihydro-2H-1,2-oxasilin-6-yl)acrylaldehyde (40.3 mg, 0.206 mmol, 1.00 eq.) in 0.2 mL THF (rinse with 0.2 mL) was added. The reaction was stirred for 2 hours and directly purified by flash column chromatography on silica gel (petroleum ether / Et_2O (9:1)) yielding the dibromide as a colourless oil (59.3 mg, 0.175 mmol, 86%).

Rf 1.00 (petroleum ether / E (9:1));

$[\alpha]_D^{20}$ +25.8 (*c* 1.0, $CHCl_3$)

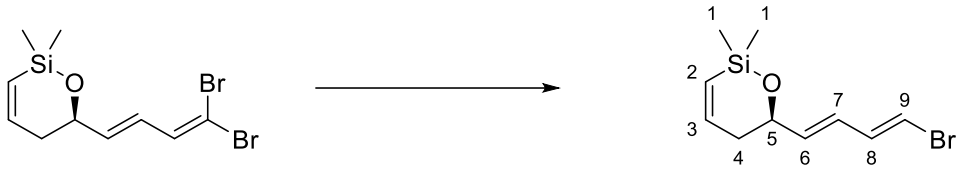
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 10.3, 0.7 Hz, 1H, H-8), 6.85 – 6.65 (m, 1H, H-3), 6.33 (ddd, *J* = 15.3, 10.3, 1.5 Hz, 1H, H-7), 5.95 (ddd, *J* = 15.3, 5.5, 0.8 Hz, 1H, H-6), 5.85 – 5.69 (m, 1H, H-2), 4.48 (dtd, *J* = 9.0, 5.3, 1.5 Hz, 1H, H-5), 2.54 – 2.02 (m, 2H, H-4), 0.21 (s, 3H, H-1), 0.21 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 139.6, 136.6, 127.7, 126.5, 91.2, 71.3, 36.2, 0.0, -0.4.

IR (thin film, ν_{max} / cm^{-1}) 2981, 2889, 2358, 2341, 1588, 1251, 958.

HRMS (ES^+) $^+$ not found.

(*R*)-6-((1*E*,3*E*)-4-bromobuta-1,3-dien-1-yl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline, 164



FRU-441-4/scale: 496-2/clean NMR: FRU-626

(*R*,*E*)-6-(4,4-dibromobuta-1,3-dien-1-yl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline (562.1 mg, 1.66 mmol, 1.0 eq.) was dissolved in diethyl phosphate (3.4 mL, 41.5 mmol, 25 eq.) and triethyl amine (1.2 mL, 8.3 mmol, 5.0 eq.) was added. The reaction was stirred for 24 hours, and its colour changed to orange. The crude mixture was diluted with 10 mL water and 1N NaOH (30 mL), extracted with pentane (3 x 20 mL), and the organic layer washed with 1N NaOH (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Purification by flash column chromatography (PE/E 19:1 (~30mL)) afforded the product as a 2:1 *E*:*Z* mixture (357.8 mg, 1.38 mmol, 84%).

The *E*/*Z* mixture (0.89g, 3.4mmol) was dissolved in ethanol (10 mL) and NaOMe (25% w/w, 3.5 mL, 1.7 mmol, 0.5 eq.) was added, before refluxing the reaction mixture for 6 hours. After cooling to room temperature, the mixture was diluted with water (20 mL) and extracted withether (3 x 20 mL). The organic layers were dried ($MgSO_4$) and concentrated, yielding a mixture of the *E* product and the terminal alkyne. This mixture was directly carried on to the following reaction.

To a solution of CuI (64.8 mg, 0.34 mmol, 0.10 eq.), $Pd(PPh_3)_4$ (198.2 mg, 0.17 mmol, 0.05 eq.) in triethylamine (34 mL) and DMF (17 mL) was added the E-vinyl bromide/alkyne mixture from the previous step. The reaction mixture was stirred over night, diluted with 10 mL water and 150 mL PE/E 1:1. The organic layer was washed with halfsaturated NH_4Cl solution (3 x 50 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (PE/E 19:1) afforded the product as pure E-isomer (476.7 mg, 87% pure with PPh_3, 1.6 mmol, 46% over 2 steps). The PPh_3 was removed by stirring with CuCl in acetone for 1 hour and subseq.uent filtration.

Rf 1.00 (petroleum ether ether/ E (9:1));

$[\alpha]_D^{20}$ +51.1 (*c* 1.0, $CHCl_3$)

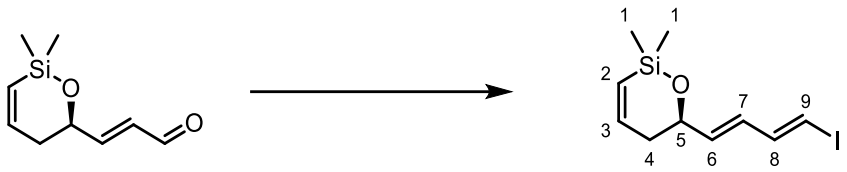
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 – 6.66 (m, 2H, H-3, H-8), 6.31 (dq, *J* = 13.5, 0.7 Hz, 1H, H-9), 6.22 (dddd, *J* = 15.2, 10.9, 1.5, 0.6 Hz, 1H, H-7), 5.89 – 5.67 (m, 2H, H-2, H-6), 4.62 – 4.29 (m, 1H, H-5), 2.25 – 2.15 (m, 2H, H-4), 0.20 (s, 3H, H-1), 0.20 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 137.1, 136.8, 127.6, 127.0, 108.8, 71.1, 36.4, –0.1, –0.4.

IR (thin film, ν_{max} / cm^{-1}). 2988, 2957, 2361, 1587, 1251, 976, 789.

HRMS (ES^+) calc. for $C_{11}H_{20}BrOSi$ $[M+MeOH+H]^+$ 293.0396, found 293.0385.

(*R*)-6-((1*E*,3*E*)-4-iodobuta-1,3-dien-1-yl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline, 159



FRU-68

Dry $CrCl_2$ (514.9 mg, 4.19 mmol, 8.0 eq.) was weighed into a dry Schlenk tube under N_2 atmosphere. It was gently heated under vacuum until the greenish colour turned grey and the solid became free-flowing. The flask was cooled to room temperature and dry THF (5.5 mL) introduced. After stirring this suspension for 10 minutes, Iodoform (412.6 mg, 1.05 mmol, 2.0 eq.) in THF (2.6 mL) was introduced which caused the solution to immediately turn red. The aldehyde in 5.5 mL THF was introduced and stirred for one hour in the dark. The reaction was quenched with aqueous $Na_2S_2O_3$ solution, and the aqueous layer extracted three times with 30 mL Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude was purified by flash column chromatography (Petroleum ether/ Et_2O 1:0 to 50:1) to yield an inseparable mixture of *E*/*Z* isomers (5:1) of the newly formed alkene (95.7 mg, 0.31 mmol, 60%).

Rf 0.20 (pure petroleum ether);

$[\alpha]_D^{25}$ +46.0 (*c* 1.0, $CHCl_3$);

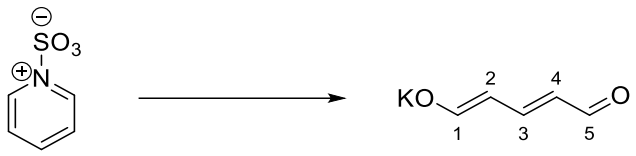
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (ddd, *J* = 14.4, 10.7, 0.7 Hz, 1H, H-8), 6.86 – 6.65 (m, 1H, H-3), 6.32 (dd, *J* = 14.4, 0.8 Hz, 1H, H-9), 6.28 – 6.13 (m, 1H, H-7), 5.85 – 5.66 (m, 2H, H-2, H-6), 4.46 – 4.39 (m, 1H, H-5), 2.36 – 2.02 (m, 2H, H-4), 0.21 (s, 3H, H-1), 0.20 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.54, 144.82, 136.51, 129.49, 127.55, 79.18, 70.99, 36.39, -0.04, -0.41.

IR (thin film, ν_{max} / cm^{-1}) 2956, 2922, 2854, 2360, 2341, 1681, 1259, 1030, 798.

HRMS (EI^+) calc. for $C_{10}H_{16}IO_2Si$ $[M+H]^+$ 307.0015, found 306.9994.

Potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate, 214



PES017 (NMR PES015-1)

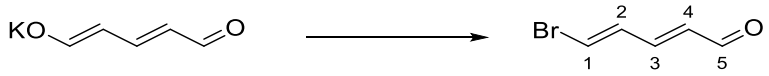
Pyridine sulfur trioxide complex (21.6 g, 98% purity, 136 mmol, 1.0 eq.) was added portionwise over 5 minutes to a 500 mL flask containing a solution of KOH (31.0 g, 550 mmol, 4.1 eq.) dissolved in H_2O (75 mL) at –20 °C. The reaction was stirred vigorously at -20°C for 1 hour 30 minutes and afterwards the ice bath was removed. The mixture was stirred for a further 1 hour 30 minutes, heated at 40 °C for 30 minutes and then cooled to 5°C overnight. A solid precipitated and was isolated by filtration. The solid was washed with acetone (2 x 30 mL) and left to dry in air. In a 1 L flask, 500 mL methanol and 1 g activated carbon were added to the solid, and the resulting mixture was refluxed for 30 minutes. The activated carbon was removed by filtration whilst the solution was still hot. The filtrate was concentrated to 30 mL and kept at 5°C for 2 hours. The solid was washed with acetone until the filtrate was colourless, then dried. A yellow solid was formed (10.0 g, 73.5 mmol, 54%).

The analytical data is in good agreement with the reported data (*Org. Synth.* **1979**, *59*, 79).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.64 (d, J = 9.2 Hz, 2H, H-1, H-5), 7.02 (t, J = 13.1 Hz, 1H, H-3), 5.08 (dd, J = 13.1, 9.2 Hz, 2H, H-2, H-4).

^{13}C NMR (101 MHz, DMSO-d6) δ 184.4, 159.9, 106.3.

(2*E*,4*E*)-5-Bromopenta-2,4-dienal, 216



PES009 (NMR PES002)

Potassium (1*E*,3*E*)-5-oxopenta-1,3-dien-1-olate (3.72 g, 27.3 mmol, 1.0 eq.) was added to a solution of dry DCM (150 mL), PPh_3 (7.16 g, 27.3 mmol, 1.0 eq.) and Br_2 (1.54 mL, 30.0 mmol, 1.1 eq.) at 0 °C in the dark. The reaction was stirred for 4 hours. 30 g of silica was added, and the solvent was removed *in vacuo*. The dry loaded crude product was purified by flash column chromatography (eluent 7:3 petroleum ether:Et_2O). The solvent was removed from the eluate to form a white solid (mixture of E,E and E,Z isomers). The solid was melted by heating it to 60 °C in a water bath and heptane (20 mL) was added under vigorous stirring. A solid precipitated immediatedly upon addition of heptane. The heptane was removed by filtration, the solid washed with 5 mL of heptane and dried under low vacuum (2.00 g, 12.4 mmol, 46%).

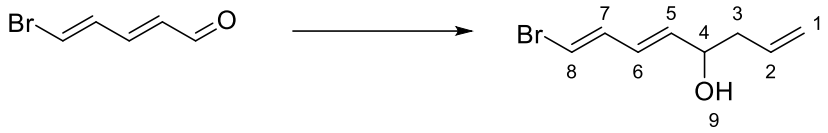
The analytical data is in good agreement with the reported data (*Journal of the Chemical Society - Perkin Transactions 1*, **1997**, 1639).

Rf (2:1 petroleum ether:Et_2O) 0.60

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J = 7.8 Hz, 1H, H-1), 7.05 – 6.92 (m, 3H, H-2/ H-3/ H-4/ H-5), 6.24 – 6.13 (m, 1H, , H-2/ H-3/ H-4/ H-5).

^{13}C NMR (101 MHz, CDCl3) δ 193.2, 147.8, 135.7, 132.1, 119.9.

(5*E*,7*E*)-8-Bromoocta-1,5,7-trien-4-ol, 264



PES010 (NMR ^{1}H PES004, ^{13}C PES010-2; IR PES008-1)

Allylmagnesium chloride (1.7 M THF, 8.7 mL, 14.8 mmol, 1.2 eq.) was added dropwise over 5 minutes to a solution of (2*E*,4*E*)-5-bromopenta-2,4-dienal (1.99 g, 12.4 mmol, 1.0 eq.) in dry THF (24 mL) at 0 °C. The reaction was stirred for 1 hour, quenched with 1 N HCl (20 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were extracted with brine (1 x 30 mL), then dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow/brown oil. The oil was purified by flash column chromatography (4:1 petroleum ether:Et_2O), and the solvent was removed from the eluate to form a yellow oil (2.34 g, 11.5 mmol, 93%).

Rf (3:1 petroleum ether:Et_2O) 0.32

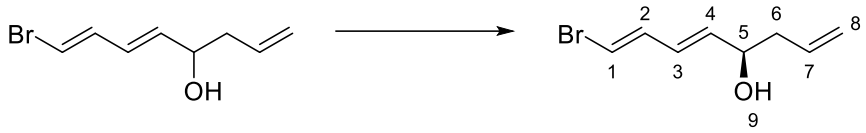
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (ddd, J = 13.5, 10.8, 0.8 Hz, 1H, H-7), 6.33 (dq, J = 13.4, 0.6 Hz, 1H, H-8), 6.19 (dddd, J = 15.3, 10.8, 1.4, 0.6 Hz, 1H, H-6), 5.86 – 5.72 (m, 2H, H-2, H-5), 5.22 – 5.12 (m, 2H, H-1), 4.21 (dddd, J = 11.1, 7.1, 4.0, 1.4 Hz, 1H, H-4), 2.43 – 2.23 (m, 2H, H-3), 1.69 (d, J = 4.1 Hz, 1H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 136.4, 133.8, 127.7, 119.0, 109.2, 70.9, 41.9.

IR (thin film, ν_{max} / cm^{-1}) 3360, 3072, 2926, 1641, 1584, 978, 919, 741.

HRMS not found.

(*R*,5*E*,7*E*)-8-Bromoocta-1,5,7-trien-4-ol, 265



PES012 (NMR PES012-1; IR PES008-1; $[\alpha]_D^{20}$ PES008)

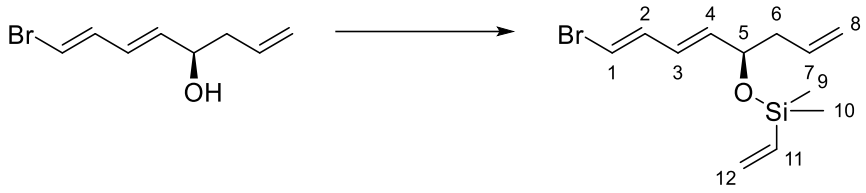
(5*E*,7*E*)-8-bromoocta-1,5,7-trien-4-ol (500 mg, 2.46 mmol, 1.0 eq.) was added dropwise to a solution of Ti(O-*i*-Pr)$_4$ (0.73 mL, 2.46 mmol, 1.0 eq.) and (+) diisopropyl-L-tartrate (0.62 mL, 2.95 mmol, 1.2 eq.) in 25 mL of DCM at -20 °C, and the reaction was stirred for 40 minutes. Tertbutylhydroperoxide (0.27 mL, 1.48 mmol, 0.6 eq.) was added dropwise over 5 minutes and the solution formed was stored in the freezer for 24 hours. 200 mg of NaOH and 10 mL of brine are added. The reaction was stirred for 1 hour, 3 g citric acid was added, and the solution formed was extracted with Et_2O (3 x 30 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to form a yellow oil. The oil was purified by flash column chromatography (5:1 petroleum ether:Et_2O) and the solvent was removed to form a yellow oil (198 mg, 0.975 mmol, 40%, 97.5 ee).

Same analytical data as (5E,7*E*)-8-bromoocta-1,5,7-trien-4-ol (p. 139)

$[\alpha]_D^{20}$ +6.9 (*c* 1.0, $CHCl_3$).

ee 97.5% (Chiralpak IC, 5% IPA/^{n}Hex, 1.0 mL/min, R – 5.7 min S – 6.0 min).

(((*R*,5*E*,7*E*)-8-Bromoocta-1,5,7-trien-4-yl)oxy)dimethyl(vinyl)silane



PES014 (NMR PES014-1; IR PES014-1; $[\alpha]_D^{20}$ PES014)

Chlorodimethylvinylsilane (0.75 mL 5.41 mmol, 1.5 eq.) is added dropwise to a solution of (*R*,5*E*,7*E*)-8-bromoocta-1,5,7-trien-4-ol (733 mg, 3.61 mmol, 1.0 eq.) and Et_3N (1.0 mL, 7.22 mmol, 2.0 eq.) in 4.0 mL DCM at 0°C. The reaction was stirred for 15 minutes, quenched using NH_4Cl (1 mL) and H_2O (1 mL), and extracted with Et_2O (1 x 2 mL then 2 x 1 mL). The organic layer is dried ($MgSO_4$), concentrated *in vacuo* to form a yellow oil, then purified by flash column chromatography (eluent 19:1 pentane:Et_2O). The solvent of the eluate is removed to yield a yellow oil (916 mg, 3.19 mmol, 89%).

Rf (19:1 petroleum ether:Et_2O) 0.91

$[\alpha]_D^{20}$ +12.6 (*c* 1.0, $CHCl_3$).

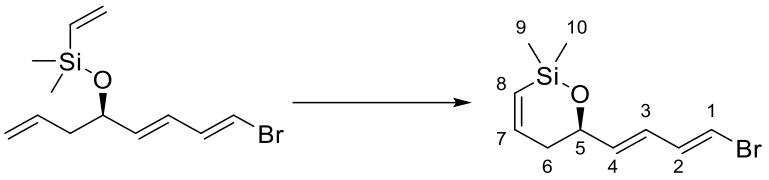
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (ddd, J = 13.4, 10.8, 0.7 Hz, 1H, H-2), 6.29 (d, J = 13.5 Hz, 1H, H-1), 6.17 – 5.97 (m, 3H, H-3/H-4/H-7/H-11/H-12), 5.81 – 5.67 (m, 3H, H-3/H-4/H-7/H-11/H-12), 5.08 – 5.01 (m, 2H, H-8), 4.24-4.10 (m, 1H, H-5), 2.34 – 2.20 (m, 2H, H-6), 0.18 (s, 3H, H-9), 0.18 (s, 3H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 137.3, 137.1, 134.5, 133.4, 127.0, 117.5, 108.6, 72.6, 42.6, –1.3, –1.4.

IR (thin film, vmax / cm-1) 3065, 2960, 1642, 1585, 1407, 1361, 1253, 1076, 978, 786.

HRMS not found.

(*R*)-6-((1*E*,3*E*)-4-Bromobuta-1,3-dien-1-yl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline, 164

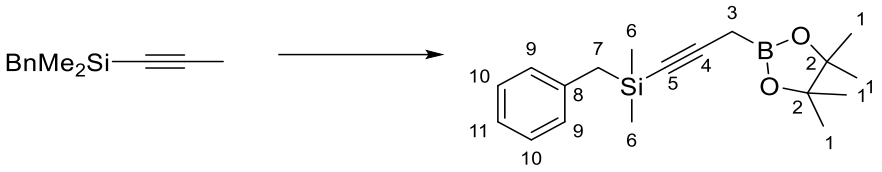


PES022 (NMR PES022-1)

(((*R*,5*E*,7*E*)-8-Bromoocta-1,5,7-trien-4-yl)oxy)dimethyl(vinyl)silane (897 mg, 3.12 mmol, 1.0 eq.) was added to a solution of Schrock's catalyst (100 mg, 0.13 mmol, 0.04 eq.) in 31 mL of degassed benzene (freeze-pump-thawed x 3) under an argon atmosphere to form a brown solution. The reaction is stirred for 17 hours at room temperature and the mixture changes colour from brown to dark green. The benzene solvent is removed *in vacuo* and the reaction is purified by flash column chromatography (19:1 petroleum ether:Et_2O) and then concentrated *in vacuo* to yield a pale orange oil (783 mg, 3.02 mmol, 97%).

Analytical data in agreement with above (R)-6-((1*E*,3*E*)-4-bromobuta-1,3-dien-1-yl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline (p. 134)

Benzyldimethyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-yn-1-yl)silane, 228



FRU-278-1 (procedure), 247-3 (NMR)

n-Butyllithium (4.1 mL of a 2.5 M solution in hexanes, 10 mmol, 1.03 eq.) was added dropwise to a solution of benzyldimethyl(prop-1-yn-1-yl)silane (2.00 g, 10.6 mmol, 1.07 eq.) in THF (18 mL) at –35 °C under N_2. The solution was stirred for one hour at –35 °C (After about 15 minutes a dark red colour was observed.). Then, magnesium chloride (944.4 mg, 9.92 mmol, 1.00 eq.) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.03 mL, 9.92 mmol, 1.00 eq.) were added subseq.uently in one portion to the alkyl lithium at -35 °C, which caused the colour to change from deep red to purple and finally to pale yellow. The solution was warmed to – 5°C over 45 minutes and quenched by the addition of acetyl chloride (0.73 mL, 10.22 mmol, 1.03 eq.). The reaction was evaporated *in vacuo* to yield a mixture of a pale-yellow oil and white solid. The residue was washed with petroleum ether (3 x 20 mL) and filtered to yield a pale-yellow oil (2.44 g, 7.76 mmol, 78%) as a mixture with remaining benzyldimethyl(prop-1-yn-1-yl)silane. The product is unstable to silica gel and Kugelrohr distillation only marginally increased the purity.

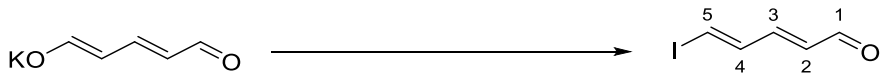
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dtd, *J* = 7.6, 5.7, 2.1 Hz, 3H, H-10, H-11), 7.14 – 7.05 (m, 2H, H-9), 2.19 (s, 2H, H-7), 1.89 (d, *J* = 1.7 Hz, 2H, H-3), 1.29 (s, 12H, H-1), 0.09 (s, 6H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 128.6 (2C), 128.2 (2C), 124.3, 104.8, 84.2, 83.3, 38.1, 26.8, 24.9, –1.8 (2C).

IR (thin film, ν_{max} / cm^{-1}) 3401, 2978, 2171, 1932, 1339, 1142, 830, 674.

HRMS (ESI^+) not found.

(2*E*,4*E*)-5-iodopenta-2,4-dienal, 215



FRU-227-16

(2*E*,4*E*)-5-iodopenta-2,4-dienal was prepared following a procedure reported in the literature (*J. Chem. Soc. Perkin Trans. 1*, **1997**, 1639).

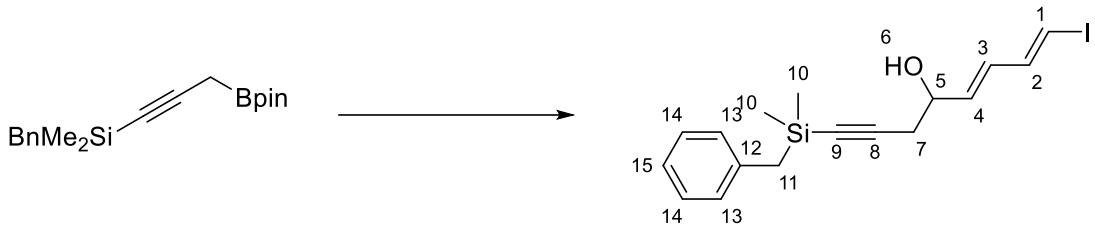
Glutaconaldehyde potassium salt (5.15 g, 37.8 mmol, 1.0 eq.) is added to a solution of triphenylphosphine (10.9 g, 41.6 mmol, 1.1 eq.) and iodine (10.6 g, 41.6 mmol, 1.1 eq.) in DCM (200 mL) at 0 °C in the dark. After 15 minutes, the ice bath is removed and stirring continued for 3 days at room temperature. The solvent is removed *in vacuo* to about 20 mL, yielding a pale-yellow solution. Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (7:3)) gives 5.05 g (24.3 mmol, 65 %) 5-iodopenta-2,4-dienal as a 1:1 mixture of (2E, 4E):(2E,4Z). Repurification by flash column chromatography on silica gel (Petroleum ether/Et_2O (49:1)) and subseq.uent trituration of the fraction containing a 4:1 mixture of (2*E*,4*E*):(2*E*,4*Z*) with *n*-Hexane (2 x 20 mL) affords 1.21 g (5.82 mmol, 16%) of pure (2*E*,4*E*)-5-iodopenta-2,4-dienal (which quickly isomerises when exposed to diethylether) along with 2.9 g (13.9 mmol, 37 %) of a mixture of (2*E*,4*E*) and (2*E*,4*Z*) 5-iodopenta-2,4-dienal (ratio 1:2).

The analytical data matched the reported data (*J. Chem. Soc. Perkin Trans. 1*, **1997**, 1639).

^{1}H NMR (400 MHz, Toluene-d_8) δ 9.16 (d, *J* = 7.6 Hz, 1H, H-1), 6.48 (ddd, *J* = 14.5, 11.0, 0.7 Hz, 1H, H-4), 6.13 (dd, *J* = 14.4, 0.7 Hz, 1H, H-5), 5.86 (ddd, *J* = 15.4, 10.9, 0.6 Hz, 1H, H-3), 5.52 (dd, *J* = 15.4, 7.7 Hz, 1H, H-2).

^{13}C NMR (101 MHz, Toluene-d_8) δ 192.0, 148.5, 143.6, 131.8, 91.0.

(5E,7E)-1-(Benzyldimethylsilyl)-8-iodoocta-5,7-dien-1-yn-4-ol, 218



FRU-280 (yield), FRU-249 (NMR)

THF (0.3 mL) was added to a mixture of CuCl (1.2 mg, 0.012 mmol, 0.05 eq.) and Xantphos (9.8 mg, 0.017 mmol, 0.07 eq.) under N_2 and the white suspension vigorously stirred for 30 minutes. Then, LiO^tBu (1M solution in THF, 0.012 mL, 0.012 mmol, 0.05 eq.) was added and stirring continued for a further hour when the reaction mixture was cooled to 0 °C and a solution of Benzyldimethyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-yn-1-yl)silane (350.0 mg, 50% purity, ~2.3 mmol, 2.3 eq.) and (2E,4E)-5-iodopenta-2,4-dienal (50.0 mg, 0.24 mmol, 1.00 eq.) in THF (0.8 mL) was added. The temperature was slowly raised to room temperature and stirring continued for 40 hours (no further conversion after 20 hours observed). The reaction was diluted with 10 mL of water, the aqueous layer extracted with Et_2O (3 x 20 mL) and the combined organic phase washed with brine (10 mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (6:1) to (4:1)) gave the alcohol (74.5 mg, 0.19 mmol, 79 %) as a pale-yellow oil.

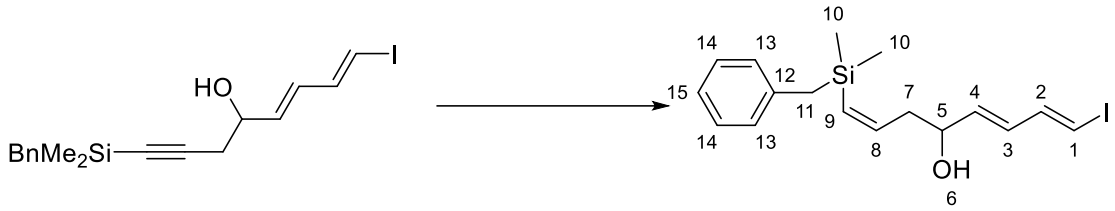
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 2H, H-14), 7.16 – 7.09 (m, 1H, H-15), 7.09 – 7.04 (m, 2H, H-13), 7.04 – 6.96 (m, 1H, H-2), 6.37 (dd, *J* = 14.4, 0.7 Hz, 1H, H-1), 6.18 (dddd, *J* = 15.3, 10.7, 1.4, 0.6 Hz, 1H, H-3), 5.72 (ddt, *J* = 15.3, 5.8, 0.8 Hz, 1H, H-4), 4.42 – 4.08 (m, 1H, H-5), 2.67 – 2.37 (m, 2H, H-7), 2.18 (s, 2H, H-11), 1.97 (d, *J* = 5.1 Hz, 1H, H-6), 0.13 (s, 6H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 139.2, 134.6, 130.8, 128.4 (2C), 128.4 (2C), 124.6, 103.7, 86.7, 80.3, 69.8, 29.2, 26.4, –1.8 (2C).

IR (thin film, ν_{max} / cm^{-1}) 3425, 2957, 2177, 1690, 1493, 1251, 837.

HRMS (ESI^+) calc. for $C_{17}H_{21}IOSiNa$ $[M+Na]^+$ 419.0299, found 419.0298.

(1*Z*,5*E*,7*E*)-1-(Benzyldimethylsilyl)-8-iodoocta-1,5,7-trien-4-ol, 163



FRU-261-3 (mass spec)/ FRU-370-2

Isopropylmagnesiumchloride (2M in THF, 0.05 mL, 0.1 mmol, 1.0 eq.) was added to a solution of (5E,7E)-1-(Benzyldimethylsilyl)-8-iodoocta-5,7-dien-1-yn-4-ol (36.9 mg, 0.09 mmol, 1.00 eq.) in Et_2O (1 mL) at -78 °C under N_2. Titaniumisopropoxide (0.06 mL, 0.19 mmol, 2.0 eq.) was added, then isopropylmagnesiumchloride (2M in Et_2O, 0.20 mL, 2.0 mmol, 4.0 eq.) was slowly added along the wall which caused the reaction to turn yellow. After 30 minutes, the temperature was raised to –42 °C (MeCN/dry ice) and kept there for 2 hours (After 1 h the reaction becomes a brown slurry.), before being quenched by the addition of 1N HCl (2 mL) in the cold. The heterogenous mixture is slowly raised to room temperature which results in a colourless solution. The aqueous layer was extracted with Et_2O (3 x 1 mL) and the combined organic phase dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/EtOAc (9:1)) gave the alcohol (11.4 mg, 0.03 mmol, 32%) as a pale-yellow oil.

Rf 0.2 (petroleum ether / Et_2O (6:1)).

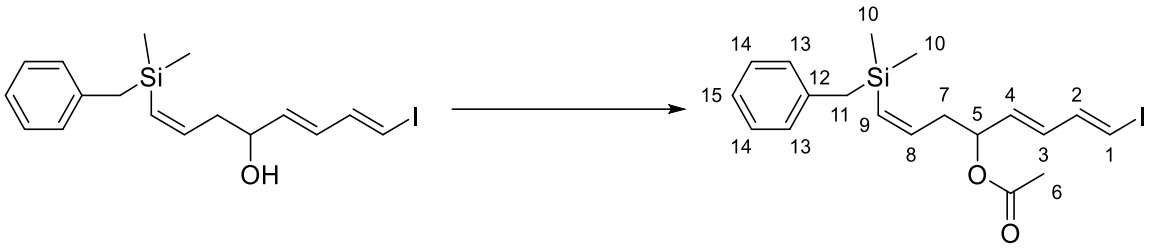
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.7 Hz, 2H, H-14), 7.14 – 6.90 (m, 4H, H-2, H-13, H-15), 6.48 – 6.22 (m, 2H, H-1, H-8), 6.16 (dd, *J* = 15.3, 10.8 Hz, 1H, H-3), 5.79 – 5.60 (m, 2H, H-4, H-9), 4.26 (d, *J* = 6.1 Hz, 1H, H-6), 4.21 – 4.00 (m, 1H, H-5), 2.36 – 2.20 (m, 2H, H-7), 2.16 (s, 2H, H-11), 0.12 (s, 6H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 144.3, 140.0, 136.2, 131.4, 130.1, 128.4, 128.3, 124.3, 79.8, 71.3, 41.1, 26.8, –1.4 (2C).

IR (thin film, ν_{max} / cm^{-1}) 3438 (br), 2956, 2917, 2358, 2341, 1686, 1600, 1252, 834.

HRMS (ES^+) calc. for $C_{17}H_{27}NIOSi$ $[M+NH_4]^+$ 416.0907, 416.0902.

(1*Z*,5*E*,7*E*)-1-(Benzyldimethylsilyl)-8-iodoocta-1,5,7-trien-4-yl acetate, 232



FRU-394-1

Acetic anhydride (0.01 mL, 0.11 mmol, 2.0 eq.) was added to a solution of (1Z,5E,7E)-1-(benzyldimethylsilyl)-8-iodoocta-1,5,7-trien-4-ol (22.7 mg, 0.06 mmol, 1.0 eq.), DMAP (crystals) and Et_3N (0.03 mL, 0.17 mmol, 3.0 eq.) in DCM (1 mL). The mixture was stirred for one hour, and quenched with 1 mL 1N HCl. The aqueous layer was extracted with diethyl ether (3x1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (1:0) to (19:1)) to give the allylic acetate as a colourless oil (19.1 mg, 0.04 mmol, 77%).

Rf 0.33 (petroleum ether);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.3, 6.9 Hz, 2H, H-14), 7.14 – 7.04 (m, 1H, H-15), 7.04 – 6.93 (m, 3H, H-2, H-13), 6.41 (d, *J* = 14.4 Hz, 1H, H-1), 6.23 (dt, *J* = 14.5, 7.2 Hz, 1H, H-8), 6.13 (ddt, *J* = 15.5, 10.8, 0.8 Hz, 1H, H-3), 5.71 – 5.54 (m, 2H, H-4, H-9), 5.38 – 5.18 (m, 1H, H-5), 2.57 – 2.23 (m, 2H, H-7), 2.16 (s, 2H, H-11), 2.04 (s, 3H, H-6), 0.11 (s, 3H, H-10), 0.10 (s, 3H, H-10).

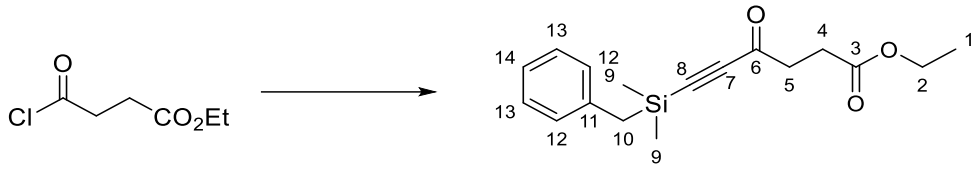
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 144.2, 143.4, 140.0, 132.2, 131.6, 130.9, 128.4, 128.3, 128.3, 124.3, 81.0, 73.1, 38.2, 26.7, 21.3, –1.5, –1.6.

IR (thin film, ν_{max} / cm^{-1}) 3379, 2956, 2361, 2342, 1740, 1234.

HRMS (ES^+) calc. for $C_{10}H_{14}IO_2$ $[M+H]^+$ 293.0038, found 293.0035.

8.5 Synthesis of the Right-hand side Fragments for RvD3 and RvE1

Ethyl 6-(benzyldimethylsilyl)-4-oxohex-5-ynoate, 167



FRU-230

A solution of methylmagnesiumbromide (5.7 mL of a 3 M solution in Et_2O, 17.2 mmol, 1.5 eq.) was added dropwise to a solution of ethynylbenzyldimethylsilane (2.00 g, 11.5 mmol, 1.0 eq.) in THF (20 mL) at 0 °C under N_2. The solution was warmed to room temperature over 20 minutes and then added dropwise to a solution of glutaric acid monoethyl ester chloride (3.3 mL, 22.9 mmol, 2.0 eq.) in THF (50 mL) at 0 °C.

The reaction was quenched with saturated NH_4Cl (10 mL) and diluted with water (20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phase washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (7:1) to (4:1)) gave ynone (1.98 g, 6.54 mmol, 57 %) as a colourless oil.

***R*$_f$** 0.18 (petroleum ether / Et_2O (9:1)).

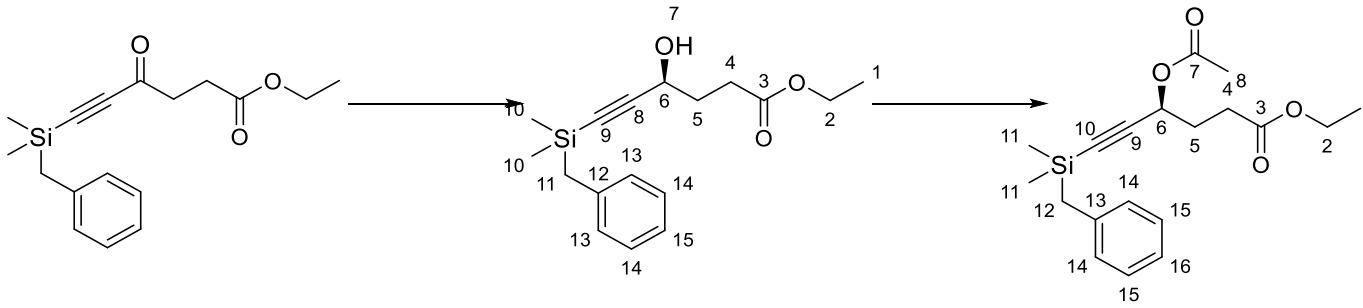
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 2H, H-13), 7.17 – 7.09 (m, 1H, H-14), 7.07 (ddd, *J* = 7.6, 1.3, 0.7 Hz, 2H, H-12), 4.15 (q, *J* = 7.1 Hz, 2H, H-2), 2.88 (t, *J* = 6.8 Hz, 2H, H-5), 2.62 (t, *J* = 6.7 Hz, 2H, H-4), 2.26 (s, 2H, H-10), 1.26 (t, *J* = 7.2 Hz, 3H, H-1), 0.20 (s, 6H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.3, 172.1, 137.9, 128.5 (2C), 128.5 (2C), 124.9, 102.6, 97.2, 61.0, 40.0, 28.0, 25.4, 14.3, –2.6 (2C).

IR (thin film, ν_{max} / cm^{-1}) 2981, 1734, 1680, 1206, 1111, 838, 700.

HRMS (ES^-) calc. for $C_{17}H_{21}O_3Si$ $[M-H]^-$ 301.1250, found 301.1263.

Ethyl (*S*)-4-acetoxy-6-(benzyldimethylsilyl)hex-5-ynoate, 168



FRU-232 (alcohol)/FRU-233/FRU-235 (rac substrate)

A solution of ynone (1.94 g, 6.43 mmol, 1.0 eq.) in isopropyl alcohol (78 mL) was degassed under vacuum until boiling and flushed with N_2 (four times), before the addition of (1*S*,2*S*)-(+)-*N*-tosyl-1,2-diphenylethane-1,2-diamine[η^6-1-isopropyl-4-methylbenzene)-ruthenium(II) (Noyori catalyst, 78.7 mg, 0.13 mmol, 0.02 eq.) as a solution in DCM (1 mL) and degassed twice. The mixture was stirred for 1.5 hours, before being concentrated under reduced pressure to give the crude propargylic alcohol.

Acetic anhydride (1.22 mL, 12.86 mmol, 2.0 eq.) was added to a solution of the crude alcohol, DMAP (2 crystals) and Et_3N (2.68 mL, 19.3 mmol, 3.0 eq.) in DCM (30 mL). The mixture was stirred for one hour, quenched with 1N HCl (10 mL) and diluted with H_2O (10 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL), and the combined organic layers washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (6:1 to 4:1)) to give the propargylic acetate (1.94 g, 5.60 mmol, 88% over two steps) as a colourless oil.

Alcohol:

***R*$_f$** 0.34 (petroleum ether / Et_2O (2:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 8.2, 6.9 Hz, 2H, H-14), 7.14 – 7.02 (m, 3H, H-13, H-15), 4.45 (app q, *J* = 5.9 Hz, 1H, H-6), 4.16 (q, *J* = 7.1 Hz, 2H, H-2), 2.67 – 2.32 (m, 2H, H-4), 2.25 (d, *J* = 5.6 Hz, 1H, H-7), 2.20 (s, 2H, H-11), 2.08 – 1.90 (m, 2H, H-5), 1.28 (t, *J* = 7.2 Hz, 3H, H-1), 0.14 (d, *J* = 0.8 Hz, 6H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 138.9, 128.5 (2C), 128.3 (2C), 124.6, 107.2, 88.7, 62.1, 60.8, 32.4, 30.1, 26.2, 14.3, -2.0 (2C).

Acetate:

Rf 0.28 (petroleum ether / Et_2O (6:1)).

$[\alpha]_D^{25}$ –67.3 (*c* 1.0, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H, H-15), 7.14 – 7.00 (m, 3H, H-14, H-16), 5.43 (t, *J* = 6.2 Hz, 1H, H-6), 4.15 (q, *J* = 7.1 Hz, 2H, H-2), 2.51 – 2.35 (m, 2H, H-4), 2.19 (s, 2H, H-12), 2.08 – 1.90 (m, 5H, H-5, H-8), 1.28 (t, *J* = 7.1 Hz, 3H, H-1), 0.13 (s, 3H, H-11), 0.13 (s, 3H, H-11).

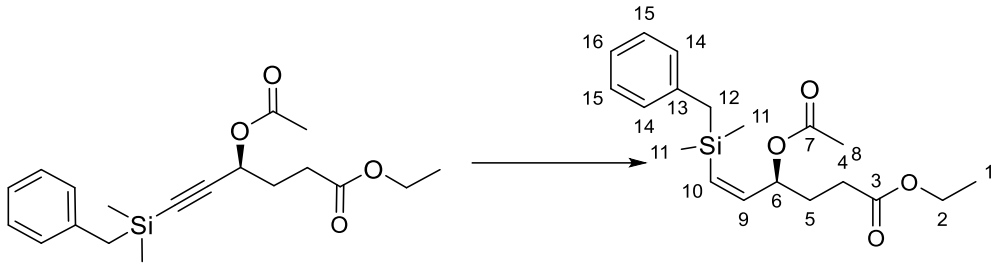
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 169.8, 138.8, 128.5 (2C), 128.3 (2C), 124.6, 103.1, 89.6, 63.3, 60.8, 29.9, 26.1, 21.1, 14.4, –2.1 (2C).

IR (thin film, ν_{max} / cm^{-1}) 2962, 1735, 1372, 1227, 1163, 1025, 837, 700.

HRMS (ES^+) calc. for $C_{19}H_{26}O_4SiNa$ $[M+Na]^+$ 369.1493, found 369.1492.

ee 97.0% (Chiralpak IB, 0.2% IPA/^{n}Hex, 1.3 mL/min, *S* – 9.9 min, *R* – 10.5 min.

Ethyl (S,Z)-4-acetoxy-6-(benzyldimethylsilyl)hex-5-enoate, 169



FRU-241

A suspension of Palladium on $CaCO_3$ (589.5 mg, 5 wt % Pd, 0.28 mmol, 0.05 eq.) in toluene (15 mL) was three times degassed under vacuum and flushed with hydrogen, and subseq.uently stirred for 15 minutes. A solution of alkynylsilane (1.92 g, 5.54 mmol, 1.0 eq.) and quinoline (0.12 mL, 1.11 mmol, 0.2 eq.) in toluene (15 mL) and cyclohexene (3.0 mL) was added to the reation mixture. After stirring for 30 minutes, the reaction mixture was filtered through celite, the filtrate was then washed with 1N HCl (2 x 10 mL) and brine (20 mL) before being dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue subjected to flash column chromatography (petroleum ether / Et_2O (6:1 to 4:1)) to give alkene (1.60 g, 4.58 mmol, *Z*:*E* > 20:1, 83%) as a pale yellow oil.

Rf 0.32 (petroleum ether / Et_2O (4:1)).

$[\alpha]_D^{25}$ -04.8 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H, H-15), 7.12 – 7.04 (m, 1H, H-16), 7.04 – 6.98 (m, 2H, H-14), 6.17 (dd, *J* = 14.4, 9.2 Hz, 1H, H-9), 5.71 (dd, *J* = 14.4, 0.8 Hz, 1H, H-10), 5.35 (dddd, *J* = 8.8, 7.8, 5.4, 0.8 Hz, 1H, H-6), 4.13 (qd, *J* = 7.2, 1.1 Hz, 2H, H-2), 2.41 – 2.25 (m, 2H, H-4), 2.20 (d, ABq, *J* = 14.5 Hz, 2H, H-12), 2.04 (s, 3H, H-8), 1.99 – 1.73 (m, 2H, H-5), 1.26 (t, *J* = 7.1 Hz, 3H, H-1), 0.16 (s, 3H, H-11), 0.16 (s, 3H, H-11).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 170.2, 145.3, 139.8, 132.3, 128.4 (2C), 128.3 (2C), 124.3, 73.6, 60.7, 30.1, 30.1, 26.5, 21.4, 14.4, –1.7, –1.7.

IR (thin film, ν_{max} / cm^{-1}) 3024, 2936, 1736, 1370, 1236, 1027, 834, 700.

HRMS (ES^+) calc. for $C_{19}H_{28}O_4SiNa$ $[M+Na]^+$ 371.1649, found 371.1648.

Ethyl (S)-3-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoate, 160

FRU-335-1

To a solution of silane (100.0 mg, 0.29 mmol, 1.0 eq.) in THF (1 mL) at room temperature was added a 1.0 M solution of trihydrate tetrabutylammonium fluoride in THF (0.30 mL, 0.30 mmol, 1.05 eq.) and the reaction stirred for 30 minutes. Then K_2CO_3 (59.5 mg, 0.43 mmol, 1.5 eq.) was added to the reaction mixture followed by water (50 µL, 5 vol. %, 14.6 eq.). After 2 h the reaction was quenched by addition ofwater (1 mL) and Et_2O (1 mL), the aqueous layer was extracted with Et_2O (3 x 1 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The alkenylsiloxane (64.9 mg, 0.302 mmol, quantitative), which was unstable to silica gel, is obtained as a pale-yellow oil without further purification.

$[\alpha]_D^{20}$ +78.6 (*c* 1.0, $CHCl_3$).

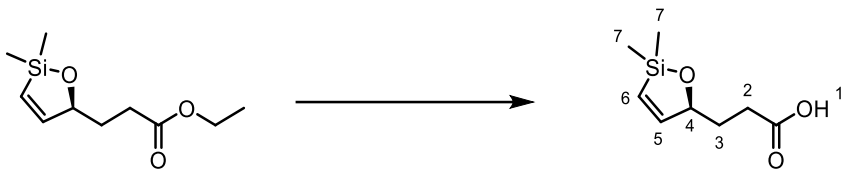
^{1}H NMR (400 MHz, $CDCl_3$) 6.78 (dd, *J* = 10.5, 1.5 Hz, 1H, H-7), 6.06 (dd, *J* = 10.5, 2.2 Hz, 1H, H-8), 4.74 (td, *J* = 6.6, 4.0 Hz, 1H, H-6), 4.12 (qd, *J* = 7.1, 1.5 Hz, 2H, H-2), 2.47 – 2.30 (m, 2H, H-4), 2.13 – 1.97 (m, 1H, H-5), 1.79 – 1.66 (m, 1H, H-5), 1.24 (t, *J* = 7.1 Hz, 3H, H-1), 0.26 (s, 3H, H-9), 0.23 (s, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) 173.9, 152.7, 127.9, 81.8, 60.4, 31.9, 30.0, 14.4, 1.4, 0.7.

IR (thin film, ν_{max} / cm^{-1}) 2958, 2855, 1734, 1251, 1162, 1035, 852, 788.

HRMS (ES^+) calc. for $C_{10}H_{18}O_3SiNa$ $[M+Na]^+$ 237.09174, found 237.09197.

(*S*)-3-(2,2-Dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoic acid, 202



FRU-342-2

Ethyl (*S*)-3-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoate (20.0 mg, 0.09 mmol, 1.0 eq.) was dissolved in a mixture of methanol and water (1mL, 1:1 v:v) and LiOH (7.8 mg, 0.186 mmol, 2.0 eq.) was added. The reaction was vigorously stirred for 1 h, diluted with 2 mL water and extracted with Et_2O (3x1mL). The organic layer was discarded. The aqueous layer was acidified with 0.5 mL 1N HCl (pH=1-2) and extracted with Et_2O (3x1mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield a white solid (14.3 mg, 0.08 mmol, 83%).

Rf not measured

$[\alpha]_D^{20}$ +87.0 (*c* 1.0, $CHCl_3$)

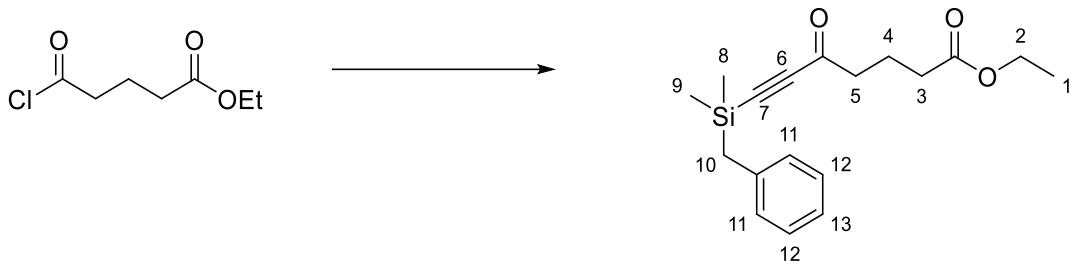
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, *J* = 10.5, 1.5 Hz, 1H, H-5), 6.08 (dd, *J* = 10.5, 2.2 Hz, 1H, H-6), 4.99 – 4.56 (m, 1H, H-4), 2.46 (m, 2H, H-2), 2.04 (m, 1H, H-3), 1.72 (m, 1H, H-1), 0.26 (s, 3H, H-7), 0.24 (s, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 152.4, 128.1, 81.8, 31.6, 29.9, 1.3, 0.7.

IR (thin film, ν_{max} / cm^{-1}) 2955, 1711, 1253, 852, 789.

HRMS (ES^-) calc. for $C_8H_{13}O_3Si$ $[M–H]^-$ 185.0639, found 185.0635.

Ethyl 7-(benzyldimethylsilyl)-5-oxohept-6-ynoate, 272



FRU-20

n-Butyllithium (0.50 mL of a 2.1 M solution / Et_2O, 1.05 mmol, 1.05 eq.) was added dropwise to a solution of ethynylbenzyldimethylsilane (177.4 mg, 1.02 mmol, 1.0 eq.) in THF (1.0 mL) at –78 °C. The solution immediately turned pale yellow and stirred for 10 minutes at –78 °C. Then, a solution of $ZnCl_2$ (1.20 mL of a 0.86 M solution in THF, 1.03 mmol, 1.0 eq.) was added to the alkynyl lithium at –78 °C, which caused the yellow colour to disappear.

The solution was stirred for a further 10 minutes at this temperature, warmed to 0°C, and stirred for 30 minutes, before neat glutaric acid monoethyl ester chloride was added. Stirring was continued for an hour at 0 °C, the solution warmed to room temperature, stirred for another hour and quenched with saturated NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phase dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (7:1)) gave ynone (171.1 mg, 0.54 mmol, 52 %) as colourless oil.

Rf 0.15 (petroleum ether / Et_2O (9:1)).

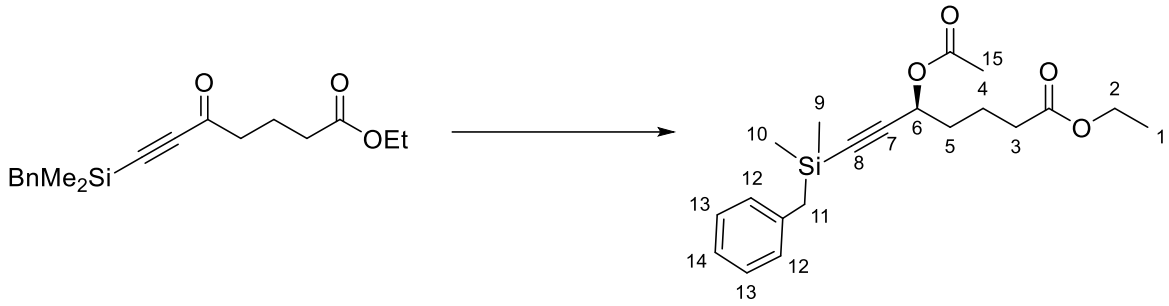
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 2H, H-12), 7.16 – 7.02 (m, 3H, H-11, H-13), 4.14 (q, *J* = 7.1 Hz, 2H, H-2), 2.63 (t, *J* = 7.2 Hz, 2H, H-5), 2.35 (t, *J* = 7.3 Hz, 2H, H-3), 2.26 (s, 2H, H-10), 1.97 (q, J = 7.2 Hz, 2H, H-4), 1.26 (t, J = 7.1 Hz, 3H, H-1), 0.20 (6H, s, H-8, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.7, 173.0, 138.0, 128.5 (2C), 128.5 (2C), 124.9, 103.0, 96.7, 60.6, 44.4, 33.2, 25.5, 19.5, 14.4, –2.6 (2C).

IR (thin film, ν_{max} / cm^{-1}) 2963, 1732, 1676, 1112, 842.

HRMS (ESI^+) calc. for $C_{18}H_{25}O_3Si$ $[M+H]^+$ 317.1574, found 317.1573.

Ethyl (*S*)-5-acetoxy-7-(benzyldimethylsilyl)hept-6-ynoate, 273



FRU-45

A solution of ethyl 7-(benzyldimethylsilyl)-5-oxohept-6-ynoate (100.0 mg, 0.32 mmol, 1.0 eq.) in isopropyl alcohol (4 mL) was degassed under vacuum until boiling and flushed with argon (four times), before the addition of (1*S*,2*S*)-(+)-*N*-Tosyl-1,2-diphenylethane-1,2-diamine[η^6-1-isopropyl-4-methylbenzene)-ruthenium(II) (Noyori catalyst, 4.6 mg, 0.006 mmol, 0.02 eq.) as a solution in DCM (0.1 mL) and degassed twice. The mixture was stirred for 1 hour, before being concentrated under reduced pressure to give the crude propargylic alcohol.

Acetic anhydride (0.07 mL, 0.64 mmol, 2.0 eq.) was added to a solution of DCM (2.0 mL) with crude alcohol, DMAP (2 crystals) and Et_3N (0.14 mL, 0.96 mmol, 3.0 eq.). The mixture was stirred for one hour, and quenched with 5 mL acqueous NH_4Cl. The aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (6:1 to 4:1)) to give the propargylic acetate (106.9 mg, 0.30 mmol, 93% over two steps) as a colorless oil.

Rf 0.40 (petroleum ether / Et_2O (2:1)).

$[\alpha]_D^{25}$ -5.8 (*c* 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.3, 6.7 Hz, 2H, H-13), 7.13 – 7.01 (m, 3H, H-12, H-14), 5.42 – 5.34 (m, 1H, H-6), 4.14 (q, *J* = 7.1 Hz, 2H, H-2), 2.38 – 2.30 (m, 2H, H-3), 2.20 (s, 2H, H-11), 2.09 (s, 3H, H-15), 1.84 – 1.68 (m, 4H, H-5, H-3), 1.26 (t, *J* = 7.1 Hz, 3H, H-1), 0.14 (3H, s, H-8), 0.13 (3H, s, H-9).

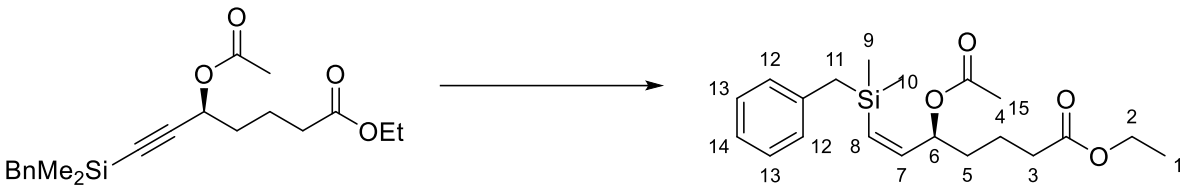
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 169.9, 138.8, 128.5, 128.5, 128.3, 128.3, 124.5, 103.7, 89.2, 64.0, 60.5, 34.1, 33.8, 26.1, 21.2, 20.6, 14.4, –2.1 (2C).

IR (thin film, ν_{max} / cm^{-1}) 2962, 1736, 1372, 1231, 1159, 1022, 840, 700.

HRMS (ESI^+) calc. for $C_{20}H_{28}O_4SiNa$ $[M+Na]^+$ 383.1649, found 383.1653.

ee 99.2% (Chiralpak IB, 0.5 IPA/^{n}Hex, 1.3 mL/min, R - 6.8 min S – 7.6 min).

Ethyl (*S*,*Z*)-5-acetoxy-7-(benzyldimethylsilyl)hept-6-enoate, 274



FRU-47

A suspension of Palladium on $CaCO_3$ (30.3 mg, 5 wt % Pd, 0.014 mmol, 0.05 eq.) in toluene (1 mL) was three times degassed under vacuum and flushed with hydrogen and stirred for 15 minutes. A solution of ethyl (*S*)-5-acetoxy-7-(benzyldimethylsilyl)hept-6-ynoate (102.6 mg, 0.284 mmol, 1.0 eq.) and quinoline (7.0 µL, 0.060 mmol, 0.2 eq.) in toluene (0.4 mL) and cyclohexene (0.14 mL) was added to the reation mixture. After stirring for 2 h, the reaction mixture was directly subjected to flash column chromatography (petroleum ether / Et_2O (6:1)) to give the alkene (76.8 mg, 0.212 mmol, 75% yield) as a pale-yellow oil.

Rf 0.45 (petroleum ether / Et_2O (2:1)).

$[\alpha]_D^{25}$ –7.2 (*c* 1.0, $CHCl_3$).

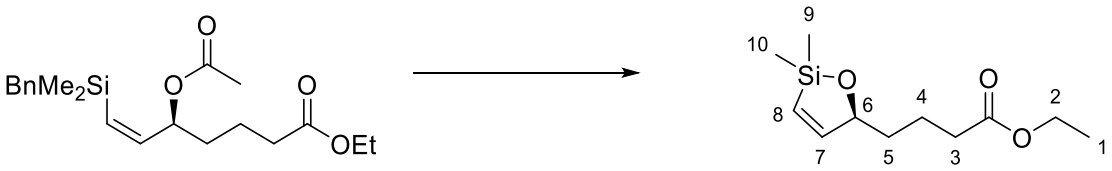
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 2H, H-13), 7.11 – 7.02 (m, 1H, H-14), 7.04 – 6.91 (m, 2H, H-12), 6.19 (dd, *J* = 14.4, 9.2 Hz, 1H, H-7), 5.69 (dd, *J* = 14.4, 0.8 Hz, 1H, H-8), 5.38 – 5.28 (m, 1H, H-6), 4.12 (q, *J* = 7.1 Hz, 2H, H-2), 2.35 – 2.22 (m, 2H, H-3), 2.19 (d, ABq, *J* = 14.5 Hz, 2H, H-11), 2.04 (s, 3H, H-15), 1.71 – 1.55 (m, 3H, H-4, H-5), 1.54 – 1.40 (m, 1H, H-4), 1.25 (t, *J* = 7.1 Hz, 3H, H-1), 0.16 (s, 3H, H-9), 0.15 (s, 3H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 170.3, 145.9, 139.8, 131.7, 128.4, 128.3, 124.2, 74.2, 60.5, 34.4, 34.1, 26.5, 21.4, 20.7, 14.4, –1.7, –1.7.

IR (thin film, ν_{max} / cm^{-1}) 2957, 1734, 1494, 1370, 1239, 1025, 833, 700.

HRMS (ESI^+) calc. for $C_{20}H_{34}O_4SiN$ $[M+NH_4]^+$ 380.2251, found 380.2261.

Ethyl (*S*)-4-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)butanoate, 162



FRU-40

A solution of silane (338.5 mg, 0.934 mmol, 1.0 eq.) in THF (3.0 mL) was stirred at room temperature then a solution of trihydrate tetrabutylammonium fluoride (1.0 M / THF, 0.98 mL, 0.98 mmol, 1.05 eq.) was added and stirred for 30 minutes. Then K_2CO_3 (192.8 mg, 1.395 mmol, 1.5 eq.) was added to the reaction mixture followed by water (150 µL, 5 vol. %). After 30 minutes the completion of the reaction was confirmed by TLC. The reaction media was quenched by addition of water (10 mL) and the aqueous layer extracted with Et_2O (3 x 10 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. The alkenylsiloxane (184.8 mg, 0.809 mmol, 87%), which was unstable to silica gel, was obtained as a pale-yellow oil without further purification.

Rf not measured.

$[\alpha]_D^{25}$ +48.9° (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 10.5, 1.5 Hz, 1H, H-7), 6.04 (dd, *J* = 10.5, 2.2 Hz, 1H, H-8), 4.71 (app ddt, *J* = 6.6, 4.0, 1.9 Hz, 1H, H-6), 4.10 (q, *J* = 7.2 Hz, 2H, H-2), 2.36 (t, *J* = 6.8 Hz, 2H, H-3), 1.84 – 1.59 (m, 3H, H-4, H-5), 1.46 (dddd, *J* = 12.4, 10.2, 6.4, 5.5 Hz, 1H, H-4), 1.24 (t, *J* = 6.9 Hz, 3H, H-1), 0.25 (s, 3H, H-9), 0.23 (s, 3H, H-10).

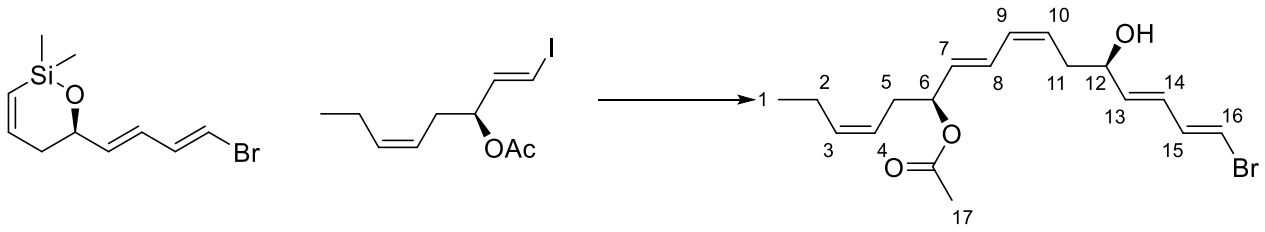
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 153.2, 127.3, 82.6, 60.4, 36.6, 34.5, 20.9, 14.4, 1.5, 0.7.

IR (thin film, ν_{max} / cm^{-1}) 2959, 1734, 1250, 1158, 1030, 853, 788.

HRMS (ESI$^+$) calc. for $C_{11}H_{21}O_3Si$ $[M+H]^+$ 229.1255, found 229.1256.

8.6 Synthesis of RvD3, RvE1 and Hybrids

(3*Z*,6*S*,7*E*,9*Z*,12*R*,13*E*,15*E*)-16-bromo-12-hydroxyhexadeca-3,7,9,13,15-pentaen-6-yl acetate, 248



FRU-509-1 FRU-504-2 (NMR)

To mixture of $Pd(dba)_2$ (5.0 mg, 0.009 mmol, 0.05 eq.), (*S*,1*E*,5*Z*)-1-iodoocta-1,5-dien-3-yl acetate (51.7 mg, 0.175 mmol, 1.00 eq.), (*R*)-6-((1*E*,3*E*)-4-bromobuta-1,3-dien-1-yl)-2,2-dimethyl-5,6-dihydro-2*H*-1,2-oxasiline (50.0 mg, 0.193 mmol, 1.10 eq.) under argon was added TBAF (1M/ THF, 0.58 mL, 0.58 mmol, 3.3 eq.). The reaction was stirred over night and directly purified by flash column chromatography on silica gel (petroleum ether / ether (9:1 to 1:1)) yielding the diol as a colourless oil (40.4 mg, 0.109 mmol, 63%).

Rf 0.2 (petroleum ether / ether (2:1)).

$[\alpha]_D^{20}$ +4.0 (*c* 0.1, $CHCl_3$).

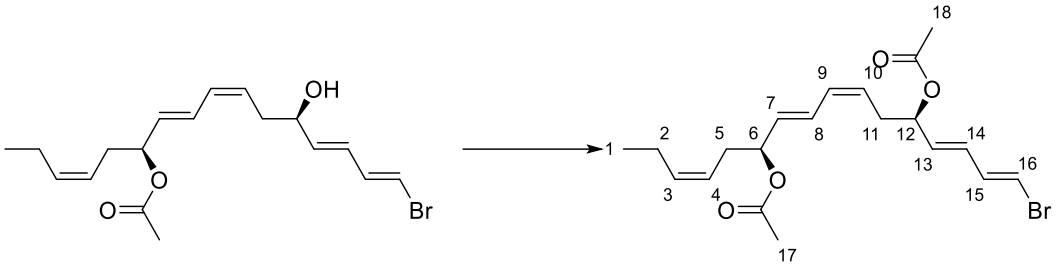
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (ddd, *J* = 13.5, 10.8, 0.7 Hz, 1H, H-15), 6.48 (ddt, *J* = 15.2, 11.1, 1.1 Hz, 1H, H-14), 6.34 (d, *J* = 13.5 Hz, 1H, H-16), 6.27 – 6.06 (m, 2H, H-8, H-9), 5.76 (ddt, *J* = 15.3, 6.0, 0.8 Hz, 1H, H-13), 5.66 (dd, *J* = 15.2, 7.2 Hz, 1H, H-7), 5.58 – 5.40 (m, 2H, H-3, H-10), 5.36 – 5.14 (m, 2H, H-4, H-6), 4.35 – 4.13 (m, 1H, H-12), 2.56 – 2.18 (m, 4H, H-5, H-11), 2.13 – 1.95 (m, 5H, H-2, H-17), 0.96 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 136.8, 136.3, 135.0, 132.3, 131.0, 128.0, 127.6, 127.5, 123.0, 109.4, 74.1, 71.6, 35.7, 32.5, 21.5, 20.9, 14.3.

IR (thin film, ν_{max} / cm^{-1}) 3434, 2963, 1734, 1372, 1238.

HRMS (ES^+) calc. for $C_{18}H_{25}BrO_3K$ $[M+K]^+$ 407.0624, found 407.0609.

(1*E*,3*E*,5*R*,7*Z*,9*E*,11*S*,13*Z*)-1-Bromohexadeca-1,3,7,9,13-pentaene-5,11-diyl diacetate, 249



FRU-513-1/scale: 518-1

Acetic anhydride (0.04 mL, 0.33 mmol, 2.0 eq.) was added to a solution of (3*Z*,6*S*,7*E*,9*Z*,12*R*,13*E*,15*E*)-16-bromo-12-hydroxyhexadeca-3,7,9,13,15-pentaen-6-yl acetate (60.9 mg, 0.16 mmol, 1.0 eq.), DMAP (crystals) and Et_3N (0.09 mL, 0.50 mmol, 3.0 eq.) in DCM (1 mL). The mixture was stirred for one hour, quenched with NH_4Cl (5 mL). The aqueous layer was extracted with dichloromethane (4 x 5 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (9:1) to (4:1)) to give the allylic acetate as a colourless oil (59.6 mg, 0.14 mmol, 88%).

Rf 0.5 (petroleum ether / ether (3:1)).

$[\alpha]_D^{20}$ +3.3 (*c* 0.1, $CHCl_3$).

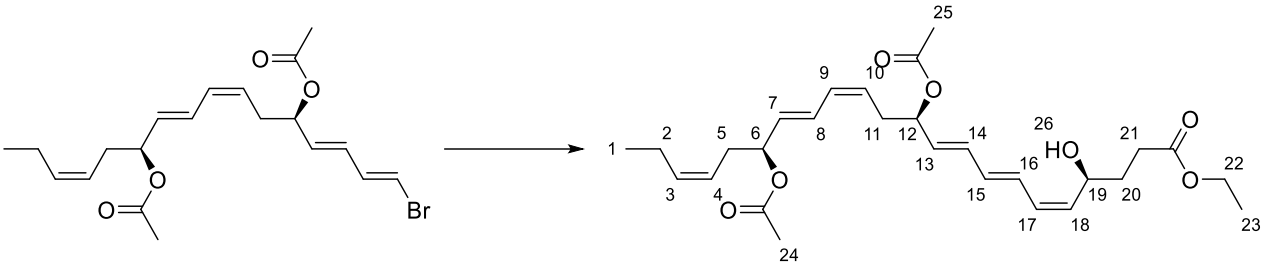
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (ddd, *J* = 13.5, 10.8, 0.8 Hz, 1H, H-15), 6.45 (ddt, *J* = 15.2, 11.1, 1.2 Hz, 1H, H-14), 6.36 (d, *J* = 13.5 Hz, 1H, H-16), 6.22 – 6.12 (m, 1H, H-8), 6.06 (dd, *J* = 11.9, 10.3 Hz, 1H, H-9), 5.74-5.59 (m, 2H, H-7, H-13), 5.56 – 5.45 (m, 1H, H-3/H-10), 5.39 (dt, *J* = 10.9, 7.7 Hz, 1H, H-3/H-10), 5.34 – 5.22 (m, 3H, H-4, H-6, H-12), 2.83 – 2.26 (m, 4H, H-5, H-11), 2.05 (m, 8H, H-2, H-17, H-18), 0.96 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 170.3, 136.5, 135.0, 132.3, 131.7, 130.7, 130.0, 127.6, 126.6, 123.0, 110.4, 74.1, 73.1, 32.8, 32.5, 21.4, 21.3, 20.9, 14.3.

IR (thin film, ν_{max} / cm^{-1}) 2931, 1738, 1372, 1235.

HRMS (ES^+) calc. for $C_{20}H_{27}BrO_4K$ $[M+K]^+$ 451.0712, found 451.0758.

(1*E*,3*E*,5*R*,7*Z*,9*E*,11*S*,13*Z*)-1-Bromohexadeca-1,3,7,9,13-pentaene-5,11-diyl diacetate, 251



FRU-520-2

To a mixture of $Pd(dba)_2$ (4.1 mg, 0.008 mmol, 0.05 eq.), (1*E*,3*E*,5*R*,7*Z*,9*E*,11*S*,13*Z*)-1-Bromohexadeca-1,3,7,9,13-pentaene-5,11-diyl diacetate (59.6 mg, 0.142 mmol, 1.00 eq.), ethyl (S)-3-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoate (52.2 mg, 0.171 mmol, 1.20 eq.) under argon was added TBAF (1M/ THF, 0.43 mL, 0.43 mmol, 3.0 eq.). The reaction was stirred overnight and directly purified by flash column chromatography on silica gel (petroleum ether / ether (4:1 to 1:1)) yielding the alcohol as a colourless oil (24.9 mg, 0.051 mmol, 36%).

Rf 0.1 (petroleum ether / ether (2:1)).

$[\alpha]_D^{20}$ +2.3 (*c* 0.19, $CHCl_3$).

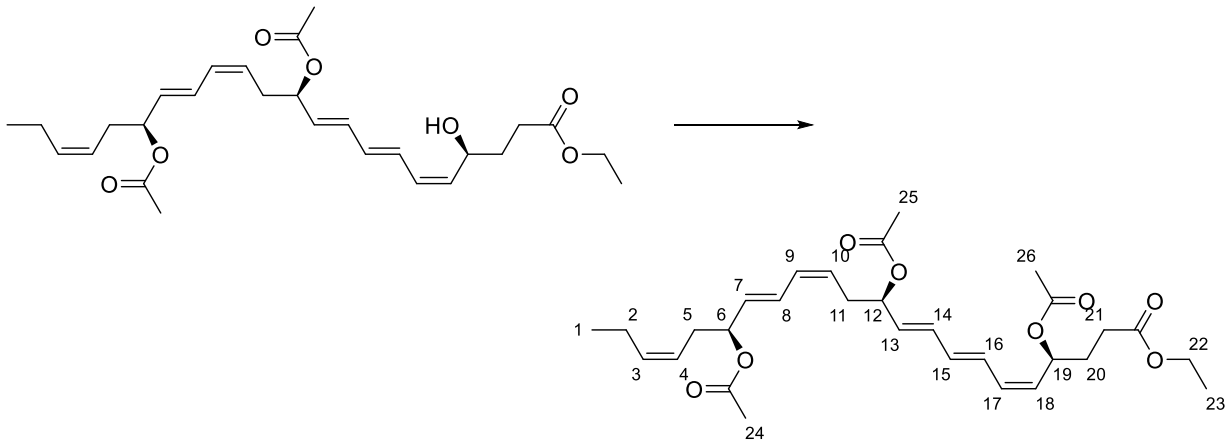
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (m, 2H, H-15, H-16), 6.32 – 6.07 (m, 2H, H-8, H-14), 6.07–5.85 (m, 2H, H-9, H-17), 5.75–5-50 (m, 2H, H-7, H-13), 5.49 – 5.14 (m, 6H, H-3, H-4, H-6, H-10, H-12, H-18), 4.58 (q, *J* = 7.4 Hz, 1H, H-19), 4.07 (q, *J* = 7.1 Hz, 2H, H-22), 2.63 – 2.23 (m, 6H, H-2, H-5, H-11), 2.20 (s, 1H, H-26), 1.97 (m, 8H, H-24,H-25, H-21), 1.90 – 1.70 (m, 2H, H-20), 1.19 (t, *J* = 7.1 Hz, 3H, H-23), 0.89 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 170.4, 170.3, 135.0, 134.0, 133.7, 132.6, 132.1, 131.8, 130.6, 130.2, 128.6, 127.5, 126.8, 123.0, 74.1, 73.4, 67.4, 60.6, 33.0, 32.5, 32.4, 30.5, 21.4, 21.3, 20.8, 14.4, 14.3.

IR (thin film, ν_{max} / cm^{-1}) 3449, 2928, 1734, 1374, 1238, 1025.

HRMS (ES^+) calc. for $C_{28}H_{40}O_7Na$ $[M+Na]^+$ 511.2672, found 511.2674.

(4*S*,5*Z*,7*E*,9*E*,11*R*,13*Z*,15*E*,17*S*,19*Z*)-1-ethoxy-1-oxodocosa-5,7,9,13,15,19-hexaene-4,11,17-triyl triacetate, 276



FRU-546-1, better NMR FRU-638-1

Acetic anhydride (0.01 mL, excess) was added to a solution of (1*E*,3*E*,5*R*,7*Z*,9*E*,11*S*,13*Z*)-1-bromohexadeca-1,3,7,9,13-pentaene-5,11-diyl diacetate (7.1 mg, 14.5 µmol, 1.0 eq.), DMAP (crystals) and Et_3N (0.02 mL, excess) in DCM (0.5 mL). The mixture was stirred for one hour, quenched with NH_4Cl (1 mL). The aqueous layer was extracted with diethyl ether (3x1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (2:1) to (1:1)) to give the allylic acetate as a colourless oil (7.0 mg, 13.2 µmol, 91%).

Rf 0.7 (petroleum ether / ether (1:1)).

$[\alpha]_D^{20}$ +49.2 (*c* 0.61, $CHCl_3$).

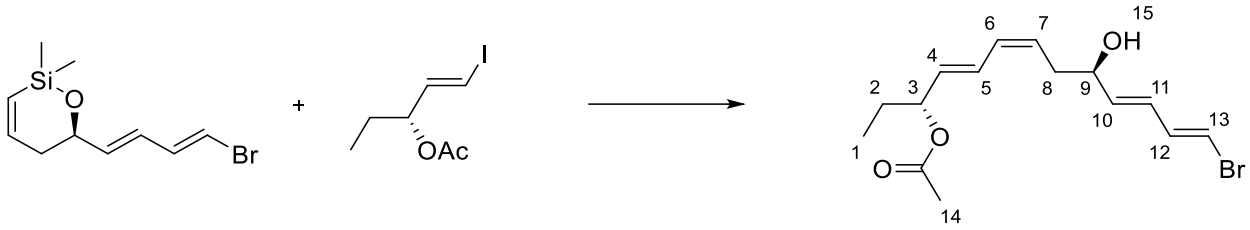
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (dd, *J* = 14.6, 11.5 Hz, 1H, H-14), 6.46 (ddt, *J* = 15.2, 11.1, 1.1 Hz, 1H, H-15), 6.33 (ddd, *J* = 15.1, 10.9, 1.1 Hz, 1H, H-16), 6.21 (dd, *J* = 14.7, 10.7 Hz, 1H, H-8), 6.16 – 6.09 (m, 1H, H-17), 6.05 (t, *J* = 10.9 Hz, 1H, H-9), 5.76 – 5.58 (m, 3H, H-7, H-13, H-18), 5.55 – 5.45 (m, 1H, H-10), 5.45 – 5.23 (m, 5H, H-3, H-4, H-6, H-12, H-19), 4.13 (q, *J* = 7.2 Hz, 2H, H-22), 2.61 – 2.36 (m, 4H, H-5, H-11), 2.33 (t, *J* = 7.6 Hz, 2H, H-21), 2.12 – 1.86 (m, 13H, H-2, H-20, H-24, H-25, H-26), 1.25 (t, *J* = 7.1 Hz, 3H, H-23), 0.96 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 170.4, 170.4, 170.3, 135.0, 134.5, 132.3, 132.2, 132.1, 131.9, 130.6, 128.9, 128.4, 127.5, 126.8, 123.0, 74.1, 73.2, 69.6, 60.7, 33.0, 32.5, 30.2, 30.0, 21.4, 21.3, 21.3, 20.9, 14.4, 14.3.

IR (thin film, ν_{max} / cm^{-1}) 2961, 2934 1736, 1372, 1236, 1021.

HRMS (ES^+) calc. for $C_{30}H_{42}O_8Na$ $[M+Na]^+$ 553.2772, found 553.2770.

(3*Z*,6*S*,7*E*,9*Z*,12*R*,13*E*,15*E*)-16-bromo-12-hydroxyhexadeca-3,7,9,13,15-pentaen-6-yl acetate



FRU-630-1

To a mixture of $Pd(dba)_2$ (20.2 mg, 0.035 mmol, 0.05 eq.), (*R*,*E*)-1-iodopent-1-en-3-yl acetate (181.6 mg, 0.70 mmol, 1.00 eq.), (*R*)-6-((1*E*,3*E*)-4-bromobuta-1,3-dien-1-yl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline (199.6 mg, 0.77 mmol, 1.10 eq.) under argon was added TBAF (1M / THF, 2.3 mL, 2.3 mmol, 3.3 eq.). The reaction was stirred over night, the solvent removed *in vacuo* and the crude reaction mixture directly purified by flash column chromatography on silica gel (petroleum ether / ether (4:1 to 1:1)) yielding the diol as a colourless oil (143.7 mg, 0.44 mmol, 63%).

Rf 0.2 (petroleum ether / ether (2:1)).

$[\alpha]_D^{20}$ +27.3 (*c* 1.0, $CHCl_3$).

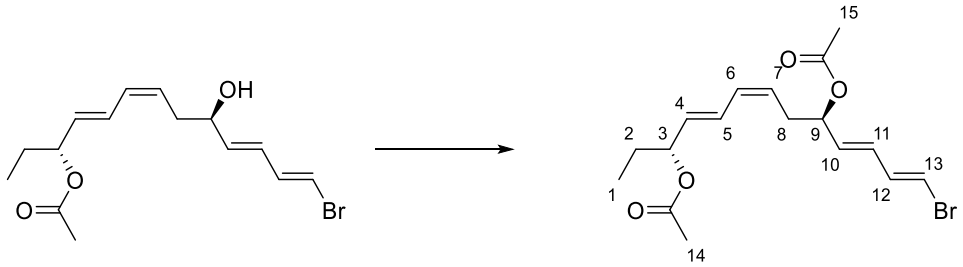
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (ddd, *J* = 13.5, 10.8, 0.8 Hz, 1H, H-12), 6.48 (ddt, *J* = 15.2, 11.1, 1.1 Hz, 1H, H-11), 6.33 (dq, *J* = 13.6, 0.6 Hz, 1H, H-13), 6.24 – 6.08 (m, 2H, H-6, H-7), 5.76 (ddt, *J* = 15.3, 6.1, 0.8 Hz, 1H, H-4), 5.68–5.56 (m, 1H, H-10), 5.55–5.40 (m, 1H, H-5), 5.22 (app q, *J* = 6.4 Hz, 1H, H-3), 4.33–4.07 (m, 1H, H-9), 2.55 – 2.39 (m, 2H, H-8), 2.06 (s, 3H, H-14), 1.81 – 1.52 (m, 3H, H-2, H-15), 0.90 (t, *J* = 7.4 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 136.8, 136.3, 132.5, 131.0, 128.0, 127.7, 127.4, 109.4, 75.9, 71.6, 35.7, 27.6, 21.5, 9.7.

IR (thin film, ν_{max} / cm^{-1}) 3416, 2969, 1729, 1372, 1241, 980.

HRMS (ES^+) calc. for $C_{15}H_{21}BrO_3Na$ $[M+Na]^+$ 351.0566, found 351.0568.

(3*R*,4*E*,6*Z*,9*R*,10*E*,12*E*)-13-bromotrideca-4,6,10,12-tetraene-3,9-diyl diacetate, 279



FRU-632-1

Acetic anhydride (0.08 mL, 0.82 mmol, 2.0 eq.) was added to a solution of (3*Z*,6*S*,7*E*,9*Z*,12*R*,13*E*,15*E*)-16-bromo-12-hydroxyhexadeca-3,7,9,13,15-pentaen-6-yl acetate (135.0 mg, 0.41 mmol, 1.0 eq.), DMAP (crystals) and Et_3N (0.17 mL, 1.23 mmol, 3.0 eq.) in DCM (1 mL). The mixture was stirred for one hour, quenched with 2 mL NH_4Cl. The aqueous layer was extracted with diethylether (3x1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (9:1) to (4:1)) to give the allylic acetate as a colourless oil (137.1 mg, 0.37 mmol, 91%).

Rf 0.5 (petroleum ether / ether (3:1)).

$[\alpha]_D^{20}$ +29.3 (*c* 1.0, $CHCl_3$).

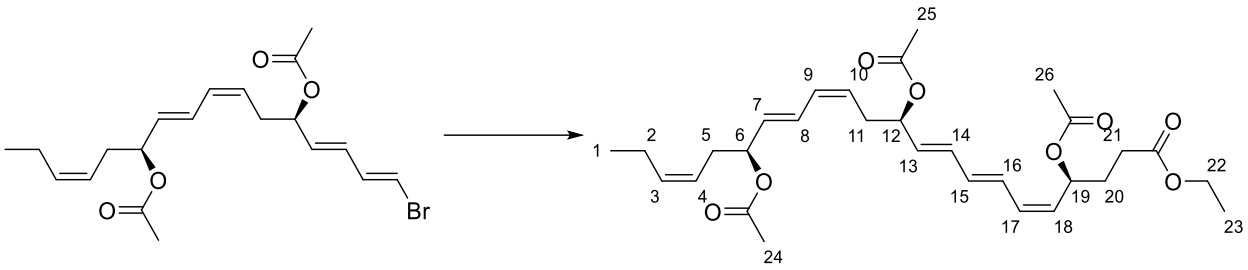
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (ddd, *J* = 13.6, 10.8, 0.8 Hz, 1H, H-12), 6.46 (ddt, *J* = 15.2, 11.1, 1.1 Hz, 1H, H-10), 6.36 (d, *J* = 13.5 Hz, 1H, H-13), 6.16 (ddt, *J* = 15.3, 10.8, 0.7 Hz, 1H, H-11), 6.07 (t, *J* = 11.0 Hz, 1H, H-6), 5.71 – 5.57 (m, 2H, H-4, H-5), 5.38 (dt, *J* = 10.8, 7.7 Hz, 1H, H-7), 5.29 (app qd, *J* = 6.6, 1.1 Hz, 1H, H-9), 5.22 (app q, *J* = 6.4 Hz, 1H, H-3), 2.63 – 2.42 (m, 2H, H-8), 2.06 (s, 3H, H-15), 2.04 (s, 3H, H-14), 1.76 – 1.57 (m, 2H, H-2), 0.90 (t, *J* = 7.4 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.3, 136.5, 132.5, 131.7, 130.8, 130.1, 127.6, 126.4, 110.4, 75.8, 73.2, 32.8, 27.7, 21.5, 21.3, 9.7.

IR (thin film, ν_{max} / cm^{-1}) 2931, 1738, 1372, 1235.

HRMS (ES^+) calc. for $C_{17}H_{23}BrO_4Na$ $[M+Na]^+$ 393.0672, found 393.0672.

(4*S*,5*Z*,7*E*,9*E*,11*R*,13*Z*,15*E*,17*S*,19*Z*)-1-ethoxy-1-oxodocosa-5,7,9,13,15,19-hexaene-4,11,17-triyl triacetate, 276



FRU-634/638-1

To mixture of $Pd(dba)_2$ (9.0 mg, 0.016 mmol, 0.10 eq.), (1*E*,3*E*,5*R*,7*Z*,9*E*,11*S*,13*Z*)-1-bromohexadeca-1,3,7,9,13-pentaene-5,11-diyl diacetate (64.3 mg, 0.142 mmol, 1.00 eq.), ethyl (*S*)-3-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoate (40.2 mg, 0.171 mmol, 1.20 eq.) under argon was added TBAF (1M/ THF, 0.47 mL, 0.47 mmol, 3.0 eq.). The reaction was stirred overnight and directly purified by flash column chromatography on silica gel (petroleum ether / ether (2:1 to 1:2)) yielding a mixture of alcohol and lactone as a colourless oil (30.4 mg, 0.062 mmol, 40%).

Acetic anhydride (0.02 mL, 0.20 mmol, 2.0 eq.) was added to the above product mixture (30.4 mg, 0.062 mmol, 1.0 eq.), DMAP (crystals) and Et_3N (0.04 mL, 0.30 mmol, 3.0 eq.) in DCM (0.5 mL). The mixture was stirred for one hour, then quenched with NH_4Cl (1 mL). The aqueous layer was extracted with diethylether (3 x 1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (3:2)) to give the allylic acetate as a colourless oil (25.6 mg, 0.048 mmol, 32% over 2 steps).

Rf 0.3 (petroleum ether / ether (3:2)).

$[\alpha]_D^{20}$ +49.2 (*c* 0.61, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (dd, *J* = 14.6, 11.5 Hz, 1H, H-14), 6.46 (ddt, *J* = 15.2, 11.1, 1.1 Hz, 1H, H-15), 6.33 (ddd, *J* = 15.1, 10.9, 1.1 Hz, 1H, H-16), 6.21 (dd, *J* = 14.7, 10.7 Hz, 1H, H-8), 6.16 – 6.09 (m, 1H, H-17), 6.05 (t, *J* = 10.9 Hz, 1H, H-9), 5.76 – 5.58 (m, 3H, H-7, H-13, H-18), 5.55 – 5.45 (m, 1H, H-10), 5.45 – 5.23 (m, 5H, H-3, H-4, H-6, H-12, H-19), 4.13 (q, *J* = 7.2 Hz, 2H, H-22), 2.61 – 2.36 (m, 4H, H-5, H-11), 2.33 (t, *J* =

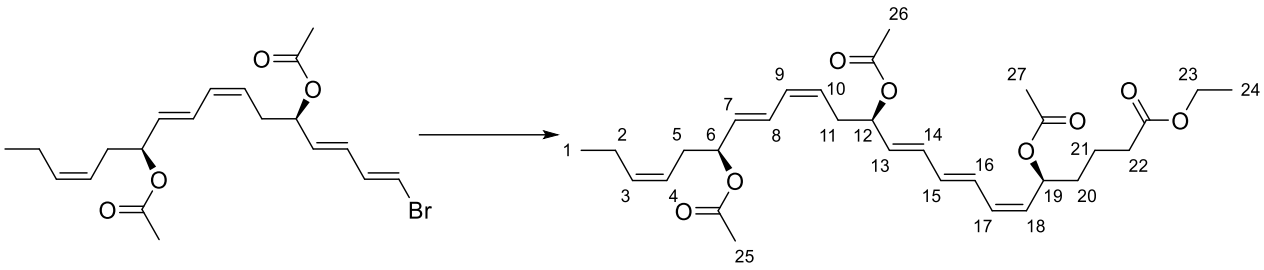
7.6 Hz, 2H, H-21), 2.12 – 1.86 (m, 13H, H-2, H-20, H-24, H-25, H-26), 1.25 (t, *J* = 7.1 Hz, 3H, H-23), 0.96 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 170.4, 170.4, 170.3, 134.9, 134.5, 132.3, 132.2, 132.1, 131.9, 130.6, 128.9, 128.4, 127.5, 126.8, 123.0, 74.1, 73.2, 69.6, 60.7, 33.0, 32.5, 30.2, 30.0, 21.4, 21.3, 21.3, 20.9, 14.4, 14.3.

IR (thin film, ν_{max} / cm^{-1}) 2961, 2934 1736, 1372, 1236, 1021.

HRMS (ES^+) calc. for $C_{30}H_{42}O_8Na$ $[M+Na]^+$ 553.2772, found 553.2770.

(5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*,16*E*,18*S*,20*Z*)-1-ethoxy-1-oxotricosa-6,8,10,14,16,20-hexaene-5,12,18-triyl triacetate, 277



FRU-635/639-1

To a mixture of $Pd(dba)_2$ (8.4 mg, 0.015 mmol, 0.10 eq.), (1*E*,3*E*,5*R*,7*Z*,9*E*,11*S*,13*Z*)-1-bromohexadeca-1,3,7,9,13-pentaene-5,11-diyl diacetate (60.4 mg, 0.146 mmol, 1.00 eq.), ethyl (*S*)-4-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)butanoate (42.5 mg, 0.175 mmol, 1.20 eq.) under argon was added TBAF (1M / THF, 0.44 mL, 0.44 mmol, 3.0 eq.). The reaction was stirred over night and directly purified by flash column chromatography on silica gel (petroleum ether / ether (2:1 to 1:2)) yielding the alcohol as a colourless oil (33.6 mg, 0.067 mmol, 46%).

Acetic anhydride (0.02 mL, 0.20 mmol, 2.0 eq.) was added to the above product (33.6 mg, 0.067 mmol, 1.0 eq.), DMAP (crystals) and Et_3N (0.04 mL, 0.30 mmol, 3.0 eq.) in DCM (0.5 mL). The mixture was stirred for one hour, then quenched with NH_4Cl (1 mL). The aqueous layer was extracted with diethylether (3 x 1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (3:2)) to give the allylic acetate as a colourless oil (31.2 mg, 0.057 mmol, 40% over 2 steps).

Rf 0.3 (petroleum ether / ether (3:2)).

$[\alpha]_D^{20}$ +15.6 (*c* 0.38, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (dd, *J* = 14.8, 11.4 Hz, 1H, H-14), 6.50 – 6.41 (m, 1H, H-15), 6.39 – 6.29 (m, 1H, H-16), 6.20 (dd, *J* = 14.8, 10.8 Hz, 1H, H-8), 6.15 – 6.08 (m, 1H, H-17), 6.06 (t, *J* = 11.0 Hz, 1H, H-9), 5.75 – 5.60 (m, 3H, H-7, H-13, H-18), 5.55 – 5.46 (m, 1H, H-10), 5.41 (dt, *J* = 11.2, 7.7 Hz, 1H, H-3/H-4), 5.38 – 5.24 (m, 4H, H-3/H-4, H-6, H-12, H-19), 4.12 (q, *J* = 7.1 Hz, 2H, H-23), 2.67 – 2.47 (m, 2H, H-11), 2.47 –

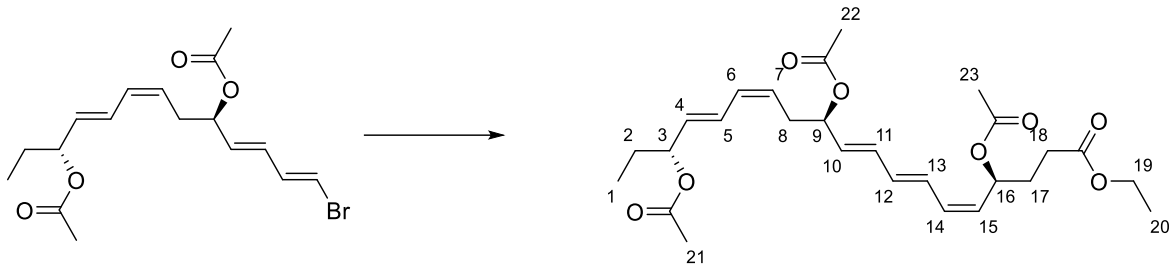
2.34 (m, 2H, H-5), 2.31 (t, *J* = 7.2 Hz, 2H, H-22), 2.11 – 1.98 (m, 13H, H-2, H-21, H-25, H-26, H-27), 1.72 (ddt, *J* = 11.5, 6.9, 3.1 Hz, 1H, H-21), 1.68 – 1.60 (m, 1H, H-21), 1.25 (t, *J* = 7.1 Hz, 3H, H-24), 0.96 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 170.5, 170.4, 170.4, 135.0, 134.3, 132.3, 132.1, 132.0, 131.6, 130.6, 129.5, 128.5, 127.5, 126.9, 123.0, 74.1, 73.3, 70.0, 60.5, 34.3, 34.1, 33.0, 32.5, 21.4, 21.4, 21.3, 20.9, 20.7, 14.4, 14.3.

IR (thin film, ν_{max} / cm^{-1}) 2963, 1735, 1372, 1236, 1021.

HRMS (ES^+) calc. for $C_{31}H_{44}O_8Na$ $[M+Na]^+$ 567.2934, found 567.2927.

(3*R*,4*E*,6*Z*,9*R*,10*E*,12*E*,14*Z*,16*S*)-19-ethoxy-19-oxononadeca-4,6,10,12,14-pentaene-3,9,16-triyl triacetate, 280



FRU-636/640-1

To a mixture of $Pd(dba)_2$ (10.5 mg, 0.018 mmol, 0.10 eq.), (3*R*,4*E*,6*Z*,9*R*,10*E*,12*E*)-13-bromotrideca-4,6,10,12-tetraene-3,9-diyl diacetate (68.2 mg, 0.183 mmol, 1.00 eq.), ethyl (*S*)-3-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoate (47.1 mg, 0.220 mmol, 1.20 eq.) under argon was added TBAF (1M / THF, 0.55 mL, 0.55 mmol, 3.0 eq.). The reaction was stirred over night and directly purified by flash column chromatography on silica gel (petroleum ether / ether (1:1 to 1:2)) yielding a mixture of the lactone and the alcohol as a colourless oil (36.6 mg, 0.082 mmol, 45%).

Acetic anhydride (0.02 mL, 0.20 mmol, 2.0 eq.) was added to the above product (36.6 mg, 0.082 mmol, 1.0 eq.), DMAP (crystals) and Et_3N (0.04 mL, 0.30 mmol, 3.0 eq.) in DCM (0.5 mL). The mixture was stirred for one hour, quenched with NH_4Cl (1 mL). The aqueous layer was extracted with diethylether (3 x 1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (3:2)) to give the allylic acetate as a colourless oil (29.3 mg, 0.060 mmol, 34% over 2 steps).

Rf 0.3 (petroleum ether / ether (3:2)).

$[\alpha]_D^{20}$ +28.5 (*c* 0.37, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (dd, *J* = 14.7, 11.5 Hz, 1H, H-11), 6.46 (ddt, *J* = 15.3, 11.2, 1.1 Hz, 1H, H-12), 6.37 – 6.27 (m, 1H, H-13), 6.21 (dd, *J* = 14.7, 10.8 Hz, 1H, H-5), 6.12 (t, *J* = 11.1 Hz, 1H, H-6), 6.07 (dd, *J* = 12.0, 10.2 Hz, 1H, H-14), 5.75 – 5.65 (m,

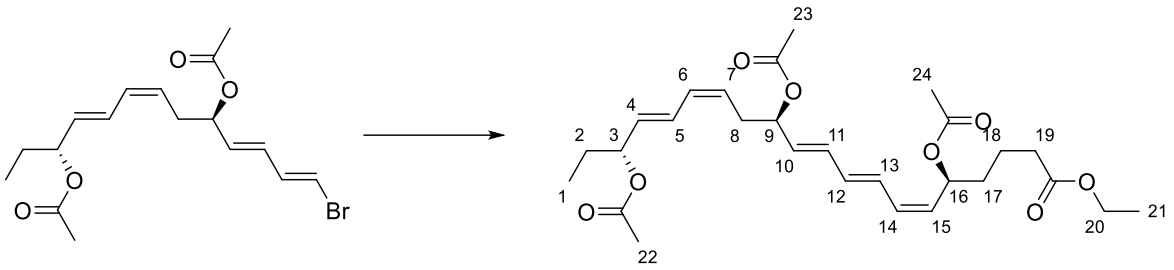
2H, H-9, H-15), 5.61 (dd, *J* = 15.2, 7.3 Hz, 1H, H-4), 5.48 – 5.27 (m, 3H, H-7, H-9, H-16), 5.23 (app q, *J* = 6.8, 6.4 Hz, 1H, H-3), 4.13 (q, *J* = 7.1 Hz, 2H, H-19), 2.58 (dddd, *J* = 14.7, 8.2, 6.7, 1.5 Hz, 1H, H-8), 2.48 (dddd, *J* = 14.8, 7.6, 6.1, 1.5 Hz, 1H, H-8), 2.33 (t, *J* = 7.6 Hz, 2H, H-18), 2.13 – 1.96 (m, 10H, H-17, H-21, H-22, H-23), 1.95 – 1.86 (m, 1H, H-17), 1.75 – 1.60 (m, 2H, H-2), 1.25 (t, *J* = 7.2 Hz, 3H, H-20), 0.90 (t, *J* = 7.4 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 170.6, 170.4, 170.3, 134.5, 132.4, 132.4, 132.2, 131.9, 130.7, 128.9, 128.4, 127.6, 126.7, 75.8, 73.3, 69.6, 60.7, 33.0, 30.2, 30.0, 27.7, 21.5, 21.3, 21.3, 14.4, 9.7.

IR (thin film, ν_{max} / cm^{-1}) 2971, 1734, 1372, 1236, 1021.

HRMS (ES^+) calc. for $C_{27}H_{38}O_8Na$ $[M+Na]^+$ 513.2465, found 513.2464.

(3*R*,4*E*,6*Z*,9*R*,10*E*,12*E*,14*Z*,16*S*)-20-ethoxy-20-oxoicosa-4,6,10,12,14-pentaene-3,9,16-triyl triacetate, 282



FRU-637/641-1

To mixture of $Pd(dba)_2$ (10.6 mg, 0.019 mmol, 0.10 eq.), (3*R*,4*E*,6*Z*,9*R*,10*E*,12*E*)-13-bromotrideca-4,6,10,12-tetraene-3,9-diyl diacetate (68.7 mg, 0.185 mmol, 1.00 eq.), ethyl (*S*)-4-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)butanoate (50.7 mg, 0.222 mmol, 1.20 eq.) under argon was added TBAF (1M/ THF, 0.56 mL, 0.56 mmol, 3.0 eq.). The reaction was stirred overnight and directly purified by flash column chromatography on silica gel (petroleum ether / ether (1:1 to 1:2)) yielding the alcohol as a colourless oil (41.7 mg, 0.090 mmol, 49%).

Acetic anhydride (0.02 mL, 0.20 mmol, 2.0 eq.) was added to the above product (41.7 mg, 0.090 mmol, 1.0 eq.), DMAP (crystals) and Et_3N (0.04 mL, 0.30 mmol, 3.0 eq.) in DCM (0.5 mL). The mixture was stirred for one hour, quenched with NH_4Cl (1 mL). The aqueous layer was extracted with diethylether (3 x 1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (3:2)) to give the allylic acetate as a colourless oil (36.0 mg, 0.071 mmol, 39% over 2 steps).

Rf 0.3 (petroleum ether / ether (3:2)).

$[\alpha]_D^{20}$ +13.0 (*c* 0.37, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (dd, *J* = 14.7, 11.5 Hz, 1H, H-11), 6.51 – 6.42 (m, 1H, H-12), 6.38 – 6.29 (m, 1H, H-13), 6.20 (dd, *J* = 14.7, 10.8 Hz, 1H, H-5), 6.15–6.03 (m, 2H, H-6, H-14), 5.72-5.64 (m, 2H, H-4, H-10), 5.61 (dd, *J* = 15.2, 7.2 Hz, 1H, H-15), 5.45

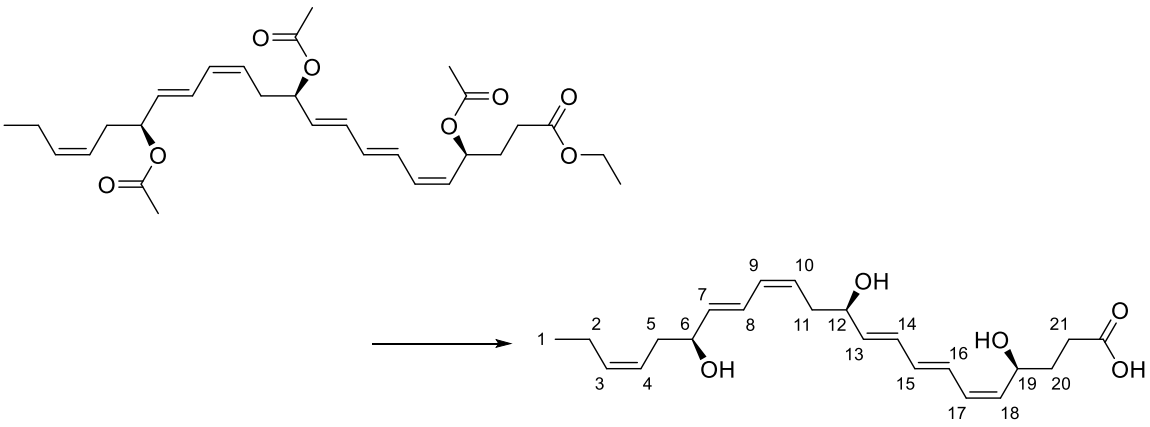
– 5.31 (m, 3H, H-7, H-9, H-16), 5.23 (app q, *J* = 6.8 Hz, 1H, H-3), 4.12 (q, *J* = 7.1 Hz, 2H, H-20), 2.58 (dddd, *J* = 14.6, 8.1, 6.7, 1.6 Hz, 1H, H-8), 2.53 – 2.43 (m, 1H, H-8), 2.31 (t, *J* = 7.2 Hz, 2H, H-19), 2.10 – 2.00 (m, 9H, H-22, H-23, H-24), 1.82 – 1.56 (m, 4H, H-2, H-17), 1.25 (t, *J* = 7.1 Hz, 3H, H-21), 0.90 (t, *J* = 7.4 Hz, 3H, H-1).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 170.5, 170.5, 170.3, 134.3, 132.4, 132.4, 132.0, 131.6, 130.7, 129.5, 128.5, 127.6, 126.7, 75.8, 73.3, 70.0, 60.5, 34.3, 34.1, 33.0, 27.7, 21.5, 21.4, 21.4, 20.7, 14.4, 9.7.

IR (thin film, ν_{max} / cm^{-1}) 2971, 1734, 1372, 1237, 1023.

HRMS (ES^+) calc. for $C_{27}H_{38}O_8Na$ $[M+Na]^+$ 527.2621, found 527.2638.

(4*S*,5*Z*,7*E*,9*E*,11*R*,13*Z*,15*E*,17*S*,19*Z*)-4,11,17-trihydroxydocosa-5,7,9,13,15,19-hexaenoic acid (RvD3), 10



FRU-742-1

To a solution of (4*S*,5*Z*,7*E*,9*E*,11*R*,13*Z*,15*E*,17*S*,19*Z*)-1-ethoxy-1-oxodocosa-5,7,9,13,15,19-hexaene-4,11,17-triyl triacetate (3.9 mg, 7 µmol, 1.00 eq.) in THF (0.3 mL) was added a solution of LiOH in water (1 M, 0.3 mL, 0.3 mmol, ~ 50 eq.). The reaction was stirred overnight, then quenched with phosphate buffer (1M pH 6, 1mL) and extracted with ethyl acetate (3 x 1 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford (4*S*,5*Z*,7*E*,9*E*,11*R*,13*Z*,15*E*,17*S*,19*Z*)-4,11,17-trihydroxydocosa-5,7,9,13,15,19-hexaenoic acid (2.7 mg, 7 µmol, quantitative yield).

Rf not measured.

$[\alpha]_D^{20}$ +7.9 (*c* 0.34, MeOH).

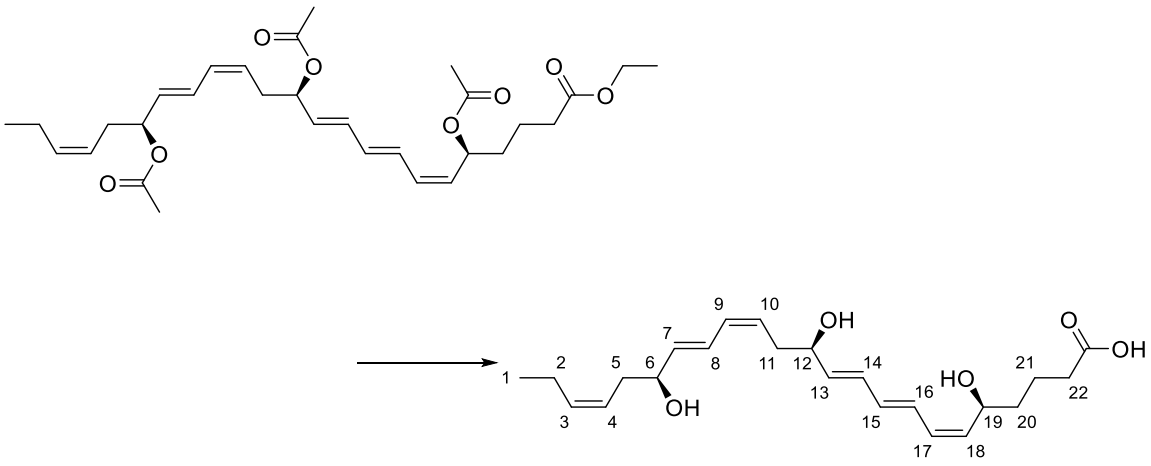
^{1}H NMR (500 MHz, Methanol-d_4) δ 6.60 – 6.44 (m, 2H, H-8, H-16), 6.36 – 6.20 (m, 2H, H-14, H-15), 6.08 (app q, *J* = 11.3 Hz, 2H, H-9, H-17), 5.76 (dd, *J* = 14.4, 6.5 Hz, 1H, H-13), 5.68 (dd, *J* = 15.2, 6.5 Hz, 1H, H-7), 5.46 (app ddt, *J* = 10.6, 8.7, 7.3 Hz, 2H, H-4, H-10), 5.41 – 5.30 (m, 2H, H-3, H-18), 4.69 – 4.52 (m, 1H, H-19), 4.26 – 4.06 (m, 2H,H-6,H-12), 2.59 – 2.16 (m, 6H, H-5, H-11, H-21), 2.13 – 1.99 (m, 2H, H-20), 1.84 (dq, *J* = 14.6, 7.5 Hz, 1H, H-2), 1.76 – 1.67 (m, 1H, H-2), 0.96 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (126 MHz, Methanol-d_4) δ 177.4, 137.9, 137.5, 135.2, 134.8, 134.6, 131.5, 131.1, 130.8, 128.7, 128.1, 126.6, 125.5, 73.2, 73.0, 67.7, 36.7, 36.2, 33.7, 30.9, 21.7, 14.6.

IR (thin film, ν_{max} / cm^{-1}) 3378, 2925, 1706, 1418, 1051, 996.

HRMS (ES^-) calc. for $C_{22}H_{31}O_5$ $[M–H]^-$ 375.2177, found 375.2175.

(5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*,16*E*,18*S*,20*Z*)-5,12,18-trihydroxytricosa-6,8,10,14,16,20-hexaenoic acid, 278



FRU-743-1

To a solution of (5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*,16*E*,18*S*,20*Z*)-1-ethoxy-1-oxotricosa-6,8,10,14,16,20-hexaene-5,12,18-triyl triacetate (4.6 mg, 8 µmol, 1.00 eq.) in THF (0.3 mL) was added a solution of LiOH in water (1 M, 0.3 mL, 0.3 mmol, ~ 50 eq.). The reaction was stirred overnight, then quenched with phosphate buffer (1 M, pH 6, 1mL) and extracted with ethyl acetate (3 x 1 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford (5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*,16*E*,18*S*,20*Z*)-5,12,18-trihydroxytricosa-6,8,10,14,16,20-hexaenoic acid (2.7 mg, 7 µmol, 87%).

Rf not measured.

$[\alpha]_D^{20}$ +4.7 (*c* 0.27, MeOH).

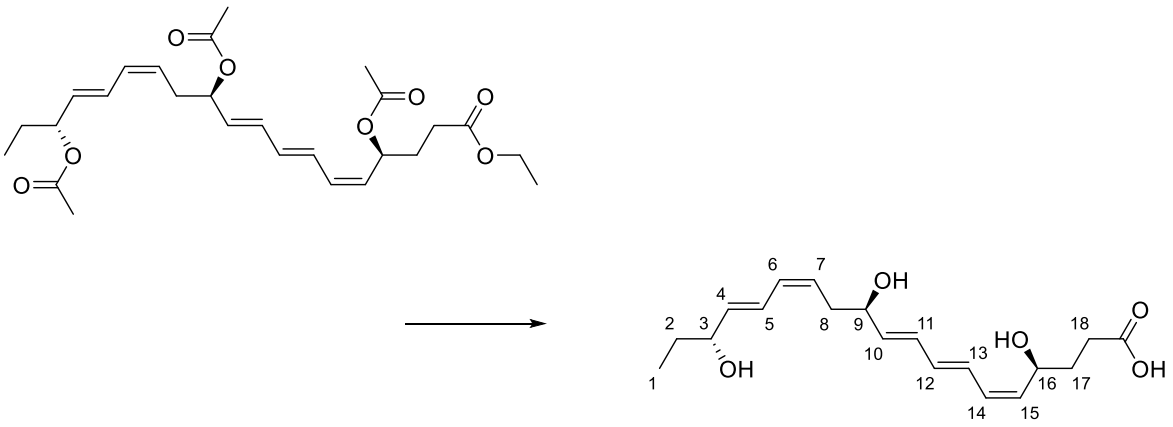
^{1}H NMR (500 MHz, Methanol-d_4) δ 6.60 – 6.44 (m, 2H, H-8, H-16), 6.37 – 6.20 (m, 2H, H-14, H-15), 6.08 (app td, *J* = 11.1, 5.4 Hz, 2H, H-9, H-17), 5.76 (dd, *J* = 14.7, 6.5 Hz, 1H, H-13), 5.68 (dd, *J* = 15.2, 6.5 Hz, 1H, H-7), 5.52 – 5.41 (m, 2H, H-4, H-10), 5.42 – 5.31 (m, 2H, H-3, H-18), 4.57 (dt, *J* = 9.0, 6.2 Hz, 1H, H-19), 4.16 (app q, *J* = 7.5 Hz, 1H, H-12), 4.14 (app q, *J* = 7.0 Hz, 1H, H-6), 2.57 – 2.37 (m, 2H, H-11), 2.37 – 2.19 (m, 4H, H-5, H-22), 2.12 – 1.97 (m, 2H, H-20), 1.65 (m, 4H, H-2, H-21), 0.96 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (126 MHz, Methanol-d_4) δ 177.5, 137.8, 137.5, 135.2, 135.1, 134.6, 131.5, 131.1, 130.5, 128.8, 128.1, 126.6, 125.5, 73.2, 73.0, 68.2, 38.0, 36.7, 36.2, 34.8, 22.1, 21.7, 14.6.

IR (thin film, ν_{max} / cm^{-1}) 3368, 2930, 1714, 1417, 996.

HRMS (ES^-) calc. for $C_{23}H_{33}O_5$ $[M–H]^-$ 389.2334, found 389.2333.

(4*S*,5*Z*,7*E*,9*E*,11*R*,13*Z*,15*E*,17*R*)-4,11,17-trihydroxynonadeca-5,7,9,13,15-pentaenoic acid, 281



FRU-744-1

To a solution of (3*R*,4*E*,6*Z*,9*R*,10*E*,12*E*,14*Z*,16*S*)-19-ethoxy-19-oxononadeca-4,6,10,12,14-pentaene-3,9,16-triyl triacetate (4.5 mg, 7 µmol, 1.00 eq.) in THF (0.3 mL) was added a solution of LiOH in water (1 M, 0.3 mL, 0.3 mmol, ~ 50 eq.). The reaction was stirred overnight, then quenched with phosphate buffer (1 M, pH 6, 1mL) and extracted with ethyl acetate (3 x 1 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford (4*S*,5*Z*,7*E*,9*E*,11*R*,13*Z*,15*E*,17*R*)-4,11,17-trihydroxynonadeca-5,7,9,13,15-pentaenoic acid (2.8 mg, 8 µmol, 92%).

Rf not measured.

$[\alpha]_D^{20}$ +2.0 (*c* 0.28, MeOH).

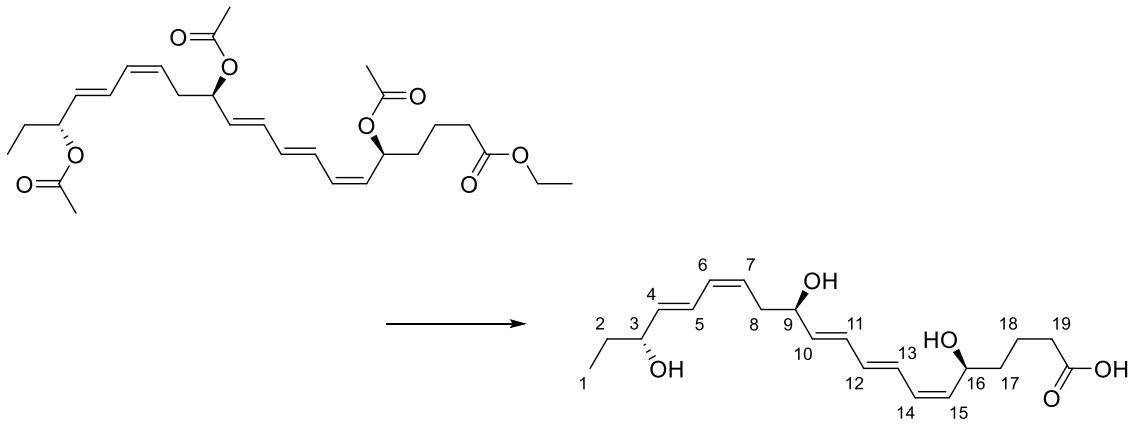
^{1}H NMR (500 MHz, Methanol-d_4) δ 6.61 – 6.42 (m, 2H, H-5, H-13), 6.41 – 6.18 (m, 2H, H-11, H-12), 6.09 (td, *J* = 11.1, 4.0 Hz, 2H, H-6, H-14), 5.77 (dd, *J* = 14.5, 6.5 Hz, 1H, H-10), 5.66 (dd, *J* = 15.2, 6.7 Hz, 1H, H-4), 5.45 (dt, *J* = 11.0, 7.5 Hz, 1H, H-7), 5.40 – 5.34 (m, 1H, H-15), 4.72 – 4.46 (m, 1H, H-16), 4.24 – 4.08 (m, 1H, H-9), 4.08 – 3.92 (m, 1H, H-3), 2.57 – 2.41 (m, 2H, H-8), 2.37 (t, *J* = 7.5 Hz, 2H, H-18), 1.84 (app dq, *J* = 14.6, 7.3 Hz, 1H, H-17), 1.73 (dtd, *J* = 13.6, 7.6, 6.0 Hz, 1H, H-17), 1.62 – 1.45 (m, 2H, H-2), 0.92 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (126 MHz, Methanol-d_4) δ 177.4, 137.9, 137.8, 135.2, 134.8, 131.5, 131.1, 130.8, 128.8, 128.0, 126.6, 74.7, 73.0, 67.8, 36.7, 33.7, 31.2, 30.9, 10.2.

IR (thin film, ν_{max} / cm^{-1}) 3336, 2924, 1708, 1412, 1055, 996.

HRMS (ES^-) calc. for $C_{19}H_{27}O_5$ $[M–H]^-$ 335.1864, found 335.1863.

(5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*,16*E*,18*R*)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid (RvE1), 13



FRU-745-1

To a solution of (3*R*,4*E*,6*Z*,9*R*,10*E*,12*E*,14*Z*,16*S*)-20-ethoxy-20-oxoicosa-4,6,10,12,14-pentaene-3,9,16-triyl triacetate (5.2 mg, 6 µmol, 1.00 eq.) in THF (0.3 mL) was added a solution of LiOH in water (1 M, 0.3 mL, 0.3 mmol, ~ 50 eq.). The reaction was stirred overnight, then quenched with phosphate buffer (1 M, pH 6, 1mL) and extracted with ethyl acetate (3 x 1 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to afford (5S,6Z,8E,10E,12R,14Z,16E,18R)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid (2.0 mg, 6 µmol, 95%).

Rf not measured.

$[\alpha]_D^{20}$ +1.1 (*c* 0.20, MeOH).

^{1}H NMR (500 MHz, Methanol-d_4) δ 6.60 – 6.43 (m, 2H, H-5, H-13), 6.40 – 6.18 (m, 2H, H-11, H-12), 6.09 (td, *J* = 11.2, 2.3 Hz, 2H, H-6, H-14), 5.76 (dd, *J* = 14.8, 6.5 Hz, 1H, H-10), 5.66 (dd, *J* = 15.2, 6.6 Hz, 1H, H-4), 5.46 (dt, *J* = 11.0, 7.5 Hz, 1H, H-7), 5.37 (dd, *J* = 10.9, 9.1 Hz, 1H, H-15), 4.57 (dt, *J* = 9.0, 6.1 Hz, 1H, H-16), 4.17 (app q, *J* = 6.5 Hz, 1H, H-9), 4.02 (app q, *J* = 6.5 Hz, 1H, H-3), 2.57 – 2.37 (m, 2H, H-8), 2.32 (t, *J* = 7.0 Hz, 2H, H-19), 1.81 – 1.44 (m, 6H, H-2, H-17, H-18), 0.92 (t, *J* = 7.4 Hz, 3H, H-1).

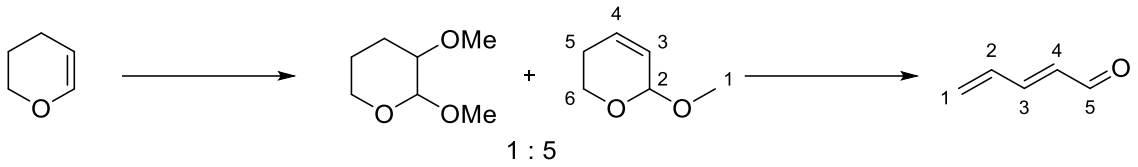
^{13}C NMR (126 MHz, Methanol-d_4) δ 177.5, 137.8, 137.8, 135.2, 135.1, 131.5, 131.1, 130.5, 128.8, 128.0, 126.6, 74.7, 73.0, 68.2, 38.0, 36.7, 34.8, 31.2, 22.1, 10.2.

IR (thin film, ν_{max} / cm^{-1}) 3350, 2925, 1709, 1412, 1246, 996.

HRMS (ES^-) calc. for $C_{20}H_{29}O_5$ $[M–H]^-$ 349.2021, found 349.2020.

8.7 Synthesis of Model Systems and their Coupling

(*E*)-Penta-2,4-dienal 219



FRU-170/FRU-174

(*E*)-penta-2,4-dienal was prepared following a modified procedure reported in the literature (*Bioorg. Med. Chem*, **2015**, 5595):

To a vigorously stirred suspension of NBS (60.0 g, 330 mmol, 1.0 eq.) in 120 mL MeOH at –10 °C was added 3,4-Dihydro-2*H*-pyran (28.3 g, 330 mmol, 1.0 eq.) dropwise over 10 minutes. After addition a slight orange colour persisted. The solution turned clear and colourless upon addition of a further drop of DHP. The reaction mixture was allowed to warm to 22°C and stirred for another hour. KOH (37.2 g, 1.02 mol, 3.1 eq.) was added and the reaction mixture was refluxed for 17 hours which caused the formation of a white precipitate. After cooling to room temperature, water (100 mL) was added and stirred vigorously to dissolve the succinimide. This also caused the separation of an oily organic layer from the aqueous methanol. The aqueous phase was extracted three times with petroleum ether (100 mL). The combined organic phase was concentrated (T=30°C, p>100mbar) to yield a mixture of the desired elimination product, 6-methoxy-3,6-dihydro-2H-pyran, and the substitution product 2,3-dimethoxytetrahydro-2H-pyran in a 5:1 ratio as a colourless oil (37.3 g, 273 mmol ,72% of 6-methoxy-3,6-dihydro-2H-pyran).

To the crude product was added 250mL 3M phosphoric acid and the mixture vigorously stirred. The heterogeneous mixture was subjected to hydrodistillation ($T_{heating\ bath}$= 100–130 °C, p= 1 atm) and a water/product azeotrope was collected (boiling point= 92–94 °C). The distillate was diluted with 100 mL of Et_2O. After separating the aqueous layer, the organic phase was washed with 10 mL of brine, dried ($MgSO_4$) and concentrated (T=40°C, p>300 mbar) to yield a pale-yellow oil (4.99 g, 54.0 mmol, 17% over 2 steps).

The analytical data matched the reported data (*Bioorg. Med. Chem*, **2015**, 5595):

6-methoxy-3,6-dihydro-2H-pyran

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (dddd, *J* = 11.2, 6.5, 2.2, 1.1 Hz, 1H, H-4), 5.73 (app dtd, *J* = 10.2, 2.8, 1.4 Hz, 1H, H-3), 4.87 – 4.72 (m, 1H, H-2), 3.92 (dtd, *J* = 15.1, 11.3, 4.0 Hz, 1H, H-6), 3.73 (ddt, *J* = 11.3, 6.2, 1.3 Hz, 1H, H-6‘), 3.42 (s, 3H, H-1), 2.51 – 2.13 (m, 1H, H-5), 2.08 – 1.75 (m, 1H, H-5‘).

^{13}C NMR (101 MHz, $CDCl_3$) δ 129.3, 125.8, 95.1, 57.4, 55.3, 24.9.

(*E*)-penta-2,4-dienal

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (dd, *J* = 7.9, 1.4 Hz, 1H, H-5), 7.10 (dd, *J* = 15.4, 10.6 Hz, 1H, H-3), 6.59 (dt, *J* = 17.0, 10.6 Hz, 1H, H-2), 6.17 (dd, *J* = 15.4, 7.9 Hz, 1H, H-4), 5.74 (d, *J* = 17.0 Hz, 1H, H-1), 5.63 (d, *J* = 9.9 Hz, 1H, H-1‘).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 152.1, 134.9, 132.5, 127.7.

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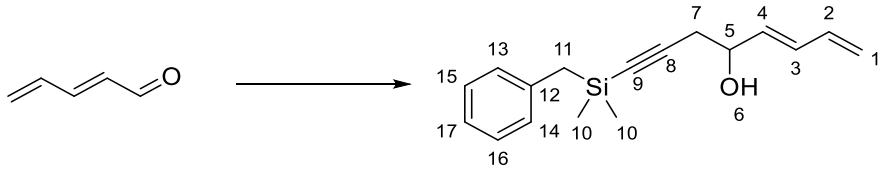
(*E*)-1-(Benzyldimethylsilyl)octa-5,7-dien-1-yn-4-ol, 217



FRU-176

sec-Butyllithium (13.0 mL of a 1.3 M solution in hexanes, 17.0 mmol, 1.4 eq.) was added dropwise to a solution of propynylbenzyldimethylsilane (3.43 g, 18.2 mmol, 1.5 eq.) in THF (100 mL) at –78 °C. The solution immediately turned pale orange and was stirred for 20 minutes at –78 °C. Then, pentadienal (1.13 mL, 12.1 mmol, 1.0 eq.) in 10 mL THF was added dropwise over 5 minutes to the alkynyl lithium at –78 °C and stirred for 1.5 hours at that temperature. The reaction was quenched at –78 °C with 5 mL NH_4Cl and 10 mL water. The aqueous layer was extracted with 3x20 mL Et_2O and the combined organic phase washed with brine (20mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (5:1)) gave the alcohol (1.49 g, 5.50 mmol, 46%) as acolourless oil.

Rf 0.20 (petroleum ether / Et_2O (5:1));

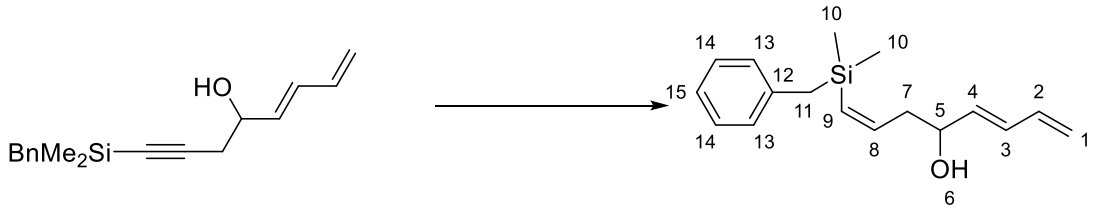
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.5 Hz, 2H, H-15/H-16), 7.18 – 7.03 (m, 3H, H-13/H-14/H-17), 6.50 – 6.06 (m, 2H, H2/H-3), 5.74 (dd, *J* = 14.7, 6.2 Hz, 1H, H-4), 5.26 (dd, *J* = 16.2, 1.8 Hz, 1H, H-1), 5.16 (dd, *J* = 9.7, 1.8 Hz, 1H, H-1‘), 4.41 – 4.22 (m, 1H, H-5), 2.70 – 2.36 (m, 2H, H-7), 2.21 (s, 2H, H-11), 2.04 (d, *J* = 4.9 Hz, 1H, H-6), 0.16 (s, 6H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 136.2, 134.1, 132.0, 128.4 (2C), 128.3 (2C), 124.5, 118.3, 104.1, 86.4, 70.3, 29.3, 26.4, –1.8 (2C).

IR (thin film, ν_{max} / cm^{-1}) 3361, 2176, 1602, 1493, 841.

HRMS (EI$^+$) calc. for $C_{17}H_{22}OSiNa$ $[M+Na]^+$ 293.1332, found 293.1332.

(1*Z*,5*E*)-1-(benzyldimethylsilyl)octa-1,5,7-trien-4-ol, 231



FRU-362-4

Isopropylmagnesiumchloride (2M in THF, 0.25 mL, 0.50 mmol, 1.0 eq.) was added to a solution of (5*E*,7*E*)-1-(Benzyldimethylsilyl)-octa-5,7-dien-1-yn-4-ol (135.2 mg, 0.50 mmol, 1.00 eq.) in Et_2O (1 mL) at –78 °C under N_2. Titaniumisopropoxide (0.30 mL, 1.00 mmol, 2.0 eq.) was added, then isopropylmagnesiumchloride (2M in Et_2O, 0.20 mL, 2.0 mmol, 4.0 eq.) was slowly added along the wall which caused the reaction to turn yellow. After 30 minutes, the temperature was raised to –42 °C (MeCN/dry ice) and kept there for 2 hours (After 1 h the reaction becomes a brown slurry.), before being quenched by the addition of 1N HCl (10 mL) in the cold. The heterogenous mixture is slowly raised to room temperature which results in a colourless solution. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic phase dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/EtOAc (9:1)) gave the alcohol (30.2 mg, 0.11 mmol, 24%) as a pale-yellow oil.

Rf 0.4 (petroleum ether / EtOAc (5:1)).

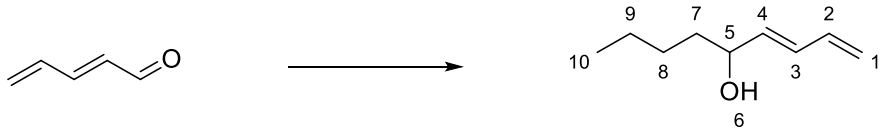
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 2H, H-13), 7.12 – 7.04 (m, 1H, H-15), 7.05 – 6.98 (m, 2H, H-14), 6.40 – 6.17 (m, 3H, H-2, H-3, H-9), 5.82 – 5.50 (m, 2H, H-4, H-8), 5.37 – 5.17 (m, 1H, H-1), 5.11 (dd, *J* = 9.8, 1.6 Hz, 1H, H-1), 4.17 (q, *J* = 6.3 Hz, 1H, H-5), 2.43 – 2.24 (m, 2H, H-7), 2.17 (s, 2H, H-11), 1.67 – 1.45 (m, 1H, H-6), 0.12 (s, 6H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 140.1, 136.3, 135.7, 131.2, 131.0, 128.4 (2C), 128.3 (2C), 124.2, 117.9, 71.8, 41.3, 26.8, –1.5 (2C).

IR (thin film, ν_{max} / cm^{-1}) 3369, 2956, 1602, 1493, 831.

HRMS (ES^+) calc. for $C_{17}H_{25}OSi$ $[M+H]^+$ 273.4708, found 273.4716.

(*E*)-1-(Benzyldimethylsilyl)octa-5,7-dien-1-yn-4-ol



FRU-188

(*E*)-Pentadienal (0.45 mL, 4.3 mmol, 1.0 eq.) was added dropwise to a solution of *n*-Butyllithium (3.53 mL of a 1.6 M solution in hexanes, 5.6 mmol, 1.3 eq.) in THF (20 mL) at –78 °C. The solution immediately turned pale yellow, the acetone/ dry ice-bath was removed and reaction warmed to room temperature over 30 minutes. The reaction was quenched with 5 mL NH_4Cl and 10 mL water. The aqueous layer was extracted with 3x20 mL Et_2O and the combined organic phase washed with brine (20mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (petroleum ether / Et_2O (9:1 to 3:1)) gave the alcohol (278.7 mg, 1.99 mmol, 46%) as a colourless oil.

Rf 0.60 (petroleum ether / Et_2O (3:1));

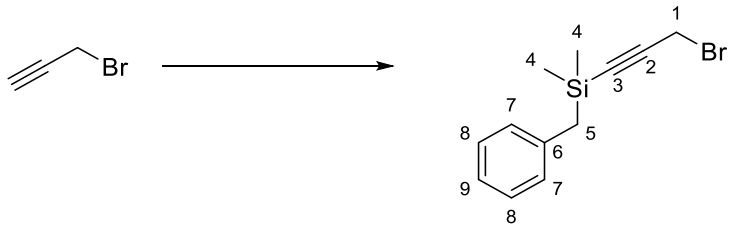
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (dt, *J* = 16.6, 10.4 Hz, 1H, H-2), 6.21 (ddd, *J* = 15.2, 10.4, 1.0 Hz, 1H, H-3), 5.79 – 5.59 (m, 1H, H-4), 5.21 (dd, *J* = 16.6, 1.5 Hz, 1H, H-1), 5.09 (dd, *J* = 9.9, 1.6 Hz, 1H, H-1‘), 4.13 (dt, *J* = 9.9, 5.0 Hz, 1H, H-5), 1.71 – 1.43 (m, 2H, H-7/H-8/H-9), 1.43-1.21 (m, 4H, H-7/H-8/H-9), 1.02 – 0.80 (m, 3H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 136.5, 131.1, 117.6, 72.7, 37.1, 27.7, 22.8, 14.2.

IR (thin film, ν_{max} / cm^{-1}) 3339, 2958, 2931, 1605, 1002.

HRMS (EI$^+$) calc. for $C_9H_{17}O$ $[M+H]^+$ 141.1274, found 141.1277.

Benzyl(3-bromoprop-1-yn-1-yl)dimethylsilane, 225



FRU-242

n-Butyllithium (4.70 mL of a 2.5 M solution in hexanes, 11.6 mmol, 1.1 eq.) was added dropwise to a solution of propargylic bromide (80% in toluene, 1.72 mL, 13.1 mmol, 1.25 eq.) in THF (32 mL) at -–78 °C. The solution was stirred for 30 minutes at –78 °C. Then, benzyldichloromethylsilane (2.00 mL, 10.5 mmol, 1.0 eq.) was added in one portion to the alkynyl lithium at –78 °C, the acetone/ dry ice bath removed and the solution was warmed to room temperature over 3 hours. The reaction was quenched with halfsaturated NH_4Cl (20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phase washed with brine (20 mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (pure petroleum ether) gave the bromide (1.76 g, 6.57 mmol, 63%) as a pale-yellow oil.

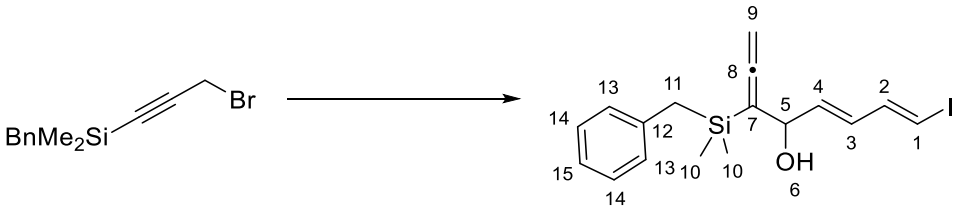
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 2H, H-8), 7.18 – 7.08 (m, 3H, H-7, H-9), 3.93 (s, 2H, H-1), 2.24 (s, 2H, H-5), 0.16 (s, 6H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 130.8 (2C), 130.6 (2C), 126.9, 103.6, 93.3, 28.3, 17.0, 0.0 (2C).

IR (thin film, ν_{max} / cm^{-1}) 3025, 2959, 2180, 1600, 1493, 1252, 1205, 1036, 833.

HRMS (ESI^+) not found

(5*E*,7*E*)-3-(Benzyldimethylsilyl)-8-iodoocta-1,2,5,7-tetraen-4-ol, 226



FRU-244-3

Magnesium turnings (46.7 mg, 1.92 mmol, 2.1 eq.) were heated to 400 °C (heat gun) under vacuum for 5 minutes. The flask was cooled to room temperature and backfilled with Argon before $HgCl_2$ (2.6 mg, 0.01 mmol, 0.01 eq.) and THF (1 mL) were added. The reaction was stirred for 10 minutes at room temperature. A drop of the propargyl bromide in 0.5 mL THF was added and the reaction stirred until slight heat evolution was perceived. Then the flask was cooled to 0 °C and the remaining propargyl bromide (385.4 mg, 1.44 mmol, 1.5 eq.) added dropwise. Stirring was continued for two hours at 0°C, then the flask was cooled to -78 °C, and (2*E*,4*E*)-5-iodopenta-2,4-dienal (200.0 mg, 0.96 mmol, 1.0 eq.) in THF (1 mL) was added quickly. After 1 hour the reaction was quenched with 1 mL sat. NH_4Cl, brought to room temperature and diluted with 5 mL water. The aqueous layer was extracted with Et_2O (3x10 mL) and the combined organic phase washed with brine (10 mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (6:1) to (4:1)) gave the alcohol (70.2 mg, 0.177 mmol, 19%) as pale-yellow oil.

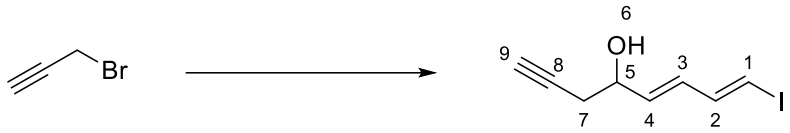
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.6 Hz, 2H, H-14), 7.14 – 7.06 (m, 1H, H-15), 7.05 – 6.95 (m, 3H, H-2, H-13), 6.35 (d, *J* = 14.4 Hz, 1H, H-1), 6.10 (ddd, *J* = 15.2, 10.7, 1.1 Hz, 1H, H-3), 5.70 (dd, *J* = 15.2, 6.3 Hz, 1H, H-4), 4.78 – 4.32 (m, 3H, H-5, H-9), 2.21 (s, 2H, H-11), 1.70 (d, *J* = 5.4 Hz, 1H, H-6), 0.11 (s, 3H, H-10), 0.11 (s, 3H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 144.5, 139.6, 135.8, 130.1, 128.5 (2C), 128.4 (2C), 124.4, 98.4, 80.0, 72.9, 71.0, 26.0, –2.7, –2.7.

IR (thin film, ν_{max} / cm^{-1}) 3426, 3024, 2957, 2361, 2342, 2177, 1599, 1493, 1251, 827.

HRMS (ESI$^+$) calc. for $C_{17}H_{21}ISiNa$ $[M+Na]^+$ 419.0299, found 419.0298.

(5*E*,7*E*)-8-Iodoocta-5,7-dien-1-yn-4-ol



FRU-332-3

Magnesium turnings (550.0 mg, 22.5 mmol, 32.0 eq.) were heated to 400°C (heatgun) under vacuum for 5 minutes. The flask was cooled to room temperature and backfilled with Argon before $HgCl_2$ (47.5 mg, 0.17 mmol, 0.24 eq.) and THF (10 mL) were added. The reaction was stirred for 10 minutes at room temperature. A drop of propargyl bromide was added and the reaction stirred until slight heat evolution was perceived. Then the flask was cooled to 0 °C and the remaining propargyl bromide (1.8 mL, 17 mmol, 23.5 eq.) added dropwise. Stirring was continued for two hours at 0°C, then the flask was cooled to –78 °C, and (2E,4E)-5-iodopenta-2,4-dienal (147.8 mg, 0.71 mmol, 1.00 eq.) in THF (3 + 1 mL) was added quickly. After 1 hour the reaction was quenched with sat. NH_4Cl (10 mL), brought to room temperature and diluted with water (5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phase washed with brine (10 mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (3:1)) gave the alcohol (178.7 mg, 0.72 mmol, quant.) as pale-yellow oil.

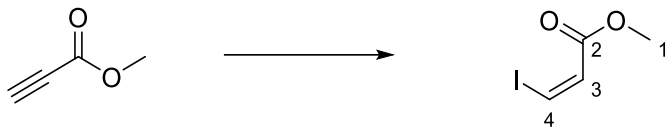
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 6.80 (m, 1H, H-2), 6.63 – 6.35 (m, 1H, H-3), 6.30 – 6.14 (m, 1H, H-1), 5.79 (dd, *J* = 15.3, 5.9 Hz, 1H, H-4), 4.31 (app p, *J* = 5.1 Hz, 1H, H-5), 2.63 – 2.30 (m, 2H, H-7), 2.16 – 1.93 (m, 1H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 134.5, 131.0, 80.6, 80.0, 71.4, 69.9, 27.6.

IR (thin film, ν_{max} / cm^{-1}) 3297, 2119, 1584, 978.

HRMS (ESI^+) calc. for $C_8H_{10}IO$ $[M+H]^+$ 248.9776, found 248.9778.

Methyl (*Z*)-3-iodoacrylate, 236



FRU-222-1

Methyl (Z)-3-iodoacrylate was prepared following a modified procedure reported in the literature (JACS, 2004, 9926).

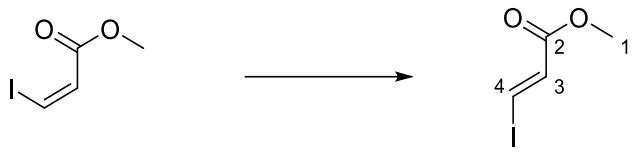
To a solution of methyl propiolate (3.56 mL, 40.0 mmol, 1.0 eq.), in acetic acid (20 mL) was added sodium iodide (12.0 g, 80 mmol) and the mixture was heated at 70 °C overnight. The solution was cooled to room temperature and diluted with water (20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phase washed with 10 % $Na_2S_2O_3$ (10 mL), K_2CO_3 sat (20 mL), $NaHCO_3$ 5% (20 mL) and brine (10 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* yields a pale-yellow oil (8.29 g, 39.1 mmol, 98%).

The analytical data matched the reported data (JACS, 2004, 9926).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.9 Hz, 1H, H-4), 6.91 (d, *J* = 8.9 Hz, 1H, H-3), 3.78 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 129.6, 95.4, 51.8.

Methyl (*E*)-3-iodoacrylate, 237



FRU-224-1

Methyl (E)-3-iodoacrylate was prepared following a modified procedure reported in the literature (Tetrahedron, 2009, 8418).

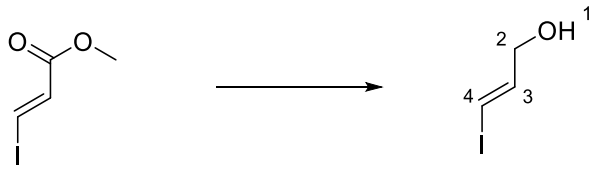
To a solution of methyl (Z)-3-iodoacrylate (8.27 g, 39.0 mmol, 1.0 eq.), in toluene (13 mL) was added hydriodic acid (55 % in H_2O, 0.37 mL, 2.7 mmol, 0.07 eq.) and the mixture was heated at 80 °C overnight. The solution was cooled to room temperature and diluted with diethylether (100 mL). The organic phase was washed with 10 % $Na_2S_2O_3$ (20 mL), K_2CO_3 half sat (20 mL) and brine (20 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* yields white crystals (7.42 g, 35.0 mmol, 90%).

The analytical data matched the reported data (Tetrahedron, 2009, 8418).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 14.9 Hz, 1H, H-4), 6.88 (d, *J* = 14.8 Hz, 1H, H-3), 3.75 (s, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 136.2, 99.8, 52.1.

(*E*)-3-Iodoprop-2-en-1-ol, 238



FRU-225-1

(E)-3-iodoprop-2-en-1-ol was prepared following a modified procedure reported in the literature (EJOC, 2016, 2110).

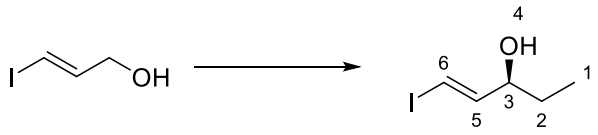
To a suspension of lithium aluminium hydride (1.45 g, 38.4 mmol, 1.1 eq.) in Et_2O (25 mL) at -78 °C under N_2, was added a solution of methyl (E)-3-iodoacrylate (7.40 g, 34.9 mmol, 1.0 eq.) in Et_2O (10 mL). After 40 minutes the temperature was raised to 0 °C and stirring continued for another 40 minutes. The reaction was quenched at 0 °C by the subseq.uent addition of H_2O (15 mL), 15 % NaOH (20 mL) and H_2O (40 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL) and the combined organic phase washed with brine (10 mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (2:1)) gave the alcohol (4.02 g, 21.8 mmol, 58%) as a pale-yellow oil.

The analytical data matched the reported data (ACIE, 2016, 2110).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (dt, *J* = 14.5, 5.4 Hz, 1H, H-3), 6.40 (dt, *J* = 14.5, 1.6 Hz, 1H, H-4), 4.11 – 3.97 (m, 2H, H-2), 1.74 (t, *J* = 5.9 Hz, 1H, H.1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 77.9, 65.3.

(S,*E*)-1-Iodopent-1-en-3-ol



FRU-266-2 (NMR, racemic), FRU-268 (enantioselective)

(E)-1-Iodopent-1-en-3-ol was prepared following a modified procedure reported in the literature (EJOC, 2016, 2110 (racemic) and Chem Comm, 1999, 1369 (enantioselective)).

Racemic:

To a mixture of molecular sieves and manganese dioxide (234.6 mg, 2.7 mmol, 10.0 eq.) under N_2 was added (E)-3-iodoprop-2-en-1-ol (50.0 mg, 0.27 mmol, 1.0 eq.) in toluene (1 mL), and the reaction mixture stirred for 2.5 hours. The reaction was filtered under N_2 and then cooled to 0 °C. Ethylmagnesium chloride (2M in THF, 0.2 mL, 0.4 mmol, 1.5 eq.) was added dropwise. After 20 minutes the reaction was quenched by addingsaturated NH_4Cl (1 mL). The aqueous layer was extracted with Et_2O (3 x 1 mL) and the combined organic phase dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (7:1) to (5:1)) gave the racemic alcohol (18.3 mg, 0.086 mmol, 32%) as a pale-yellow oil.

Enantioselective:

To a mixture of molecular sieves and manganese dioxide (869.0 mg, 10.0 mmol, 10.0 eq.) under N_2 was added (*E*)-3-iodoprop-2-en-1-ol (184.0 mg, 1.00 mmol, 1.0 eq.) in toluene (1 mL), and the reaction mixture stirred for 4 hours. The reaction was filtered under N_2 and then cooled to 0 °C. (2R)-(+)-3-exo-(Morpholino)isoborneol (4.8 mg, 0.02 mmol, 0.02 eq.) was added, and then diethyl zinc (1M solution hexane, 2.0 mL, 2.0 mmol, 2.0 eq.) was carefully added along the wall. The colour changed immediatedly from red to yellow. Stirring at 0°C was maintained for 2.5h, and then the reaction was quenched with 1 mL NH_4Cl saturated. The solids were filtered and the residue purified by flash

column chromatography on silica gel (Petroleum ether/Et_2O (4:1)) gave the enantioenriched alcohol (49.5 mg, 0.23 mmol, 24%) as a pale-yellow oil.

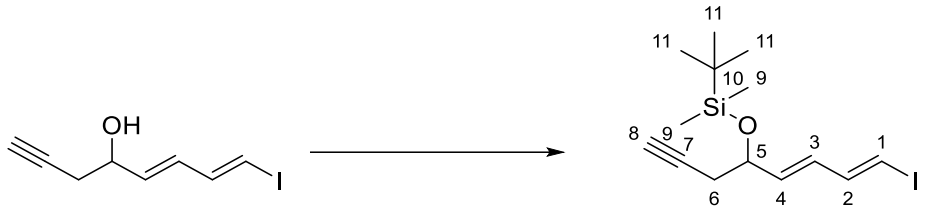
The analytical data matched the reported data (EJOC, 2016, 2110).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (dd, *J* = 14.5, 6.4 Hz, 1H, H-5), 6.35 (dd, *J* = 14.5, 1.2 Hz, 1H, H-6), 4.12 – 3.88 (m, 1H, H-3), 1.68 (d, *J* = 3.4 Hz, 1H), 1.57 (qd, *J* = 7.4, 6.4 Hz, 2H, H-2), 0.94 (t, *J* = 7.5 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 77.4, 76.1, 29.6, 9.6.

ee 3.0% (Chiralpak IC, 2% IPA/^{n}Hex, 1.3 mL/min, S – 6.8 min R – 7.2 min.

Tert-butyl(((5*E*,7*E*)-8-iodoocta-5,7-dien-1-yn-4-yl)oxy)dimethylsilane



FRU-338-1

A solution of TBSCl (33.4 mg, 0.22 mmol, 1.1 eq.) in DMF (0.5 mL) was to a solution of (5*E*,7*E*)-8-iodoocta-5,7-dien-1-yn-4-ol (50.0 mg, 0.20 mmol, 1.0 eq.) and imidazole (16.5 mg, 0.24 mmol, 1.2 eq.) in DMF (1 mL) at 0 °C. The ice bath was removed, the reaction mixture gradually warmed to room temperature and stirred for a further 3 hours. The reaction was quenched with NH_4Cl (1 mL) /H_2O (1 mL). The aqueous layer was extracted with 3x5 mL pentane and the combined organic phase dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (1:0 to 9:1)) gave the TBS-protected alcohol (72.0 mg, 0.20 mmol, 99%) as a pale-yellow oil.

Rf 0.99 (petroleum ether / Et_2O (2:1));

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (ddd, *J* = 14.5, 10.7, 0.8 Hz, 1H, H-2), 6.33 (d, *J* = 14.4 Hz, 1H, H-1), 6.17 (dddd, *J* = 15.2, 10.7, 1.4, 0.6 Hz, 1H, H-3), 5.81 (ddt, *J* = 15.2, 5.6, 0.8 Hz, 1H, H-4), 4.43 – 4.17 (m, 1H, H-5), 2.58 – 2.25 (m, 2H, H-6), 1.99 (t, *J* = 2.7 Hz, 1H, H-8), 0.89 (s, 9H, H-11), 0.08 (s, 3H, H-9), 0.05 (s, 3H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 136.1, 129.9, 80.9, 79.6, 71.2, 70.4, 28.4, 26.0, 18.4, –4.5, –4.7.

IR (thin film, ν_{max} / cm^{-1}) 3309, 2954, 2929, 2857. 1471, 1256, 980, 836.

HRMS (ES^+) calc. for $C_{14}H_{24}IOSi$ $[M+H]^+$ 362.0563, found 362.0557.

(5*E*,7*E*)-8-Iodoocta-5,7-dien-1-yn-4-yl acetate

FRU-366-1

Acetic anhydride (0.03 mL, 0.24 mmol, 2.0 eq.) was added to a solution of (5*E*,7*E*)-8-iodoocta-5,7-dien-1-yn-4-ol (27.4 mg, 0.11 mmol, 1.0 eq.), DMAP (2 crystals) and Et_3N (0.06 mL, 0.36 mmol, 3.0 eq.) in DCM (1 mL). The mixture was stirred for one hour, quenched with 1N HCl (1 mL) and diluted with H_2O (1 mL). The aqueous layer was extracted with diethyl ether (3x1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (19:1) to (9:1)) to give the propargylic acetate as a colourless oil (28.3 mg, 0.10 mmol, 89%).

Rf 0.23 (petroleum ether / Et_2O (19:1));

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (ddd, *J* = 14.4, 10.6, 0.8 Hz, 1H, H-2), 6.45 (dd, *J* = 14.5, 0.7 Hz, 1H, H-1), 6.24 (dddd, *J* = 15.3, 10.7, 1.1, 0.6 Hz, 1H, H-3), 5.74 (ddt, *J* = 15.3, 6.9, 0.8 Hz, 1H, H-4), 5.50 – 5.27 (m, 1H, H-5), 2.55 (ddd, *J* = 6.3, 2.7, 1.1 Hz, 2H, H-7), 2.08 (s, 3H, H-6), 2.02 (t, *J* = 2.7 Hz, 1H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 144.1, 133.1, 130.1, 81.7, 79.1, 71.4, 71.0, 24.7, 21.2.

IR (thin film, ν_{max} / cm^{-1}) 3294, 2917, 1736, 1220, 1024, 977.

HRMS (ES^+) not found.

(S,Z)-5-Styryldihydrofuran-2(3H)-one, 205

FRU-348-5

To a mixture of KOTMS (36.9 mg, 0.29 mmol, 4.00 eq.), PdAPC (0.8 mg, 0.002 mmol, 0.025 eq.) and (S)-3-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoic acid (13.4 mg, 0.072 mmol, 1.00 eq.) in THF (0.2mL) and water (13.7 µl, 0.720 mmol, 10.0 eq.) was added phenyl iodide (9.7 µl, 0.087 mmol, 1.20 eq.). The reaction was stirred over night, diluted with 3mL 1N HCl and extracted with Et_2O (3x1mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (7:1)) gave the lactone (10.8 mg, 0.056 mmol, 78%) as white solid.

$[\alpha]_D^{20}$ not measured

m.p. not measured

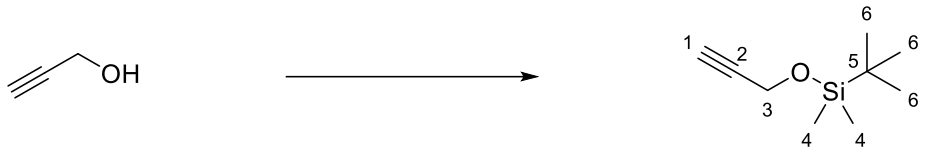
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.12 (m, 5H, H-8 – H-10), 6.68 (d, *J* = 11.5 Hz, 1H, H-6), 5.63 (dd, *J* = 11.4, 9.2 Hz, 1H, H-5), 5.20 (dddd, *J* = 9.2, 8.2, 6.5, 1.0 Hz, 1H, H-4), 2.61 – 2.41 (m, 2H, H-2), 2.35 (dddd, *J* = 13.1, 8.6, 6.5, 4.5 Hz, 1H, H-3), 1.98 (dtd, *J* = 12.8, 9.6, 8.2 Hz, 1H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.2, 135.7, 135.0, 128.9, 128.8 (2C), 128.6 (2C), 128.1, 29.5, 29.2.

IR (thin film, ν_{max} / cm^{-1}) 2918, 1772, 1775.

HRMS (ES^+) calc. for $C_{12}H_{12}O_2Na$ $[M+Na]^+$ 211.0730, found 211.0731.

Tert-butyl(((5*E*,7*E*)-8-iodoocta-1,5,7-trien-4-yl)oxy)dimethylsilane



FRU-392-1

TBSCl (2.78 g, 18.5 mmol, 1.1 eq.) was added to a solution of propargyl alcohol (1.0 mL, 17 mmol, 1.0 eq.) and imidazole (1.37 g, 20.2 mmol, 1.2 eq.) in DMF (20 mL) at 0 °C. The ice bath was removed, the reaction mixture gradually warmed to room temperature and stirred for a further hour. The reaction was diluted with H_2O (100 mL). The aqueous layer was extracted with pentane (3x50 mL) and the combined organic phases dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (1:0 to 19:1)) gave the TBS-protected alcohol (2.00 g, 11.8 mmol, 71%) as colourless oil.

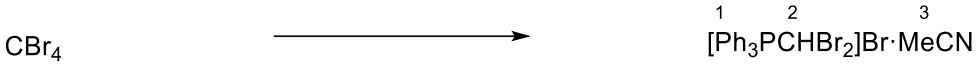
The analytical data matched the reported data (*Angewandte Chemie - International Edition*, **2017**, *56*, 847):

Rf 0.8 (petroleum ether);

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (d, *J* = 2.4 Hz, 2H, H-3), 2.39 (t, *J* = 2.4 Hz, 1H, H-1), 0.91 (s, 9H, H-6), 0.13 (s, 6H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 82.6, 73.0, 51.7, 25.9, 18.4, -5.0.

(Dibromomethyl)triphenylphosphonium bromide Acetonitrile complex



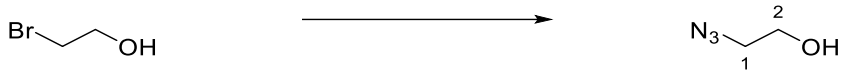
FRU-451-1

To a solution of triphenylphosphine (10.50 g, 40.0 mmol, 2.0 eq.) in DCM (100 mL) was added tetrabromomethane (6.64g, 20.0 mmol, 1.0 eq.) in small portions. The resulting solution turned bright red and warms slightly. The mixture was stirred for 30 minutes, before being quenched with water (50 mL) and separated. The aqueous layer was extracted with DCM (1x100 mL), and the combined organic layers dried (Na_2SO_4) and concentrated. The crude reaction mixture was dissolved in acetonitrile (60 mL) and sonicated for 20 minutes. A white solid crashed out, was collected by filtration and washed with additional acetonitrile (2 x 30 mL) to yield the product (7.41 g, 13.3 mmol, 67%).

The analytical data matched the reported data (*Org. Lett.*, **2016**, 1162):

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (d, *J* = 2.4 Hz, 1H, H-2), 8.28 – 8.05 (m, 6H, H-1), 7.85 – 7.76 (m, 3H, H-1), 7.75 – 7.61 (m, 6H, H-1), 1.99 (s, 3H, H-3).

2-Azidoethan-1-ol



FRU-494-3

Caution: Azides are potentially explosive. All operations were carried out behind a blast shield.

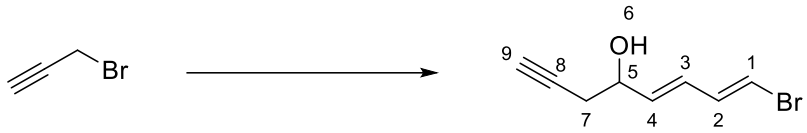
A supsension of sodium azide (3.90 g, 60.0 mmol, 2.0 eq.) and tetrabutylammonium bromide (0.19 g, 0.6 mmol, 0.02 eq.) in 2-bromo ethanol (2.2 mL, 30.0 mmol, 1.0 eq..) was stirred for 7 hours at 110 °C. After cooling to room temperature, it was diluted with 10 mL Et_2O and filtered. The filter cake was rinsed with an additional portion of Et_2O (10 mL). The solvent was removed *in vacuo* to yield the product (1.90 g, 20.0 mmol, 66%) as colourless oil.

The analytical data matched the reported data (*JOC*, **2005**, 4746):

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 – 3.68 (m, 2H, H-2), 3.44 (ddd, *J* = 6.5, 4.1, 1.7 Hz, 2H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 61.6, 53.7.

(5*E*,7*E*)-8-Bromoocta-5,7-dien-1-yn-4-ol, 229



FRU-516-3

Magnesium turnings (660.0 mg, 27.0 mmol, 2.0 eq.) were heated to 400 °C (heat gun) under vacuum for 5 minutes. The flask was cooled to room temperature and backfilled with Argon before $HgCl_2$ (55.0 mg, 0.2 mmol, 0.01 eq.) and THF (10 mL) were added. The reaction was stirred for 10 minutes at room temperature. A drop of propargyl bromide was added and the reaction stirred until slight heat evolution was perceived. Then the flask was cooled to 0 °C and the remaining propargyl bromide (2.3 mL, 20 mmol, 1.50 eq.) added dropwise. Stirring was continued for two hours at 0 °C, then the flask was cooled to -78 °C, and a 1:1 mixture of (2*E*,4*E*) and (2*E*,4*Z*)-5-bromopenta-2,4-dienal (2.18 g, 13.2 mmol, 1.00 eq.) in THF (3 + 1 mL) was added quickly. After 1 hour the reaction was quenched with 10 mL sat. NH_4Cl, brought to room temperature and diluted with 5 mL water. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic phase washed with brine (10 mL) and dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (5:1)) gave the alcohol (324.0 mg, 1.19 mmol, 12%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (ddd, *J* = 13.5, 10.8, 0.8 Hz, 1H, H-2), 6.37 (d, *J* = 13.5 Hz, 1H, H-1), 6.25 (ddd, *J* = 15.3, 10.8, 1.4 Hz, 1H, H-3), 5.80 (ddt, *J* = 15.3, 5.9, 0.8 Hz, 1H, H-4), 4.33 (app p, *J* = 6.3 Hz, 1H, H-5), 2.67 – 2.35 (m, 2H, H-7), 2.08 (t, *J* = 2.6 Hz, 1H, H-9), 2.03 (d, *J* = 4.9 Hz, 1H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 134.7, 128.7, 110. 0, 80.0, 71.4, 70.0, 27.6.

IR (thin film, ν_{max} / cm^{-1}) 3297, 2119, 1584, 978.

HRMS (ESI^+) not found.

(5*E*,7*E*)-1-(Benzyldimethylsilyl)-8-bromoocta-5,7-dien-1-yn-4-ol, 230

FRU-536-2

To a solution of (5*E*,7*E*)-8-bromoocta-5,7-dien-1-yn-4-ol (97.1 mg, 0.49 mmol, 1.00 eq.) in THF (1 mL) at 0 °C under argon was added MeMgCl (3M in Et_2O, 0.38 mL, 1.12 mmol, 2.30 eq.). The solution was stirred for 1.5 hours, and BDMSCl (0.20mL, 1.25 mmol, 2.50 eq.) was added in one portion. After 20 minutes, 1N HCl (2 mL) was added and the mixture stirred for a further 30 minutes before being diluted with 10 mL of water. The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic phase dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (3:1)) gave the alcohol (71.4 mg, 0.21 mmol, 42%) as a pale-yellow oil.

Rf 0.35 (petroleum ether / E (2:1));

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 2H, H-11), 7.15 – 7.09 (m, 1H, H-12), 7.08 – 7.04 (m, 2H, H-10), 6.70 (ddd, *J* = 13.5, 10.8, 0.7 Hz, 1H, H-2), 6.33 (dq, *J* = 13.6, 0.7 Hz, 1H, H-1), 6.18 (dddd, *J* = 15.4, 10.9, 1.5, 0.6 Hz, 1H, H-3), 5.73 (ddt, *J* = 15.3, 5.7, 0.8 Hz, 1H, H-4), 4.40 – 4.11 (m, 1H, H-5), 2.58 – 2.40 (m, 2H, H-7), 2.17 (s, 2H, H-9), 2.02 – 1.97 (m, 1H, H-6), 0.13 (s, 6H, H-8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 136.7, 134.8, 128.4, 128.4, 128.4, 124.6, 109.8, 103.7, 86.7, 69.9, 29.2, 26.4, -1.8.

IR (thin film, ν_{max} / cm^{-1}) 3362, 2176, 1493, 1250, 977, 834.

HRMS (ESI^+) $[M+H]^+$ not found.

(*E*)-1-Bromo-3-iodoprop-1-ene

FRU-534-1

To a cooled (0 °C) suspension of triphenyl phosphine (2.01 g, 7.67 mmol, 1.05 eq.), imidazole (0.55 g, 8.03 mmol, 1.10 eq.) and (*E*)-3-bromoprop-2-en-1-ol (1.00 g, 7.30 mmol, 1.00 eq.) in DCM (20 mL) was added a solution of iodine (1.95 g, 7.67 mmol, 1.05 eq.). After 10 minutes, the ice bath was removed and stirring was continued at room temperature for one hour, before being quenched with water (10 mL), NH_4Cl (10 mL) and $Na_2S_2O_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with DCM (1 x 10 mL). The combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether/Et_2O (1:0)) gave the desired iodide (1.39 g, 5.60 mmol, 78%) as a pale-yellow oil.

Rf 1.0 (petroleum ether / (1:0));

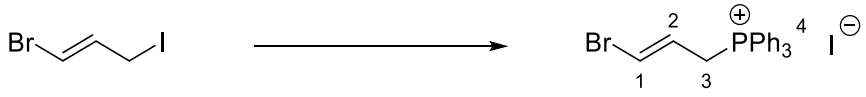
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 – 5.88 (m, 2H, H-1, H-2), 4.06 – 3.66 (m, 2H, H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 109.4, 2.0.

IR (thin film, ν_{max} / cm^{-1}) not recorded.

HRMS (ESI^+) not recorded.

(*E*)-(3-Bromoallyl)triphenylphosphonium iodide, 258



FRU-535-1

To a solution of (*E*)-1-bromo-3-iodoprop-1-ene (1.39 g, 5.62 mmol, 1.00 eq.) in toluene (2 mL) at 0 °C was added triphenylphosphine (1.47 g, 5.62 mmol, 1.00 eq.). The reaction was stirred for 20 minutes at room temperature and then heated to 50°C over night. A solid precipitated. The reaction was filtered and the solid washed with toluene (3 x 5 mL). The solid was dried under vaccum to afford the desired phosphonium salt (1.88 g, 3.68 mmol, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.78 (m, 9H, H-4), 7.76 – 7.65 (m, 6H, H-4), 7.00 (ddt, *J* = 13.4, 5.5, 1.2 Hz, 1H, H-1), 6.03 (dtd, *J* = 13.4, 7.7, 5.5 Hz, 1H, H-2), 5.01 (ddd, *J* = 14.9, 7.7, 1.3 Hz, 2H, H-3).

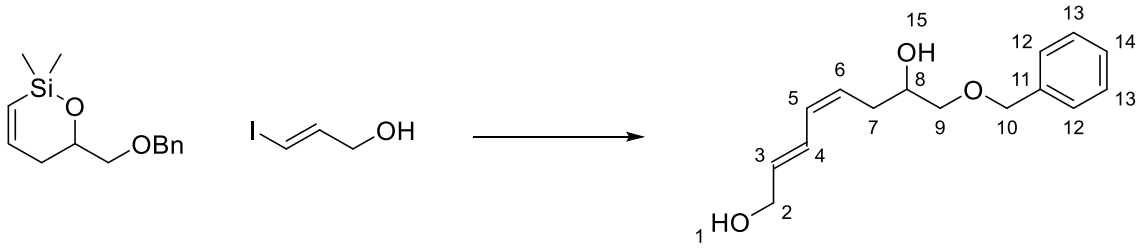
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5, 135.4, 134.3, 134.2, 130.7, 130.5, 122.0, 121.9, 117.9, 117.1, 116.8, 116.7, 29.0, 28.5. (mulitplicity because of phosphorous)

m.p. not measured

IR (thin film, ν_{max} / cm^{-1}) not recorded.

HRMS (ESI^+) not recorded.

(2*E*,4*Z*)-8-(Benzyloxy)octa-2,4-diene-1,7-diol, 239



FRU-405-1

To mixture of $Pd(dba)_2$ (2.9 mg, 0.005 mmol, 0.05 eq.), (*E*)-3-iodoprop-2-en-1-ol (18.4 mg, 0.100 mmol, 1.00 eq.), 6-((benzyloxy)methyl)-2,2-dimethyl-5,6-dihydro-2H-1,2-oxasiline (29.8 mg, 0.120 mmol, 1.20 eq.) under argon was added TBAF (1 M/ THF, 0.30 mL, 0.30 mmol, 3.0 eq.). The reaction was stirred over night and directly purified by flash column chromatography on silica gel (petroleum ether / EtOAc (19:1 to 1:1)) yielding the diol as a colourless wax (8.1 mg, 0.033 mmol, 33%).

Rf 0.18 (petroleum ether / EtOAc (1:1));

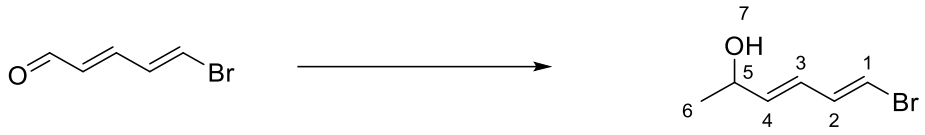
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, H-12, H-13, H-14), 6.53 (ddq, *J* = 15.2, 11.0, 1.5 Hz, 1H, H-4), 6.14 (ddt, *J* = 12.6, 11.0, 1.5 Hz, 1H, H-5), 5.85 (dt, *J* = 15.2, 5.8 Hz, 1H, H-3), 5.49 (dt, *J* = 10.9, 7.8 Hz, 1H, H-6), 4.55 (s, 2H, H-10), 4.19 (dd, *J* = 5.8, 1.5 Hz, 2H, H-2), 3.88 (tt, *J* = 6.7, 3.4 Hz, 1H, H-8), 3.53 (dd, *J* = 9.5, 3.4 Hz, 1H, H-9), 3.39 (dd, *J* = 9.5, 7.2 Hz, 1H, H-9), 2.42 (ddt, *J* = 7.9, 6.3, 1.5 Hz, 2H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.05, 133.07, 130.43, 128.61, 127.96, 127.86, 127.39, 126.35, 73.90, 73.55, 70.34, 63.55, 31.91.

IR (thin film, ν_{max} / cm^{-1}) 3371, 2913, 2861, 1454, 1080.

HRMS (ES^+) calc. for $C_{15}H_{21}O_3$ $[M+H]^+$ 249.1490, found 249.1489.

(3*E*,5*E*)-6-Bromohexa-3,5-dien-2-ol, 234



FRU-407-1

To a solution of (2*E*,4*E*)-5-bromoopenta-2,4-dienal (200.0 mg, 1.24 mmol, 1.0 eq.) in 3 mL Et_2O at –78 °C under argon was added dropwise a solution of methyl magnesium bromide (0.62 mL, 3 M/ Et_2O, 1.86 mmol, 1.2 eq.). After 1 hour the reaction was quenched with sat. NH_4Cl (5 mL) and water (1 mL) in the cold and brought to room temperature. The aqueous layer was extracted with EtOAc (2 x 2 mL) and the combined organic phase dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (3:1)) gave the alcohol (120.3 mg, 0.68 mmol, 55%) as a pale-yellow oil.

Rf 0.25 (petroleum ether / Et_2O (3:1));

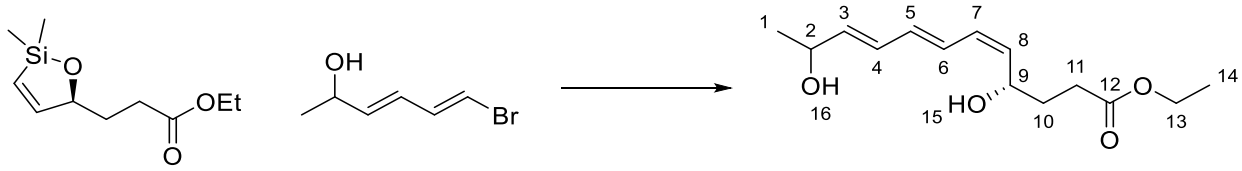
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (ddd, *J* = 13.5, 10.8, 0.7 Hz, 1H, H-2), 6.32 (dq, *J* = 13.5, 0.7 Hz, 1H, H-1), 6.15 (dddd, *J* = 15.3, 10.8, 1.3, 0.6 Hz, 1H, H-3), 5.78 (ddt, *J* = 15.4, 6.0, 0.7 Hz, 1H, H-4), 4.47 – 4.17 (m, 1H, H-5), 1.50 (d, *J* = 4.1 Hz, 1H, H-7), 1.29 (d, *J* = 6.4 Hz, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.43, 136.89, 126.78, 109.10, 68.26, 23.36.

IR (thin film, ν_{max} / cm^{-1}) 3064, 1584, 1265, 1186, 1059, 977.

HRMS (ES^+) calc. for C_6H_9BrONa $[M+Na]^+$ 198.9735, found 198.9731.

Ethyl (4S,5*Z*,7*E*,9*E*)-4,11-dihydroxydodeca-5,7,9-trienoate, 240



FRU-410-3

To mixture of $Pd(dba)_2$ (2.9 mg, 0.005 mmol, 0.05 eq.), (3*E*,5*E*)-6-bromohexa-3,5-dien-2-ol (17.7 mg, 0.10 mmol, 1.00 eq.), ethyl (*S*)-3-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoate (25.7 mg, 0.12 mmol, 1.20 eq.) under argon was added TBAF (1 M/ THF, 0.40 mL, 0.40 mmol, 4.0 eq.). The reaction was stirred over night and directly purified by flash column chromatography on silica gel (petroleum ether / EtOAc (19:1 to 1:1)) yielding the diol as a colourless oil (14.4 mg, 0.057 mmol, 57%).

Rf 0.10 (petroleum ether / EtOAc (1:1));

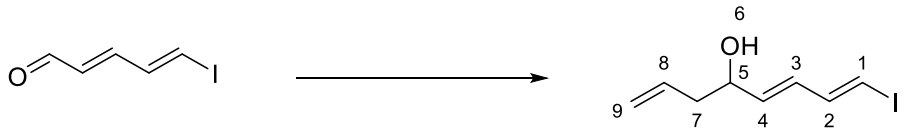
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 – 6.40 (m, 1H, H-6), 6.38 – 6.14 (m, 2H, H-4, H-5), 6.08 (td, *J* = 10.9, 1.1 Hz, 1H, H-8), 5.79 (ddd, *J* = 14.3, 6.2, 1.5 Hz, 1H, H-3), 5.41 (ddd, *J* = 10.7, 8.7, 1.1 Hz, 1H, H-7), 4.64 (dddd, *J* = 8.7, 7.1, 5.6, 1.1 Hz, 1H, H-9), 4.37 (m, 1H, H-2), 4.13 (qd, *J* = 7.1, 0.7 Hz, 2H, H-13), 2.41 (td, *J* = 7.3, 1.7 Hz, 2H, H-11), 2.13 – 1.71 (m, 2H, H-10), 1.29 (d, *J* = 6.3 Hz, 3H, H-1), 1.25 (td, *J* = 7.1, 0.8 Hz, 3H, H-14).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.78, 138.56, 134.11, 133.26, 130.24, 129.25, 127.45, 68.45, 67.29, 60.53, 32.25, 30.29, 23.29, 14.22.

IR (thin film, ν_{max} / cm^{-1}) 3410, 2973, 2931, 1770, 1729, 1179.

HRMS (ES^+) calc. for $C_{14}H_{23}O_4$ $[M+H]^+$ not found.

(5*E*,7*E*)-8-iodoocta-5,7-dien-1-yn-4-ol, 206



FRU-358-3

To a solution of (2*E*,4*E*)-5-iodopenta-2,4-dienal (300.0 mg, 1.44 mmol, 1.0 eq.) in THF (3.0 mL) at –78°C under argon was added dropwise a solution of allyl magnesium bromide (1.73 mL, 1M/Et_2O, 1.73 mmol, 1.2 eq.). After 1 hour the reaction was quenched with sat. NH_4Cl (5 mL) and water (1 mL) in the cold and then brought to room temperature. The aqueous layer was extracted with Et_2O (3 x 2 mL) and the combined organic phase dried ($MgSO_4$). Purification by flash column chromatography on silica gel (Petroleum ether/Et_2O (5:1)) gave the alcohol (246.8 mg, 0.987 mmol, 69%) as a pale-yellow oil.

Rf 0.2 (petroleum ether / Et_2O (5:1));

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (ddd, *J* = 14.4, 10.7, 0.7 Hz, 1H, H-2), 6.35 (dd, *J* = 14.4, 0.7 Hz, 1H, H-1), 6.19 (dddd, *J* = 15.3, 10.7, 1.4, 0.6 Hz, 1H, H-3), 5.95 – 5.69 (m, 2H, H-4, H-8), 5.26 – 5.16 (m, 1H, H-9), 5.16 – 5.11 (m, 1H, H-9), 4.34 – 4.02 (m, 1H, H-5), 2.60 – 1.99 (m, 2H, H-7), 1.74 (d, *J* = 4.1 Hz, 1H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 136.2, 133.8, 130.1, 119.0, 79.8, 70.8, 41.8.

IR (thin film, ν_{max} / cm^{-1}) 3451, 3073, 2923, 1681, 1599, 983.

HRMS (ES^-) calc. for $C_8H_{10}IO$ $[M–H]^-$ 248.9771, found 248.9771.

(5*E*,7*E*)-8-Iodoocta-1,5,7-trien-4-yl acetate, 207

FRU-363-1

Acetic anhydride (0.08 mL, 0.80 mmol, 2.0 eq.) was added to a solution of (5*E*,7*E*)-8-iodoocta-5,7-dien-1-yn-4-ol (98.0 mg, 0.39 mmol, 1.0 eq.), DMAP (2 crystals) and Et_3N (0.17 mL, 1.20 mmol, 3.0 eq.) in DCM (1 mL). The mixture was stirred for one hour, quenched with 1N HCl (10 mL) and diluted with H_2O (10 mL). The aqueous layer was extracted with diethyl ether (3 x 20 mL), and the combined organic layers washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The crude material was purified via flash column chromatography on silica gel (petroleum ether / Et_2O (9:1)) to give the allylic acetate as a colourless oil (101.4 mg, 0.347 mmol, 89%).

Rf 0.6 (petroleum ether / Et_2O (9:1));

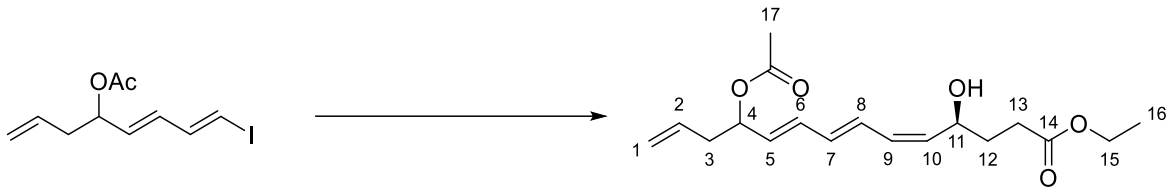
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (ddd, *J* = 14.4, 10.7, 0.8 Hz, 1H, H-2), 6.47 – 6.32 (d, *J* = 14.5 Hz, 1H, H-1), 6.16 (dddd, *J* = 15.3, 10.7, 1.1, 0.6 Hz, 1H, H-3), 5.81 – 5.68 (m, 1H, H-8), 5.64 (ddt, *J* = 15.3, 6.9, 0.8 Hz, 1H, H-4), 5.29 (app qd, *J* = 6.5, 1.1 Hz, 1H, H-5), 5.14 – 5.09 (m, 1H, H-9), 5.09 – 5.05 (m, 1H, H-9), 2.47 – 2.33 (m, 2H, H-7), 2.05 (s, 3H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 144.3, 132.9, 132.3, 131.6, 118.5, 81.0, 72.9, 38.9, 21.3.

IR (thin film, ν_{max} / cm^{-1}) 3077, 2935, 1736, 1371, 1235.

HRMS (ES^+) calc. for $C_{18}H_{26}O_5Na$ $[M+Na]^+$ 345.1673, found 345.1673.

Ethyl (4*S*,5*Z*,7*E*,9*E*)-11-acetoxy-4-hydroxytetradeca-5,7,9,13-tetraenoate, 209



FRU-364-1

To a mixture of $Pd(dba)_2$ (2.3 mg, 0.004 mmol, 0.05 eq.), (5*E*,7*E*)-8-iodoocta-1,5,7-trien-4-yl acetate (23.4 mg, 0.080 mmol, 1.00 eq.), ethyl (*S*)-3-(2,2-dimethyl-2,5-dihydro-1,2-oxasilol-5-yl)propanoate (20.6 mg, 0.096 mmol, 1.20 eq.) under argon was added TBAF (1M / THF, 0.29 mL, 0.29 mmol, 3.6 eq.). The reaction was stirred over night, the solvent removed *in vacuo* and the crude reaction mixture directly purified by flash column chromatography on silica gel (petroleum ether / ethylacetate (7:1) yielding the diol as a colourless oil (16.8 mg, 0.053 mmol, 55%).

Rf 0.1 (petroleum ether / ethylacetate (7:1)).

$[\alpha]_D^{20}$ not recorded.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, *J* = 14.4, 11.6 Hz, 1H, H-8), 6.35 – 6.13 (m, 2H, H-5/H-6/H-7/H-10), 6.07 (t, *J* = 11.2 Hz, 1H, H-9), 5.83 – 5.55 (m, 2H, H-5/H-6/H-7/H-10), 5.54 – 5.38 (m, 1H, H-2), 5.34 (q, *J* = 6.6 Hz, 1H, H-4), 5.16 – 5.04 (m, 2H, H-1), 4.64 (app q, *J* = 7.9 Hz, 1H, H-11), 4.13 (qd, *J* = 7.1, 0.7 Hz, 2H, H-15), 2.46 – 2.35 (m, 4H, H-3, H-13), 2.10 – 2.02 (s, 3H, H-17), 1.95 – 1.81 (m, 2H, H-12), 1.25 (td, *J* = 7.1, 0.6 Hz, 3H, H-16).

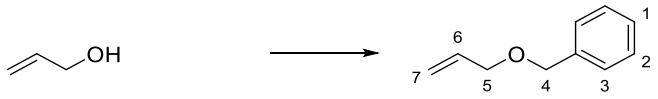
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 170.4, 133.9, 133.7, 133.1, 132.5, 132.0, 130.2, 128.5, 118.3, 73.4, 67.4, 60.7, 39.1, 32.3, 30.4, 21.4, 14.4.

IR (thin film, ν_{max} / cm^{-1}) 3469, 2982, 1731, 1372, 1235, 998.

HRMS (ES^+) calc. for $C_{15}H_{21}BrO_3Na$ $[M+Na]^+$ 351.0566, found 351.0568.

8.8 Synthesis of Bridge-substituted Bicyclo[1.1.1]pentanes

((Allyloxy)methyl)benzene, 388



FRU-660-1

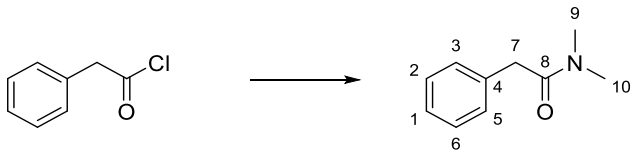
Potassium hydroxide (1.40 g, 25.0 mmol, 1.00 eq.) was dissolved in allylic alcohol (4.3 mL, 62.5 mmol, 2.50 eq.) and cooled to 20 °C in a water bath. Benzylchloride (2.9 mL, 25.0 mmol, 1.00 eq.) was added in small portions over 5 minutes, then the reaction mixture was heated to 60 °C for 3 hours. The reaction was cooled to 0 °C and quenched by the addition of water (10 mL) and diluted with pentane (40 mL). The phases were separated, and the organic phase washed with water (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the product as a colourless oil (3.23 g, 19.7 mmol, 79%).

The analytical data matched the reported data (*TL*, **2011**, 7000):

^{1}H NMR (400 MHz, CDCl3) δ 7.44 – 7.27 (m, 5H, H1-H-3), 5.97 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H, H-6), 5.32 (dq, *J* = 17.3, 1.7 Hz, 1H, H-7), 5.27 – 5.14 (m, 1H, H-7), 4.54 (s, 2H, H-4), 4.04 (dt, *J* = 5.6, 1.4 Hz, 2H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 134.9, 128.5 (2C), 127.9 (2C), 127.7, 117.3, 72.3, 71.3.

N,N-Dimethyl-2-phenylacetamide, 387



FRU-661-1

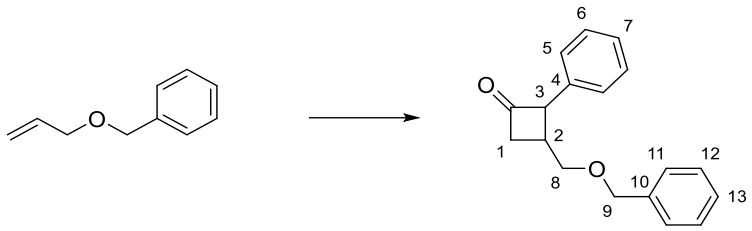
To a solution of sodium hydroxide (3.2g, 80.0 mmol, 2.6 eq.) in water (18 mL) was added dimethylamine hydrochloride (5.87 g, 72 mmol, 2.4 eq.) in 2 eq.ual portions over 5 minutes at 0 °C. This solution was then added dropwise to phenylacetyl chloride (4.0 mL, 30 mmol, 1.0 eq.) in DCM (40 mL) at 0 °C. The ice bath was removed and stirring continued overnight. The reaction was diluted with pentane (40 mL), the phases were separated, and the organic phase washed with 1N HCl (20 mL) and saturated $NaHCO_3$. The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the product as a white solid (4.77 g, 29.2 mmol, 98%).

The analytical data matched the reported data (*JOC*, **2001**, 6719):

^{1}H NMR (400 MHz, CDCl3) δ 7.41 – 7.28 (m, 2H, H-2, H-6), 7.28 – 7.22 (m, 3H, H-1, H-3, H-5), 3.72 (s, 2H, H-7), 2.99 (s, 3H, H-9), 2.97 (s, 3H, H-10).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 135.2, 128.9 (2C), 128.8 (2C), 126.8, 41.2, 37.9, 35.8.

3-((Benzyloxy)methyl)-2-phenylcyclobutan-1-one, 389



FRU-662-4

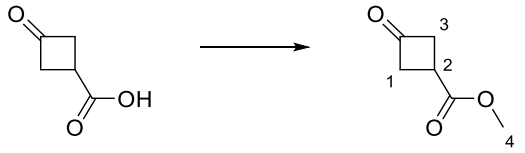
To a solution of *N*,*N*-dimethyl-2-phenylacetamide (168.2 mg, 1.00 mmol, 1.0 eq.) in dry DCM (2 mL) was added triflic anhydride (0.20 mL, 1.2 mmol, 1.2 eq.) dropwise over 5 minutes at –30°C. After stirring for 15 minutes, a solution of ((allyloxy)methyl)benzene (0.23 mL, 1.50 mmol, 1.5 eq.) and collidine (0.16 mL, 1.20 mmol, 1.2 eq.) in DCM (1.5 mL) was added. The solution was gradually warmed to room temperature over the course of 3 hours and stirred overnight. The reaction was cooled to 0 °C, then quenched by the addition of water (20 mL) and diluted with DCM (10 mL). The aqueous layer was extracted with DCM (2 x 10 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (4:1) to (2:1)) to give the cyclobutanone as a colourless oil (47.6 mg, 0.17 mmol, 17%).

The analytical data matched the reported data (*JOC*, **2001**, 6719):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.06 (m, 10H, H-11 to H-13, H-5 to H-7), 4.61 (s, 2H, H-9), 4.38 (d, *J* = 7.7 Hz, 1H, H-8), 3.80 (d, *J* = 5.4 Hz, 2H, H-3), 3.09 (ddd, *J* = 8.3, 2.6, 1.2 Hz, 2H, H-1), 2.87 (tdd, *J* = 8.3, 5.5, 2.8 Hz, 1H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 206.1, 138.2, 136.1, 128.8 (2C), 128.6 (2C), 127.9, 127.8 (2C), 127.3 (2C), 127.2, 73.4, 72.1, 66.6, 47.4, 32.5.

Methyl 3-oxocyclobutane-1-carboxylate, 398



FRU-664-4

To a solution of 3-oxocyclobutane-1-carboxylic acid (10.0 g, 87.6 mmol, 1.00 eq.) in methanol (18.0 mL, 438 mmol, 5.0 eq.) was added conc. sulfuric acid (0.23 mL, 4.3 mmol, 0.05 eq.) and the resulting solution was refluxed for 5 hours. The reaction was cooled to room temperature and diluted with toluene (50 mL) and water (10 mL) and stirred for one hour. The layers were separated and the aqueous layer extracted with Et_2O (2x10 mL), and the combined organic layers washed with brine (20 mL) and dried ($MgSO_4$) and concentrated. The crude product was a 3:2 mixture of ketone and ketal.

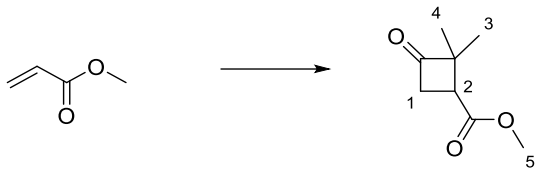
The mixture was redissolved in toluene (50 mL) and HCl (1 N, 10 mL) was added. The mixture was vigorously stirred for one hour. The layers were separated, and the aqueous layer extracted with Et_2O (2x10 mL), and the combined organic layers washed with brine (20 mL) and dried ($MgSO_4$) and concentrated. The crude product was a 20:1 mixture of ketone and ketal. Repition of this step afforded pure product (5.62 g, 43.9 mmol, 50%).

The analytical data matched the reported data (EP3235819, 2017, A1):

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H, H-4), 3.55 – 3.06 (m, 5H, H-1 to H-3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7, 174.6, 52.5, 51.8, 27.4.

Methyl 2,2-dimethyl-3-oxocyclobutane-1-carboxylate, 392



FRU-666-2

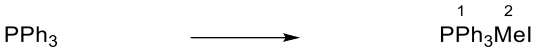
To a solution of dry $ZnCl_2$ (817.8 mg, 6.00 mmol, 1.2 eq.) in dry DCM (2.2 mL) was added methyl acrylate (0.45 mL, 5.0 mmol, 1.0 eq.) and then Ghosez's reagent (0.73 mL, 5.5 mmol, 1.1 eq.) dropwise over 5 minutes at room temperature. A slight exotherm was observed and the suspended solid dissolved into a biphasic reaction mixture. The reaction was heated to reflux overnight, cooled to room temperature, and quenched by the addition of water (5 mL) and diluted with DCM (10 mL). The layers were separated, the aqueous layer was extracted with Et_2O (2x10 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (2:1)) to give the cyclobutanone as a colourless oil (500.0 mg, 3.20 mmol, 64%).

The analytical data matched the reported data (*ACIE*, **1981**, 782):

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H, H-5), 3.54 (dd, *J* = 17.9, 7.4 Hz, 1H, H-1), 3.09 (dd, *J* = 17.9, 9.0 Hz, 1H, H-1), 2.95 (dd, *J* = 8.9, 7.4 Hz, 1H, H-2), 1.31 (s, 3H, H-3), 1.11 (s, 3H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 172.6, 64.5, 52.1, 44.9, 40.8, 23.2, 18.6.

Methyltriphenylphosphonium iodide



FRU-680-1

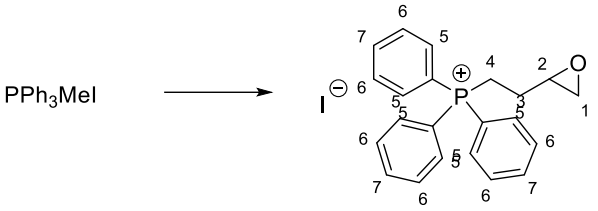
To a solution of triphenylphosphine (50.0 g, 190 mmol, 1.00 eq.) in toluene (240 mL) at room temperature was added methyl iodide (12.4 mL, 200 mmol, 1.05 eq.), and the reaction stirred overnight. A white solid precipitated from the mixture and was filtered, washed with toluene (2x20 mL) and dried to yield the product as a white solid (73.0 g, 181 mmol, 96%).

The analytical data matched the reported data (US 2009/54714):

^{1}H NMR (400 MHz, CDCl3) δ 8.00 – 7.44 (m, 15H, H-1), 3.25 (d, *J* = 13.2 Hz, 3H, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.4 (d, *J* = 2.9 Hz), 133.5 (d, *J* = 10.7 Hz), 130.6 (d, *J* = 13.1 Hz), 119.2 (d, *J* = 88.5 Hz), 12.0 (d, *J* = 57.2 Hz).

(2-(Oxiran-2-yl)ethyl)triphenylphosphonium iodide



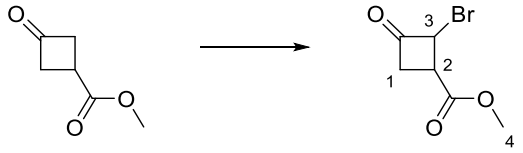
FRU-688-1

To a solution of methyltriphenylphosphonium iodide (10.11 g, 25.0 mmol, 1.00 eq.) in THF (37.5 mL) at 0 °C was added *n*-BuLi (1.6 M in hexanes, 17.2 mL, 27.5 mmol, 1.1 eq.) dropwise over 5 minutes. The red solution was cooled to –50 °C and epichlorohydrine (2.1 mL, 27.0 mmol, 1.08 eq.) was added dropwise causing the solution to turn orange. After 5 minutes a thick solid precipitates that prevents stirring, the reaction mixture was gradually warmed to –5 °C over 2 hours, quenched by addition of water and warmed to room temperature. Stirring resumed shortly after the addition of water and a white fine crystalline solid precipitated from the mixture. The solid was filtered and washed with methanol (5 mL) to yield the product (6.04 g, 13.1 mmol, 50%) as a white solid.

The analytical data matched the reported data (*JOC*, **1993**, 5915):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 – 7.58 (m, 15H, H-5 to H-7), 4.14 (dddd, *J* = 15.7, 13.4, 11.3, 4.6 Hz, 1H, H-4), 3.83 (dddd, *J* = 15.9, 13.0, 11.5, 4.8 Hz, 1H, H-4), 3.45 (td, *J* = 6.3, 3.8 Hz, 1H, H-2), 2.83 (app t, *J* = 4.2 Hz, 1H, H-1), 2.72 (dd, *J* = 4.4, 2.6 Hz, 1H, H-1), 2.23 (app tdd, *J* = 15.3, 7.6, 4.3 Hz, 1H, H-3), 1.89 – 1.60 (m, 1H, H-3).

Methyl 2-bromo-3-oxocyclobutane-1-carboxylate, 399



FRU-690-2

To a solution of methyl 3-oxocyclobutane-1-carboxylate (128.1 mg, 1.00 mmol, 1.00 eq.) in chloroform (2 mL) was added bromine (0.06 mL, 1.0 mmol, 1.0 eq.) and the resulting solution stirred overnight. The reaction was diluted with pH7 phosphate buffer (2 mL), the layers were separated and the aqueous layer extracted with Et_2O (2 x 1 mL), and the combined dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (9:1) to (4:1)) to give the cyclobutanone (63.3 mg, 0.31 mmol, 31%) as a colourless oil.

Rf 0.5 (petroleum ether / Et_2O (2:1)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 – 5.22 (m, 1H, H-3), 3.82 (s, 3H, H-4), 3.54 – 3.21 (m, 3H, H-1, H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 171.8, 53.1, 51.2, 48.9, 39.2.

IR (thin film, ν_{max} / cm^{-1}) 1797, 1731, 1437, 1208.

HRMS (APCI) calc. for $C_6H_6O_3Br$ $[M–H]^-$ 204.9495, found 204.9497.

2,2,2-Triphenyl-3-oxa-2λ^5-phosphabicyclo[3.1.0]hexane, 405

FRU-695-1

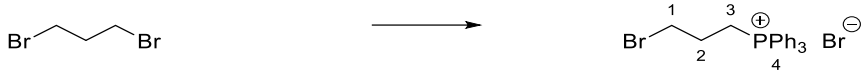
A solution of (2-(oxiran-2-yl)ethyl)triphenylphosphonium iodide (2.01 g, 4.3 mmol, 1.0 eq.) and sodium hydride (60% in paraffin, 0.20 g, 5.0 mmol, 1.15 eq.) in THF (2.2 mL) was refluxed for 4 hours. The reaction was cooled to room temperature and concentrated. The solid was extracted with hot Et_2O (5 x 10mL), and the combined organic layers concentrated to give the product (1.21 g, 3.64 mmol, 80%) as a white solid.

The analytical data matched the reported data (*JOC*, **1993**, 5915):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.29 (m, 5H, H-1), 7.32 – 7.16 (m, 10H, H-1), 3.58 (dd, *J* = 13.9, 8.9 Hz, 1H, H-3), 3.01 (dd, *J* = 8.9, 3.1 Hz, 1H, H-3), 1.46 (app dq, *J* = 15.8, 4.4 Hz, 1H, H-5), 1.36 (m, 1H, H-4), 1.24 – 1.12 (m, 1H, H-6), 0.94 – 0.79 (m, 1H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 130.9, 127.6, 127.5, 127.4, 57.9, 14.7, 12.5, 7.1.

(3-Bromopropyl)triphenylphosphonium bromide



FRU-700-1

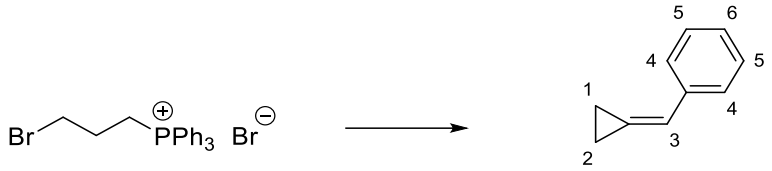
To a solution of triphenyl phosphine (10.0 g, 38.1 mmol, 1.00 eq.) in toluene (20 mL) at room temperature was added 1,3-dibromopropane (3.9 mL, 38.1 mmol, 1.00 eq.) and the reaction refluxed overnight. The reaction was cooled to room temperature and the white precipitate was filtered, washed with toluene (2 x 20 mL) and dried to yield the product (12.91 g, 27.8 mmol, 73%) as a white solid.

The analytical data matched the reported data (*Chem Comm*, **2014**, 5993):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.75 (m, 9H, H-4), 7.73 – 7.60 (m, 6H, H-4), 4.28 – 4.08 (m, 2H, H-3), 3.87 (td, *J* = 6.2, 1.5 Hz, 2H, H-1), 2.40 – 2.02 (m, 2H, H-2).

^{13}C NMR (101 MHz, CDCl3) δ 135.3 (d, *J* = 3.0 Hz), 133.9 (d, *J* = 10.2 Hz), 130.7 (d, *J* = 12.6 Hz), 118.2 (d, *J* = 86.3 Hz), 33.7 (d, *J* = 20.4 Hz), 26.5, 21.8 (d, *J* = 52.4 Hz).

(Cyclopropylidenemethyl)benzene, 409



FRU-701-1

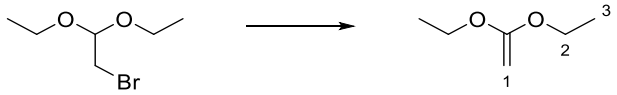
Potassium *tert*-butoxide (2.24g, 20.0 mmol, 3.0 eq.) was added to a solution of (3-bromopropyl) triphenylphosphonium bromide (4.64 g, 10.0 mmol, 1.5 eq.) at 0 °C. After 10 minutes the ice bath was removed and the reaction refluxed for 1 hour. Benzaldehyde (0.68 mL, 6.7 mmol, 1.0 eq.) was added and the reflux maintained for another 1.5 hours. The reaction was cooled to room temperature, diluted with pentane (30 mL), filtered and the filtrate concentrated. The crude product was purified *via* flash column chromatography on silica gel (petroleum ether) to give the cyclopropane (0.66 g, 5.1 mmol, 77%) as a colourless oil.

The analytical data matched the reported data (*OL*, **2018**, 409):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 2H, H-4), 7.34 (app t, *J* = 7.2 Hz, 2H, H-5), 7.22 (t, *J* = 7.2 Hz, 1H, H-6), 6.80 – 6.73 (m, 1H, H-3), 1.48 – 1.38 (m, 2H, H-1/H-2), 1.28 – 1.06 (m, 2H, H-1/H-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 128.6, 126.8, 126.8, 124.4, 118.4, 4.4, 0.7.

1,1-Diethoxyethene, 412



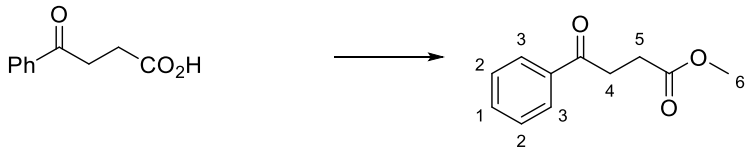
FRU-720-6

To solid potassium *tert*-butoxide (11.5 g, 102 mmol, 1.00 eq.) at 0 °C was added 2-bromo-1,1, diethoxyether (15.4 mL, 102.0 mmol, 1.00 eq.). The reaction was stirred for 30 minutes and then vacuum was attached (10 mbar) and the reaction distilled. A forerun (3.36g, P: tBuOH 2:1, 48-52 °C), a middle fraction (1.08 g, P: *t*-BuOH 10:1, 52-62 °C) and a main fraction (5.08 g, P: tBuOH 4:1, 62 °C) were collected (in total: 1.57g *t*-BuOH, 7.95g P, 68% yield, 75% purity).

The analytical data matched the reported data (US88859763):

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (q, *J* = 7.0 Hz, 4H, H-2), 3.09 (s, 2H, H-1), 1.33 (t, *J* = 7.0 Hz, 6H, H-3).

Methyl 4-oxo-4-phenylbutanoate, 417



FRU-728-1

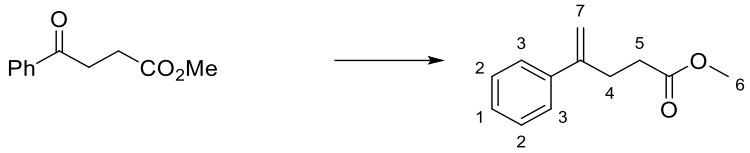
To a solution of 4-oxo-4-phenylbutanoic acid (5.00 g, 28.0 mmol, 1.00 eq.) in methanol (12 mL) was added conc. sulfuric acid (0.11 mL) and the reaction refluxed for 4 hours. After cooling to room temperature the solvent was removed in vacuo and the residue taken up in ether (100 mL). The organic layer was washed with $NaHCO_3$ (sat., 25 mL) and dried ($MgSO_4$). The solvent was removed under vacuum to afford the product as a colourless oil (4.94 g, 25.7 mmol, 92%).

The analytical data matched the reported data (US 2003/96109):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.3, 1.1 Hz, 2H, H-3), 7.65 – 7.51 (m, 1H, H-1), 7.51 – 7.41 (m, 2H, H-2), 3.71 (s, 3H, H-6), 3.33 (t, *J* = 6.6 Hz, 2H, H-4), 2.77 (t, *J* = 6.6 Hz, 2H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 173.5, 136.7, 133.4, 128.8, 128.2, 52.0, 33.6, 28.2.

Methyl 4-phenylpent-4-enoate, 418



FRU-810/FRU-725-1 (NMR)

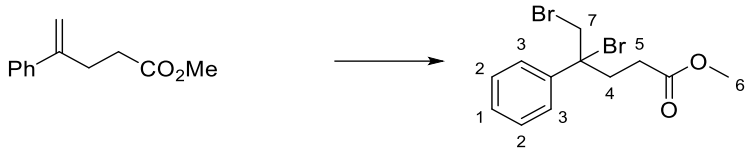
Potassium *tert*-butoxide (5.49 g, 47.9 mmol, 1.9 eq.) was added to a solution of methyl triphenylphosphonium bromide (17.45 g, 47.9 mmol, 1.9 eq.) in THF (50 mL) at 0 °C. After 15 minutes the ice bath was removed, and the reaction stirred for 30 minutes. The so prepared ylid was then added quickly to a solution of methyl 4-oxo-4-phenylbutanoate (4.86 g, 25.2 mmol, 1.0 eq.) in THF (25 mL) at 0°C. After 45 minutes the reaction was quenched with NH_4Cl (sat, 25 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2 x 50 mL), and the combined organic layers washed with brine (25 mL), dried ($MgSO_4$) and concentrated. The crude was purified via flash column chromatography on silica gel (petroleum ether / Et_2O (9:1)) to give the ester (3.95 g, 20.8 mmol, 83%) as a colourless oil.

The analytical data matched the reported data (*CEJ*, **2016**, 7381):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.16 (m, 5H, H-1 to H-3), 5.34 – 5.14 (m, 1H, H-7), 5.02 (app q, *J* = 1.3 Hz, 1H, H-7), 3.59 (s, 3H, H-6), 2.89 – 2.69 (m, 2H, H-5), 2.50 – 2.32 (m, 2H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 147.0, 140.7, 128.5, 127.7, 126.2, 113.0, 51.7, 33.2, 30.6.

Methyl 4,5-dibromo-4-phenylpentanoate, 419



FRU-758-1

Bromine (0.75 mL, 14.6 mmol, 1.0 eq.) was added to a solution of methyl 4-phenylpent-4-enoate (2.78 g, 14.6 mmol, 1.0 eq.) in DCM (15 mL) at 0 °C. After 15 minutes the reaction was quenched with NaS_2O_3 (sat, 2 drops), dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (19:1)) to give the dibromide (2.78 g, 7.9 mmol, 55%) as a colourless oil.

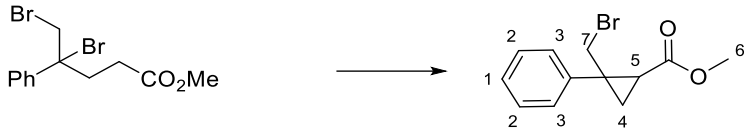
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.51 (m, 2H, H-2), 7.48 – 7.29 (m, 3H, H-1, H-3), 4.21 (d, *J* = 10.7 Hz, 1H, H-7), 4.08 (d, *J* = 10.7 Hz, 1H, H-7), 3.72 (s, 3H, H-6), 2.99 – 2.84 (m, 1H, H-5), 2.75 – 2.58 (m, 3H, H-4, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 140.6, 128.8 128.7, 127.4, 69.7, 52.1, 41.8, 35.5, 31.2.

IR (thin film, ν_{max} / cm^{-1}) 1783, 1737, 1161.

HRMS (ES^+) not found.

Methyl 2-(bromomethyl)-2-phenylcyclopropane-1-carboxylate, 420



FRU-793-2

n-Butyllithium (1.6 M / hex, 1.71 mL, 2.74 mmol, 3.0 eq.) was added to a solution of HMDS (0.59 mL, 3.1 mmol, 3.1 eq.) in THF (2 mL) at –78 °C. After 5 minutes the prepared LHMDS solution was added dropwise to methyl 4,5-dibromo-4-phenylpentanoate (0.32 g, 0.91 mmol, 1.00 eq.) in THF (1mL) at –78 °C. The reaction stirred for 30 minutes and quenched at –78 °C with NH_4Cl (sat, 2 mL). After warming to room temperature the reaction was diluted with water (10 mL) and ether (10 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2x50 mL), and the combined organic layers washed with brine (25 mL), dried ($MgSO_4$) and concentrated. The crude was purified via flash column chromatography on silica gel (petroleum ether / Et_2O (20:1)) to give the cyclopropane (137.2 mg, 0.51 mmol, 57%) as a colourless oil.

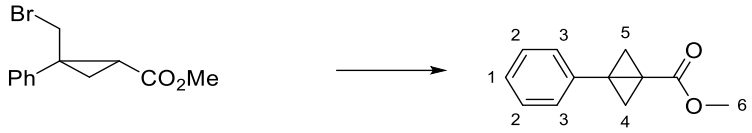
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.27 (m, 5H, H-1 to H-3), 4.04 – 3.84 (m, 2H, H-7), 3.80 (s, 3H, H-6), 2.29 (dd, *J* = 8.2, 6.1 Hz, 1H, H-5), 1.74 (dd, *J* = 6.1, 4.9 Hz, 1H, H-4), 1.60 (dd, *J* = 8.2, 4.9 Hz, 1H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 141.3, 129.4, 128.6, 127.8, 52.5, 38.9, 36.9, 28.5, 23.2.

IR (thin film, ν_{max} / cm^{-1}) 1726, 1440, 1393, 1197, 1173.

HRMS (ES^+) calc. for $C_{12}H_{14}O_2Br$ $[M+H]^+$ 269.0172, found 269.0173.

Methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate, 346



FRU-750-1

Butyllithium (1.6 M / hex, 0.27 mL, 0.42 mmol, 1.2 eq.) was added to a solution of DIPA (0.07 mL, 0.45 mmol, 1.3 eq.) in THF (1 mL) at –78°C. After 5 minutes the thus prepared LDA solution was added dropwise to methyl 2-(bromomethyl)-2-phenylcyclopropane-1-carboxylate (93.0 mg, 0.34 mmol, 1.0 eq.) in THF (1mL) at –78°C. The reaction stirred for 15 minutes and quenched in the cold with NH_4Cl (sat, 1 mL). After warming to room temperature, the reaction was diluted with water (1 mL) and ether (1 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2 x 1 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (30:1)) to give the bicyclobutane (43.6 mg, 0.23 mmol, 69%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 6.98 (m, 5H, H-1 to H-3), 3.45 (s, 3H, H-6), 2.89 (t, *J* = 1.1 Hz, 2H, H-4, H-5), 1.57 (t, *J* = 1.1 Hz, 2H, H-4, H-5).

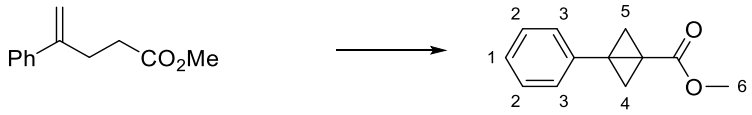
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 133.8, 128.6, 127.1, 126.1, 52.0, 35.9, 33.1, 23.4.

IR (thin film, ν_{max} / cm^{-1}) 1700, 1440, 1344, 1151, 744.

melting point 67-68 °C

HRMS (ES^+) calc. for $C_{12}H_{12}O_2Na$ $[M+Na]^+$ 211.0740, found 211.0731.

Methyl 3-phenylbicyclo[1.1.0]butane-1-carboxylate, 346

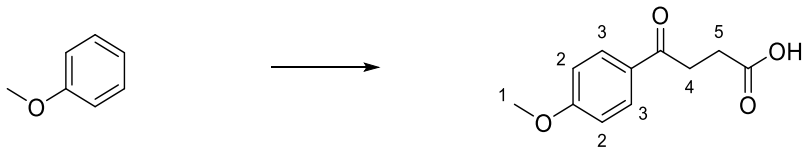


FRU-811-1

Bromine (1.08 mL, 20.8 mmol, 1.0 eq.) was added to a solution of methyl 4-phenylpent-4-enoate (3.95 g, 20.8 mmol, 1.0 eq.) in THF (20 mL) at 0 °C. After 10 minutes, the reaction is cooled to -78°C. Meanwhile, in a separate flask, *n*-butyllithium (2.5 M / hex, 25.0 mL, 62.4 mmol, 3.0 eq.) was added to a solution of HMDS (13.5 mL, 64.5 mmol, 3.1 eq.) in THF (40 mL) at –78°C. After 5 minutes the prepared LHMDS solution was added slowly to the first flask, containing brominated starting material, and the LHMDS flask washed with THF (5 mL) to ensure complete transfer. The reaction was stirred for 30 minutes at –78°C, then the acetone/ dry ice bath was removed, and the reaction gradually warmed up to room temperature over 2.5 hours. The reaction was then cooled to 0 °C and quenched with NH_4Cl (halfsat, 20 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2 x 20 mL), and the combined organic layers washed with brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (20:1) to (14:1)) to give the bicyclobutane (1.57 g, 8.3 mmol, 40%) as a white solid.

analytical data as before (p. 228)

4-(4-Methoxyphenyl)-4-oxobutanoic acid



FRU-795-1

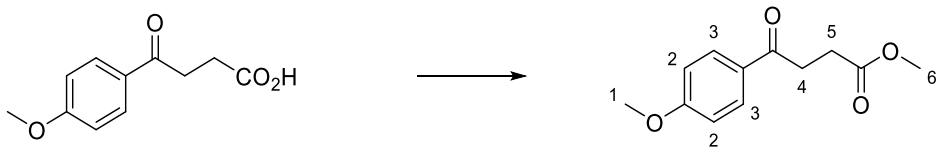
To a suspension of aluminium trichloride (8.50 g, 66.0 mmol, 1.10 eq.) in DCM (60 mL) at 15°C (cold water bath) was added succinic anhydride (6.01 g, 60.0 mmol, 1.00 eq.) in one portion and then anisole (6.5 mL, 60 mmol, 1.0 eq.) in 1 mL portions over 10 minutes. The cold bath was removed, and the reaction stirred overnight (deep red homogeneous solution). The reaction mixture was poured on a slurry of conc HCl (10 mL) and crushed ice (100 g) and a white solid precipitated. After vigorous stirring for 1h the white solid was isolated by filtration and washed with water (2 x 20mL) and petroleum ether (2 x 20 mL) to yield the product (9.14 g, 43.9 mmol, 74%).

The analytical data matched the reported data (*OPRD*, **2004**, 291):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.9 Hz, 2H, H-2), 7.09 – 6.74 (m, 2H, H-3), 3.87 (s, 3H, H-1), 3.27 (t, *J* = 6.6 Hz, 2H, H-4), 2.80 (t, *J* = 6.6 Hz, 2H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 177.9, 163.8, 130.5, 129.6, 113.9, 55.6, 33.0, 28.2.

Methyl 4-(4-methoxyphenyl)-4-oxobutanoate



FRU-799-1

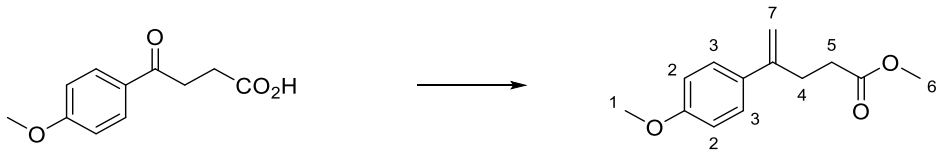
To a solution of 4-(4-methoxyphenyl)-4-oxobutanoic acid (9.14 g, 43.9 mmol, 1.00 eq.) in methanol (18 mL) was added conc. sulfuric acid (0.18 mL) and the reaction refluxed overnight. After cooling to room temperature, the solvent was removed *in vacuo* and the residue taken up in ether (100 mL). The organic layer was washed with $NaHCO_3$ (sat., 25 mL) and dried ($MgSO_4$). The solvent was removed under vacuum to afford the product as a white solid (7.74 g, 34.8 mmol, 80%).

The analytical data matched the reported data (*Adv Synthesis and Catalysis*, **2018**, 686):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 – 7.86 (m, 2H, H-2), 7.07 – 6.74 (m, 2H, H-3), 3.87 (s, 3H, H-1), 3.71 (s, 3H, H-6), 3.28 (t, *J* = 6.7 Hz, 2H, H-4), 2.75 (t, *J* = 6.7 Hz, 2H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 173.7, 163.7, 130.5, 129.8, 113.9, 55.6, 52.0 33.2, 28.3.

Methyl 4-(4-methoxyphenyl)pent-4-enoate, 422



FRU-804-2

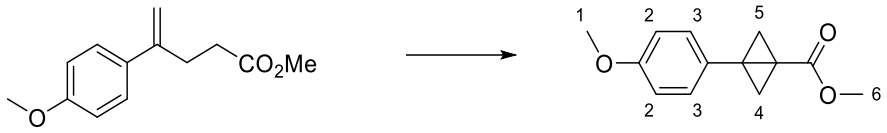
Potassium *tert*-butoxide (7.57 g, 66.1 mmol, 1.9 eq.) was added to a solution of methyl triphenylphosphonium bromide (24.1 g, 66.1 mmol, 1.9 eq.) in THF (66 mL) at 0°C. After 15 minutes the icebath was removed and the reaction stirred for 30 minutes. The prepared ylid was then added quickly to a solution of methyl 4-(4-methoxyphenyl)-4-oxobutanoate (7.74 g, 34.8 mmol, 1.0 eq.) in THF (33 mL) at 0 °C. After 45 minutes the reaction was quenched with NH_4Cl (halfsat, 100 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2 x 50 mL), and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (9:1) to (4:1)) to give the ester as a colourless oil (6.94 g, 31.5 mmol, 91%).

The analytical data matched the reported data (*JACS*, **2010**, 3298):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 2H, H-2), 6.94 – 6.79 (m, 2H, H-3), 5.30 – 5.11 (m, 1H, H-7), 5.00 (q, *J* = 1.2 Hz, 1H, H-7), 3.81 (s, 3H, H-1), 3.66 (s, 3H, H-6), 2.98 – 2.65 (m, 2H, H-5), 2.48 (dd, *J* = 8.8, 6.9 Hz, 2H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 159.3, 146.3, 133.0, 127.3, 113.9, 111.4, 55.4, 51.7, 33.3, 30.7.

Methyl 3-(4-methoxyphenyl)bicyclo[1.1.0]butane-1-carboxylate, 423



FRU-825-2

Bromine (0.64 mL, 12.4 mmol, 1.0 eq.) was added to a solution of methyl 4-(4-methoxyphenyl)pent-4-enoate (2.73 g, 12.4 mmol, 1.0 eq.) in THF (12 mL) at 0°C. After 10 minutes, the reaction is cooled to –78°C. Meanwhile, in a separate flask, *n*-butyllithium (2.5M / hex, 14.9 mL, 37.2 mmol, 3.0 eq.) was added to a solution of HMDS (8.0 mL, 38 mmol, 3.1 eq.) in THF (40 mL) at –78°C. After 5 minutes the prepared LHMDS solution was added slowly to the first flask, containing brominated starting material, and the LHMDS flask washed with THF (2mL) to ensure complete transfer. The reaction was stirred for 30 minutes at –78 °C, then the icebath was removed and the reaction gradually warmed up to room temperature over 2.5 hours. The reaction was then cooled to 0 °C and quenched with NH_4Cl (halfsat, 20 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2x20 mL), and the combined organic layers washed with brine (25 mL), dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (20:1) to (14:1)) to give the bicyclobutane as a white solid (0.77 g, 3.50 mmol, 30%).

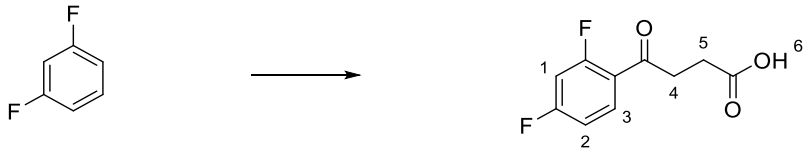
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.09 (m, 2H, H-3), 6.91 – 6.79 (m, 2H, H-2), 3.79 (s, 3H, H-1), 3.49 (s, 3H, H-6), 2.88 (t, *J* = 1.1 Hz, 2H, H-4/H-5), 1.58 (t, *J* = 1.1 Hz, 2H, H-4/H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 159.1, 127.3, 125.5, 114.2, 55.4, 51.9, 36.0, 33.5, 22.6.

IR (thin film, ν_{max} / cm^{-1}) 1731, 1601, 1509, 1250, 1171.

HRMS (ES^+) calc. for $C_{13}H_{14}O_3Na$ $[M+Na]^+$ 241.0835, found 241.0837.

4-(2,4-Difluorophenyl)-4-oxobutanoic acid



FRU-800-1

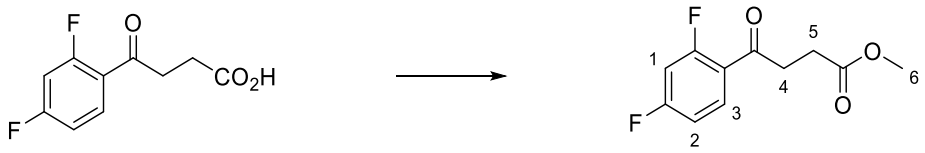
To a suspension of aluminium trichloride (16.80 g, 126.0 mmol, 2.1 eq.) in DCM (60 mL) at room temperature was added succinic anhydride (6.01 g, 60.0 mmol, 1.0 eq.) in one portion and then 1,3 difluorobenzene (5.9 mL, 60 mmol, 1.0 eq.) and the reaction refluxed overnight. The reaction mixture was poured on a slurry of conc HCl (20 mL) and crushed ice (150 g). After vigorous stirring for 1h the layers were separated, the aqueous layer was extracted with DCM (2x20 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude solid was reslurried in DCM (10 mL) and petroleum ether (50 mL) and isolated by filtration and washed with petroleum ether (2x30 mL) to yield a beige solid (9.49 g, 44.3 mmol, 74%).

The analytical data matched the reported data (*EJMC*, **2019**, 320):

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (s, 1H, H-6), 7.94 (td, *J* = 8.6, 6.6 Hz, 1H, H-1), 7.01 – 6.91 (m, 1H, H-2/H-3), 6.86 (ddd, *J* = 11.1, 8.7, 2.4 Hz, 1H, H-2/H-3), 3.26 (td, *J* = 6.3, 3.5 Hz, 2H, H-4), 2.77 (t, *J* = 6.3 Hz, 2H, H-5).

^{13}C NMR (101 MHz, CDCl3) δ 194.6 (d, *J* = 4.2 Hz), 179.2, 166.1 (dd, *J* = 257.5, 12.5 Hz), 163.1 (dd, *J* = 257.5, 12.5 Hz), 132.8 (dd, *J* = 10.6, 4.2 Hz), 121.6 (dd, *J* = 13.1, 3.3 Hz), 112.4 (dd, *J* = 21.5, 3.3 Hz), 104.9 (dd, *J* = 27.6, 25.6 Hz), 37.9 (d, *J* = 8.8 Hz), 28.1 (d, *J* = 2.4 Hz).

Methyl 4-(2,4-difluorophenyl)-4-oxobutanoate



FRU-805-1

To a solution 4-(2,4-difluorophenyl)-4-oxobutanoic acid (9.49 g, 44.3 mmol, 1.00 eq.) in methanol (18 mL) was added conc. sulfuric acid (0.18 mL) and the reaction refluxed overnight. After cooling to room temperature, the solvent was removed in vacuo and the residue was taken up in ether (100 mL). The organic layer is washed with $NaHCO_3$ (sat., 25 mL) and dried ($MgSO_4$). The solvent was removed under vacuum to afford the product as an orange oil (8.89 g, 39.0 mmol, 88%).

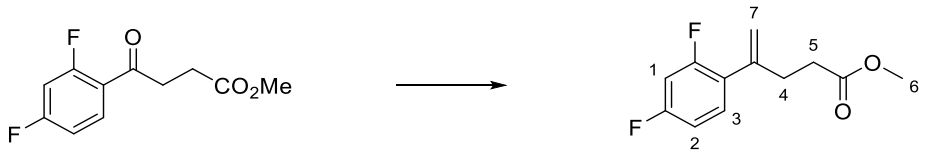
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (td, *J* = 8.7, 6.7 Hz, 1H, H-1), 6.92 – 6.85 (m, 1H, H-2/H-3), 6.81 (ddd, *J* = 11.1, 8.7, 2.4 Hz, 1H, H-2/H-3), 3.61 (s, 3H, H-6), 3.20 (td, *J* = 6.4, 3.5 Hz, 2H, H-4), 2.66 (t, *J* = 6.4 Hz, 2H, H-5).

^{13}C NMR (101 MHz, CDCl3) δ 194.6 (d, *J* = 4.7 Hz), 173.1, 165.8 (dd, *J* = 257.6, 12.6 Hz), 162.9 (dd, *J* = 257.6, 12.6 Hz), 132.6 (dd, *J* = 10.6, 4.7 Hz), 121.6 (dd, *J* = 13.2, 3.6 Hz), 112.1 (dd, *J* = 21.5, 3.6 Hz), 104.7 (dd, *J* = 27.8, 25.5 Hz), 51.7, 38.0 (d, *J* = 8.6 Hz), 27.8 (d, *J* = 2.3 Hz).

IR (thin film, ν_{max} / cm^{-1}) 1736, 1687, 1609, 1428, 1167, 1099.

HRMS (ES^+) calc. for $C_{11}H_{10}O_3F_2Na$ $[M+Na]^+$ 251.0490, found 251.0491.

Methyl 4-(2,4-difluorophenyl)pent-4-enoate, 424



FRU-808-3

Potassium *tert*-butoxide (8.25 g, 72.1 mmol, 1.9 eq.) was added to a solution of methyl triphenylphosphonium bromide (26.3 g, 72.1 mmol, 1.9 eq.) in THF (72 mL) at 0°C. After 15 minutes the icebath was removed and the reaction stirred for 30 minutes. The prepared ylid was then added quickly to a solution of methyl 4-(2,4-difluorophenyl)-4-oxobutanoate (8.66 g, 37.9 mmol, 1.0 eq.) in THF (38 mL) at 0°C. After 45 minutes the reaction was quenched with NH_4Cl (halfsat, 100 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2x50 mL), and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (9:1)to (4:1)) to give the ester as a colourless oil (5.36 g, 23.7 mmol, 63%).

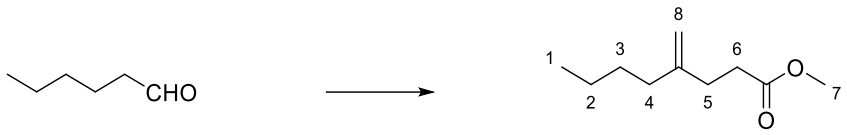
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (td, *J* = 8.6, 6.6 Hz, 1H, H-1), 6.92 – 6.67 (m, 2H, H-2/H-3), 5.24 (s, 1H, H-7), 5.15 (s, 1H, H-7), 3.64 (s, 3H, H-6), 2.77 (t, *J* = 7.7 Hz, 2H, H-4), 2.45 – 2.34 (m, 2H, H-5).

^{13}C NMR (101 MHz, CDCl3) δ 173.3, 162.4 (dd, *J* = 248.6, 11.9 Hz), 160.0 (dd, *J* = 249.9, 11.6 Hz), 142.5, 130.9 (dd, *J* = 9.4, 5.9 Hz), 125.44 (dd, *J* = 14.8, 3.9 Hz), 116.8, 111.3 (dd, *J* = 21.0, 3.6 Hz), 106.0 – 100.2 (m), 51.7, 32.9, 31.7 (d, *J* = 3.2 Hz).

IR (thin film, ν_{max} / cm^{-1}) 1736, 1502, 1265, 1140, 968, 850.

HRMS (ES^+) calc. for $C_{12}H_{13}O_2F_2$ $[M+H]^+$ 227.0878, found 227.0881.

Methyl 4-methyleneoctanoate, 425



FRU-803/FRU-806/FRU-807-4

A mixture of dimethylamine hydrochloride (9.78 g, 0.12 mol, 1.2 eq.), formaldehyde (37% in water, 9.0 mL, 0.12 mol, 1.2 eq.) and hexanal (12.2 mL, 0.10 mol, 1.0 eq.) was heated at 70 °C overnight. After cooling to room temperature, the reaction was extracted with Et_2O (3 x 20 mL), and the combined organic layers washed with brine (20 mL), dried ($MgSO_4$) and concentrated. The crude colourless oil was used directly for the next step (9.84 g, 87.7 mmol, 88%).

To a solution of 2% $NaHCO_3$ in water (25 mL) at 0 °C was added sodium borohydride (3.45 g, 87.7 mmol, 1.0 eq.) and then dropwise a solution of crude 2-methylenehexanal (9.84 g, 87.7 mmol, 1.0 eq.) in methanol (100 mL). After 1.5 hours, the reaction was diluted with water (50 mL) and quenched with conc. HCl (10 mL). The icebath was removed and the reaction was extracted with Et_2O (3 x 100 mL), and the combined organic layers washed with brine (2 x 50 mL), dried ($MgSO_4$) and concentrated. The crude material was filtered through a short pad of silica (rinsed with petroleum ether / ether (4:1)) to give crude 2-methylenehexan-1-ol (8.15 g, 71.4 mmol, 82%).

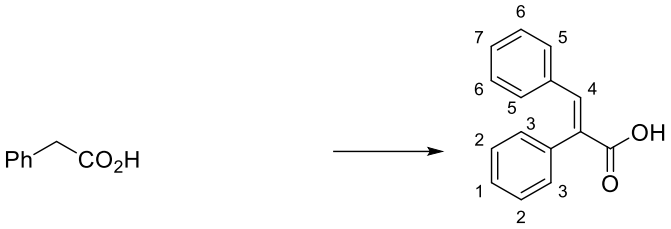
A mixture of 2-methylenehexan-1-ol (8.15 g, 71.4 mmol, 1.0 eq.), trimethylorthoacetate (36.5 mL, 286 mmol, 4.00 eq.) and propionic acid (4 drops) was heated to reflux overnight (142 °C). The reaction poured on a mixture of crushed ice (100 g) and $NaHCO_3$ (10 mL) and then extracted with Et_2O (3 x 100 mL), and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The crude was purified via flash column chromatography on silica gel (petroleum ether / Et_2O (19:1)) to give methyl 4-methyleneoctanoate (8.04 g, 47.2 mmol, 67%) as a colourless oil.

The analytical data matched the reported data (*J Agric Food Chem*, **2007**, 5050):

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1H, H-8), 4.70 (s, 1H, H-8), 3.67 (s, 3H, H-7), 2.54 – 2.41 (m, 2H, H-6), 2.39 – 2.26 (m, 2H, H-5), 2.05 – 1.95 (m, 2H, H-4), 1.47 – 1.34 (m, 2H, H-3), 1.35 – 1.22 (m, 2H, H-2), 0.90 (t, *J* = 7.2 Hz, 3H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 148.4, 109.2, 51.7, 36.1, 32.7, 31.0, 30.1, 22.6, 14.1.

(*E*)-2,3-diphenylacrylic acid, 429



FRU-840-1

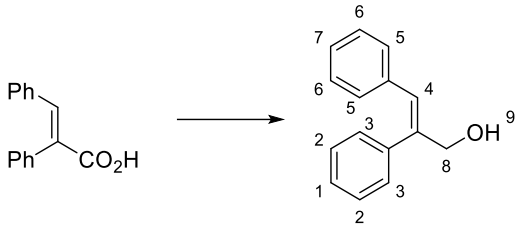
A solution of phenylacetic acid (11.0 g, 80.0 mmol, 1.00 eq.), benzaldehyde (12.0 mL, 118 mmol, 1.45 eq.) and triethylamine (8.0 mL, 58 mmol, 0.71 eq.) in acetic anhydride (23.0 mL, 240 mmol, 3.00 eq.) was heated to reflux overnight (140 °C). The reaction was cooled to room temperature, poured on 10% HCl (100 mL) and extracted with Et_2O (100 mL). The aqueous phase was discarded, and the organic layer was extracted with 5% NaOH (300 mL). The organic layer was dicarded and the aqueous layer acidified with conc. HCl (15 mL) to precipitate a white solid which was collected by filtration and washed with water (2 x 20 mL). The solid was dried to constant mass (5.34 g, 23.8 mmol, 30%).

The analytical data matched the reported data (*JACS*, **2018**, 16821):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H, H-4), 7.47 – 7.32 (m, 4H, H-1/H-2/H-3/H-5/H-6/H-7), 7.31 – 7.14 (m, 4H, H-1/H-2/H-3/H-5/H-6/H-7), 7.12 – 7.04 (m, 2H, H-1/H-2/H-3/H-5/H-6/H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 142.6, 135.5, 134.5, 131.8, 131.0, 130.0, 129.6, 128.9, 128.4, 128.2.

(*E*)-2,3-Diphenylprop-2-en-1-ol, 430



FRU-843-1

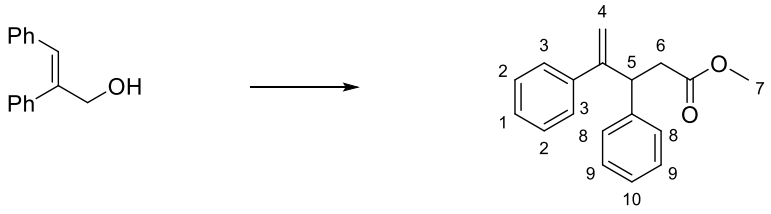
To a suspension of lithium aluminium hydride (1.10 g, 28.6 mmol, 1.2 eq.) in THF (20 mL) was added a solution of (*E*)-2,3-diphenylacrylic acid (5.31 g, 23.8 mmol, 1.0 eq.) in THF (10 mL) at 0 °C over 10 minutes. The icebath was removed and stirring was continued at room temperature. After 2 hours the reaction mixture was cooled to 0 °C and 1 mL H_2O, 1 mL 15% NaOH, and 3 mL H_2O were subseq.uently added dropwise. After vigorous stirring for 15 minutes, the reaction was dried ($MgSO_4$) and filtered through celite (rinse with Et_2O, 50 mL). The solvent was removed *in vacuo* and the crude purified via flash column chromatography on silica gel (petroleum ether / Et_2O (1:1)) to give the alcohol (3.98 g, 18.9 mmol, 80%) as a colourless oil.

The analytical data matched the reported data (*Chem Comm*, **2014**, 978):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 3H, H-1/H-2/H-3/H-5/H-6/H-7), 7.25 – 7.21 (m, 2H, H-1/H-2/H-3/H-5/H-6/H-7), 7.11 (qd, *J* = 4.4, 1.4 Hz, 3H, H-1/H-2/H-3/H-5/H-6/H-7), 7.00 (dd, *J* = 7.2, 2.4 Hz, 2H, H-3/H-5), 6.70 (s, 1H, H-4), 4.47 (dd, *J* = 6.3, 1.4 Hz, 2H, H-8), 1.71 – 1.59 (m, 1H, H-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 138.7, 136.6, 129.4, 129.0, 128.9, 128.1, 127.7, 127.0, 126.7, 68.7.

Methyl 3,4-diphenylpent-4-enoate, 427



FRU-844-2

A mixture of (*E*)-2,3-diphenylprop-2-en-1-ol (3.98 g, 18.9 mmol, 1.0 eq.), trimethylorthoacetate (9.7 mL, 76 mmol, 4.0 eq.) and propionic acid (4 drops) is heated to reflux overnight (142 °C). The reaction poured into $NaHCO_3$ (10 mL sat $NaHCO_3$ and 50 mL water), extracted with Et_2O (3 x 20 mL), and the combined organic layers washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified via flash column chromatography on silica gel (petroleum ether / EtOAc (100:1) to (30:1)) to give the ester as a colourless oil (3.19 g, 12.0 mmol, 64%).

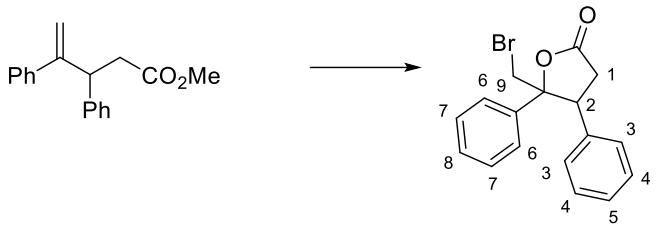
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.14 (m, 10H, H-1/H-2/H-3/H-8/H-9/H-10), 5.41 (s, 1H, H-4), 5.28 – 5.10 (m, 1H, H-4), 4.66 – 4.35 (m, 1H, H-5), 3.62 (s, 3H, H-7), 2.96 (dd, *J* = 15.6, 7.9 Hz, 1H, H-6'), 2.81 (dd, *J* = 15.6, 7.9 Hz, 1H, H-6).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 150.7, 141.9, 141.8, 128.6, 128.3, 128.0, 127.6, 127.0, 126.8, 113.5, 51.8, 46.5, 40.5.

IR (thin film, ν_{max} / cm^{-1}) 1737, 1493, 1453, 1156, 700.

HRMS (ES^+) calc. for $C_{18}H_{18}O_2Na$ $[M+Na]^+$ 289.1199, found 289.1200.

5-(Bromomethyl)-4,5-diphenyldihydrofuran-2(3H)-one, 431



FRU-847-2

Bromine (0.10 mL, 1.94 mmol, 1.0 eq.) was added to a solution of methyl 3,4-diphenylpent-4-enoate (516.7 mg, 1.94 mmol, 1.0 eq.) in THF (2 mL) at 0 °C. After 10 minutes, the reaction was cooled to –78 °C. Meanwhile, in a separate flask, *n*-butyllithium (2.5 M / hex, 2.3 mL, 5.8 mmol, 3.0 eq.) was added to a solution of HMDS (1.26 mL, 6.0 mmol, 3.1 eq.) in THF (4 mL) at –78 °C. After 5 minutes the prepared LHMDS solution is added slowly to the first flask**,** containing brominated starting material, and the LHMDS flask washed with THF (1mL) to ensure complete transfer. The reaction was stirred for 30 minutes at –78 °C, then the icebath was removed and the reaction gradually warmed up to room temperature over 2.5 hours. The reaction was then cooled to 0 °C and quenched with NH_4Cl (halfsat, 10 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2 x 20 mL), and the combined organic layers washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude solid was purified by trituration (2 x 2mL petroleum ether/0.1 mL DCM) to afford the desired lactone as a white solid (145.9 mg, 0.44 mmol, 23%).

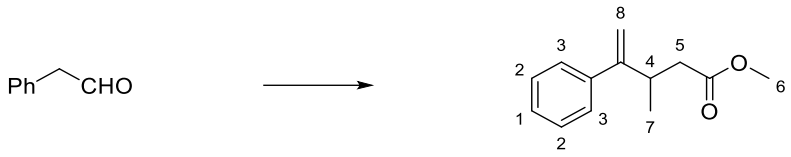
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 8H, H-3/H-4/H-5/H-6/H-7/H-8), 7.18 – 7.05 (m, 2H, H-3/H-4/H-5/H-6/H-7/H-8), 3.78 (t, *J* = 6.9 Hz, 1H, H-2), 3.27 (s, 2H, H-9), 2.77 (d, *J* = 6.9 Hz, 2H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 141.1, 136.5, 129.3, 128.9, 128.7, 128.6, 128.4, 125.1, 89.1, 52.3, 37.8, 36.2.

IR (thin film, ν_{max} / cm^{-1}) 1775, 1180, 1140, 1031, 995, 756, 698.

HRMS (ES^+) calc. for $C_{17}H_{15}O_2BrNa$ $[M+Na]^+$ 353.0148, found 353.0149.

Methyl 4-methyleneoctanoate, 432



FRU-854/FRU-860/FRU-861-1

A mixture of phenylacetaldehyde (5.8 mL, 50.0 mmol, 1.0 eq.), acetaldehyde (2.8 mL, 50.0 mol, 1.0 eq.) and ethanol (5 mL) was added to a solution of NaOAc (2.67 g, 32.5 mmol, 0.65 eq.) in water (5 mL) over 3 minutes. The reaction was heated at 85 °C overnight. After cooling to room temperature, the reaction was diluted with water (20 mL), extracted with Et_2O (3 x 20 mL), and the combined organic layers washed with brine (20 mL), dried ($MgSO_4$), fltered and concentrated. The crude was purified via flash column chromatography on silica gel (petroleum ether / EtOAc (50:1) to (10:1)) to afford the desired aldehyde as a colourless oil (3.13 g, 23.7 mmol, 48%, *E*:*Z*= 6:1).

To a solution of 2% $NaHCO_3$ in water (7 mL) at 0 °C was added sodium borohydride (0.90 g, 23.7 mmol, 1.0 eq.) and then dropwise a solution of (*E*)-2-phenylbut-2-enal (3.13 g, 23.7 mmol, 1.0 eq.) in methanol (40 mL). After 1.5 hours, the reaction was diluted with water (50 mL) and quenched with conc. HCl (10 mL). The reaction was warmed to room temperature and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (2 x 50 mL), dried ($MgSO_4$) and concentrated. The crude material was filtered through a short pad of silica (petroleum ether/ ether (19:1)) to give crude (*E*)-2-phenylbut-2-en-1-ol (2.71 g, 20.2 mmol, 86%).

A mixture of (*E*)-2-phenylbut-2-en-1-ol (2.71 g, 20.2 mmol, 1.0 eq.), trimethylorthoacetate (10.2 mL, 80.0 mmol, 4.0 eq.) and propionic acid (4 drops) is heated to reflux overnight (142 °C). The reaction poured on $NaHCO_3$ (sat, 10 mL) and extracted with Et_2O (3 x 10 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography (petroleum ether / Et_2O (100:1) to (30:1)) to give the ester as a colourless oil (1.71 g, 8.37 mmol, 42%).

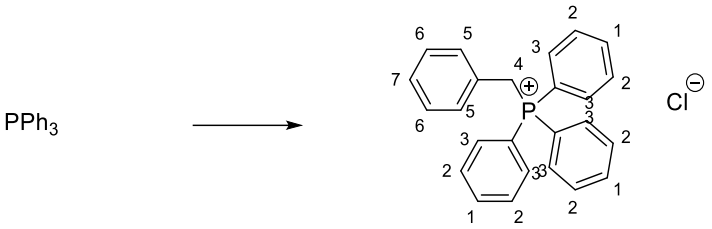
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 6.92 (m, 5H, H-1/H-2/H-3), 5.20 (app s, 1H, H-8), 5.06 (app s, 1H, H-8), 3.65 (s, 3H, H-6), 3.41 – 3.12 (m, 1H, H-4), 2.73 – 2.56 (m, 1H, H-5), 2.30 (dd, *J* = 15.3, 8.7 Hz, 1H, H-5), 1.15 (d, *J* = 6.8 Hz, 3H, H-7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 153.4, 142.1, 128.4, 127.5, 126.9, 111.5, 51.6, 40.9, 34.9, 20.0.

IR (thin film, ν_{max} / cm^{-1}) 1735, 1436, 1167, 900, 778, 702.

HRMS (ES^+) calc. for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1226.

Benzyltriphenylphosphonium chloride



FRU-864-1

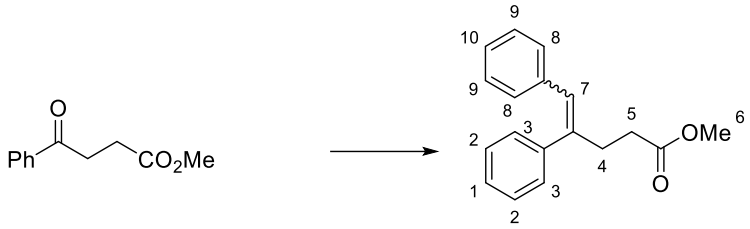
To a solution of triphenyl phosphine (5.25 g, 20.0 mmol, 1.0 eq.) in toluene (20 mL) at room temperature was added benzyl chloride (2.30 mL, 20.0 mmol, 1.0 eq.) and the reaction heated at reflux (110 °C) overnight. The white precipitate was filtered, washed with toluene (2 x 20 mL) and dried *in vacuo* to yield the product as a white solid (3.46 g, 8.9 mmol, 45%).

The analytical data matched the reported data (*EJOC*, **2009**, 5788):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.66 (m, 10H, H-1/H-2/H-3/H-5/H-6/H-7), 7.64 – 7.51 (m, 6H, H-1/H-2/H-3/H-5/H-6/H-7), 7.23 – 7.13 (m, 1H, H-1/H-2/H-3/H-5/H-6/H-7), 7.12 – 7.01 (m, 3H, H-1/H-2/H-3/H-5/H-6/H-7), 5.47 (d, *J* = 14.5 Hz, 2H, H-4).

^{13}C NMR (101 MHz, CDCl3) δ 135.0 (d, *J* = 3.0 Hz), 134.5 (d, *J* = 9.7 Hz), 131.7 (d, *J* = 5.6 Hz), 130.2 (d, *J* = 12.6 Hz), 128.9 (d, *J* = 3.3 Hz), 128.4 (d, *J* = 3.9 Hz), 127.5 (d, *J* = 8.7 Hz), 118.1 (d, *J* = 85.6 Hz), 30.7 (d, *J* = 46.4 Hz).

Methyl 4,5-diphenylpent-4-enoate, 426



FRU-869-1

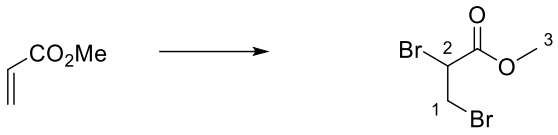
n-BuLi (1.56 mL, 3.9 mmol, 1.3 eq.) was added to a solution of benzyltriphenylphosphonium chloride (1.52 g, 3.9 mmol, 1.3 eq.) in THF (4 mL) at 0 °C. After 15 minutes the resultant solution was added to a solution of methyl 4-oxo-4-phenylbutanoate (576.6 mg, 3.0 mmol, 1.0 eq.) in THF (1 mL) and the reaction heated at reflux (66 °C) overnight. The reaction was cooled to room temperature, diluted with water (20 mL), the aqueous layer was extracted with DCM (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (30:1)) to give the ester as a colourless oil (168.4 mg, 0.63 mmol, 22%, E:Z=1:1.3).

The analytical data matched the reported data (*CL*, **2010**, 723):

NMR of E/Z isomers (ratio 1:1.3):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.3, 1.2 Hz, 3H), 7.40 (tt, *J* = 6.0, 1.8 Hz, 5H), 7.37 – 7.32 (m, 6H), 7.32 – 7.29 (m, 3H), 7.22 – 7.16 (m, 3H), 7.16 – 7.05 (m, 6H), 7.01 – 6.89 (m, 3H), 6.78 (s, 1H, H-7 (E)), 6.51 (s, 1H, H-7 (Z)), 3.67 (s, 3H), 3.62 (s, 3H), 3.09 (dd, *J* = 9.2, 7.3 Hz, 3H), 2.91 – 2.69 (m, 2H), 2.58 – 2.32 (m, 4H).

Methyl 2,3-dibromopropanoate, 446



FRU-898-1

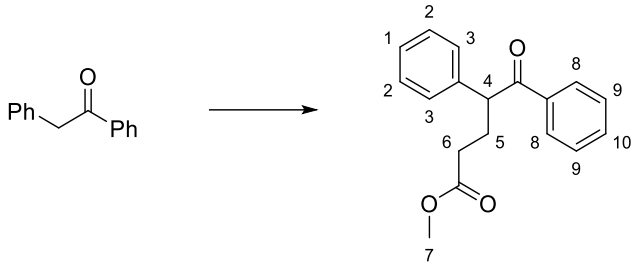
Bromine (2.0 mL, 40.0 mmol, 1.0 eq.) was added to a solution of methyl acrylate (3.2 mL, 36.2 mmol, 1.0 eq.) in DCM (40 mL) at 0 °C and was allowed to warm to rt. The reaction was stirred overnight, cooled to 0 °C and quenched with NaS_2O_3 (10 mL). The layers were separated, and the aqueous layer extracted with DCM (1 x 10 mL). the combined organic layers were dried ($MgSO_4$) and concentrated to afford the desired dibromide as a colourless oil (8.53 g, 34.7 mmol, 96%).

The analytical data matched the reported data (*OL*, **2019**, 3281):

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (dd, *J* = 11.3, 4.4 Hz, 1H, H-2), 3.98 – 3.87 (m, 1H, H-1), 3.84 (s, 3H, H-3), 3.68 (dd, *J* = 9.9, 4.4 Hz, 1H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 53.5, 40.9, 29.8.

Methyl 5-oxo-4,5-diphenylpentanoate, 443



FRU-905-2

To a solution of phenylacetophenone (197.0 mg, 1.00 mmol, 1.0 eq.) in THF (3 mL) at 0 °C was added potassium *tert*-butoxide (1 M solution in THF, 0.10 mL, 0.1 mmol, 0.1 eq.) and methyl acrylate (0.09 mL, 1.0 mmol, 1.0 eq.). After 45 minutes, the reaction was warmed to rt and the solvent removed *in vacuo*. The crude was purified via flash column chromatography (petroleum ether / EtOAc (100:1) to (5:1)) to give the ester as a colourless oil (149.8 mg, 0.53 mmol, 54%).

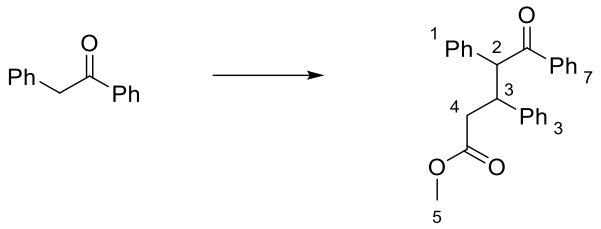
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 – 7.63 (m, 2H, H-1/H-2/H-3/H-8/H-9/H-10), 7.53 – 7.44 (m, 1H, H-1/H-2/H-3/H-8/H-9/H-10), 7.43 – 7.33 (m, 2H, H-1/H-2/H-3/H-8/H-9/H-10), 7.32 – 7.27 (m, 4H, H-1/H-2/H-3/H-8/H-9/H-10), 7.24 – 7.18 (m, 1H, H-1/H-2/H-3/H-8/H-9/H-10), 4.67 (t, *J* = 7.3 Hz, 1H, H-4), 3.65 (s, 3H, H-7), 2.61 – 2.39 (m, 1H, H-6), 2.31 (dd, *J* = 7.8, 6.5 Hz, 2H, H-5, H-6), 2.26 – 2.10 (m, 1H, H-5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 173.8, 138.9, 136.8, 133.1, 129.2, 128.9, 128.7, 128.5, 127.4, 52.6, 51.7, 31.7, 28.9.

IR (thin film, ν_{max} / cm^{-1}) 1733, 1679, 1447, 1214, 1175, 698.

HRMS (ES^+) calc. for $C_{18}H_{18}O_3Na$ $[M+Na]^+$ 305.1148, found 305.1147.

Methyl 5-oxo-3,4,5-triphenylpentanoate, 445



FRU-907-1

To a solution of phenylacetophenone (197.0 mg, 1.00 mmol, 1.0 eq.) in THF (3 mL) at 0 °C was added potassium *tert*-butoxide (1M solution in THF, 0.10 mL, 0.1 mmol, 0.1 eq.) and methyl cinnamate (162.2 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred overnight, diluted with water (10 mL) and Et_2O (5 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / EtOAc (100:1) to (5:1)) to give the ester (80.6 mg, 0.22 mmol, 23%, mixture of diastereomers 1:1.3) as a white solid.

NMR of diastereomeric mixture (ratio 1:1.3):

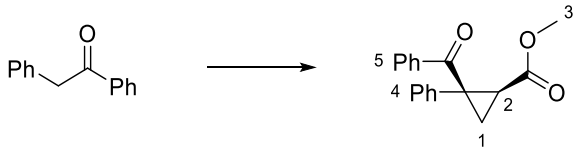
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dt, *J* = 8.6, 1.7 Hz, 3H), 7.81 (dd, *J* = 8.4, 1.3 Hz, 4H), 7.58 – 7.45 (m, 7H), 7.46 – 7.17 (m, 28H), 7.17 – 6.96 (m, 20H), 5.09 (d, *J* = 11.0 Hz, 1H), 4.95 (d, *J* = 10.6 Hz, 1H), 4.20 (ddd, *J* = 11.0, 8.9, 5.8 Hz, 2H), 4.10 (td, *J* = 10.0, 4.5 Hz, 1H), 3.49 (s, 3H, H-5 ds1), 3.41 (s, 4H, H-5 ds2), 2.98 – 2.76 (m, 2H), 2.61 – 2.43 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 198.5, 172.3, 172.2, 142.2, 141.0, 137.1, 137.0, 136.8, 133.2, 132.8, 129.2, 129.0, 128.7, 128.7, 128.5, 128.5, 128.4, 128.4, 128.1, 128.1, 127.8, 127.1, 126.8, 126.6, 58.8, 58.6, 51.5, 51.4, 45.8, 45.0, 39.2, 39.1.

IR (thin film, ν_{max} / cm^{-1}) 1735, 1678, 1448, 1266, 698.

HRMS (ES^+) calc. for $C_{24}H_{22}O_3Na$ $[M+Na]^+$ 381.1461, found 381.1461.

Methyl *cis*-2-benzoyl-2-phenylcyclopropane-1-carboxylate, 447



FRU-939-1

To a vigorously stirred solution of phenylacetophenone (7.04 g, 35.9 mmol, 1.0 eq.) in DCM (180 mL) at 0 °C was added NaOH (50% w/w in water, 11.5 mL, 215 mmol, 6.0 eq.), benzyltriethyl ammonium chloride (16.4 g, 71.8 mmol, 2.0 eq.) and methyl 2,3-dibromopropanoate (5.0 mL, 39.5 mmol, 1.1 eq.). After 3 hours, the reaction was quenched with water (50 mL), the layers separated, and the aqueous layer was extracted with DCM (1 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / EtOAc (20:1) to (8:1)) to give the ester as a white solid (2.14 g, 7.63 mmol, 22%).

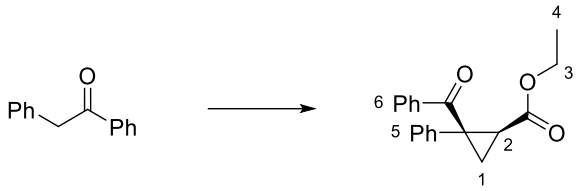
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.67 (m, 2H, H-5), 7.47 – 7.34 (m, 1H, H-4/H-5), 7.34 – 7.14 (m, 7H, H-4/H-5), 3.42 (s, 3H, H-3), 3.12 (dd, *J* = 8.4, 6.4 Hz, 1H, H-2), 2.43 (dd, *J* = 6.4, 4.9 Hz, 1H, H-1), 1.67 (dd, *J* = 8.4, 4.9 Hz, 1H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1, 170.1, 136.1, 135.0, 132.6, 129.9, 129.6, 128.5, 128.2, 127.8, 51.9, 43.6, 27.5, 18.7.

IR (thin film, ν_{max} / cm^{-1}) 1735, 1677, 1447, 1265, 1204, 1171.

HRMS (ES^+) calc. for $C_{18}H_{17}O_3$ $[M+H]^+$ 281.1172, found 281.1174.

Ethyl *cis*-benzoyl-2-phenylcyclopropane-1-carboxylate



FRU-944-1

To a vigorously stirred solution of phenylacetophenone (98.1 mg, 0.50 mmol, 1.0 eq.) in DCM (2.5 mL) at 0 °C was added NaOH (50% w/w in water, 0.27 mL, 5.0 mmol, 10.0 eq.), benzyltriethyl ammonium chloride (2.3 mg, 0.01 mmol, 0.02 eq.) and ethyl 2,3-dichloropropanoate (0.10 mL, 0.65 mmol, 1.3 eq.). After 3 hours, the reaction was quenched with water (4 mL), the aqueous layer was extracted with Et_2O (2 x 4 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography on silica gel (petroleum ether / EtOAc (20:1) to (8:1)) to give the ester as a white solid (20.8 mg, 0.08 mmol, 14%).

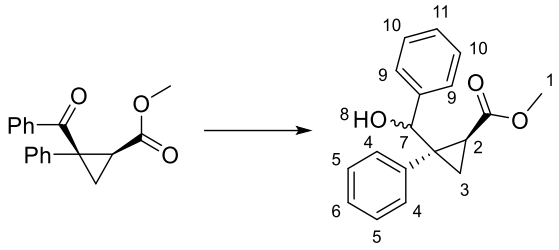
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.64 (m, 2H, H-6), 7.45 – 7.34 (m, 1H, H-5/H-6), 7.34 – 6.96 (m, 7H, H-5/H-6), 3.85 (qd, *J* = 7.1, 3.0 Hz, 2H, H-3), 3.11 (dd, *J* = 8.4, 6.4 Hz, 1H, H-2), 2.43 (dd, *J* = 6.4, 4.9 Hz, 1H, H-1), 1.65 (dd, *J* = 8.4, 4.9 Hz, 1H, H-1), 0.96 (t, *J* = 7.1 Hz, 3H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2, 169.5, 136.2, 135.1, 132.5, 130.0, 129.5, 128.5, 128.2, 127.7, 60.7, 43.5, 27.4, 18.6, 14.1.

IR (thin film, ν_{max} / cm^{-1}) 1728, 1674, 1262, 1171, 1002, 697.

HRMS (ES^+) calc. for $C_{19}H_{18}O_3Na$ $[M+Na]^+$ 317.1148, found 317.1148.

Methyl *cis*-2-(hydroxy(phenyl)methyl)-2-phenylcyclopropane-1-carboxylate, 447



FRU-912

To methanol (8 mL) at 0 °C was added sodium borohydride (0.29 g, 7.6 mmol, 1.0 eq.) and then dropwise a solution of methyl *cis*-2-benzoyl-2-phenylcyclopropane-1-carboxylate (2.14 g, 7.6 mmol, 1.0 eq.) in methanol (2 mL). After 1.5 hours, the reaction was quenched with 1N. HCl (30 mL). The reaction was warmed to rt, extracted with Et_2O (3 x 30 mL), and the combined organic layers washed with brine (30 mL), dried ($MgSO_4$) and concentrated. The crude material was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (2:1)) to give the alcohol as a colourless oil (1.56 g, 5.5 mmol, 73%, 1:1 mixture of diastereomers).

Diastereomer 1

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.29 (m, 2H, Ar-H), 7.24 (dd, *J* = 3.6, 1.3 Hz, 2H, Ar-H), 7.19 – 7.11 (m, 2H, Ar-H), 7.14 – 7.02 (m, 2H, Ar-H), 7.01 – 6.86 (m, 2H, Ar-H), 4.87 (d, *J* = 3.8 Hz, 1H, H-6), 3.44 (s, 3H, H-3), 2.48 (dd, *J* = 8.2, 5.6 Hz, 1H, H-2), 1.71 (dd, *J* = 5.6, 4.7 Hz, 1H, H-1), 1.63 (dd, *J* = 8.2, 4.7 Hz, 1H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 141.6, 137.7, 130.7, 129.0, 128.6, 128.0, 127.1, 126.8, 51.7, 41.4, 32.1, 23.9, 15.0.

Diastereomer 2

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.14 (m, 6H, Ar-H), 7.05 (ddt, *J* = 9.6, 4.5, 2.5 Hz, 4H, Ar-H), 4.59 (d, *J* = 3.5 Hz, 1H, H-6), 3.44 (s, 3H, H-3), 2.22 (dd, *J* = 8.1, 5.7 Hz, 1H, H-2), 2.07 (d, *J* = 3.6 Hz, 1H, H-7), 1.72 – 1.61 (m, 1H, H-1), 1.48 (dd, *J* = 8.1, 4.9 Hz, 1H, H-1).

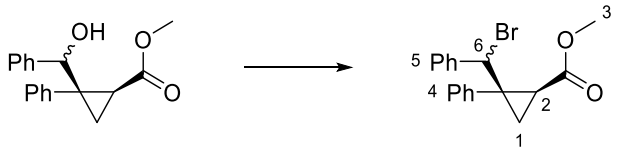
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 140.8, 136.8, 131.0, 128.1, 128.1, 127.9, 127.5, 126.9, 79.9, 51.8, 41.5, 25.6, 15.8.

Mixture of ds:

IR (thin film, ν_{max} / cm^{-1}) 3459, 1718, 1440, 1219, 1168, 670.

HRMS (ES^+) calc. for $C_{18}H_{18}O_3Na$ $[M+Na]^+$ 305.1148, found 305.1148.

Methyl *cis*-2-(bromo(phenyl)methyl)-2-phenylcyclopropane-1-carboxylate, 448



FRU-945-1/FRU-913-1 (C NMR)

To a solution of methyl cis-2-(hydroxy(phenyl)methyl)-2-phenylcyclopropane-1-carboxylate (1.56 g, 5.5 mmol, 1.0 eq.) in DCM (25 mL) at 0 °C was added carbon tetrabromide (1.92 g, 5.8 mmol, 1.05 eq.) and then triphenylphosphine (1.52 g, 5.8 mmol, 1.05 eq.). After 1.5 hours, the reaction was warmed to rt and concentrated *in vacuo*. The crude material was purified *via* flash column chromatography on silica gel (petroleum ether / Et_2O (15:1) to (10:1)) to give the bromide as a colourless oil (0.81 g, 2.4 mmol, 43%, 1:1 mixture of diastereomers).

Data are of a mixture of diastereomers:

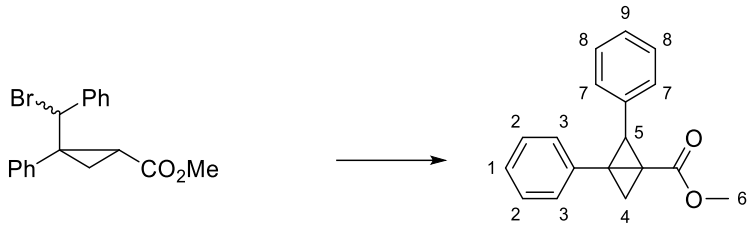
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.06 (m, 10H, H-4/H-5), 7.01 – 6.88 (m, 3H, H-4/H-5), 5.05 (s, 1H, H-6), 4.95 (s, 0H), 3.47 (s, 1H), 3.39 (s, 3H, H-3), 2.55 (dd, *J* = 8.3, 5.8 Hz, 1H, H-2), 2.20 (dd, *J* = 8.3, 6.1 Hz, 0H), 1.95 – 1.88 (m, 1H, H-1), 1.89 – 1.85 (m, 0H), 1.68 (dd, *J* = 8.3, 5.1 Hz, 1H, H-1), 1.66 – 1.62 (m, 0H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 139.2, 138.5, 136.5, 135.9, 131.4, 131.3, 128.8, 128.6, 128.6, 128.5, 128.1, 127.8, 127.8, 127.7, 63.4, 62.9, 52.0, 51.9, 41.5, 41.2, 29.1, 28.7, 20.0, 19.2.

IR (thin film, ν_{max} / cm^{-1}) 1734, 1446, 1383, 1212, 1169, 706.

HRMS (ES^+) calc. for $C_{18}H_{17}O_2BrNa$ $[M+Na]^+$ 367.0304, found 367.0305.

Methyl 2,3-diphenylbicyclo[1.1.0]butane-1-carboxylate, 377



FRU-946-1 (scale)/ FRU-916-2 (analytical data)

n-Butyllithium (2.5M / hex, 1.10 mL, 2.76 mmol, 1.2 eq.) was added to a solution of DIPA (0.42 mL, 3.0 mmol, 1.3 eq.) in THF (4 mL) at –78 °C. After 5 minutes this solution was added dropwise to methyl cis-2-(bromo(phenyl)methyl)-2-phenylcyclopropane-1-carboxylate (0.81 g, 2.3 mmol, 1.0 eq.) in THF (4mL) at –78 °C. The reaction was stirred for 15 minutes and quenched in the cold with NH_4Cl (sat, 3 mL). After warming to room temperature, the reaction was diluted with water (1 mL) and ether (2 mL), the layers were separated, the aqueous layer was extracted with Et_2O (2 x 2 mL), and the combined organic layers dried ($MgSO_4$) and concentrated. The crude was purified *via* flash column chromatography (petroleum ether / Et_2O (15:1)) to give the bicyclobutane as a white solid (237.2 mg, 0.90 mmol, 40%, 1:1 mixture of diastereomers).

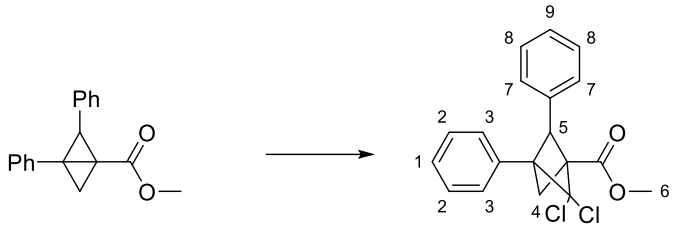
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.11 (m, 20H), 7.03 – 6.91 (m, 1H), 6.76 (s, 0H), 4.82 (d, *J* = 4.7 Hz, 1H), 3.66 (s, 2H, H-6 ds1), 3.56 (s, 3H, H-6 ds2), 3.11 (dd, *J* = 4.6, 2.4 Hz, 1H), 2.65 (d, *J* = 7.2 Hz, 1H), 2.50 – 2.33 (m, 0H), 2.05 (s, 0H), 1.89 (d, *J* = 2.3 Hz, 1H), 1.50 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 134.8, 134.1, 129.4, 128.8, 128.7, 128.6, 128.5, 128.4, 127.5, 127.2, 127.1, 126.8, 126.5, 126.5, 126.2, 53.5, 52.1, 51.8, 51.3, 39.4, 36.5, 35.4.

IR (thin film, ν_{max} / cm^{-1}) 1712, 1441, 1328, 1199, 1153.

HRMS (ES^+) calc. for $C_{18}H_{17}O_2$ $[M+H]^+$ 265.1223, found 265.1225.

Methyl 2,2-dichloro-3,4-diphenylbicyclo[1.1.1]pentane-1-carboxylate, 449, 450



FRU-947-6

A solution of methyl 2,3-diphenylbicyclo[1.1.0]butane-1-carboxylate (233.9 mg, 0.90 mmol, 1.0 eq.) in tetrachloroethylene (7.5 mL) and diglyme (1.5 mL) was heated to 120°C. Sodium trichloroacetate (0.59 g, 3.15 mmol, 3.5 eq.) was added and the temperature raised to 140 °C. Heating was continued overnight, the reaction cooled to room temperature and consumption of starting material monitored by crude NMR. This addition/heating cycle was repeated 4 more times (5 in total) until the starting material was fully consumed. The reaction was filtered through celite (rinse with Et_2O) and the crude was purified *via* flash column chromatography on silica gel (petroleum ether / EtOAc (40:1)) to give the bicyclobutane as a white solid (28.8 mg, 0.08 mmol, 10%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.15 (m, 3H, Ar-H), 7.08 (app dd, *J* = 7.8, 1.7 Hz, 2H, Ar-H), 7.01 (app dd, *J* = 5.2, 1.9 Hz, 2H, Ar-H), 6.84 (app dd, *J* = 6.6, 2.9 Hz, 2H, Ar-H), 6.67 (app s, 1H, Ar-H), 5.55 (s, 1H, H-5), 3.93 (s, 1H, H-4), 3.63 (s, 3H, H-6), 3.37 (s, 1H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 139.9, 137.2, 136.6, 130.8, 129.1, 128.6, 127.9, 117.3, 61.8, 53.4, 52.4, 52.2, 42.9, 30.3.

IR (thin film, ν_{max} / cm^{-1}) 1731, 1276, 1203, 834, 698.

HRMS (ES^+) calc. for $C_{19}H_{16}O_2Cl_2Na$ $[M+Na]^+$ 369.0420, found 369.0421.

The aromatic region of both proton and carbon spectrum are not very clean and the picked peaks might not be an accurate depiction of the aromatic substituents' environment.

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